REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF NEUROGENIC OVERACTIVE BLADDER IN STROKE SURVIVORS

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Repetitive Transcranial Magnetic Stimulation for the Treatment of Neurogenic Overactive Bladder in Stroke Survivors

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CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma except where due acknowledgement has been made in the text.

_____(Signed)

Mohammed Usman Ali (Name of student)

DEDICATION

I dedicate my PhD thesis to my beloved father, Malam Usman Muhammad Ali.

ABSTRACT

Background: Neurogenic overactive bladder (OAB) causes significant distress to stroke survivors. Current treatments for neurogenic OAB are invasive, expensive, or lack standardized regimens. Therefore, evaluating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for managing neurogenic OAB among stroke survivors remains crucial.

Objectives: To (1) determine the effects of nonsurgical, minimally or non-invasive therapies on urgency urinary incontinence (UUI) in neurogenic OAB, (2) identify psychometrically sound measures for assessing OAB symptoms, (3) identify psychometrically sound measures for evaluating quality of life in neurogenic OAB, (4) investigate the effectiveness of active rTMS compared to sham rTMS in alleviating neurogenic OAB symptoms among stroke survivors, (5) estimate the cost of active and sham rTMS in managing neurogenic OAB symptoms among stroke survivors, (6) explore the experiences of stroke survivors with neurogenic OAB symptoms after rTMS.

Methods: A meta-analysis was conducted to determine the effects of non-invasive therapies on UUI symptoms in neurogenic OAB. Two systematic reviews were conducted to identify psychometrically sound measures for evaluating OAB symptoms and quality of life in neurological disorders. A total of 110 stroke survivors with neurogenic OAB symptoms were screened for eligibility; 60 participants were eligible

and were randomly assigned to either the active (n = 30) or sham rTMS (n = 30) groups. The active rTMS group received low-frequency rTMS of 1200 pulses per session lasting 20 min thrice weekly. The sham rTMS group received low-frequency stimulation at a 20 % resting motor threshold. The primary (Overactive Bladder Symptom Score [OABSS]) and secondary (Incontinence Quality of Life [I-QOL] and Brief Resilience Scale [BRS]) outcome measures were assessed. The analysis of covariance (ANCOVA) analysis compared changes in the study groups. An estimate of the mean cost per patient was determined for study groups. Thematic analysis was utilised to explore the experiences of participants after active rTMS.

Results: The meta-analysis revealed that electrical stimulations (intravaginal and neuromuscular stimulations) are efficacious in decreasing UUI symptoms due to multiple sclerosis and stroke. Among the identified clinical tools for neurogenic OAB symptoms and quality of life, OABSS and I-QOL, respectively, were the most psychometrically sound. The between-group mean difference (MD) of OABSS (effect size [ES]: 0.62) at the primary and secondary endpoints were 1.66 (95% CI = 1.22–2.10, $p < 0.001$) and 1.81 (95% CI = 1.42–2.20, $p < 0.001$), respectively. The between-group MD of I-QOL (ES: 0.74) at the primary and secondary endpoints were 16.50 (95% CI = 13.73–19.28, $p < 0.001$) and 17.48 (95% CI = 14.18–20.79, $p < 0.001$), respectively. The between-group MD of BRS (ES: 0.10) differed significantly between the active and sham rTMS groups at the primary (MD = 0.12, 95% CI = 0.20–0.22, $p = 0.018$) and secondary (MD = 0.25, 95% CI = 0.09–0.41, $p = 0.002$) endpoints. The cost-effectiveness (expressed as the cost-utility) study also identified a lower cost in the active rTMS group compared to the sham rTMS group. The active rTMS participants demonstrated positive experiences following the intervention.

Conclusion: Low-frequency rTMS is a promising therapeutic approach for addressing neurogenic OAB symptom severity among stroke survivors.

LIST OF PUBLICATIONS DURING THE COURSE OF PhD STUDY

Ph.D. related articles:

1. **Ali, M. U.,** Fong, K. N. K., Kannan, P., Bello, U. M., & Kranz, G.S. (2022). Effects of nonsurgical, minimally or non-invasive therapies for urinary incontinence due to neurogenic bladder: a systematic review and meta-analysis. ***Therapeutic advances in chronic disease***, 13: 20406223211063059, https://doi:10.1177/20406223211063059. [Appendix A1]

2. **Ali, M.U.,** Fong, K.N, Kannan, P., Winser, J.S., U.M Bello, D. Salihu., Kranz, G.S. (2023) Measures for evaluating the quality of life among people with neurogenic overactive bladder: A systematic review of psychometric properties. ***European Journal of Obstetrics & Gynecology and Reproductive Biology.*** https://doi.org/10.1016/j.ejogrb.2023.11.010 [Appendix A2]

3. **Ali, M.U.,** Kranz, G.S., Fong, K.N.K., Kannan, P., (2024) Does repetitive transcranial magnetic stimulation (rTMS) induce long-lasting neuroplastic changes to improve detrusor muscle function among stroke survivors with neurogenic overactive bladder? ***Medical Hypotheses.*** https://doi.org/10.1016/j.mehy.2024.111300 [Appendix A3]

4. **Ali, M.U.,** Kwan, C., Fong, K.N.K., Kranz, G.S., Winser, S.J., Kannan, P. (2024), Evaluating repetitive transcranial magnetic stimulation for neurogenic overactive bladder management in stroke survivors: A randomised sham-controlled trial protocol. ***European Journal of Obstetrics & Gynecology and Reproductive Biology.*** https://doi.org/10.1016/j.ejogrb.2024.07.034 [Appendix A4]

5. **Ali, M.U.,** Winser, J.S., Kannan, P., Kranz, G.S., Fong, K.N. (2024) "Clinical tools for evaluating the severity of overactive bladder: A systematic review of psychometric properties" ***Clinical Rehabilitation.*** https://doi.org/10.1177/02692155231225662 [Appendix A5]

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1. Khan, M. J., **Ali, M. U.,** Ganesan, B., Abdullahi, A., Hasan, S. M., Khan, A. R., ... & Winser, S. J. (2025). A Nationwide Cross-Sectional Survey of the Prevalence of and Association of Physical Activity With Suicidal, Psychosocial and Health-Risk Indicators Among Adolescents in Bangladesh. *Child: care, health and development*, *51*(1), e70021.https://doi.org/10.1111/cch.70021

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LIST OF CONFERENCE PRESENTATIONS ARISING FROM THE THESIS

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3. **Ali, M.U.,** Fong, K.N., Kranz, G.S., Kannan, P. Randomised Controlled Trials Assessing Efficacy of Neurogenic Overactive Bladder Therapies: A Meta-Analysis. **Hong Kong Physiotherapy Association (HKPA) 60th Anniversary Conference 23 to 25 June 2023 [Poster Presentation-P 25]**

4. **Ali, M.U.,** Winser, S.J., Kannan, P., Kranz, G.S., Fong, K.N. Measures for evaluating the severity of urge urinary incontinence among people with overactive bladder: A systematic review of psychometric properties. **World Physiotherapy Asia Western Pacific (AWP) Regional Congress with Hong Kong Physiotherapy Association (HKPA) Conference 18 to 20 June 2022 [Platform Presentation]**

5. **Ali, M.U.,** Fong, K.N., Kannan, P., Bello, U.M., Kranz, G.S. Effects of non-surgical, minimally or non-invasive therapies for urinary incontinence due to neurogenic bladder: A systematic review and meta-analysis. **12th Pan-Pacific Conference on Rehabilitation (PPCR), 27 and 28 November 2021, Hong Kong. (Virtual). [Platform Presentation]**

LIST OF CONFERENCE PRESENTATIONS NON-RELATED TO THE THESIS

1. Liu, X., **Ali, M.U.,** Khan, M.J., Kannan, P., Cheing, G. The effectiveness of invasive and non-invasive biofeedback for treatment of stress urinary incontinence in women: a systematic review with meta-analysis and meta-regression of randomised controlled trials. **World Physiotherapy Asia Western Pacific (AWP) Regional Congress with Hong Kong Physiotherapy Association (HKPA) Conference 18 to 20 June 2022 [Accepted Platform Presentation]**

2. Maina, H.A., Bello, U.M., Muhammad, A.S., Mahmud, F.A., Jalo, H.A., Sulaiman, S.K. **Ali, M.U**. & Bello, I.M. Effect of telerehabilitation in facilitating upper extremity home programs and associated functional regain among chronic stroke survivors: a pilot study. **8Th European Stroke Organization Conference (ESOC) 2022, Lyon, May 4 – 6 (Virtual). [Poster presentation]**

3. Bello, U.M., Chutiyami, M., Salihu, D., Muhammad, A.S., Kannan, P., Pun, J.W., Mahmud, F.A., Jalo, H.A., **Ali, M.U**., Maharaj, R., Miller, T., Bello, I.M. & Winser, S.J. Effect of Covid-19 Pandemic on the Prevalence of Anxiety and Depression among the General Population in Nigeria: A Systematic Review –

Nigeria Society of Physiotherapy 61st Scientific Conference 2021, Jigawa, Nigeria, 1-5 November 2021. (Virtual). [Platform presentation]

4. Ali, H.M., Bello, U.M., Muhammad, A.S., Mahmud, F.A., Sa'ad, F.S., Shitu, A., Jalo, H.A., Sulaiman, S.K., **Ali, M.U.,** Effect of Telerehabilitation in Facilitating Upper Extremity Home Programs and Associated Functional Regain Among Chronic Post-Stroke Patients: A Pilot Study. **Nigeria Society of Physiotherapy 61st Scientific conference, Jigawa, Nigeria, 1 to 5 November 2021 (Virtual). [Platform Presentation]**

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

APPENDICES

LIST OF ABBREVIATIONS

ABSST: Actionable bladder symptom screening tool.

ANCOVA: Analysis of covariance.

ATP: Adenosine triphosphate.

BFLUTS: Bristol female lower urinary tract symptoms instrument.

BRS: Brief resilience scale.

B-SAQ: Bladder control self-assessment questionnaire.

CI: Confidence interval.

COSMIN: COnsensus-based standards for selecting health status measurement instruments.

CSRI: Client service recipient inventory.

DALYs: Disability-adjusted life years.

DAN-PSS-1: Danish prostate symptom score.

EEG: Electroencephalography.

EMG: Electromyography.

FDA: Food and drug administration.

fMRI: Functional magnetic resonance imaging.

GRADE: Grading of recommendations, assessment, development, and evaluation.

ICC: Intra-class correlation coefficient.

ICER: Incremental cost-effectiveness ratio.

ICIQ-BD: International consultation on incontinence questionnaire bladder diary.

ICIQ-FLUTS: International consultation on incontinence questionnaire in females lower urinary tract symptoms.

ICIQ-MLUTS: International consultations on incontinence questionnaire in male's lower urinary tract symptoms.

ICIQ-OAB: International consultation on incontinence questionnaire.

ICIQ-OABqol: International consultation on incontinence questionnaire overactive bladder symptoms quality of life.

ICIQ-UI-SF: International consultation on incontinence questionnaire-urinary incontinence short form.

ICS: International continence society.

IIQ: Incontinence impact questionnaire.

IIQ-7: Incontinence impact quality of life.

IIQ-7: SF-Incontinence impact questionnaire.

I-QOL: Incontinence quality of life questionnaire.

ISS: Incontinence symptom severity.

ISS: Incontinence symptom severity index.

IUI: Incontinence utility index.

IUI: Incontinence utility index.

IUSS: Indevus urgency severity scale.

IVES: intravaginal electrical stimulation.

KHQ: King health questionnaire.

LTD: Long-term depression.

LTP: Long-term potentiation.

M1: Primary motor cortex.

MCID: Minimal clinically important difference.

MEPs: Motor-evoked potentials.

MTR: Mass transit railway.

NBSS: Neurogenic bladder symptom score questionnaire.

NHS: National Health Service.

NICE: National institute for health and care excellence.

NMDA: N-methyl D-aspartate.

NMES: Neuromuscular electrical stimulation.

OAB: Overactive bladder.

OAB-BAT: Overactive bladder questionnaire bladder assessment tool.

OAB-q: Overactive bladder questionnaire.

OAB-SAT-q: Overactive bladder satisfaction with treatment questionnaire.

OABSS: Overactive bladder symptom score.

OAB-V8: Overactive bladder-validated 8-question.

PAG: Periaqueductal gray.

PEDro: Physiotherapy evidence database.

PFLUTS: Persian female lower urinary tract symptoms.

PFMT: Pelvic floor muscle training.

PMC: Pontine micturition center.

PPIUS: Patients' perception of the intensity of urgency scale.

PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

PROSPERO: Prospective register of systematic reviews.

QALY: Quality-adjusted life-years.

RCT: Randomised controlled trial.

rTMS: Repetitive transcranial magnetic stimulation.

ROB: Risk of bias.

SF-Qualiveen: Short form Qualiveen.

SMDs: Standardised mean differences.

SUR: Seemingly unrelated regression.

TENS: Transcutaneous electrical nerve stimulation.

TTNS: Transcutaneous tibial nerve stimulation.

UDI-6: Urogenital distress inventory.

UQ: Urgency questionnaire.

UUI: Urgency urinary incontinence.

WMDs: Weighted mean differences.

WTP: Willingness to pay.

Chapter 1

Introduction

This thesis focuses on the clinical and cost-effectiveness (expressed as the cost-utility) of repetitive transcranial magnetic stimulation (rTMS) for treating neurogenic overactive bladder (OAB) symptoms in stroke survivors. This chapter provides an overview of stroke, OAB, and rTMS. It begins with a brief overview of stroke, including its epidemiology, risk factors, and clinical features. Next, it explains the definition, prevalence, aetiology, physiology, pathophysiology, individual and societal impacts, and economic impact of OAB. Then, it provides a brief background on TMS and the mechanisms of rTMS in neurogenic OAB. Finally, it concludes with the study's aims, research questions, hypotheses, and the structure of the thesis.

1.1 Stroke

1.1.1 Overview of stroke

The World Health Organisation defines stroke as 'rapidly developing clinical signs of (usually focal) disturbance of cerebral function lasting for more than 24 hours or leading to death, with no apparent cause other than of vascular origin' [1, 2]. Stroke is the second leading cause of mortality globally, after ischaemic heart disease, and ranks third in disability, as measured by disability-adjusted life years (DALYs) lost [3].

Despite advances in preventive strategies and a decrease in age-adjusted stroke incidence over the last decade, approximately 77 million individuals are affected by stroke annually worldwide [3]. It has been estimated that 12% of stroke survivors are lost annually, and 50% experience chronic disability, resulting in a significant clinical and economic burden [2].

Stroke is not a singular disease but a condition caused by various modifiable and non-modifiable risk factors [4]. Hypertension is a major modifiable risk factor, contributing to over 80% of stroke cases globally, although its distribution varies among different stroke subtypes [4]. Most strokes (85%) are predominantly ischaemic, resulting from cardioembolism, arteriolosclerosis, and atherothromboembolism [5]. However, approximately 15% of strokes globally result from intracerebral haemorrhage [5]. Other risk factors for stroke include diabetes mellitus, obesity smoking, lipid profile, atrial fibrillation, cardiac failure and myocardial infarction [4].

Ischemic stroke occurs when the cerebral arteries are blocked, with different types of occlusion accounting for varying proportions of cases [6]. Thrombotic or atherosclerotic occlusion, embolic occlusion, and small-vessel occlusion/lacunar stroke account for approximately 50%, 25%, and 25% of cases, respectively [7-9]. Blood vessel occlusions reduce the blood supply to specific brain regions by narrowing blood vessel lumens and triggering an ischemic cascade [8, 10]. If ischemia persists for more than 24 hours, it can cause oxygen deprivation, leading to the cessation of neural function unless reperfusion occurs to salvage the cells in the penumbra [11, 12].

Another significant occurrence in ischemic tissue is the activation of anaerobic glycolysis [13], primarily due to the inhibition of mitochondrial metabolism caused by oxygen deprivation [13].

Embolic infarction occurs when a thrombus formed elsewhere in the circulatory system migrates and occludes distal cerebral arteries, leading to a lack of perfusion in brain tissue and subsequent cerebral ischemia, often associated with atrial fibrillation [14]. The embolic infarction depletes brain tissue energy, leading to anaerobic metabolism, reduced production of cellular adenosine triphosphate, degradation of macromolecules and the presence of lactic acid, which disrupts ion homeostasis and normal acid-base balance in the brain [13].

Haemorrhagic stroke occurs primarily from the spontaneous rupture of blood vessels or aneurysms in the brain or trauma [15]. This type of stroke includes different forms, such as intracerebral, subarachnoid, intraventricular and subdural haemorrhages [15]. Haemorrhagic strokes are classified based on their underlying pathology [15]. Intracerebral haemorrhages typically occur in the supratentorial region (85%–95%) [16], with the predominant aetiological factors being hypertension (30%–60%), cerebral amyloid angiopathy (10%–30%), anticoagulation (1%–20%) and vascular structural abnormalities (3%–8%) [16]. These types of strokes result in brain tissue damage due to compression caused by the expansion of a hematoma [17]. This compression can damage and distort the brain tissue, and the pressure can lead to

hypoxia, inducing infarction [17]. Additionally, the haematoma appears to have harmful effects on both the brain tissue and the blood vessels [18].

1.1.2 Epidemiology of stroke

The global incidence and prevalence of stroke have significantly increased by 70% and 85%, respectively, over the last three decades [19]. According to the Global Burden of Disease Study 2021, stroke resulted in an estimated 2.59 million deaths and 55.2 million DALYs [20]. The incidence of stroke among the Chinese population accounted for over one-third of global annual cases of stroke [21]. A recent population-based study utilizing a nationally representative survey estimated that around 2.6% of individuals over the age of 40 in China have experienced a stroke [21]. The study also found that the incidence rate is approximately 505.2 new stroke cases per 100,000 person-years, and the mortality rate is about 343.4 deaths per 100,000 person-years [21]. Mortalities and DALYs attributed to stroke have also increased by 43% and 32%, respectively. This increase in stroke burden has been notably higher in low and middle-income countries than in high-income countries [19]. Interestingly, studies in high-income countries have demonstrated a substantial decline in age-standardised stroke incidence and mortality, with a reduction of 42% in stroke incidence over the last four decades [22, 23]. However, low and middle-income countries have experienced a staggering 100% increase in stroke incidence, with 70% of stroke cases and 87% of stroke-related mortalities and DALYs occurring in these regions [23].

The incidence of stroke tends to double with each decade after the age of 55 [2]. Among adults aged 35–44 years, the annual incidence of stroke ranges from 30 to 120 cases per 100,000 individuals [24]. The incidence is even higher for those aged 65–74 years, ranging from 670 to 970 cases per 100,000 individuals [25]. While among adults aged ≥75 years, it rises to 1151 to 1216 cases per 100,000 individuals [25]. Additionally, women tend to have strokes at a younger age, with an adjusted incidence rate 1.25 times greater than that of men [26, 27].

1.1.3 Risk factors of stroke

According to the American Stroke Association [28, 29], there are several modifiable risk factors for stroke, such as hypertension (stroke -level: 180/120 mmHg), diabetes mellitus, smoking (20 cigarettes per day), high cholesterol (higher than 130 milligrams per deciliter [mg/dL]), reduced physical activity, abdominal obesity, atrial fibrillation, haematological disorders (such as sickle cell anaemia), excessive alcohol consumption (five or more drinks per day) and illegal drug use (such as cocaine, heroin and amphetamines). These factors can be modified or controlled to reduce the risk of stroke through lifestyle modification, medication, and other clinical interventions [30, 31]. Hypertension, high cholesterol, carotid stenosis and atrial fibrillation have been associated with an increased risk of stroke [31-34]. Clinical trials have provided evidence that interventions targeting modifiable risk factors can effectively decrease the incidence of stroke [31-34]. Hypertension is the most significant modifiable risk factor globally, accounting for approximately 80% of stroke cases [31, 35]. The risk

associated with hypertension declines after the age of 60, where it has a relative risk of 3.5, and becomes an insignificant risk factor by the age of 80 [4].

Furthermore, according to the American Stroke Association, non-modifiable risk factors for stroke include advancing age, sex, race-ethnicity and genetics or family history [30, 31]. The risk of developing stroke increases significantly after the age of 55, nearly doubling in incidence [36]. The higher prevalence of stroke in females than in males globally may be attributed mainly to their longer life expectancy [37]. Since females tend to live longer than males on average, they are at greater risk of having a stroke [37]. Additionally, females are more likely to be widowed, unmarried or living alone and have a greater level of disability in their daily activities than males when they experience a stroke [38]. This demographic discrepancy in life expectancy between males and females contributes to the overall higher prevalence of stroke in females [37]. Those of African-American and Hispanic-Latino ancestry are at greater risk of developing stroke than those of white ancestry [39]. Previously, genetics has been considered a non-modifiable risk factor for stroke [39]. However, with advances in gene therapy, genetics is now considered at the intersection between modifiable and non-modifiable risk factors [39].

1.1.4 Clinical features of stroke

The clinical features of a stroke are influenced by the specific region of the brain that is impacted and the extent of the injury [40, 41]. The primary symptom of a stroke is

the abrupt onset of hemiparesis or hemiplegia and paresthesia in the face and upper and lower extremities [40]. Additional symptoms might be delirium, dysphasia, dysphagia, hemianopia, gait disorders, vertigo, impaired balance or incoordination, migraine or coma [40]. The typical signs and symptoms of a stroke include the sudden appearance of muscle weakness in one or more limbs (hemiparesis, monoparesis, or quadriparesis), sensory deficits on one side of the body, partial or complete loss of vision in one or both eyes, visual field impairments, diplopia, dysarthria, facial nerve palsy, coordination problems, vertigo (rarely occurring alone), aphasia, neurogenic OAB and a sudden decrease in consciousness [25]. While these symptoms can occur individually, they are more likely to manifest in combination [25]. Stroke survivors with neurogenic OAB experience significant OAB symptoms such as urinary urgency, urgency incontinence, frequency and nocturia as a result of spontaneous involuntary contractions of the detrusor (detrusor overactivity) [42]. Neurogenic OAB among stroke survivors is reported to occur from damage to the suprapontine neural circuitry, leading to the removal of tonic inhibition of the pontine micturition center resulting in involuntary detrusor contractions [43]. Details of the definition, prevalence, aetiology, physiology, pathophysiology, individual and societal impact, economic impact, diagnosis, prognosis and management of the neurogenic OAB among stroke survivors are presented below.

1.2 OAB

1.2.1 Definition, prevalence and aetiology of OAB

The International Continence Society (ICS) defines OAB as ‘urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia’ [44]. Urgency is defined as ‘a sudden compelling desire to void that is difficult to defer, while urgency urinary incontinence [UUI] refers to the involuntary leakage of urine accompanied by or immediately preceded by urgency’ [45, 46]. OAB is projected to impact over 500 million people globally, with a high prevalence in the adult population [47]. The prevalence of OAB in Hong Kong is estimated to be 15% [48].

In 2021, Abu Faraj et al. reported that neurogenic OAB is a significant concern in clinical practice in the United States, as evidenced by its increasing prevalence ranging from 26.1% to 31.1% [49]. This increase in prevalence indicates a growing number of individuals experiencing neurogenic OAB-related symptoms, which can substantially impact their quality of life and healthcare needs. Additionally, the prevalence of OAB has been documented as 31% in men and 25% in women, with its prevalence increasing with age [50, 51].

However, the epidemiology of neurogenic OAB is diverse, with various underlying conditions contributing to its prevalence. For example, neurogenic OAB is commonly associated with multiple sclerosis, with a prevalence ranging from 40% to 90% [52].

Neurogenic OAB is also highly associated with Parkinson's disease, with a prevalence ranging from 37% to 72% [52, 53]. Additionally, OAB is associated with spina bifida and spinal cord injury, with prevalences ranging from 40% to 60.9% and 40% to 84%, respectively [52, 53]. The prevalence of neurogenic OAB is notably higher among stroke survivors, with reported prevalences ranging from 32% to 79% [54-59] in hospital-based assessments and 37.6% among community-dwelling stroke survivors [60]. These figures are substantially higher than the prevalence of OAB in the general population, which is reported to be around 24% [59]. Among stroke survivors, the prevalence of neurogenic OAB was reported to be 53% at three months following the stroke event [61].

Neurogenic OAB can develop due to various underlying conditions, many of which involve detrusor overactivity [62], which can lead to symptoms such as urgency incontinence, where individuals experience a sudden and compelling desire to void, often resulting in UUI [62]. Detrusor overactivity is also characterised by involuntary contractions of the detrusor muscle during the filling phase, leading to increased frequency of urination and urinary incontinence [46, 63]. Dysfunctions that can contribute to detrusor overactivity and neurogenic OAB include a range of neurological disorders, including stroke, multiple sclerosis, Parkinson's disease and spinal cord injury [63]. These dysfunctions can disrupt the normal functioning of the cortical and subcortical structures, leading to abnormal signals to the bladder [63].

In addition to the primary causes of neurogenic OAB, such as detrusor muscle dysfunction, it is important to recognise that other factors can contribute to the development of OAB symptoms. Bladder outlet obstruction, urinary tract infections, and certain medications are known to potentially lead to OAB symptoms [62]. For example, bladder outlet obstruction may result in incomplete emptying of the urinary bladder, leading to symptoms consistent with those of OAB [62]. Urinary tract infections may irritate the bladder and cause urinary urgency and increased urinary frequency [62]. Furthermore, some medications, particularly diuretics and some neurological medications, may contribute to OAB symptoms [62]. Understanding the underlying conditions that contribute to detrusor overactivity and neurogenic OAB is crucial in providing appropriate management and treatment. By addressing the specific aetiology of detrusor overactivity, healthcare professionals can tailor interventions to effectively manage symptoms and enhance the quality of life of those with neurogenic OAB.

1.2.2 Symptoms and clinical presentation of neurogenic OAB in stroke survivors

The most common symptoms of neurogenic OAB are urinary frequency, experienced by 85% of individuals; urgency, reported by 54%; and UUI and nocturia, affecting 36% [61, 64]. Additionally, 79% of those with neurogenic OAB experience these symptoms for at least one year, with 49% having symptoms lasting more than three years [64]. These neurogenic OAB symptoms are often reported by stroke survivors [62, 65].

The symptoms of neurogenic OAB usually result from involuntary detrusor muscle contractions during the micturition cycle's filling phase, which is called detrusor overactivity [66]. The ICS defines detrusor overactivity as 'a urodynamic observation characterised by involuntary detrusor muscle contractions during the filling phase, which may be spontaneous or provoked' [66]. The detrusor muscle is highly innervated and supports bladder function by rhythmically contracting and relaxing under neural control provided via complex central and peripheral neurological mechanisms [67]. Any disruption to the neurological systems involved in bladder control can affect the contraction and relaxation of the detrusor muscles, leading to reduced bladder compliance, deterioration of the urinary tract and increased bladder overactivity due to the loss of suprapontine inhibition [56, 68].

Involuntary detrusor contraction caused by detrusor overactivity may be attributable to the effects on the sensory mechanisms resulting in the initiation of urgency bladder emptying in small quantities [69]. Urodynamic findings reveal positive detrusor overactivity in around 64% of people with neurogenic OAB, while 83% also indicate the presence of OAB symptoms with detrusor overactivity [70]. If neurogenic OAB symptoms are left untreated, detrusor overactivity can lead to urinary tract infections, bladder stones, fibrosis, trabeculation and automatic dysreflexia in those with a neurological condition such as spinal cord injuries and rarely occurs in stroke survivors [63].

1.2.3 Physiology of neurogenic OAB in stroke survivors

The coordination of multiple central nervous system pathways, such as parasympathetic and sympathetic preganglionic and somatic motor neurons, is crucial for the proper functioning of the lower urinary tracts, including the bladder [62, 67]. These pathways facilitate the transmission of signals between the brain and the spinal cord, allowing for the modulation of bladder function [62, 67]. During urine storage, the periaqueductal grey matter (PAG) plays a role in transmitting signals from the cerebrum, amygdala and hypothalamus to the ventrolateral medulla indicating that the bladder is filling [67]. These signals are transmitted to supraspinal centres, such as the prefrontal cortex and hypothalamus, which then suppress the voiding process [71]. This suppression prevents the voiding reflex initiation, allowing for urine storage [72]. However, during voiding, the suppression of the pontine micturition centre (PMC) is disrupted by the activity of the primary motor cortex (M1), prefrontal cortex, and hypothalamus [73]. The disruption of PMC suppression leads to the excitation of the PMC, which activates descending neural pathways to the spinal cord [74]. Noradrenaline is released by sympathetic fibres from the T10–L2 spinal cord (hypogastric nerve) and acts on β3-adrenoceptors to relax the smooth muscles in the bladder wall [75]. The effect of noradrenaline on the detrusor muscles leads to detrusor muscle contraction and urethral smooth muscle relaxation, resulting in increased bladder compliance and sustained low-pressure filling of the bladder, allowing for the passage of urine [75]. The efferent parasympathetic fibres mediated by the pelvic nerves via the intermediolateral nucleus in S2–S4 of the spinal cord release acetylcholine, which is responsible for the detrusor muscle contraction during the voiding process [71]. In contrast, the sympathetic

nervous system, mediated by the hypogastric nerves, is responsible for relaxing the bladder neck and urethral smooth muscle during urine storage [67, 76].

1.2.4 Pathophysiology of OAB in stroke survivors

Neurogenic OAB is reported to occur when there is damage to the central inhibitory pathways in the brain and spinal cord or sensitisation of the peripheral afferent terminals in the bladder [77-79]. This damage can lead to the re-emergence of the primitive voiding reflex, causing detrusor overactivity, frequent urination, urinary urgency, elevated bladder storage and voiding pressure [77]. While the exact cause of the neurogenic OAB after a stroke is unclear, it is believed to be related to the disruption of normal physiological functions of the detrusor muscle [80]. Targeting specific pathways or receptors involved in micturition can help restore normal bladder function and improve the quality of life of those with neurogenic OAB [62].

Since the pathophysiology of neurogenic OAB is complex, two theories have been proposed (neurogenic and myogenic) to elucidate its underlying mechanisms [81]. These theories aim to provide insights into the pathophysiological processes that contribute to the symptoms of neurogenic OAB, such as urinary urgency, urinary frequency and urgency incontinence [81]. The neurogenic theory suggests that a decrease in inhibitory signals supports the storage of urine, and an increase in excitatory signals stimulates the act of voiding [82]. This imbalance in neural signalling may contribute to the symptoms associated with neurogenic OAB and other urinary

dysfunctions [82]. The neurogenic theory suggests that urgency originating from the nervous system initiates the detrusor contractions [62]. This theory can explain neurogenic OAB dysfunctions, including neurological conditions such as stroke, spinal cord injury and multiple sclerosis [83]. These explanations include abnormalities in the bladder urothelium and suburothelial afferent nerves, alterations in the central nervous system signalling related to bladder control, and dysregulation of the autonomic nervous system [83]. Factors such as inflammation, changes in bladder smooth muscle function, and alterations in neurotransmitter activity have also been suggested as potential contributors to neurogenic OAB pathophysiology [62].

Conversely, the myogenic theory describes an increased sensitivity of the detrusor muscle to excitatory stimuli, leading to muscle contractions [84]. This theory suggests that the detrusor muscle may play a significant role in the development of neurogenic OAB symptoms, highlighting the importance of understanding the physiological mechanisms underlying neurogenic OAB [84]. The increased pressure and hypertrophy of the detrusor muscles can lead to symptoms such as urgency, frequency, and nocturia, which are characteristic of neurogenic OAB [85]. Brain transection studies in animals with an intact neuroaxis have demonstrated that suprapontine areas typically exert a tonic inhibitory influence on the PMC [86]. In humans, it is believed that the cerebral cortex (medial frontal lobes) and the basal ganglia play a role in suppressing the micturition reflex. Consequently, damage to the brain can induce bladder overactivity by reducing this suprapontine inhibition (Figure 1.1).

By gaining insights into the underlying pathophysiological mechanisms, physiotherapists can tailor management strategies to address the specific factors contributing to neurogenic OAB in each patient, ultimately improving the outcomes and quality of life of those with neurogenic OAB.

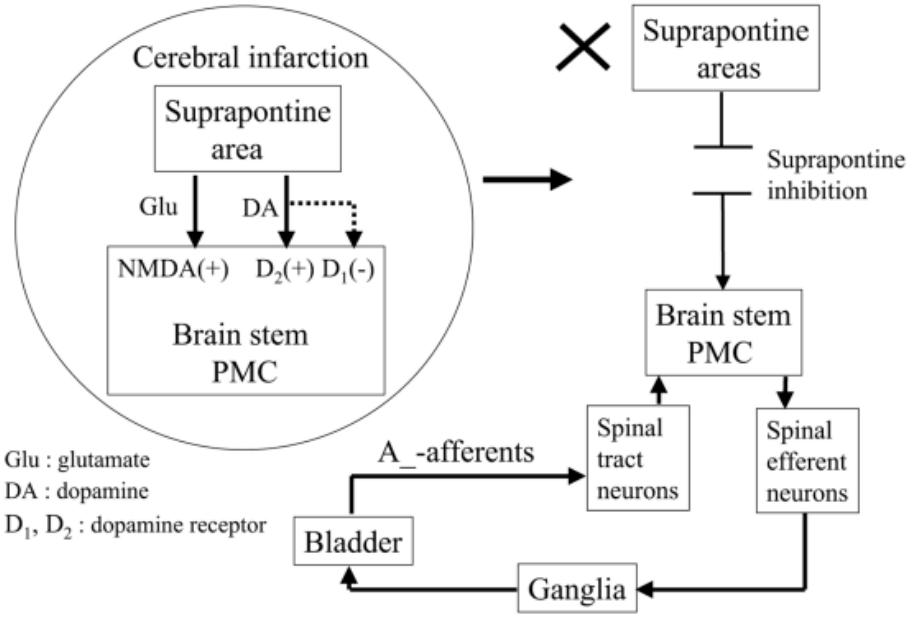

Figure 1. 1 Suprapontine lesions causing detrusor overactivity (Mostwin et al 2005 [86])

1.2.5 Individual and societal impact of OAB among stroke survivors

OAB has been reported to adversely affect the basic activities of daily living, such as domestic activities, socialisation, occupation, travel, physical activity, sleep disturbances and sexual activity [64]. Neurogenic OAB is also associated with an increased risk of psychological distress [87, 88]. Stroke survivors with neurogenic OAB were reported to have compromised functioning, reduced life satisfaction and elevated risk of institutionalisation compared to those without neurogenic OAB [89, 90]. In addition, one study found that 45% of patients with stroke with neurogenic OAB were institutionalised, with 5% living in institutional settings one year after the stroke [91]. At two years post-stroke, the risk of mortality was greater among stroke survivors with than without neurogenic OAB [92]. These factors have a cumulative, multidimensional impact on various quality-of-life domains, including physical, social, psychological and domestic [93]. In society, those with neurogenic OAB may experience anxiety in unfamiliar environments since they may be preoccupied with navigating to the nearest restroom, seeking aisle seating, and estimating the time until their next opportunity for a work break [94].

There are reported cases of under-treatment of neurogenic OAB resulting from the reluctance of individuals to seek healthcare due to the social stigma associated with the condition [95]. This social stigma leads to isolation, a lack of adherence to treatment regimens and poor communication about continence needs. There may also be insufficient information sharing among clinicians, further hindering the effective management of neurogenic OAB [95]. If not adequately managed, neurogenic OAB

will increase the risk of developing complications such as falls, severe depression and urinary tract infections [93], placing a personal financial burden on patients and their caregivers and reducing their self-dependency [93]. Neurogenic OAB has also been reported to place substantial physical and psychological burdens on family caregivers [96]. A focus group qualitative study revealed that the family caregivers of those with neurogenic OAB are constrained by the increased urinary frequency during travel and leisure activities, significantly limiting their activities of daily living [97]. Family caregivers also experience significant bouts of emotional disturbance, such as feelings of embarrassment, frustration, anger and anxiety [98].

1.2.6 Economic impact of OAB

The total annual direct medical cost associated with an OAB in six Western countries (Canada, Germany, Italy, Spain, Sweden and the United Kingdom) was estimated at €3.9 billion [99]. Additionally, the estimated annual nursing home expenses for OAB were €4.7 billion, and the annual cost of OAB-related work absenteeism was estimated at €1.1 billion [99]. In the United Kingdom, the National Health Service (NHS) has estimated that annual medical and nonmedical costs associated with an OAB are as high as £1.8 billion, with the annual cost associated with self-purchased incontinence pads being around £750 million [100]. In the United States (US), the annual national cost for caring for those with neurogenic OAB was estimated to be $65.9 billion ($49.1 billion in direct medical costs, $2.3 billion in direct nonmedical costs, and $14.6 billion in indirect costs from lost productivity) [101]. National medical and nonmedical cost

projections in the US indicate that the current cost of $65.9 billion will rise to $82.6 billion [101]. Additionally, the annual medical and nonmedical costs for community-dwelling older adults with an OAB are reported to be $4.2 billion, while those of institutionalised older adults with an OAB are reported to be $5.3 billion [101]. Furthermore, the global diaper market reached a total value of $69.5 billion in 2020 and was projected to grow by $3.02 billion between 2020 and 2024 [102, 103].

No specific economic cost data appears available for managing OAB in Hong Kong. However, we can infer potential costs by examining the expenses related to stroke rehabilitation. For example, the cost of stroke rehabilitation in 2006 was reported to be HKD 719.4 million and was projected to increase to HKD 1.9875 billion by 2036 [104]. In addition, medical and nonmedical costs were 2.5 times higher for patients with than without OAB [105]. The symptoms of OAB could be exacerbated by loss of productivity and wages and increased medical and nonmedical costs [90]. These costs reflect the expenses associated with managing and treating OAB [103]. Effective management and support are crucial to alleviating these costs and burdens and improving outcomes for those with neurogenic OAB [101].

1.2.7 Diagnosis of OAB

Following a stroke, individuals may experience physical, visual and language complications that can impair their functional abilities and potentially contribute to symptoms of neurogenic OAB [106]. The most common risk factors for neurogenic

OAB after a stroke are severe paresis, cognitive or perceptual decline, aphasia, altered consciousness and visual field defects [107]. A thorough and comprehensive examination is essential to achieve optimum clinical decision-making and evidence-based therapy and improve clinical outcomes and recovery.

The clinical diagnosis of neurogenic OAB is primarily based on a patient's symptoms, present and past medical history, and thorough urological and physical evaluations [108]. It is essential to rule out conditions such as bladder stones, bladder cancer, benign prostatic enlargement and urinary tract infection since they can present with symptoms similar to OAB [45]. The ICS offers definitions of OAB that provide a symptomatic diagnosis, serving as a simplified and accurate benchmark for diagnosis based on patient-specific symptom evaluation [66]. Therefore, given the emphasis on clinical reasoning, judgment and subjective assessment are crucial useful tools for diagnosing neurogenic OAB [109]. Additionally, clinical tools such as the Overactive Bladder Symptom Score, Incontinence Quality of Life questionnaire and the International Consultation on Incontinence Questionnaire-Short Form are frequently used to aid in clinical diagnosis, symptom monitoring and recovery evaluation [110-112]. Therefore, further differential diagnosis, such as urine analysis, imaging studies and symptom evaluation for pain and hematuria, are essential for holistic and proper diagnosis and better therapeutic outcomes.

1.2.8 Prognosis of OAB

Stroke is a common condition, and OAB is a significant predictor of mortality, dependency, institutionalisation and poor treatment prognosis in stroke survivors [113]. Neurogenic OAB due to stroke has been identified in at least two level A studies (Cochrane collaboration criteria) and has been associated with poor functional outcome prediction in activities of daily living [114]. Neurogenic OAB due to stroke predicted favourable outcomes related to bladder control and toileting with 82% accuracy [115]. The presence of neurogenic OAB and comorbidities such as depression, arthritis, hypertension, heart disease, neurological conditions, mobility limitations, benign prostatic hyperplasia, recurrent urinary tract infection and prostatitis could be indicative of the prognostic status [116, 117]. While the prognosis for urinary retention after a stroke is generally favourable, typically lasting for a few weeks or months, the prevalence of neurogenic OAB can persist one year after the onset of a stroke in 15% to 30% of cases [91, 106, 118]. This observation suggests that while urinary retention may improve over time, neurogenic OAB symptoms can persist in a significant proportion of stroke survivors. Notably, 6.5%–17% of stroke survivors may have experienced neurogenic OAB before the stroke, which can be attributed to multiple causative factors and could predict the prognosis [119, 120].

The prognosis of neurogenic OAB among stroke survivors can vary depending on the severity of the stroke, the extent of neurological damage, and the individual's overall health [56]. In some cases, neurogenic OAB symptoms may improve over time as the patient recovers from the stroke [121]. However, in other cases, neurogenic OAB

symptoms may persist or worsen due to the neurological impact of the stroke on bladder function [122]. Patients with stroke with neurogenic OAB need to receive comprehensive medical care and management to address both their stroke-related issues and neurogenic OAB symptoms [123]. A healthcare professional can provide a more specific prognosis based on the patient's medical history and current condition [124].

1.2.9 Management of OAB

The ICS recommends conservative management as the first-line therapy for managing neurogenic OAB symptoms, which includes lifestyle modifications, behavioural therapy, bladder training and pelvic floor muscle training (PFMT) [125]. First-line therapy is usually the initial nonsurgical and safe therapy with relatively low risks of adverse effects [126]. The conservative management is consistently tailored to the individual needs of those with neurogenic OAB [127]. The current physiotherapy treatments for neurogenic OAB include PFMT [128], with or without electromyography (EMG) biofeedback [129] or electrical stimulation [130, 131]. Clinically-delivered PFMT with EMG biofeedback could be invasive due to the insertion of a vaginal (women) or anal (men) probe, which could cause pain and discomfort [132, 133]. Recent systematic reviews have demonstrated the effectiveness of PFMT in improving patient symptomatology, pelvic floor muscle function and overall quality of life in those with neurogenic OAB [134-137]. The PFMT involves executing a voluntary contraction of the pelvic floor muscles while resisting pelvic floor muscle relaxation until the urinary urgency is suppressed, an effect known as the 'guard

reflex’ [138]. According to the National Institute for Health and Care Excellence (NICE) guidelines, PFMT should be performed for at least three months, consisting of at least eight contractions thrice daily [139].

Electrical stimulation involves applying specific voiding parameters of frequencies (low: 5–20 Hz, high: 50 Hz), modes, and types of electrical impulses to alleviate symptoms associated with the lower urinary tract [140-142]. This therapy can involve increasing bladder capacity and compliance or reducing detrusor pressure to address lower urinary tract symptoms [143, 144]. Neural signalling occurs during electrical stimulation, involving the transmission of action potentials through electrical and chemical processes [145, 146]. This process leads to the release of neurotransmitters and the activation of afferent and efferent neurons and skeletal and smooth muscles [147, 148]. A meta-analysis examining studies involving those with neurogenic OAB showed that electrical stimulation improved bladder compliance, reduced residual urine, and decreased the urinary frequency of enuresis and urinary urgency [149]. Similarly, another meta-analysis on vaginal electrical stimulation found that it reduced urgency episodes, nocturia, and the number of pads used and improved the quality of life of women with an OAB [150].

The pharmacological management of neurogenic OAB typically involves using anticholinergic drugs and alpha-adrenergic blockers [151]. However, these medications can have various adverse effects, including blurred vision, dry mouth, drowsiness, constipation, somnolence, and impaired renal function [151]. These side effects can

impact patients' compliance with medication and their long-term management of neurogenic OAB. In addition to pharmacological approaches, non-pharmacological treatment options are available for neurogenic OAB. Catheterisation, colposuspension, bladder neck needle suspension and periurethral injections are other treatment options that have been used with varying degrees of success [152]. However, these interventions pose risks such as being bothersome, semi-invasive, or invasive, can be expensive and may lead to long-term complications [152].

1.3 TMS

1.3.2 TMS mechanisms in neurogenic OAB

TMS is a technique that stimulates the cortex using magnetic fields based on Faraday's principle of electromagnetic induction [153]. It is a safe and painless method that activates cortical neuron fibres by delivering intense and brief magnetic fields [154-156]. By directing alternating magnetic fields through a wire coil, TMS can modulate neurons and either excite or inhibit cortical activity depending on the frequency [157]. High-frequency TMS (typically >5 Hz) is known to increase cortical excitability, leading to enhanced neuronal firing and synaptic transmission in the targeted brain area [158], which can be beneficial for stimulating specific brain regions and promoting cognitive or motor functions.

The magnetic field is reduced by extracerebral tissue, such as the scalp, bone, and meninges, while maintaining sufficient potency to induce an electrical field that can depolarise superficial axons and activate cortical networks [158]. However, it is important to note that the magnetic field strength decreases as it passes through these extracerebral tissues due to their magnetic properties and conductivity [159]. Despite this reduction, the magnetic field can still induce an electrical current in the underlying neural tissue [160]. When applied correctly, TMS can depolarise neurons and generate action potentials [158]. However, its effectiveness in depolarising neurons and generating action potentials depends on various factors, including the specific stimulation parameters, the targeted brain region and individual differences in brain anatomy and physiology [161]. Proper positioning of the TMS coil and the intensity, frequency and duration of stimulation are all critical factors influencing the outcome of TMS [162]. Long-term changes in synaptic strength can be achieved through high- or low-frequency rTMS, resulting in long-term potentiation (LTP) or depression, respectively [154, 155].

Synaptic plasticity refers to the ability of synapses to strengthen or weaken over time in response to neural activity [163]. Long-term changes in synaptic strength, especially spatiotemporal configurations, have been established as a prerequisite to understanding the mechanisms of long-term plasticity of intrinsic excitability in the brain and learning rules [164]. The spatiotemporal configurations affect the signal propagation in the axon, dendrites and soma, resulting in the formation of a coherent engram [164]. Synaptic

plasticity is critical for the formation of memories and the adaptation of neural circuits in the brain [165].

rTMS has been investigated as a means to induce long-term changes in synaptic strength [165]. High-frequency rTMS involves delivering repeated magnetic pulses rapidly, typically >5 Hz, to a specific brain region [166]. High-frequency rTMS has been associated with the induction of LTP, a process that strengthens synaptic connections [158]. LTP is a crucial mechanism emanating from a 'long-lasting increase in synaptic efficacy following high-frequency stimulation of afferent fibres', underlying learning and memory formation in the brain [167]. By inducing LTP-like effects, high-frequency rTMS can enhance synaptic transmission and promote neural plasticity in targeted brain areas [167]. The LTP works by activating a double-gated N-methyl D-aspartate (NMDA) receptor, which acts as a molecular coincidence detector. These glutamatergic receptors, permeable to calcium, can enhance postsynaptic signals for an extended period after being activated by a stimulus sufficient to depolarise the postsynaptic membrane and alleviate tonic Mg^{2+} inhibition.

Conversely, low-frequency rTMS (typically <1 Hz) has been used to reduce cortical excitability, effectively inhibiting neuronal excitation in the targeted area. When low-frequency rTMS was applied to the M1, it significantly decreased the motor-evoked potentials (MEPs) of the contra-lesional M1 [168]. Low-frequency rTMS induces long-term depression at synapses by modulating synaptic plasticity and altering the strength of synaptic connections [169, 170]. Low-frequency rTMS may decrease synaptic

efficacy and contribute to the modulation of neural networks [170]. Low-frequency rTMS applied to the motor cortex for a 15-minute train of suprathreshold 0.9 Hz leads was reported to decrease the size of MEPs (Figure 1.2) [171].

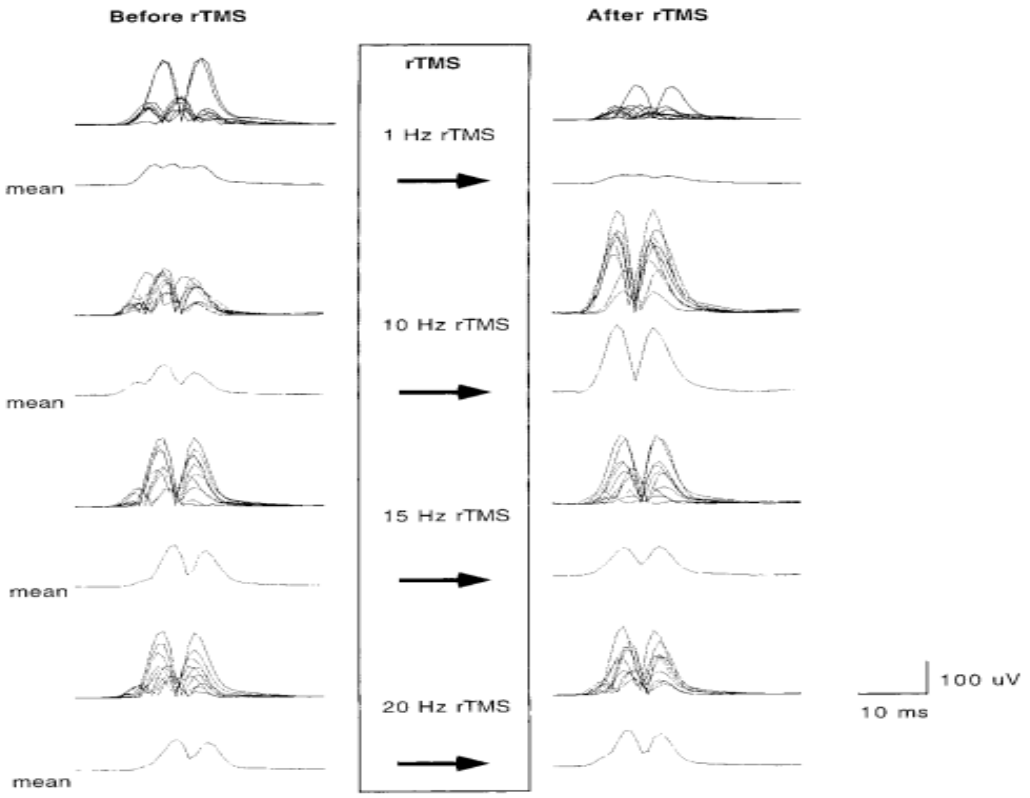

Figure 1. 2 Motor evoked potentials at baseline and post-rTMs. The neuromodulatory effect at 1 Hz is inhibitory, while 10 Hz is excitatory (Maeda et al., 2000 [172])

By targeting cortical areas related to the pelvic region, rTMS can modulate cortical excitability and induce long-lasting neuroplastic changes [173]. The rationale behind targeting cortical areas related to the pelvic region with rTMS lies in understanding the brain's role in regulating bladder and pelvic floor function. Studies have shown that the brain, particularly its cortical and subcortical regions, plays a significant role in controlling bladder and pelvic floor activity. The M1 is crucial in controlling pelvic floor muscles and detrusor stability [174]. The M1, located in the cerebral cortex, is involved in initiating and coordinating voluntary movements, including those related to bladder control [174]. The M1 is associated with neuro-urologic conditions such as neurogenic OAB [69, 175] and is a target for rTMS interventions [176]. Applying low-frequency rTMS to the M1 aims to induce cortical inhibition and reduce neural excitability, thereby alleviating lower urinary tract symptoms such as neurogenic OAB symptoms and quality of life [177, 178]. This mechanism could improve bladder capacity and filling by reducing detrusor overactivity [179]. By influencing the cortical control of pelvic floor muscles and detrusor stability, rTMS may offer a promising approach to managing bladder dysfunction in these patients [174].

Studies related to micturition disorders have identified the latency of MEPs from the striated urethral sphincter as a reliable response to rTMS [180]. The latency of these MEPs, which refers to the time interval between the TMS pulse and the resulting EMG response, serves as a quantitative measure of the neural conduction time and can provide information about the integrity and function of the neural pathways involved in urinary control (Figure 1.3) [180]. By examining the latency of MEPs from the striated

urethral sphincter in response to TMS, researchers and clinicians can better understand the neural mechanisms underlying micturition disorders, which could have implications for diagnostic procedures, treatment evaluation, and developing targeted interventions for patients with micturition disorders [180]. Low-frequency rTMS has also been shown to improve neurogenic OAB in individuals with advanced Parkinson's disease by enhancing bladder capacity and the first sensation of the filling phase [179]. By modulating pelvic floor tonicity and reducing detrusor overactivity, low-frequency rTMS of the M1 can reverse OAB symptoms and enhance bladder capacity and filling [179].

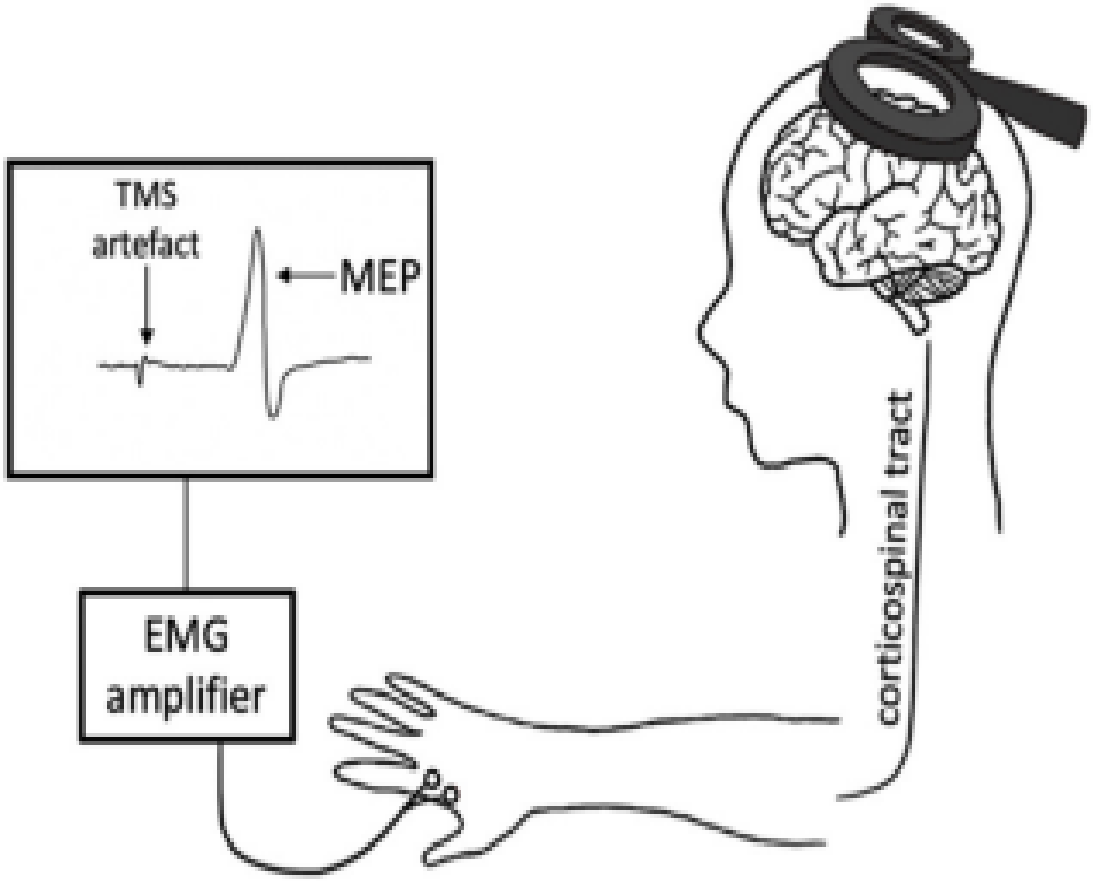

Figure 1. 3 Transcranial magnetic stimulation (TMS) schematic presentation. An electric current is generated in the TMS coil, producing a magnetic field perpendicular to the coil. (Turco and Nelson, 2021[181])

1.3.3 Low-frequency rTMS for cortical excitability inhibition and long-lasting neuroplastic changes

High-frequency rTMS at a frequency of ≥5 Hz increased motor cortical excitability beyond the stimulation period, while low-frequency rTMS at a frequency of 1 Hz decreased motor cortical excitability [182]. This modulation of cortical excitability has been associated with therapeutic efficacy and patient satisfaction [182]. Lesions in the corticospinal tract due to a brain injury reduce the excitability of cortical motor neurons and cause an imbalance in connectivity [183, 184], which activates inhibitory circuits within the M1 [183, 184]. Using low-frequency rTMS to suppress the contralesional M1 and achieve increased excitability of motor neurons can improve cortical performance by modulating and balancing the altered connectivity in the motor network [185, 186]. The contralesional M1 is suppressed by establishing effective communication between the ipsilesional M1 and the ipsilesional supplementary motor area.

Resting-state functional magnetic resonance imaging studies have shown that effective connectivity from the premotor cortex to the ipsilesional M1 improves three weeks after low-frequency rTMS in patients with subacute stroke [187]. These changes lead to the remodelling of the neural network architecture, resulting in improved motor performance after the intervention [188].

Low-frequency rTMS stimulation for 15–25 minutes suppressed MEPs and enhanced the efficiency of excitatory synaptic transmission without significantly increasing Ca levels [179]. This neural suppression of MEPs could inhibit cortical excitability, ultimately inhibiting the descending pathways of the corticospinal tracts projecting to the detrusor muscles [179]. Multiple sessions of low-frequency rTMS significantly reduced the resting and active motor threshold of the affected M1 and were sustained for three months post-intervention [189]. By inhibiting cortical excitability, low-frequency rTMS provides neuroprotection against cellular mechanisms such as excitotoxicity, energy depletion and free radical formation [190]. At low intensities, low-frequency rTMS preferentially activates low-threshold inhibitory interneurons over higher-threshold excitatory interneurons, while pyramidal tract neurons are indirectly activated through synaptic inputs without causing them to discharge [191].

The clinical effectiveness of low-frequency rTMS may be due to its effects on the PMC, which is responsible for descending excitatory projections to the parasympathetic sacral centre and/or the PAG, where the afferent proprioceptive projection of the bladder terminates [192]. The details are outlined in Figure 1.1. Given the consistent evidence of the inhibitory effects of low-intensity, low-frequency rTMS on the human M1, it can be safely considered a treatment approach in various clinical settings [171, 193, 194]. Low-frequency rTMS is a safe and effective therapeutic technique that has been shown to yield positive clinical outcomes, including increased bladder capacity and improved lower urinary tract symptoms.

1.4 Hypotheses of the thesis

1.4.1 Formulating the research question

The people with neurogenic OAB and their families are confronted with distressing psychological, social, and financial burdens [80]; and were reported to be sub-optimally managed with a consequent high incidence of complications such as urinary tract disorders, isolation, anxiety, depression, hospitalisation, increased disability, and increased risk of mortality [195]. This under-treatment could not be unconnected to the feeling of embarrassment for health care seeking, social stigma, low patient adherence, poor communication of the continence needs of the neurogenic OAB, and insufficient patient information sharing among the clinicians [95]. Neurogenic OAB demands significant attention from people with stroke and their caregivers because it correlates negatively with functional outcomes and is strongly linked with institutionalisation [91]. Kolominsky-Rabas et al. found that 45% of the people with neurogenic OAB due to stroke were institutionalised, with 5% living in a custodial setting at 12 months after stroke with an evident personal, economic burden and low self-dependency [91]. In the United States, the annual national cost of care for people with neurogenic OAB was estimated as high as $65.9 billion in 2007 and is projected to rise to 82.6 billion in 2020 [101], with $4.2 billion and $5.3 billion as annual costs for the community-dwelling adults and institutionalised elderly, respectively [196].

Pharmacological interventions for managing neurogenic OAB symptoms include anticholinergic drugs, beta-adrenergic agents, and selective serotonin reuptake

inhibitors, which are frequently associated with adverse side effects that can adversely impact patient adherence and the sustainability of long-term treatment regimens [152]. Alternative therapeutic strategies have shown varying effectiveness, including behavioral therapies, PFMT, intermittent urethral catheterisation, colposuspension, periurethral injections, and bladder neck needle suspension [130]. Nonetheless, these interventions pose certain risks, as they may be bothersome, semi-invasive, or invasive, incur significant costs, and lead to long-term complications.

Currently, available physiotherapy interventions for the treatment of neurogenic OAB include PFMT [128], both alone and in combination with EMG biofeedback [129, 197] or electrical stimulation [131]. However, based on a review of the current literature [198], no standardised PFMT regimen currently exists or is not preferred due to invasiveness. EMG biofeedback and transvaginal or anal electrical stimulation are often not preferred by individuals with detrusor overactivity because it is invasive and causes pain/discomfort associated with the insertion of the vaginal or anal probe [132, 133]. Additionally, individuals with functional limitations due to stroke may have difficulty inserting the vaginal (women) or anal probe (men) of the biofeedback device or electrical stimulator [199].

PFMT is a first-line therapy for those with a neurogenic OAB and its is an individualised treatment tailored to the needs and goals of each patient [200]. PFMT was found to demonstrate moderate efficacy [201], with meta-analyses showing no significant effect and low Grading of Recommendations, Assessment, Development,

and Evaluation (GRADE) evidence quality in improving the symptoms and quality of life of those with neurogenic OAB [130, 201]. However, the included systematic reviews and meta-analyses had small sample sizes [130, 201]. PFMT was also found to be more effective than conservative therapy in improving the quality of life of those with neurogenic OAB [201].

Regarding electrical stimulation, transcutaneous electrical nerve stimulation (TENS) was found to have moderate efficacy, with it being more effective than the sham control in reducing the number of nocturia episodes [201]. A meta-analysis also indicated a beneficial effect of transcutaneous tibial nerve stimulation (TTNS) in improving the symptoms and quality of life of those with neurogenic OAB, although the quality of evidence ranged from low to moderate according to the GRADE criteria [130]. It also found TENS and behavioural therapy to improve UUI symptoms in those with neurogenic OAB [130]. Moreover, it suggested that TTNS and behavioural therapy might improve the quality of life of those with neurogenic OAB [130]. A Cochrane systematic review revealed moderate GRADE evidence quality supporting the superiority of electrical stimulation over PFMT with or without EMG biofeedback in improving OAB symptoms [202]. In addition, individuals with an OAB reported a therapeutic benefit twice as often when using electrical stimulation compared to PFMT, with low GRADE evidence quality [202].

Nonetheless, whether electrical stimulation is more effective than sham/placebo in treating symptoms of neurogenic OAB remains unclear [202]. Individuals with

neurogenic OAB found electrical stimulation/PFMT with EMG biofeedback to be associated with pain and discomfort due to some of its invasiveness in men (intra-anal probe) and women (intra-vaginal probe) [132]. This discomfort and pain hindered their compliance with the treatment regimen and overall treatment outcomes [132].

Neuromodulation, such as rTMS, is an emerging non-invasive and safe therapeutic approach for managing the symptoms of neurogenic OAB [179, 203]. rTMS can painlessly deliver a magnetic field to the brain, inducing neural activity in the pelvic floor muscles and striated sphincter motor afferents [154]. Furthermore, it can modulate cortical excitability and induce long-lasting neuroplastic changes [155]. rTMS treatment has yielded positive clinical outcomes, including increased bladder capacity and improved lower urinary tract symptoms [179, 203]. Promising findings have been observed among individuals with neuro-urologic symptoms due to Parkinson's disease and multiple sclerosis [179, 203]. Given the high prevalence of neurogenic OAB among stroke survivors, ranging from 32% to 79% [54, 59, 204], and the significant individual, societal, and economic burden associated with this condition, investigating the effectiveness of rTMS among stroke survivors with neurogenic OAB is crucial.

1.4.2 Research questions

1. How do nonsurgical, minimally or non-invasive therapies affect UUI symptoms and quality of life in individuals with neurogenic OAB?

2. What evidence describes the psychometric properties of clinical measures for assessing neurogenic OAB symptoms (urinary urgency with or without UUI, urinary frequency and nocturia)? What is the quality of this evidence based on the COnsensus-based Standards for selecting health status Measurement INstruments (COSMIN) checklist and GRADE framework?
3. What is the psychometrically sound quality-of-life outcome measure for evaluating the quality of life of individuals with neurogenic OAB?
4. What is the clinical effectiveness of the active rTMS compared to sham rTMS in alleviating neurogenic OAB symptoms in stroke survivors?
5. What are the experiences and perceptions of stroke survivors with neurogenic OAB after rTMS?
6. Is the estimated cost of rTMS intervention low in managing neurogenic OAB symptoms in stroke survivors?

1.5 Aims, objectives and hypothesis of the thesis

The primary aim of this thesis is to evaluate the effectiveness of active rTMS compared to sham rTMS in managing the neurogenic OAB symptoms of stroke survivors. It also aims to explore stroke survivors' experiences and perspectives about using rTMS to treat neurogenic OAB symptoms and compare the cost estimation of active versus sham rTMS in managing the symptoms of neurogenic OAB in stroke survivors.

Its specific objectives and hypotheses are:

Objective 1: To determine the effects of nonsurgical, minimally or non-invasive therapies on UUI symptoms and quality of life in individuals with neurogenic OAB.

Hypothesis 1: Nonsurgical, minimally or non-invasive therapies will improve the UUI symptoms and quality of life of individuals with neurogenic OAB.

Objective 2: To systematically evaluate the evidence describing the psychometric properties of clinical measures for assessing OAB symptoms and the quality of this evidence based on the COSMIN checklist and GRADE framework.

Hypothesis 2: The psychometric properties of clinical measures used to assess OAB symptoms will vary significantly among different instruments, and a systematic evaluation will identify measures with superior psychometric properties for use in clinical and research settings.

Objective 3: To identify psychometrically robust quality-of-life outcome measures for evaluating the quality of life of individuals with neurogenic OAB.

Hypothesis 3: The psychometric properties of clinical measures used to assess OAB-related quality of life will vary significantly among different outcome measures, and a systematic evaluation will identify measures with superior psychometric properties for use in clinical and research settings.

Objective 4: To investigate the clinical effectiveness of active rTMS compared to sham rTMS in alleviating neurogenic OAB symptoms in stroke survivors.

Hypothesis 4: Stroke survivors with neurogenic OAB randomly assigned to receive active rTMS for 4 weeks will evidence a significantly greater reduction in neurogenic OAB symptoms than stroke survivors with neurogenic OAB randomly assigned to receive sham rTMS 4 weeks after randomisation (primary endpoint).

Objective 5: To explore the experiences and perceptions of stroke survivors with neurogenic OAB symptoms treated with rTMS.

Hypothesis 5: Stroke survivors with neurogenic OAB randomly assigned to receive active rTMS for 4 weeks will demonstrate a positive experience and perception of the 4-week rTMS intervention.

Objective 6: To compare the cost estimate of active and sham rTMS in managing neurogenic OAB symptoms in stroke survivors.

Hypothesis 6: Stroke survivors with neurogenic OAB receiving active rTMS for 4 weeks will evidence a significantly lower cost estimate than stroke survivors with neurogenic OAB randomly assigned to receive sham rTMS 4 weeks after randomisation.

1.6 Structure of the thesis

The objectives of the thesis were investigated and addressed through six study designs conducted in the following order:

Objective 1 was addressed by investigating the effects of nonsurgical, minimally or non-invasive therapies on UUI symptoms and quality of life in individuals with neurogenic OAB through a systematic review and meta-analysis of randomised

controlled trials (RCTs). It aimed to provide a comprehensive understanding of the effectiveness of these therapies in managing symptoms and improving the overall quality of life of individuals with neurogenic OAB.

Objective 2 was addressed by conducting a psychometric systematic review to identify the most reliable and valid clinical tools for evaluating symptoms in individuals with neurogenic OAB. It aimed to ensure that the tools used to assess symptoms are robust and accurate, providing valuable insights into the symptoms of neurogenic OAB.

Objective 3 was addressed by conducting a psychometric systematic review to identify the most reliable and valid clinical tools for evaluating the quality of life of individuals with neurogenic OAB. It aimed to establish the most robust clinical measures for evaluating the quality of life of individuals with neurogenic OAB in terms of overall well-being and daily functioning.

Objective 4 was addressed by conducting a full-scale RCT comparing the effectiveness of active rTMS to sham rTMS in alleviating neurogenic OAB symptoms in stroke survivors. It aimed to provide direct evidence of the efficacy of rTMS as a potential treatment for neurogenic OAB, particularly in the context of stroke-related symptoms.

Objective 5 was addressed by conducting a qualitative study exploring the experiences and preferences of stroke survivors with neurogenic OAB regarding rTMS in alleviating their symptoms. It aimed to capture the personal perspectives and insights of stroke survivors undergoing rTMS treatment, providing valuable qualitative data to complement the quantitative findings.

Objective 6 was addressed by estimating the cost of active rTMS to sham rTMS interventions in alleviating neurogenic OAB symptoms in stroke survivors. It aimed to evaluate the economic implications of implementing rTMS as a treatment option, considering its potential benefits and costs in managing neurogenic OAB after a stroke. These six studies are examined over Eight chapters, as illustrated in Figure 1.2.

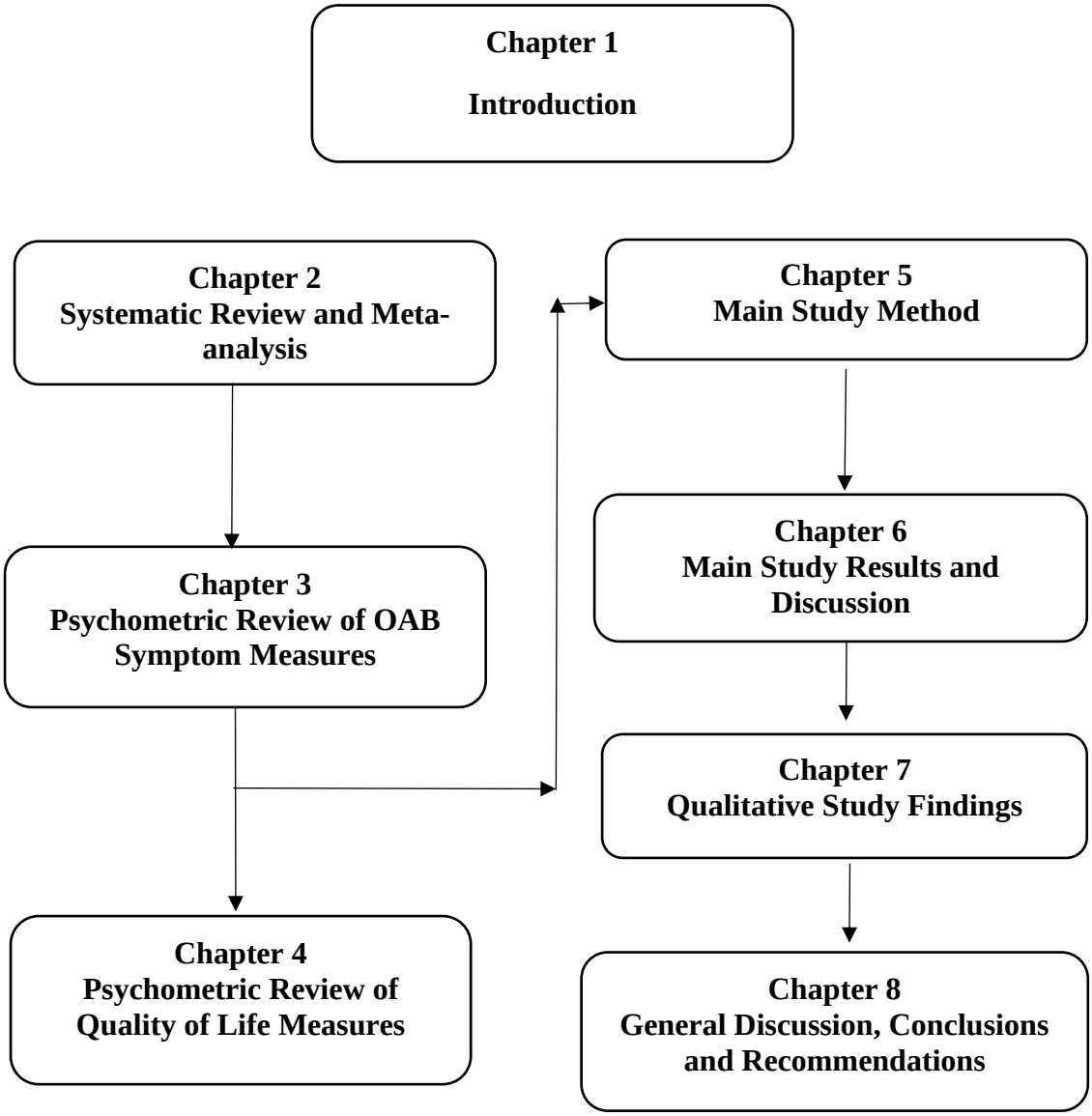

Figure 1.4: Flowchart of the chapters of this thesis.

Chapter descriptions

Chapter 2: This chapter describes the conduct and findings of a systematic review and meta-analysis investigating the effects of nonsurgical, minimally or non-invasive therapies on UUI symptoms and quality of life in individuals with neurogenic OAB, identifying a research gap regarding the lack of existing RCTs that investigated the impact of rTMS on neurogenic OAB.

Chapter 3: This chapter presents the findings of the systematic review of psychometric properties to identify the most robust and psychometrically sound clinical measure for evaluating UUI symptoms in individuals with neurogenic OAB symptoms.

Chapter 4: This chapter presents the findings of the systematic review of psychometric properties to identify the most robust and psychometrically sound clinical measure for evaluating the quality of life of individuals with neurogenic OAB symptoms.

Chapter 5: This chapter describes the methodology of the RCT and economic evaluation. It begins by outlining the methodology of the RCT. It describes the study design, including participant selection, randomisation, and allocation concealment. It also discusses the interventions the RCT compares, including the specific treatment protocols and sham interventions. Finally, it describes the methodology of the economic evaluation, including the economic perspectives it adopted, such as a societal perspective. It also describes the data sources used to estimate costs and outcomes and the methods used to analyse the data and generate the cost estimation.

Chapter 6: The chapter begins by presenting the sociodemographic and clinical characteristics of the participants included in this RCT. It also presents the key findings

of the study, including the RCT and cost-estimating findings. We aimed to determine whether four weeks of active low-frequency rTMS is significantly more effective than sham rTMS in reducing neurogenic OAB symptoms, improving quality of life, and enhancing patient satisfaction. We also aimed to evaluate whether any improvements observed could be sustained beyond the immediate post-intervention at the four- and eight-week follow-ups. The findings from this RCT and cost estimation are anticipated to have implications for decreasing healthcare-related expenses. By providing an effective therapeutic intervention for neurogenic OAB management in stroke survivors, we could potentially alleviate the socioeconomic burdens associated with this condition.

Chapter 7: This chapter describes the qualitative study and its justification. It also describes the research approach, such as phenomenology, and the methods used for data collection, such as focus groups. It also discusses the sampling strategy for selecting participants. The Chapter also discusses the strengths and limitations, conclusions, clinical implications and recommendations of the study.

Chapter 8: This chapter presents a general discussion of this thesis project, including its strengths and limitations, clinical implications and recommendations.

Chapter 2

Effects of non-surgical minimally- or non-invasive therapies for urinary incontinence due to neurogenic overactive bladder: A systematic review and meta-analysis

2.1 Commentary

This chapter reports the background, methods, results, discussions and conclusions of the systematic review and meta-analysis. It identifies a critical research gap: the absence of existing randomised controlled trials (RCTs) investigating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) on neurogenic overactive bladder (OAB) symptoms among stroke survivors. This gap necessitates the main study of this thesis.

2.2 Background

Neurogenic OAB is a condition that arises from neurological dysfunctions affecting the bladder's normal function [205, 206]. It disrupts the regulation of detrusor muscle pressure, which is responsible for bladder emptying, leading to urgency urinary incontinence (UUI) [205, 206]. Individuals with neurogenic OAB experience a range of symptoms, including increased urinary frequency, urgency and involuntary urine leakage [207], which are often triggered by a sudden, strong urge to urinate, making it

difficult for individuals to control their bladder [207]. The impact of UUI due to neurogenic OAB extends beyond the physical symptoms. The condition can significantly affect an individual's quality of life, leading to social isolation, depression and embarrassment [208]. The involuntary nature of urine leakage can reduce self-esteem and limit social, sexual and occupational activities [195]. The psychological stress associated with managing UUI can further restrict participation in social engagements, exacerbating feelings of isolation and depression [209]. The severity of neurogenic OAB and its implications highlight the importance of its adequate management and treatment. Without proper intervention, neurogenic OAB can not only reduce the quality of life but also pose life-threatening risks, particularly in severe cases where it leads to complications such as recurrent urinary tract infections or renal damage [210, 211]. Therefore, it is crucial for individuals experiencing symptoms of neurogenic OAB to seek medical advice for diagnosis and treatment.

Pharmacological options for managing neurogenic OAB include oral medications such as anticholinergic drugs (antimuscarinics), beta-adrenergic agents and selective serotonergic reuptake inhibitors. Additional therapeutic modalities involve intravesical injections and transdermal agents [212]. However, the long-term response rate to medication is low, with only 12%–39% of individuals experiencing sustained compliance after one year [213]. A significant number of individuals with neurogenic OAB discontinue medication due to adverse effects or a lack of symptom improvement [213, 214]. Surgical interventions may be considered for those who do not respond to conservative or less invasive treatments. However, surgical management of neurogenic

OAB symptoms is costly and can be associated with postoperative complications [215]. Some surgical procedures, such as tension-free vaginal tape and translabial ultrasound, are used to assess technical errors following mid-urethral transobturator tape placement [216].

Non-surgical minimally- or non-invasive therapies for neurogenic OAB encompass diverse treatment modalities. These include rTMS [217], transcranial direct current stimulation [218], transcutaneous electrical nerve stimulation (TENS) [218], neuromuscular electrical stimulation (NMES) [219], biofeedback [220], transcutaneous tibial nerve stimulation (TTNS) [221], intravaginal electrical stimulation (IVES) [222], pelvic floor muscle training (PFMT) [220], cognitive behavioural training, and the use of vaginal cones [223]. Previous systematic reviews have evaluated the effectiveness of these interventions [210, 224-228]. However, these reviews had some limitations. They either did not include meta-analyses [144, 229, 230], focused on a single intervention [224-227], yielded inconclusive results due to a limited number of included studies [230], or were conducted more than five years ago [224, 226]. Therefore, this meta-analysis is the first to encompass all non-surgical minimally- or non-invasive therapies for managing UUI due to neurogenic OAB [210, 224-228].

2.3 Aims

The primary aim was to assess the effects of non-surgical minimally- or non-invasive therapies for managing UUI and reduced quality of life caused by neurogenic OAB.

2.4 Methods

2.4.1 Search strategy and study screening

This review was developed and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [231] and registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42021236522) before the databases were searched. Six electronic databases were searched from inception to 30 September 2021: Cochrane Library, Excerpta Medica Database (EMBASE), MEDLINE, Physiotherapy Evidence Database (PEDro), Scopus and Web of Science. The search terms were formulated into three themes: neurogenic OAB, treatments and study design (Appendix 2.1). The defined search terms within each theme were combined using the Boolean operator 'OR', and the three themes were combined using the Boolean operator 'AND'. The EMBASE database search strategy is described in detail in Appendix 2.2. The studies were selected for this review based on the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework [232]. The articles identified through electronic database searches were exported to the EndNote X9 citation manager (Clarivate Analytics, Philadelphia, PA, USA) for screening.

2.4.2 Study selection

Studies were included in this systematic review if they (1) were RCTs (full, pilot, cluster or crossover) reported in published articles; (2) included adults (of both sexes) with

UUI caused by neurogenic OAB due to spinal cord injury, stroke, Parkinson's disease, or multiple sclerosis; (3) compared therapies, such as IVES, TENS, NMES, TTNS, PFMT or behavioural therapy (BT), against control therapies, such as no treatment, sham, or PFMT; and (4) used the OAB-Validated 8-Question Screener (OAB-V8), the Overactive Bladder Symptom Score (OABSS) questionnaire or a voiding diary to evaluate UUI symptoms or used the Qualiveen questionnaire, Incontinence Impact Questionnaire-7 (IIQ-7) or International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) to measure quality of life. Studies were excluded if they (1) were not published in English; (2) were quasi-experimental trials, crossover studies, or wait-list studies; (3) involved medical or surgical interventions; or (4) were conference proceedings.

2.4.3 Data extraction

One reviewer (MUA) performed the electronic database searches and the title and abstract screening. Two reviewers (MUA and Umar Muhammad Bello) independently performed the full-text screening. Discrepancies between the two reviewers were resolved through discussion until a consensus was reached. For unresolved discrepancies, a third reviewer (PK) was consulted. The reference lists for included studies and relevant systematic reviews were manually searched to identify any potentially relevant articles. Two reviewers (MUA and UMB) independently performed the data extraction for each included study. The following data were extracted from each included study: first author, publication year, country of origin, participant

characteristics (mean and standard deviation of age), the sample size of each group, intervention, control, outcome measure(s), and pre- and post-treatment results.

2.4.4 Quality assessment

The methodological quality and quality of evidence of each included study were evaluated using the PEDro scale [233, 234] and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [235], respectively. Among the many available scales for assessing the quality of clinical trials, the PEDro scale has emerged as a widely adopted and commonly used instrument [233]. Its popularity can be attributed to its ease of use, established psychometric properties and ability to provide a reliable and standardised assessment of trial quality. Consequently, it has become an integral tool in critically appraising clinical trials within the research community [233]. The PEDro scale has been reported as a reliable and valid tool for evaluating methodological quality [233]. It is an 11-item checklist: item 1 assesses external validity, items 2–9 assess internal validity, and items 10 and 11 assess interpretability [236]. Each item of the PEDro scale is scored as "1 (yes) or 0 (no)'', resulting in a maximum score of 10, with higher scores indicating higher study quality. Studies scoring ≥7 are considered high quality, 5–6 are considered moderate quality, and 0–4 are considered low quality [233]. Over 61,000 trials, reviews and guidelines evaluating physiotherapy interventions are indexed in the PEDro database. In order to facilitate the interpretation of research findings, all trials indexed in the PEDro database are assessed for methodological quality [237]. The efficient access to the most methodologically robust trials in the PEDro database is enhanced by their ranking

according to a set of quality criteria [238]. This ranking enables researchers and clinicians to promptly identify and prioritise high-quality evidence, thereby streamlining the process of interpreting research findings [238]. One reviewer (MUA) evaluated the methodological quality of the included studies, and the scores were compared against existing scores reported on the PEDro database [239]. Disagreements in scores between the author and the PEDro database were resolved through discussion with a second reviewer (UMB).

The quality of evidence (GRADE) was evaluated using the GRADEpro software [240]. According to the GRADE system, the quality of a body of evidence can be categorised as ‘very low’, ‘low’, ‘moderate’ or ‘high’ [241]. The overall quality of evidence for an outcome measure was based on the lowest quality score for the assessed outcome [241]. The following factors were considered when grading the quality of evidence.

2.4.4.1 Study limitations

Evidence was rated according to the presence of methodological flaws, such as the absence of concealed allocation, inadequate follow-ups and inadequate reporting of outcome measures [242]. Given the nature of the intervention, studies were not downgraded for the lack of participant blinding; however, studies were downgraded by one level for the lack of either therapist or assessor blinding and by two levels for the lack of both therapist and assessor blinding [242].

2.4.4.2 Indirectness of evidence

Studies were downgraded if a substantial difference was identified between the intervention and control populations across the studies and when surrogate outcome measures were used, which may reduce the quality of evidence [243].

2.4.4.3 Imprecision

Studies were downgraded for imprecision if the confidence interval (CI) around the estimated treatment effect was not sufficiently narrow in the presence of a small total sample size [244].

2.4.4.4 Inconsistency of results across studies

Studies were downgraded for minimal or no overlap or evidence of statistical heterogeneity, as indicated by a large chi-square statistic [245].

2.4.4.5 Publication bias

It has been proposed that industry bias should be considered a 'meta-bias,' as industry sponsorship itself does not directly cause bias—unlike, for example, lack of allocation concealment—but rather acts as a risk factor that increases the likelihood of biases occurring [246]. Publication bias from underreporting or overreporting of evidence is downgraded by one level. A funnel plot was planned if more than 10 studies were included in a meta-analysis.

2.4.5 Ethical Approval

Ethical approval was not sought for this meta-analysis, and each included study independently obtained ethical approval before conducting the RCTs included in this meta-analysis [247].

2.4.6 Data analysis

The meta-analysis of the included studies was conducted using the Comprehensive Meta-Analysis software (CMA Version 3.0; Biostat, Inc., Englewood, New Jersey 07631, USA) [248, 249]. Trials that used similar interventions and outcome measures were pooled. Weighted mean differences (WMDs), standardised mean differences (SMDs) and 95% CIs were used to assess the intervention effects of continuous outcomes. Where studies used different outcome measures to assess the same outcome, SMD was computed using Hedges' *g*. Statistical heterogeneity was evaluated using the chi-square test (I^2 > 50% was considered substantial heterogeneity). When minimal heterogeneity was identified (I^2 < 50%), a fixed-effects model was used, whereas a random-effects model was used when maximum heterogeneity was identified (I^2 > 50%) [250, 251]. Asymmetry could not be evaluated using funnel plot analyses because fewer than 10 studies were included in the pooled meta-analyses [252].

2.5 Results

2.5.1 Study selection

Figure 2.1 presents a PRISMA flowchart of the screening process used to select studies, with the reasons for exclusion at each stage. The electronic database searches identified 3,953 potentially relevant articles. After importing them into the EndNote citation manager, 1,391 duplicate records were identified and removed. The review of the study titles and abstracts excluded 2,360 and 148 articles, respectively. The full-text screening of the remaining 54 articles led to the exclusion of 45, and nine were determined to meet the study's inclusion criteria. A manual search of the reference lists of the included articles (forward search) and relevant systematic reviews revealed an additional five articles, resulting in 14 studies being included in this review. The interventions identified in the included studies included IVES [253, 254], TENS [255, 256], NMES [219, 257], TTNS [221, 258], PFMT [259-261] and BT [262, 263]. Studies evaluating the effects of other therapies, such as rTMS [217] and functional magnetic stimulation [264-268], were also identified during the database searches; however, these interventions [264-268] could not be included in this review because they were evaluated in quasi-experimental trials lacking a control group.

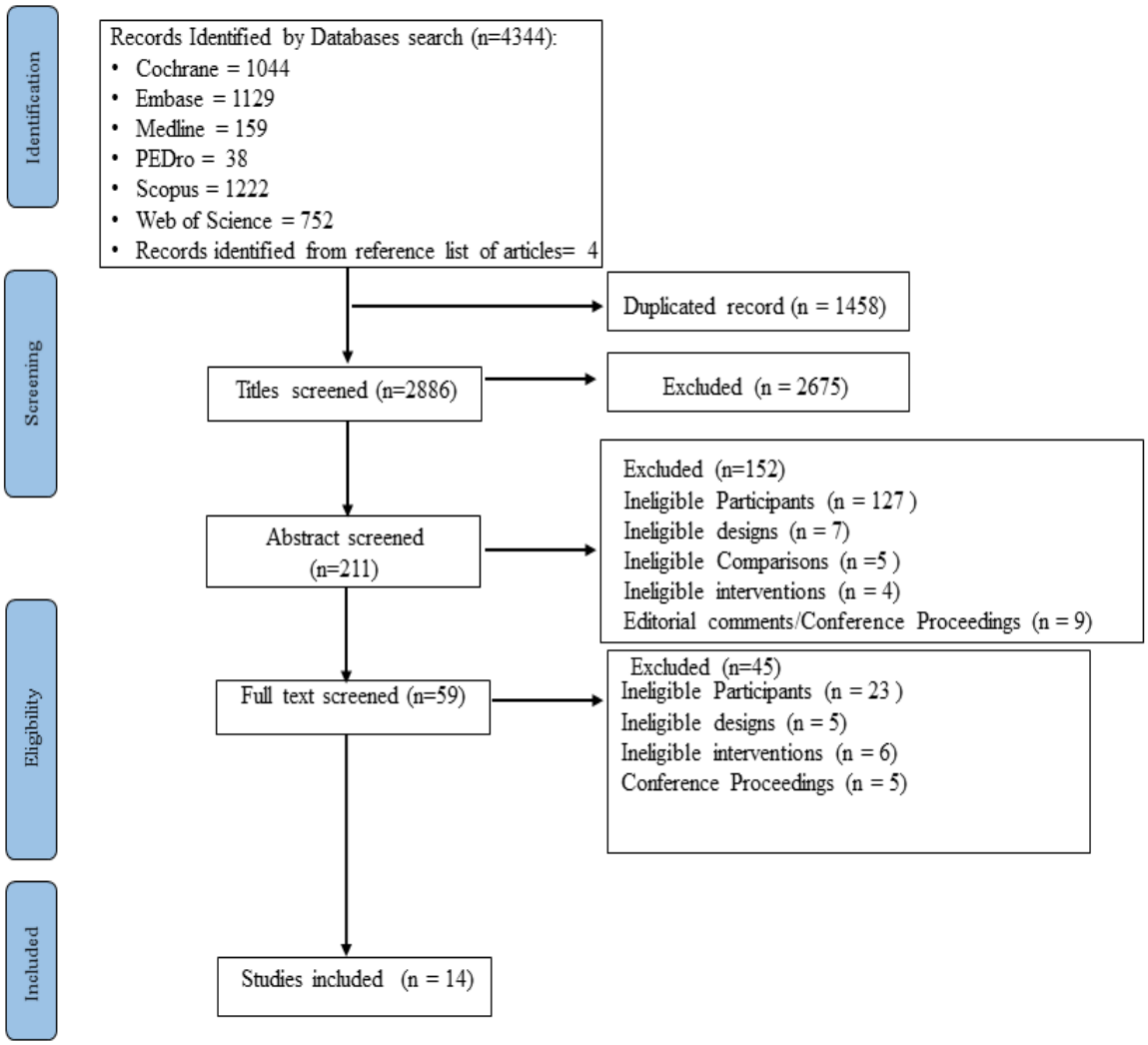

Figure 2.1: Flowchart of study identification and screening.

2.5.2 Study characteristics

The characteristics of the included studies are presented in Table 2.1. The 14 included studies included 804 participants, with sample sizes ranging from 13 to 82. The participants' ages ranged from 18 to 90 years. The included studies were published between 2004 and 2021, with 11 of the 14 studies published within the last seven years (2014–2021). Five studies were conducted in Brazil [221, 253, 254, 258, 269], three in Denmark [259-261], three in China [219, 255, 256], two in the United Kingdom [257, 262] and one in the United States [263]. Twelve studies evaluated UUI [219, 253-257, 259-263, 269], and four studies evaluated quality of life [221, 258, 262, 263].

Table 2.1 Characteristics of included studies (n =14)

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure (s)	Pre-treatment results	Post-treatment results
Araujo et al., 2021 Brazil **8/10**	**Exp**: 64.2+ 2.5 **Con**: 68.2+ 2.3 **Exp**: *n* = 15 **Con**: *n* = 15	**TTNS** **Frequency:** 10 Hz **Pulse Duration**: 200 µs **Intensity:** 1mA at 1KΩ **Duration:** 20 min for 12 weeks	**TTNS** **Frequency:** <0.5 Hz **Pulse Duration**: 200 µs **Intensity:** not sufficient to trigger rhythmic toe flexion **Duration:** 20 min for 12-weeks	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp:** 27.8 ± 8.9 **Con**: 29.4 ± 8.4	**Exp:** 15.0 ± 6.9 **Con:** 25.9 ± 8.1
Ferreira et al 2016 Brazil., **5/10**	**Exp**: 43.25 ± 10.68 **Con:** 49.8 ± 16.5 **Exp:** *n* = 12 **Con**: *n* = 12	**NMES** **Frequency:** 2 Hz **Pulse Duration**: 1 msec **Intensity:** tolerable for the patient. **Duration**: 48 sessions twice weekly for 6 months **PFMT** 3 sets of 10 reps daily for 6-months	**PFMT** 3 sets of 10 reps per day for 6 months	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp:** 1.69 (0.59) **Con:** 1.58 (0.71)	**Exp:** 0.62 (0.62) **Con:** 0.88 (0.62)
Ferreira et al., 2019 Brazil **5/10**	**Exp:** 38.6 ± 13.5 **Con:** 49.8 ± 16.5 **Exp:** *n* = 15 **Con**: *n* = 15	**PFMT** During stimulation, participants perform 20 fast and slow contractions twice weekly for 6 months **IVES** **Frequency:** 2 Hz **Pulse Duration**: 1 msec **Intensity:** tolerable for the patient. **Duration**: 30 min 48 sessions twice weekly for 6 months	**PFMT** 3 sets of 8-10 close-to-maximal contractions and 10s sustenance daily for 6 months.	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp:** 1.1 ± 1.1 **Con:** 0.7 ± 0.7	**Exp:** 0.3 ± 0.3 **Con:** 0.4 ± 0.4
Guo et al., 2014 China **4/10**	**Exp**: 68.1±7.1 **Con**: 65.1±9.8 **Exp**: *n* = 32 **Con**: *n* = 29	**PFMT+TENS** 30 minutes daily/60 days Pulse duration: 70 µS Frequency: 75 Hz Current: 16 mA (1 kΩ)	**PFMT** Basic therapy	OABSS	***UUI symptoms*** **OABSS** **Exp:** 5±0.94 **Con**: 5±0.69	**Exp:** 2.64±0.98 **Con:** 4.09±0.71

Guo and Kang, 2018 China **9/10**	**Exp**: 64.3 (11.8) **Con**: 62.5 (12.2) **Exp**: *n* = 41 **Con**: *n* = 41	**NMES** **Frequency**: 50 Hz **Pulse Duration**: 250µs **Treatment duration**: 30 minutes (10 seconds on and 30 seconds off) Graded intensity based on patient's tolerance. Once daily 5 sessions weekly for 10 weeks	**Sham** NMES without active probe	OABSS	***UUI symptoms*** **OABSS:** **Exp**: 4.02±0.76 **Con:** 4.18±0.65	**Exp:** 1.61±0.32 **Con:** 3.86±0.74
Liu et al., 2016 China **7/10**	**Exp I**: 66.30 (10.84) **Exp II**: 63.75 (8.92) **Con**: 67.91 (7.39) **Exp I**: *n* = 27 **Exp II**: *n* = 27 **Con:** *n* = 27	**TENS I** **Frequency**: 20 Hz **Pulse Duration**: 150µs **Treatment duration**: 30 mins once daily for 90 days **TENS II** **Frequency**: 75 Hz **Pulse Duration**: 150µs **Treatment duration**: 30 mins once daily for 90 days	**No-treatment** Only assessment of OABSS, BI, Urodynamics and Voiding diary on the first day and the 90th day.	Voiding diary	***UUI symptoms*** **Voiding diary: incontinence episodes in 24 hours** **Exp I:** 10.07 (3.98) **Exp II:** 11.84 (3.05) **Con:** 10.63 (1.82)	**Exp I**: 2.10 (0.78) **Exp II:** 4.69 (1.05) **Con:** 9.54 (3.51)
Lúcio et al. 2016 Brazil **5/10**	**Exp I**: 42 (27-54) **Exp II**: 45 (22-52) **Con:** 43.5 (25-51) **Exp I**: *n* = 10 **Exp II:** n = 10 **Con**: *n* = 10	**NMS+ EMG Biofeedback +PFMT** **Frequency**: 10 Hz **Pulse Duration**: 200 µs **Treatment duration**: 30 mins **TTNS+ EMG Biofeedback +PFMT** **Frequency**: 10 Hz **Pulse Duration**: 200 µs **Treatment duration**: 30 mins	**Sham NMS+PFMT** **Frequency**: 2 Hz **Pulse Duration**: 50 milsec **Treatment duration**: 2 sec with 60 sec rest 30 mins once daily for 90 days 30 slow maximal effort followed by 3 minutes of fast maximal effort	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp I**: 5.0 (0-8.3) **Exp II**: 4.0 (1.7-5.7) **Con:** 3 (1.7-6.3)	**Exp I**: 0.2 (0-2.3) **Exp II**: 0.7 (0-4.3) **Con:** 0.5 (0-3)
McClurg et al., 2008 UK **9/10**	**Exp:** 48.3 (11.5) **Con**: 52.0 (8.8) **Exp:** *n* = 37 **Con:** *n* = 37	**PFMT + Biofeedback + Active NMES** **Ist Parameter Frequency**: 40 Hz **Pulse Duration**: 250 µs **Treatment duration**: 5 sec of stimulation and 10 sec of no stimulation with a ramp of 1 sec at clinic and home for 30 mins **2nd Parameter Frequency**: 10 Hz **Pulse Duration**: 450 µs	**PFMT + Biofeedback + Placebo NMES** **Frequency**: 2 Hz **Pulse Duration**: 50 µs **Treatment duration**: 2 sec of stimulation and 60 sec of no stimulation with a ramp of 8 sec at clinic and clinic for 30 mins	Voiding Diary	***UUI symptoms*** **Voiding diary: Incontinence episodes per in 24 hours** **Exp:** 2.1±4.1 **Con:** 2.1±4.0	**Exp**: 0.3±1 **Con:** 1.1±2.8

		Treatment duration: 10 sec of stimulation and 3 sec of no stimulation with a ramp of 3 sec at clinic and home for 30 mins				
McDonald et al., 2020 UK **8/10**	**Exp**: 63.6 (1.7) **Con:** 69.8 (1.8) **Exp**: *n* = 20 **Con:** *n* = 18	**Bladder training Programme** -Instructions on urge suppression and distraction techniques -Coaching in PFMT -A personalised voiding schedule -A DVD training For 12 weeks	Conservative advice	Voiding diary ICIQ-OAB	***UUI symptoms*** **Voiding diary: 72 hours Episodes of urgency** **Exp:** 4.7 (1.1) **Con:** 6.7 (1.9) ***QoL*** **ICIQ-QOL Score** **Exp**: 63 (4.7) **Con:** 60 (6.3)	**Exp:** 2.1 (1.0) **Con**: 4.7 (1.2) **Exp**: 50 (7.0) **Con:** 59 (4.1)
Perissinotto et al., 2015 Brazil **6/10**	**Exp**: 63.5 (51.0-80.0) **Con**: 57.0 (50.0-68.0) **Exp**: *n* = 8 **Con**: *n* = 5	**TTNS** Pulse Width: 200 µs Frequency: 10 Hz Duration: 30 min for 5 weeks	**Sham** No active electrical stimulation	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp:** 18.0 (6.0-27.0) **Con:** 29 (11.0-33.0)	**Exp:** 16.0 (6.0-25.0) **Con**: 21.5 (6.0-21.5)
Tibaek et al., 2004 Denmark **6/10**	**Exp:** 59 (56–72) **Con**: 62 (52–75) **Exp**: *n* = 12 **Con**: *n* = 12	**Standardised PFMT** - -Close-to maximum contraction (6 s contraction/ 6 sec rest). -30% of maximum contraction possible (max 30 s contraction/30 s rest). -All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. -Group treatment in this population	**Normal rehabilitation programme** -No specific Urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary: Voiding Frequency Totally/24 hours** **Exp**: 11 (6-10) **Con:** 11 (8-12)	**Exp:** 7 (5-10) **Con**: 8 (7-12)
Tibaek et al., 2005 Denmark **7/10**	**Exp**: 59 (56–72) **Con**: 62 (52–75) **Exp**: *n* = 14 **Con**: *n* = 12	**Standardised PFMT** -Close-to maximum contraction (6 s contraction/ 6 sec rest). -30% of maximum contraction possible (max 30 s contraction/30 s rest).	**Normal rehabilitation programme** -No specific Urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary: Voiding Frequency Totally/24 hours** **Exp:** 10 (8-12) **Con:** 9 (8-13)	**Exp:** 8 (7-9) **Con:** 8 (7-12)

		-All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. -Group treatment in this population				
Tibaek et al., 2015 Denmark **7/10**	**Exp**: 68 (57-73) **Con:** 70 (64-75) **Exp**: *n* = 15 **Con**: *n* = 15	**Standardised PFMT** -Close-to maximum contraction (6 s contraction/ 6 sec rest). -30% of maximum contraction possible (max 30 s contraction/30 s rest). -All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. -Group treatment in this population	**General Rehabilitation** -No specific Urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary:** **Voiding frequency, total per 24 hours** **Exp:** 11 (6-10) **Con:** 11 (8-12)	**Exp:** 7 (5-10) **Con:** 8 (7-12)
Vaughan et al., 2019 US **8/10**	**Exp:** 71.0 ± 6.1 **Con**: 69.7 ± 8.2 **Exp**: *n* = 26 **Con:** *n* = 21	**Behavioural Therapy** -Isolated PFMT without abdominal muscle recruitment (45 contractions and relaxation divided into 3 sets of 15 with one in each of the three positions: lying, sitting, standing) -Fluid management education (Decrease caffeine, daily drinking 6-8 ounce glasses of fluid) -Constipation management education (increase physical activity, fibre, fruit, and fluid) -Urge suppression strategy	-Maintain 7-day bladder diaries for 8 weeks -Mirrored-shaped drawing exercises	Voiding Diary ICIQ-OAB	***QoL*** **ICIQ-OAB QoLscore** **Exp**: 69.7 ± 23.8 **Con**: 74.7 ± 23.8 ***UUI symptoms*** **Voiding diary:** **Weekly Frequency** **Exp**: 13.9 ± 9.6 **Con**: 15.1 ± 11.1	**Exp:** 58.4 ± 21.5 **Con**: 81.0 ± 24.2 **Exp:** 7.7 ± 10.5 **Con**: 8.5 ± 10.0

Exp: Experimental Group; Con: Control Group; TTNS: Transcutaneous Tibial Nerve stimulation; PFMT: pelvic floor muscle training; IVES: intravaginal electrical stimulation; OAB-V8: Overactive Bladder –V8 Questionnaire; ICIQ-UI-OAB: International Consultation on Incontinence Questionnaire OAB: Overactive Bladder; IIQ: Incontinence Impact Questionnaire; UUI: Urgency Urinary Incontinence

2.5.3 Methodological quality

The PEDro scores for the included studies are presented in Table 2.2. The mean PEDro score among the included studies was 6 out of 10, ranging from 4 to 9. Out of the 14 included studies, eight were classified as having high methodological quality, five as moderate and one as low. Among these 14 included studies, seven did not report allocation concealment, 10 lacked intention-to-treat analysis, 10 lacked assessor blinding, and three had a loss to follow-up of more than 15% of participants. Additionally, none of the 14 studies used therapist blinding.

Table 2.2 Summary of methodological quality of the included studies according to the PEDro scale (n=14)

PEDro Scale	Random allocation	Concealed allocation	Baseline Similar	Subject blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between-group comparison	Points estimate	Total Score/10
Araujo et al., 2021	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8
Ferreira et al., 2016	Y	N	Y	N	N	N	Y	N	Y	Y	5
Ferreira et al., 2019	Y	N	Y	N	N	N	Y	N	Y	Y	5
Guo et al., 2014	Y	N	Y	N	N	N	N	N	Y	Y	4
Guo and Kang 2018	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Liu et al., 2016	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Lucio et al., 2016	Y	N	Y	N	N	Y	N	N	Y	Y	5
McClurg et al., 2008	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
McDonald et al., 2020	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Perissinotto et al., 2015	Y	N	Y	Y	N	Y	N	N	Y	Y	6
Tibaek et al., 2004	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Tibaek et al., 2005	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Tibaek et al., 2015	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Vaughan et al., 2019	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8

Y = Yes; N = No.

2.5.4 Risk of bias

The Cochrane Risk of Bias assessment tool was used to evaluate the methodological quality of the included studies in this review. The 14 included studies were categorised as having low, intermediate or high risk of biases. All 14 included studies used randomisation in their design. Regarding bias assessment, 21% of the included studies had a risk of bias related to blinding of the outcome assessment (detection bias) and incomplete outcome data (attrition bias). The most common bias observed was the lack of blinding of participants and personnel (selection bias), which was present in 50% of the included studies, followed by a lack of allocation concealment, which was present in 33% of the studies (Figures 2.2 and 2.3).

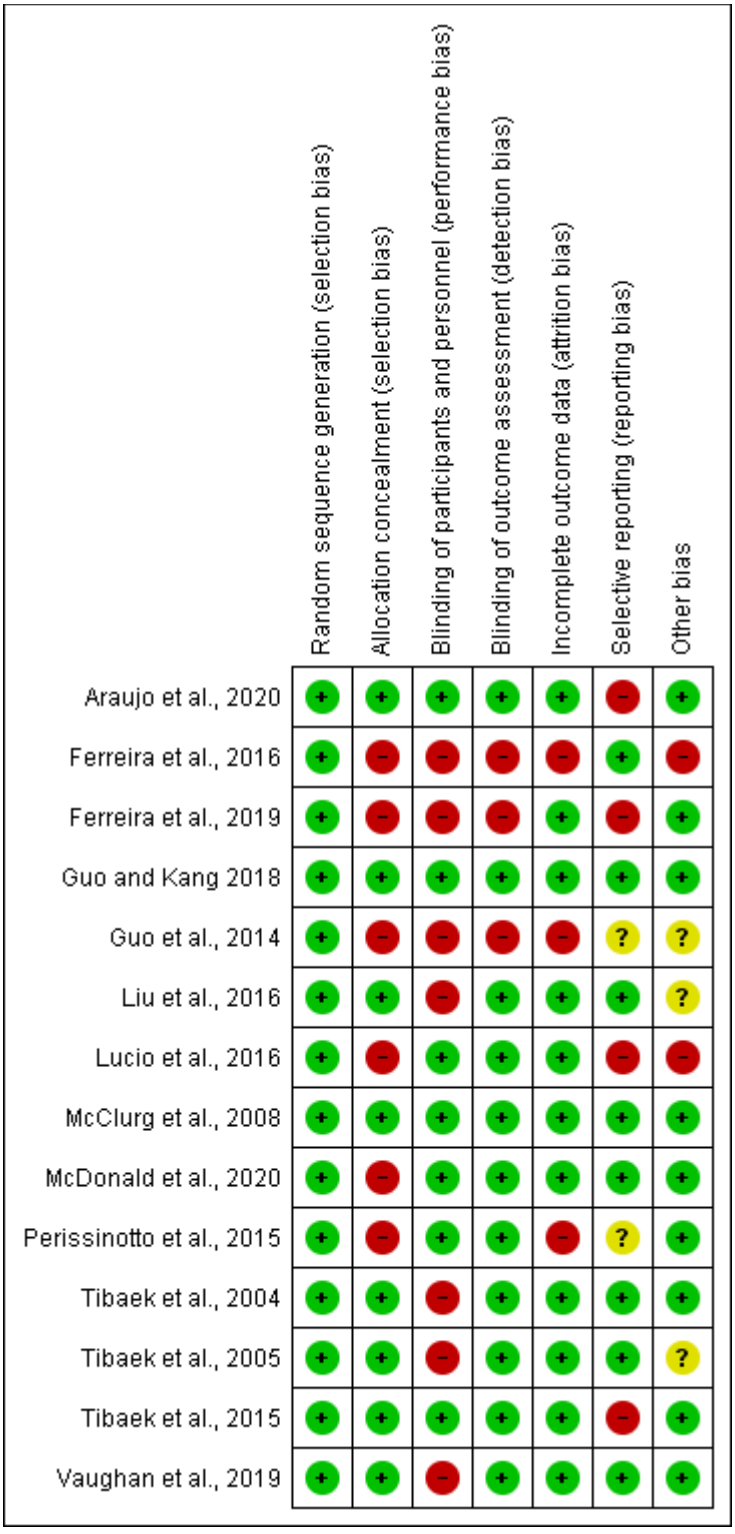

Figure 2.2: Risk of bias summary: reviewers' judgements about each risk of bias item for each included study.

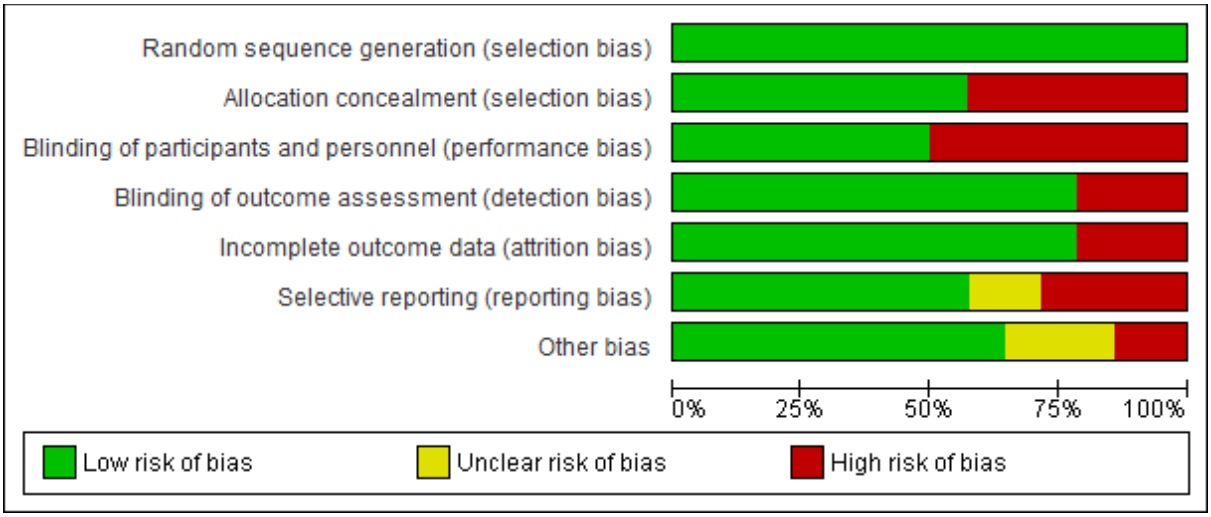

Figure 2.3: Risk of bias graph: reviewers' judgements about each risk of bias item presented as percentages across all included studies.

2.5.5 Quality of evidence

The findings generated by the GRADE profiler software are presented in Table 2.3. The quality of evidence, as determined by GRADE, varied from ‘low’ to ‘moderate’ for the 14 studies included in the five meta-analyses. The overall quality of evidence for the included studies was rated as ‘low’ to ‘moderate’ for UUI and moderate for quality of life.

Table 2.3 Summary of the findings (GRADE) for the effects of interventions compared to control

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention group	Control group	Relative (95% CI)	Absolute (95% CI)	
4 McClurg 2008 Ferreira 2016 Lucio 2016F Ferreira 2019	RCT	very serious [a]	not serious	not serious	not serious	none	74	74	-	(1.055 lower to 0.208 lower)	⊕⊕◯◯ LOW
3 Tibaek 2004 Tibaek 2005 Tibaek 2015	RCT	very serious [b]	not serious	not serious	not serious	none	41	39	-	(0.628 lower to 0.225 higher)	⊕⊕◯◯ LOW
3 Guo 2014 Liu 2016 Guo and Kang 2018	RCT	serious [c,d]	not serious	not serious	not serious	none	100	97	-	(4.219 lower to 1.635 lower)	⊕⊕⊕◯ MODERATE
2 Vaughan 2019 McDonald 2020	RCT	serious [e]	serious [f]	not serious	not serious	none	46	39	-	(16.015 lower to 8.797 lower)	⊕⊕◯◯ LOW
2 Perrissinotto 2015 Araujo 2021	RCT	serious [g,h]	not serious	not serious	not serious	none	23	20	-	(14.746 lower to 3.487 lower)	⊕⊕⊕◯ MODERATE
2 Vaughan 2019 McDonald 2020	RCT	serious [e]	serious [f]	not serious	not serious	none	46	39	-	SMD **1.365 SD lower** (2.598 lower to 0.131 lower)	⊕⊕◯◯ LOW

CI: Confidence interval
RCT: Randomised Controlled Trial

Explanations
a. Lack of intention-to-treat analysis (Ferrira 2016, Lucio 2016 and Ferreira 2019)
b. Lack of Intention-to-treat analysis (Tibaek 2004, Tibaek 2005 and Tibaek 2015)
c. Lack of concealed allocation (Guo 2014)
d. Lack of intention-to-treat analysis (Guo 2014 and Liu 2016)

e. Lack of concealed allocation (McDonald 2020)
f. Evidence of Statistical/Methodology (I squared value> 50%)
g. Lack of concealed allocation (Perissinotto 2015)
h. Lack of Intention-to-treat analysis (Araujo 2021, Perissinotto 2015)

2.5.6 Effects of the interventions on UUI

2.5.6.1 Electrical stimulation vs PFMT on UUI due to multiple sclerosis

Four studies [253, 254, 257, 269] compared the effects of electrical stimulation (IVES and NMES) with PFMT on UUI among individuals with multiple sclerosis. Regarding the stimulation parameters used in the four studies, session length ranged from 18 to 52 treatment sessions, the frequency ranged from 2 to 40 Hz, the intensity ranged from 450 microseconds to 1 millisecond, and the duration ranged from 20 to 30 minutes. Among the four studies, three [253, 254] measured UUI using OAB-V8 and one using a voiding diary.

The methodological quality of the four studies [253, 254, 257, 269] was moderate to high, and the quality of evidence quality was moderate. A pooled analysis of the studies trials (n = 74) revealed a significant reduction in UUI symptoms in the intervention group compared to the control group (SMD: −0.614, 95% CI: −1.023–−0.206, p = 0.003; Figure 2.4a).

2.5.6.2 PFMT vs no treatment on UUI due to stroke

Three studies [259-261] compared the effects of PFMT on UUI symptoms to a no-treatment control among individuals with stroke. In the three studies, PFMT consisted of 6 seconds of maximum contractions, followed by 6 seconds of rest, for a total of 30 seconds of maximum contractions and 30 seconds of rest. All exercises were repeated

gradually 6–10 times while lying, standing or seated, 1–2 times daily, seven days a week. All three studies [259-261] measured UUI using a voiding diary.

The methodological quality of the three studies [259-261] was evaluated as moderate to high, and the quality of evidence was low. The pooled analysis of the three studies (n = 80) revealed a nonsignificant reduction in daytime voiding frequency in the intervention group compared to the control group (WMD: −0.751, 95% CI: −2.426–0.924, p = 0.380; Figure 2.4b).

2.5.6.3 Electrical stimulation vs no treatment on UUI due to stroke

Three studies [219, 255, 256] compared the effects of electrical stimulation (NMES [219] or TENS [255, 256]) on UUI to a no-treatment control group among individuals with stroke. Across the three studies, the stimulation parameters ranged from five to seven times weekly, for a total of 40–90 treatment sessions, at frequencies ranging from 20 to 75 Hz, with intensities ranging from 70 to 250 microseconds and lasting from 20 to 30 minutes. Of the three studies, two [219, 255] measured UUI using the OABSS and one [256] using a voiding diary.

The methodological and evidence qualities of the three studies [219, 255, 256] were moderate. The pooled analysis of the three studies (n = 224) revealed a significant effect of the intervention on UUI symptoms compared to the control intervention (SMD: −2.637, 95% CI: −3.804–−1.474, p = 0.000; Figure 2.4c).

2.5.6.4 BT vs no treatment on UUI due to Parkinson's disease

Two studies [262, 263] compared the effects of BT to usual care (reduced alcohol and caffeine intake and advice about managing constipation and available containment products) on UUI symptoms in individuals with Parkinson's disease. The BT intervention delivered in the included studies involved isolated PFMT without abdominal muscle recruitment (45 contractions and relaxation, divided into three sets of 15, each performed in a different position: lying, sitting and standing), fluid management education (decreased caffeine and daily intake of six 8-ounce glasses of fluid), constipation management education (increased physical activity, increased intake of fibre, fruits and fluids) and urge suppression strategies. The two studies [262, 263] measured UUI using a voiding diary.

The methodological quality of both studies [262, 263] was high, and the quality of evidence was low. The pooled analysis of the two studies (n = 85) revealed a nonsignificant effect of the intervention on UUI symptoms compared to the control intervention (WMD: −0.597, 95% CI: −1.278–0.083, p = 0.085; Figure 2.4d).

2.5.6.5 Effects of interventions on quality of life in individuals with Parkinson's disease

2.5.6.5.1 BT vs no treatment

Two studies [262, 263] compared the effects of BT to usual care (reduced alcohol and caffeine intake and advice about managing constipation and available containment products) on quality of life in individuals with Parkinson's disease. The two studies [262, 263] measured quality of life using the ICIQ-SF.

The methodological quality of both studies [262, 263] was high, and the quality of evidence was low. The pooled analysis of the two studies (n = 85) revealed a significant effect of BT on quality of life compared to the control intervention (WMD: −0.9117, 95% CI: −14.746–−3487, p = 0.002; Figure 2.4e).

2.5.6.5.2 TTNS vs no treatment

Two studies [221, 258] compared the effects of TTNS on quality of life to a no-treatment control group in individuals with Parkinson's disease. The stimulation parameters used in the two studies included session lengths ranging from 5 to 12 weeks, a frequency of 10 Hz at an intensity of 200 microseconds and a duration of 20–30 minutes. Both studies [221, 258] measured quality of life using the OAB-V8.

The methodological quality of the two studies [221, 258] ranged from moderate to high, and the quality of evidence was moderate. The pooled analysis of the two studies (n = 43) revealed a significant improvement in quality of life in the intervention group compared to the control group (WMD: −12.406, 95% CI: −16.015–−8.797, p = 0.000; Figure 2.4f).

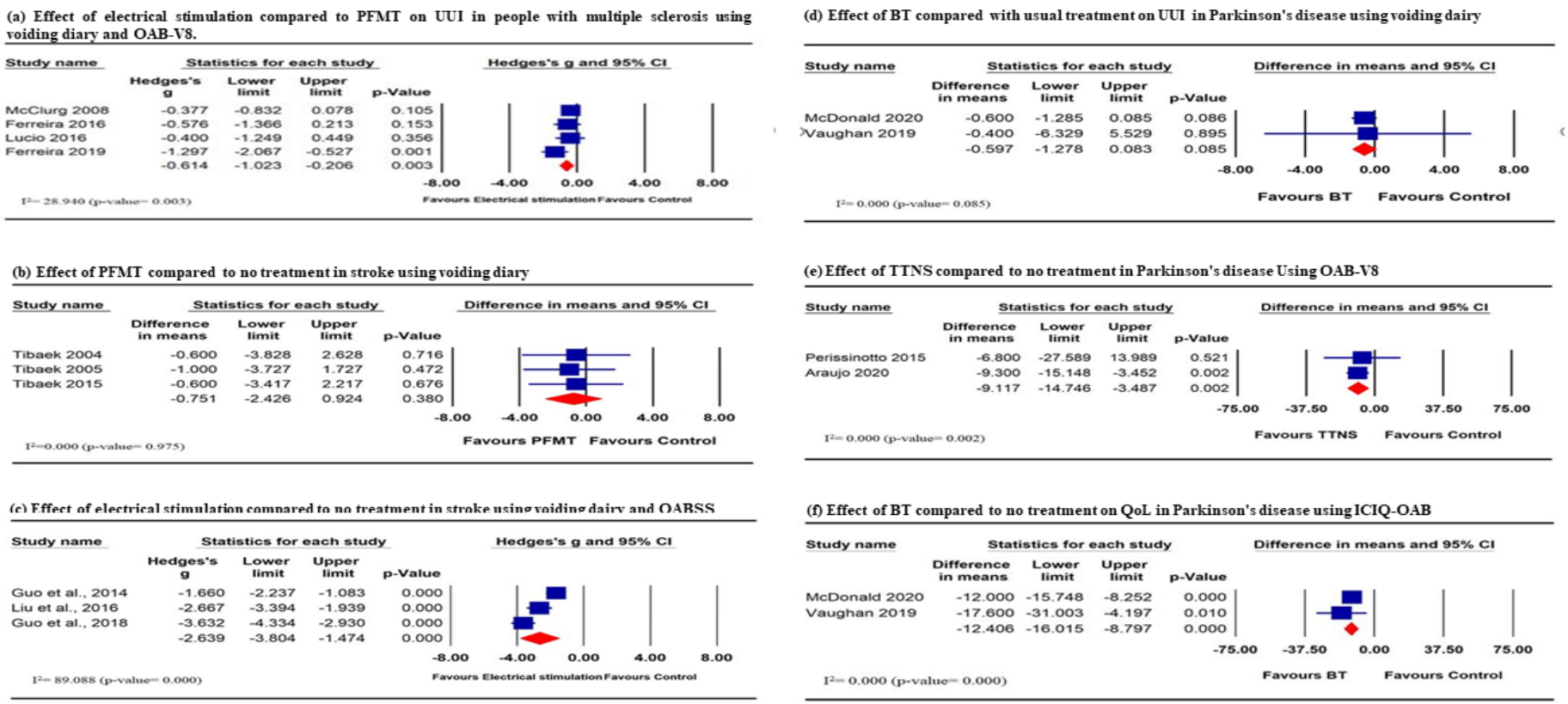

Figure 2.4: Forest Plots

OAB-V8: Overactive Bladder Questionnaire; PFMT: Pelvic Floor Muscle Training; UUI: Urge Urinary Incontinence; OABSS: Overactive Bladder Symptom Score; BT: Behavioural Therapy; TTNS: Transcutaneous Tibial Nerve Stimulation; ICIQ-OAB: International Consultation on Incontinence Questionnaire Overactive Bladder Module (ICIQ-OAB); QoL: Quality of Life

2.6 Discussion

This review aimed to assess the effects of non-surgical minimally- or non-invasive therapies on symptoms of UUI and quality of life in individuals with neurogenic OAB. The database searches identified 14 studies with 804 participants. The meta-analyses demonstrated a significant effect of electrical stimulation on UUI due to multiple sclerosis or stroke. Additionally, the pooled analyses of TTNS revealed significant effects of these interventions on quality of life in individuals with Parkinson's disease. However, the meta-analyses revealed nonsignificant effects of PFMT on UUI due to Parkinson's disease.

The pooled analysis of four studies [253, 254, 257, 269] with moderate to high methodological quality and moderate quality of evidence showed a significant effect of electrical stimulations (IVES, NMES, and TENS) compared to PFMT on UUI symptoms in individuals with multiple sclerosis. IVES, specifically, has been reported to significantly increase pelvic floor muscle strength in women with UUI [270]. IVES depolarises the somatic lumbar and sacral afferent fibres, inhibiting bladder overactivity [271]. IVES has also been reported to cause profound bladder inhibition in animal models [272]. IVES at frequencies below 12 Hz has shown beneficial effects on UUI and mixed urinary incontinence [273], as frequencies below 12 Hz stimulate the pudendal nerve, reducing involuntary detrusor contractions [274, 275]. Among the four studies providing evidence for the effects of electrical stimulation in this review, three [253, 254, 257] used IVES at the recommended frequency to achieve maximum benefits.

The IVES procedure involves the participants being placed in a supine position with 45° of hip and knee flexion and the intravaginal electrode inserted in the vagina [276]. The acceptance and satisfaction of invasive IVES among women with UUI remain inconclusive, and previous studies [275, 277] have reported mixed results. One reported that women experienced pain and discomfort due to the vaginal probe used for IVES [278]. However, another examining women with mixed urinary incontinence reported that 80% of the study participants were satisfied with IVES [275]. These findings highlight the need for further investigation into the acceptance and satisfaction of women with UUI regarding the IVES procedure.

The mean estimated effect size for electrical stimulation, when compared to PFMT, in reducing the symptoms of UUI was found to be moderate (0.6) [275, 279]. The effect of electrical stimulation was much larger than no treatment (2.6), which could be attributed to the effect of PFMT. However, the difference was not statistically significant in the limited meta-analysis of only three pooled studies. The substantial effect size, combined with the methodological quality of the included studies, suggests that electrical stimulation might be considered a viable treatment option for UUI due to multiple sclerosis. However, further studies with adequate power to investigate the safety and acceptance of electrical stimulation (specifically IVES and TENS) for treating UUI due to neurogenic dysfunction are required.

The pooled analyses of three studies [219, 255, 256] with moderate methodological quality and moderate quality of evidence demonstrated a significant effect of electrical

stimulation (NMES or TENS) on UUI due to stroke. The mean estimate of the effect size was large (SMD: −2.637, $p = 0.000$). A recent review also indicated that NMES is generally safe for treating post-stroke urinary incontinence in women [280]. Given its safety and substantial effect size observed in this review, electrical stimulation may be a viable clinical option.

A meta-analysis of three studies [259-261] with moderate to high methodological quality and low-quality evidence found no significant effect of PFMT compared to no treatment on UUI symptoms due to stroke. However, the National Institute for Health and Care Excellence (NICE) guidelines recommend PFMT for neurogenic OAB when voluntary pelvic floor muscle contraction is preserved [281]. PFMT for UUI involves contracting the pelvic floor muscles and avoiding pelvic floor relaxation until the urinary urgency is suppressed, an effect known as the 'guard reflex' [281]. NICE guidelines suggest that PFMT should be performed for at least three months, with a minimum of eight contractions three times daily [282]. The participants of the three included studies [259-261] performed PFMT 6–10 times daily in various positions, such as lying, sitting and standing, for three months. Based on the findings of this review, the efficacy of PFMT for UUI in neurogenic OAB remains inconclusive. Future studies evaluating the effect of PFMT for UUI due to neurogenic OAB should adhere to the NICE guidelines.

The pooled analysis of two studies on those with Parkinson's disease [262, 263] with high methodological quality and low evidence quality found that BT had a nonsignificant effect on UUI symptoms compared to the no-treatment control. The

rationale underlying BT is based on the premise that a potential precipitant of detrusor instability is the habit of frequent voiding and can indicate uninhibited detrusor contraction and reduced bladder capacity [283]. BT aims to moderate the habit of frequent voiding by practising resisting the urge to void, delaying micturition and increasing the voiding interval, improving bladder capacity and decreasing detrusor instability [284]. However, the evidence suggests that BT alone, without other adjunctive treatments, might not yield positive results [285]. Therefore, based on this review, the effects of BT on UUI among individuals with Parkinson's disease remain inconclusive. It is recommended that future studies explore integrating BT with other interventions, such as electrical stimulations, for neurogenic OAB to achieve better outcomes.

UUI has been found to negatively affect the quality of life of individuals with Parkinson's disease [286]. The degree of quality of life impairment is associated with various social predictors (e.g. age, sex, rural living, the number of household members and financial problems) and clinical predictors (e.g. disease severity, disability, disease duration, motor impairment, depressive symptoms, complications of therapy and gait impairment) [287]. A pooled analysis of two studies [262, 263] with high methodological quality and low evidence quality revealed a significant effect of BT on the quality of life of individuals with Parkinson's disease compared to no-treatment control, with a large effect size (0.9). Similarly, other pooled analyses [221, 258] found that TTNS improved the quality of life of individuals with Parkinson's disease compared to the no-treatment control, with a large effect size (12.4). Based on these results, TTNS and BT may be considered potential interventions in clinical practice to improve the quality of life in individuals with UUI due to Parkinson's disease.

2.7 Study strengths and limitations

This systematic review had several notable strengths. Firstly, it adopted a comprehensive search strategy, using relevant search terms to identify RCTs evaluating the effects of non-surgical minimally- or non-invasive therapies for managing UUI. Secondly, it used a rigorous and systematic methodology to identify and evaluate the included studies. The robustness of the pooled meta-analyses was ensured by including only RCTs. Thirdly, it used psychometrically sound quality assessment tools to evaluate the methodology quality and evidence reported by the included studies.

However, this systematic review also had some limitations. Firstly, the pooled analysis had a relatively small size, which may impact the generalizability of the findings. Secondly, some interventions lacked RCTs, preventing their inclusion. Thirdly, while systematic reviews of RCTs are considered to provide the highest level of clinical evidence, excluding studies based on their design may have limited the scope of our systematic review. Fourthly, our systematic review may be affected by language bias since only studies published in English or Chinese were included, potentially excluding relevant studies in other languages.

2.8 Conclusions

Our meta-analysis found that electrical stimulation (IVES and NMES) is effective in reducing symptoms of UUI among individuals with multiple sclerosis. Electrical stimulation (NMES and TENS) was also found to be beneficial for reducing UUI symptoms among individuals with stroke. These findings were based on studies with moderate to high methodological quality and moderate evidence quality. Furthermore,

our review demonstrated that TTNS and BT could improve the quality of life of individuals with neurogenic OAB due to Parkinson's disease. These results were derived from studies with moderate to high methodological quality and low to moderate evidence quality. However, the specific effects of PFMT and BT on UUI remain uncertain. Further studies evaluating the effects of PFMT, BT and other interventions that have received less attention, such as rTMS and functional magnetic stimulation, on neurogenic OAB-related outcomes are warranted.

2.9 Clinical message

Electrical stimulation has the strongest effects, although not all patients may prefer it. Electrical stimulation is superior to PFMT.

Chapter 3

Clinical tools for evaluating the severity of overactive bladder: A systematic review of psychometric properties

3.1 Commentary

This chapter reports the rationale, methodology, findings, discussions and conclusions of the systematic review of psychometric properties to identify the most psychometrically sound clinical tool for evaluating the overactive bladder (OAB) symptoms of individuals with neurogenic OAB.

3.2 Introduction

OAB is a profoundly debilitating condition that significantly limits individuals' capacity to participate in the activities of daily living and social engagements [288]. It is associated with a spectrum of adverse effects, including psychological distress, depression, restrictions in participation, reduced productivity in work-related activities, disruptions in sleep patterns, deterioration of sexual function and an overall decline in quality of life [209]. OAB can be caused by various pathophysiological mechanisms, including reduced inhibitory control from suprapontine centres over the micturition reflex and disruption of axonal pathways within the spinal cord [288, 289]. Additionally, heightened sensory input from afferent nerves, a reduction in peripheral inhibitory mechanisms and an increase in excitatory neurotransmitter activity within the neural circuitry regulating the micturition reflex could contribute to the development

of neurogenic OAB by altering the normal regulation of bladder function [288-290]. The common pathophysiological signs exhibited by the unstable bladder include intravesical pressure and spontaneous myogenic activity increase, tetanic contractions, enlarged sensory neurons, anatomic changes in smooth muscle ultrastructure, patchy denervation, hypertrophic ganglion cells and an enhanced spinal micturition reflex [65]. Any neurological insult in the diencephalic and cerebral cortex could disrupt the inhibitory influence in the modulation of bladder control and timing, resulting in uninhibited detrusor contractions and bladder overactivity [291].

Neurogenic OAB is assessed to ascertain its severity and confirm an accurate diagnosis [292]. Typically, this assessment involves using a validated outcome measure with strong psychometric properties, which is essential for clinical practice and research [293]. Psychometric properties encompass the fundamental attributes of validity, reliability and responsiveness [294] and are crucial in facilitating rigorous evaluations that integrate evidence-based practice [295]. The precision of any outcome assessment is contingent upon the psychometric quality of the outcome measure employed [296]. Therefore, it is imperative to accurately identify the clinical issue by employing psychometrically robust outcome measures to enhance patient care and facilitate recovery. This critical step ensures that the assessment tools used are valid, reliable and sensitive to changes in the patient's condition, thereby providing a solid foundation for evidence-based clinical decision-making.

Given the profound adverse effects of OAB and the substantial costs associated with its management, there is a need to identify clinical tools that are psychometrically validated for assessing symptom severity and tracking recovery after interventions [297]. Prior psychometric

systematic reviews of instruments for reporting OAB symptoms have primarily concentrated on identifying and categorising the clinical tools used to screen for OAB symptoms [298], assess quality of life in individuals with spinal cord injuries [299] and evaluate both generic and condition-specific instruments in female cohorts [300]. However, these reviews have not extensively evaluated the psychometric properties of the clinical tools, and only two have objectively appraised evidence quality [298, 300].

Researchers and clinicians are increasingly concerned with selecting psychometrically sound and condition-specific clinical tools to improve the evaluation of treatment effects and the monitoring of symptom improvements [301, 302]. Individuals with neurological disorders may have difficulty responding to some clinical tools, and their response rate and accuracy can be affected by subjective responses, a lack of motivation among patients to respond accurately, language or cultural barriers, cognitive decline or senility [303, 304]. Currently, no consensus exists on recommended clinical tools for evaluating OAB symptoms. Therefore, identifying psychometrically strong clinical tools for evaluating OAB symptoms is paramount. Consequently, this review aimed to systematically evaluate the evidence on the psychometric properties of clinical measures for assessing OAB symptoms (urinary urgency with or without urgency urinary incontinence [UUI], urinary frequency and nocturia). The methodological and evidence quality were evaluated using the COnsensus-based Standards for selecting health status Measurement INstruments (COSMIN) checklist and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tools, respectively.

3.3 Methods

3.3.1 Search strategy and study screening

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [231] guidelines and prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42022297811). Two reviewers (MUA and Stanley John Winser) searched the following databases from inception to 30 August 2023: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), MEDLINE, Scopus and Web of Science. Three themes were developed for the search terms: psychometric properties, clinical tools and OAB (Appendix 3.1). The themes for OAB and lower urinary tract symptoms were developed according to the International Continence Society definitions of OAB and adult neurogenic lower urinary tract dysfunction. The search terms developed for the MEDLINE database search are described in detail in Appendix 3.2. This systematic review selected appropriate studies according to the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework [252].

3.3.2 Study selection

Studies were included in this systematic review if they (1) tested the psychometric properties of clinical tools assessing OAB symptoms; (2) tested one or more of the following psychometric properties: internal consistency, test-retest reliability, inter-rater reliability, intra-rater reliability, content validity, structural validity, criterion validity, construct validity, convergent validity, divergent validity or responsiveness; and (3) included adult patients aged ≥18 years of both sexes with OAB. Studies were excluded if (1) the full-text article could not be retrieved (even after contacting the authors); (2) they were systematic reviews,

commentaries or editorials; (3) they were conference proceedings, abstracts or event annals; (4) they were published in languages other than English; or (5) they were unpublished theses/reports.

All studies identified through the electronic database searches were exported to the EndNote 21 citation manager (Clarivate Analytics, Philadelphia, PA, USA). After duplicate removal, two reviewers (MUA and SJW) independently screened the titles, abstracts and full-texts. Any disagreements between the two reviewers during the screening process were discussed until a consensus was reached. A third reviewer (Priya Kannan) was consulted for unresolved disagreements. The reference lists of the included studies and relevant systematic reviews were manually searched to identify any potentially relevant studies.

3.3.3 Data extraction

Two reviewers (MUA and SJW) independently extracted the data. A third reviewer (PK) was consulted for unresolved discrepancies during the extraction process. The following data were extracted from each included study: first author, publication year, country of origin, participant characteristics (the mean and standard deviation of participants' age and the sample size of each group), population, clinical tool(s), psychometric properties tested and authors' conclusions.

3.3.4 Quality appraisal

For each included study and clinical tool, methodological quality was evaluated using the COSMIN risk of bias checklist [305], and the evidence quality was evaluated using the

modified GRADE tool [235]. The COSMIN checklist evaluates the methodological quality of studies designed to measure the psychometric properties of a given clinical tool. It can be used to assess and select the most appropriate instrument for use in clinical practice and research [294]. It assesses nine psychometric domains: reliability (relative measures, including test-retest, inter-rater and intra-rater reliability), internal consistency, measurement error, content validity (including face validity), hypotheses testing, structural validity, criterion validity, cross-cultural validity and responsiveness [305]. Based on the scores obtained for each domain, the methodological quality of the tested psychometric properties is rated using a four-point rating scale as 'very good', 'adequate', 'doubtful', or 'inadequate'. An overall methodological quality score can be obtained for the psychometric properties of any clinical tool, which corresponds to the lowest score assigned to any item on the checklist for that tested property [305]. Two independent reviewers (MUA and PK) independently evaluated the methodological quality of each clinical tool assessed in the included studies. A third reviewer was consulted (SJW) for any unresolved disagreements.

The modified GRADE approach was used to evaluate the cumulative quality of the evidence supporting each psychometric property of the identified clinical tools [306]. The quality of the evidence supporting the psychometric properties in each study was investigated and categorised as 'sufficient', 'insufficient' or 'indeterminate' according to the updated criteria for good psychometric properties proposed by Prinsen et al. [306]. For each clinical tool examined in the included study, the quality of evidence supporting the psychometric properties was pooled and summarised using the modified GRADE approach, which categorises it as 'high', 'moderate', 'low', or 'very low' [306]. The modified GRADE approach begins by assuming a high quality of evidence, and the quality of evidence is then downgraded for risk of bias, inconsistency, indirectness or imprecision [307]. The risk of bias was determined by evaluating reporting bias

(selective outcome reporting), attrition bias (incomplete outcome data) and the availability of an a priori protocol. When applying the modified GRADE approach, we first considered the risk of bias, categorised as not serious, serious, very serious or extremely serious [308]. For a clinical tool to have no risk of bias, at least two studies with adequate or better evidence quality or at least one study with very good evidence quality had to be identified [308]. A serious risk of bias was assigned when multiple studies of doubtful quality or at least one study with adequate quality were identified. A very serious risk of bias was assigned when multiple studies of inadequate quality were identified. An extremely serious risk of bias was assigned to clinical tools associated with only one study of inadequate quality [308].

The COSMIN evaluation of the psychometric performance of a given measure can be either quantitively pooled or qualitatively summarised for comparison against the criteria for good psychometric properties, resulting in an assessment of whether the overall psychometric properties of the clinical tool in question are sufficient (+), insufficient (−), inconsistent (±), or indeterminate (?). The psychometric performance of the tools used in each included study was evaluated using the COSMIN checklist, and the quality of the evidence presented for each tool was evaluated using GRADE to determine the confidence and trustworthiness of the pooled results or the overall rating [306].

For example, we found an Actionable Bladder Symptom Screening Tool (ABSST) that had been reported by two studies with sufficient results. Five of the six psychometric properties were found to be of very good quality, and only one psychometric property was of doubtful quality. Therefore, the level of risk of bias was downgraded from high to low. Inconsistency was assessed based on the results of the included studies on ABSST, which was sufficient,

meaning no downgrading for the inconsistency. The rating for imprecision was based on the study's total sample size; when the total sample size of the study evaluating a specific outcome measure was over 100, the study was not downgraded for imprecision [306]. Studies were downgraded for indirectness if they differed in population [306].

3.3.5 Data analysis

The data analysis was analysed in three steps. In the first step, the quality of included studies was rated using the COSMIN checklist. In the second step, each measurement property of each study was classified as 'sufficient', 'insufficient' or 'undetermined' according to the criteria for good measurement properties in the COSMIN guidelines for systematic reviews of outcome measures. In the third step, the overall classification of evidence for each measurement property was conducted to evaluate the level of evidence quality according to the modified GRADE approach using the updated COSMIN methodology appraisal assessment, development and rating approach. In this modified GRADE approach, the overall quality of the evidence was rated either as 'high', 'moderate', 'low', or 'very low' based on the GRADE assessment [306]. For an outcome measure to be recommended for clinical practice, the studies should meet the acceptable threshold of psychometric robustness (i.e. if all/most of the psychometric properties are evaluated with a rating of 'good' or above for the methodological quality according to the COSMIN checklist and 'high' evidence quality according to the modified GRADE evaluation) [309, 310].

3.4 Results

3.4.1 Study selection

The database searches identified 7112 potentially relevant articles for screening, among which 1328 duplicate records were identified and excluded. After all screening procedures, 40 studies met our eligibility criteria and were included in this review. The reasons for exclusion during the full-text screening phase can be found in Appendix 3.3. Figure 3.1 presents a PRISMA flowchart illustrating the study process.

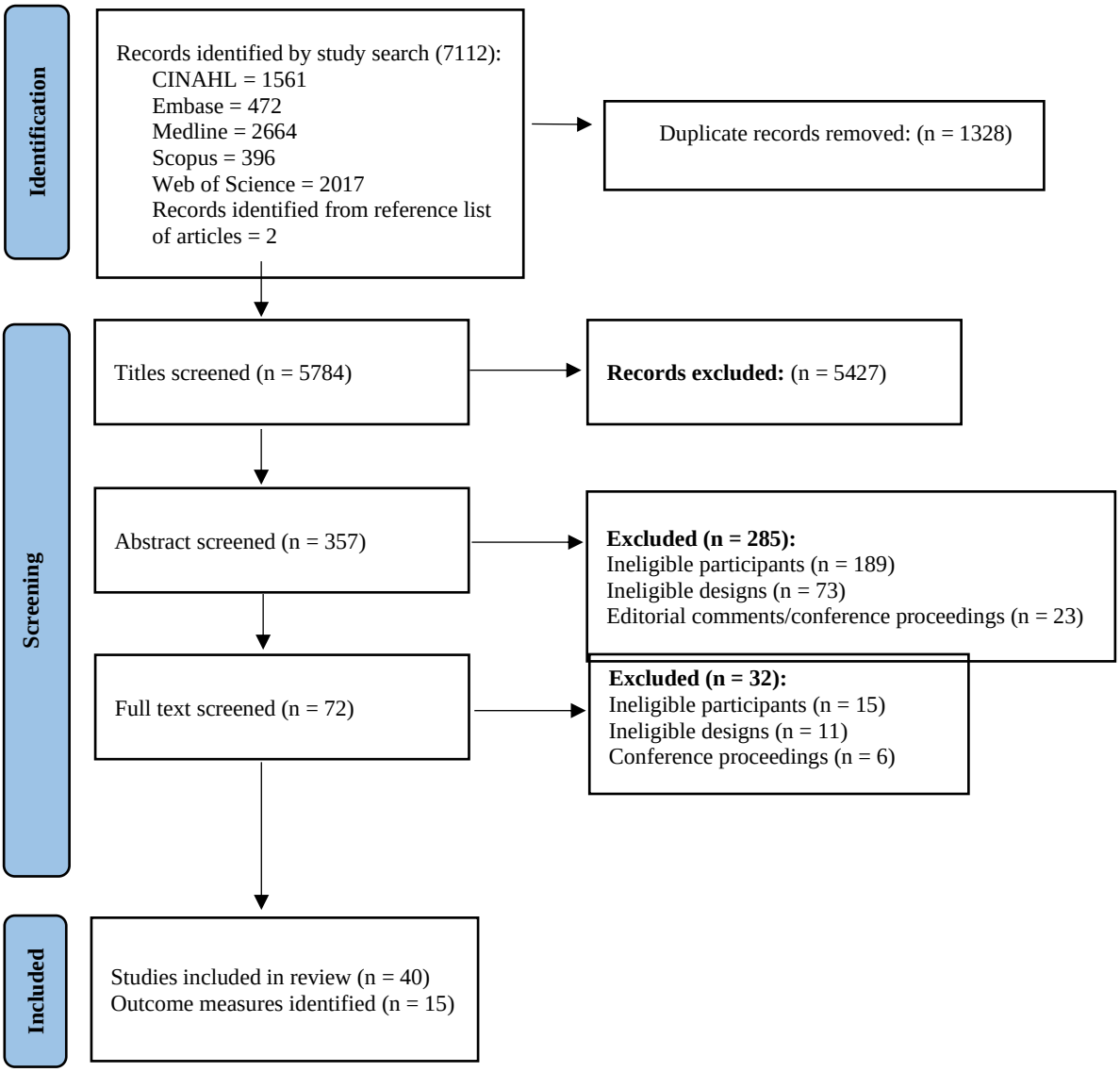

Figure 3.1: Flowchart of screened studies

3.4.2 Study characteristics of the included studies

Table 3.1 presents the characteristics of the included studies. This review included 40 studies with 10,634 participants, with sample sizes ranging from 20 [311] to 1,839 [312]. The participants' ages ranged from 18 to 89 years. The 40 included studies were published between 2002 and 2022, with 31 published within the last decade (2011–2022). They involved patients with OAB due to stroke (*n* = 3) [313-315], multiple sclerosis (*n* = 1) [311], multiple sclerosis and spinal cord injuries (*n* = 3) [316-318], and without specified underlying causes (*n* = 31) [312, 319-346].

Table 3.1: Characteristics of included studies (n =40)

First author, year, country of study	Participant characteristics (mean age of participants (SD); sample size)	Population	Study design and Study setting	Outcome measure(s)	Psychometric property
Stroke					
Tibaek et al., 2005 Denmark [314]	65 (56-75) N=71	Stroke	A prospective questionnaire-based survey at an acute stroke and neurology unit at Copenhagen University Hospital, Glostrup, Denmark.	The Danish Prostatic Symptom Score	Test-retest reliability
Tibaek and Dehlendorff 2009 Denmark [313]	59 (52–65) N=482	Stroke	An observational cross-sectional survey at the urology department, University Hospital, Herlev and the neurology unit at Copenhagen University Hospital, Glostrup, Denmark	The Danish Prostatic Symptom Score	Content validity Face validity
Yesil et al., 2017 Turkey [315]	66.66±8.72 N=50	Stroke	An observational cross-sectional survey at the Physical Medicine and Rehabilitation Department of Afyon Kocatecepe University Medical Faculty, Turkey	Turkish version The Danish Prostatic Symptom Score	Internal consistency Test-retest Reliability Simulation validity
Multiple Sclerosis					
Burks et al., 2013 United States [311]	48.2±12.11 N=20	Multiple sclerosis	Observational US-based, non-randomised multicentre stand-alone study	Actionable bladder symptom screening tool	Internal Consistency Test-retest Reliability Concurrent Validity Predictive Validity Sensitivity Specificity
Stroke, Spinal cord injury and Multiple sclerosis					
Talebi et al., 2022, Iran [347]	45.8±17.6 N=279	Stroke and Multiple sclerosis	Cross-cultural adaptation and validation study	Persian version Neurogenic bladder symptoms score questionnaire	Face and content validity Construct validity Criterion validity Interna; consistency Test-retest reliability
Cintra et al. 2019 Brazil [316]	38.9±14.7 N=68	Spinal cord injury Multiple sclerosis	Cross-cultural adaptation and validation study from the daily schedule of the psychiatrist or urologist medical consultations at the clinic in Brazil	Brazilian version Neurogenic Bladder Symptom Score	Cross-cultural adaptation Test re-test reliability Internal consistency
Gular et al., 2020 Turkey [317]	40.18±10.87 N=102	Spinal cord injury Multiple sclerosis	Cross-cultural adaptation Rehabilitation clinic in Gaziosmanpasa Training and Research Hospital.	Turkish version Neurogenic Bladder Symptom Score	Internal consistency Test-retest reliability Face and content validity Concurrent validity
Przydacz et al., 2020 Poland [318]	MS: 46.8 (IQR 32.4-59.9) SCI: 49.8 (IQR 35.9-62.1) N=210	Spinal cord injury Multiple sclerosis	A single-centre, prospective cohort validation study.	Polish version Neurogenic Bladder Symptom Score	Internal consistency Test-retest reliability Content validity

					Criterion validity
Moreno-Palacios et al., 2021, Mexico [348]	43.9 (18-78) N= 82	Stroke, Spinal cord injury, Multiple sclerosis, Parkinson's disease and other neurological conditions	Cross-cultural adaptation and validation study	Spanish version Neurogenic bladder symptoms score questionnaire	Internal Consistency Test-retest Reliability
Overactive Bladder					
Al-Shaiji et al. 2019, Kuwait [319]	Exp: 42.7± 12.8 Con: 36±9.2 Exp: n = 46 Con: n = 58	Overactive bladder	A validation study at Almiri Hospital Kuwait	Arabic version Overactive Bladder -V8	Internal consistency Test-retest reliability
Bunyavejchevin 2015, Thailand [322]	60.4±9.6 N=56	Overactive bladder	A single-centre, prospective cohort validation study in the Urogynaecology clinic at King Chulalongkorn Memorial Hospital	Thai-Version Overactive Bladder Symptom Score	Internal consistency Test-retest reliabilities
Cardozo et al. 2014, United States [320]	Exp: 54.6±11.6 Con: 40.4±14.3 Exp: N = 45 Con: N = 47	Overactive bladder	Prospective observational study Six gynaecological clinics across the United States	Actionable Bladder Symptom Screening Tool	Internal consistency Concurrent validity Predictive validity Known-groups validity Sensitivity and specificity
Chapple et al., 2021 United Kingdom [321]	Exp: 59 (30–84) Con: 40.4±14.3 Exp: n = 45 Con: n = 47	Overactive bladder	A prospective observational noninterventional psychometric testing study across six US-based urology clinics	Overactive Bladder-Bladder Assessment Tool	Internal consistency Test-retest reliability Convergent and divergent validity Known-groups validity
Chou et al., 2012 Taiwan [323]	55.3±13.8 N=60	Overactive bladder	A reproducibility and responsiveness in Taiwan	Chinese version Overactive Bladder Symptom Score	Test-retest reliability Internal consistency Responsiveness
Coyne et al., 2002 United States [324]	58.5±16.6 N= 990	Overactive bladder	A clinical validation study of community sample and clinical study across the United States	Overactive Bladder Questionnaire	Internal consistency Concurrent validity Discriminant validity
Coyne et al., 2005 United States [327]	61.0±14.7 N=865	Overactive bladder	Secondary analysis of baseline and 12-week clinical trials across the United States	Overactive Bladder Questionnaire	Responsiveness
Coyne et al. 2006 United States [326]	58.7±13.2 58.8±13.8 N1=548 N2=520	Overactive bladder	12-week randomised, double-blind, placebo-controlled across the United States	Overactive Bladder Questionnaire	Minimally important difference
Coyne et al., 2007 United States [325]	62.5±14.1 61.0±13.1 N=292 N=260	Overactive bladder	A posthoc analysis of 12-week trials of open-label trials and randomised, double-blind, placebo-controlled trials in the United States and the United Kingdom	Overactive Bladder Questionnaire	Responsiveness
Coyne et al., 2011 United States [312]	59.6±13.6 59.4±13.5	Overactive bladder	Secondary analysis of three 12-week clinical trials across the United States	Overactive Bladder Questionnaire	Responsiveness Internal consistency

	59.9±13.3 N=516 N=441 N=882				Discriminant validity
Culha et al., 2019 Turkey [328]	46.79±14.26 (18–78) N=117	Overactive bladder	A non-invasive observational study at a urology clinic in Turkey	Turkish version Overactive Bladder Symptom Score	Test-retest reliability Concurrent validity
Gotoh et al., 2011 Japan [329]	56.7±13.6 N=214	Overactive bladder	12-week trials of open-label trials and randomised, double-blind, placebo-controlled trials in Japan	Overactive Bladder Questionnaire	Responsiveness Minimal Clinically Important Difference
Homma and Fujimura, 2014 United States and Japan [330]	54.8 (23-83) N=149	Overactive bladder	A psychometric validation online study in Japan	English Version Overactive Bladder Symptom Score	Test-retest reliability Concurrent validity
Huang et al. 2008 Korea [331]	Exp: 53.2 ± 11.6 52.3 ± 12.9 Exp: 85 Con: 65	Overactive bladder	An observational validation study at Beijing Obstetrics and Gynaecology Hospital, China	Chinese Version International Consultation on Incontinence Questionnaires	Content/face validity Internal consistency Test-retest reliability
Jeong et al., 2014 Korea [332]	64.4 ± 10.3 64.1 ± 10.2 N=42 N=50	Overactive bladder	A prospective trial at two teaching hospitals in Korea.	Korean version Overactive Bladder Symptom Score	Internal consistency Test-retest reliability Content validity Discriminant validity Convergent validity
Margolis et al., 2009 United States [333]	57.8 ± 13.7 N=375	Overactive bladder	Secondary analysis of randomised, open-label clinical study at clinical setting in the United States	Overactive Bladder Satisfaction with Treatment Questionnaire	Internal Consistency Concurrent validity Discriminant validity
Matza et al., 2005 United States [334]	66.0 66.8 63.8 N=47 N=35 N=12	Overactive bladder	Validation study of five urology clinics in the United States	Overactive Bladder Questionnaire	Test-retest reliability
Mertoğlu et al., 2015 Turkey [335]	58.9±10.5 N=117	Overactive bladder	A validation study in Turkish Urology Clinics	Turkish version International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms	Internal consistency Test-retest reliability
Motlagh et al., 2015 Iran [342]	41.4±11.5 N=50	Overactive bladder	An observational validation study at four outpatient clinics.	Persian version International Consultation on Incontinence Questionnaire Overactive Bladder Module	Content validity Internal consistency Test-retest reliability
Nixon et al., 2005 United States [336]	62.46±0.49 N=658	Overactive bladder	Parallel, randomised, double-blind, placebo-controlled phase III study 51 sites in the United States.	Indevus Urgency Severity Scale	Responsiveness Test-retest reliability content validity
Notte et al., 2012 United States [337]	59.1±15.23 61.6±13.5 N=39 N=12	Overactive bladder	Observational non-interventional study of five clinical sites across the United States	Patient Perception of Intensity of Urgency Scale	Content validity Test-retest reliability
Oh et al., 2012 Korea [338]	N=58	Overactive bladder	A prospective multi-centre cohort study involving Seoul National University Hospital and Borame Medical Centre Seoul, Korea.	Korean version Overactive Bladder Questionnaire	Face and content validity Discriminant validity Convergent validity Responsiveness Test-retest reliability

					Internal consistency
Pourmomeny and Mazdak, 2017 Iran [340]	58.3 ± 14 20 and 88 N=22	Overactive bladder	An observational cross-sectional study at state and private university hospitals in Istafan	International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms	Content/face validity Construct/criterion validity Internal consistency Test-retest reliability
Pourmomeny et al., 2017 Iran [341]	48.8 ± 5 N=114	Overactive bladder	An observational validation study at two medical centres in Iran	Persian version Bristol Female Lower Urinary Tract Symptoms instrument	Content/face validity Construct/criterion validity Internal consistency Test-retest reliability
Pourmomeny et al., 2018 Iran [339]	60.5 (29–85) N=121	Overactive bladder	A cross-sectional observational study at outpatient clinics at Isfahan University Medical Sciences	Persian version International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms	Content/face validity Construct validity Internal consistency test-retest reliability
Przydacz et al., 2021 Polish [349]	Exp: 59.3±12.4 Con: 57.9±11.2 N=150 N=150	Overactive bladder	A prospective and single centre study at the Department of Urology Jagiellonian University Medical College, Krakow, Poland	Polish version International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms	Content validity Construct validity Internal consistency Test-retest reliability
Sawaqed and Suoub, 2021 Jordan [343]	N=235 (64–78)	Overactive bladder	A prospective study at urology outpatient clinics of Karak Governorate Teaching Hospital in Jordan	Arabic version Overactive Bladder Symptom Score	Internal consistency Test-retest reliability Discriminatory validity
Shen et al., 2020 China [350]	46.16 ± 14.55 (19–8) N=86	Overactive bladder	An observational validation study at two comprehensive tertiary institutions in China	Chinese version International Consultation on Incontinence Questionnaires bladder diary	Face/content validity Construct/criterion validity Internal consistency Test-retest reliability Responsiveness
Sumardi et al., 2012 Indonesia [344]	49.41 (11.11) N=50	Overactive bladder	Observational study in a local Indonesian population	Indonesian Version Overactive Bladder Symptom Score	Test-retest reliability
Weinberg et al., 2012 United States [345]	55±18 N=117	Overactive bladder	A clinical validation study Boston Medical Centre, United States	Spanish version Overactive Bladder Symptom Score	Test-Retest Reliability Internal consistency Content validity Discriminant Validity
Yiu et al., 2013 Hong Kong [346]	53±13 53 (26-86) N=51	Overactive bladder	A validation study at five urology clinics of regional hospitals in Hong Kong.	Hong Kong Chinese version Overactive Bladder Symptom Score	Construct validity Internal consistency Test-Retest Reliability

3.4.3 Description of the outcome measures identified in the included studies

The included studies reported 15 clinical tools for evaluating urinary symptoms among individuals with OAB due to stroke, multiple sclerosis, spinal cord injuries or other causes. Ten studies had evaluated the Overactive Bladder Symptom Score (OABSS) [322, 323, 328-330, 332, 343-346]; seven had evaluated the Overactive Bladder Questionnaire (OAB-q) [312, 324-327, 334, 338]; three had evaluated the Danish Prostate Symptom Score (DAN-PSS-1) [313-315], International Consultations on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) [347, 351, 352]; and Neurogenic Bladder Symptom Score (NBSS) questionnaire [316-318, 347, 348]; two had evaluated the ABSST [311, 320] and International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) [331, 349]; and one had evaluated the International Consultation on Incontinence Questionnaire-Bladder Diary (ICIQ-BD) [350], Bristol Female Lower Urinary Tract Symptoms (BFLUTS) [341], International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB) [342], Overactive Bladder Questionnaire-Bladder Assessment Tool (OAB-BAT) [321], Overactive Bladder Satisfaction with Treatment Questionnaire (OAB-SAT-q) [333], OAB-Validated 8-Question Screener (OAB-V8) [319], Patient Perception of Intensity of Urgency Scale (PPIUS) [337], and Indevus Urgency Severity Scale (IUSS) [336].

The COSMIN criteria require modified versions of outcome measures to be evaluated separately, even if they differ by one item from the original scale. Based on this criterion, of the 15 outcome measures examined in this review, eight were modified versions that were considered independent outcome measures in the included studies (ICIQ-BD [350], ICIQ-

FLUTS [331, 349], ICIQ-MLUTS [335, 339, 340], ICIQ-OAB [342], OAB-BAT [321], OAB-q [312, 324-327, 338, 351], OAB-SAT-q [333] and OAB-V8 [319]), and the remaining seven were original versions (ABSST [311, 320], BFLUTS [341], DAN-PSS-1 [311, 313-315, 320, 341], IUSS [336], NBSS [316-318, 347, 348], OABSS [322, 323, 328-330, 332, 343-346] and PPIUS [337]).

Sixteen studies evaluated the original English version of the outcome measures [311, 312, 319-321, 324-327, 329, 330, 333, 334, 336, 337, 343, 345]. two had evaluated the Arabic [319, 343]; four evaluated the Chinese [322, 323, 346, 350] , Persian [339-342] or Turkish [316-318] versions; two had evaluated the Arabic [319, 343], Danish [313, 314], Korean [332, 338], or Polish [318, 349] versions; and one evaluated the Brazilian Portuguese [316], Indonesian [344] or Thai [322] versions. The characteristics of the identified clinical tools, such as the languages of instruction, descriptions of the items and scoring schemes used, the duration necessary to complete the clinical tools, costs, strengths, limitations, and populations tested, are presented in Table 3.2.

Table 3.2: Description of the identified outcome measures

Outcome measures	Language of instruction Number of items Description of the item Scoring scheme	Duration to complete Cost of the outcome measure: Free/licensed/ need to purchase	Strengths and limitations of the Outcome measures Population tested
Actionable Bladder Symptom Screening Tool [311, 320]	**Language of instruction:** English, Turkish, Persian, Spanish, Dutch **Number of items: Eight** items (Urinary frequency, urinary leakage, urinary urgency, nighttime voiding, social relations impact, embarrassment, and occupational interference) **Description of the item:** 4-point Likert scale with a seven-day recall period question. **Scoring scheme** -total scores (range 0–24) from summing the +responses; Cut-off points for positivity: 6; ≥3 indicating further urogynaecological evaluations and interventions; higher scores indicating severe symptoms; zero scores signify the absence of bladder symptoms.	**Duration to complete:** average of 5.33 minutes **Cost of the outcome measure:** Available free online	**Strengths:** -Brief and useful questionnaire, easy-to-use items, and facilitates communication between medical practitioners and people with Urinary incontinence due to multiple sclerosis. **Limitations:** Educational level disparity could affect the generalisation of their counterparts. **Population tested:** Multiple sclerosis
Bristol Female Lower Urinary Tract Symptoms instrument [341]	**Language of instruction:** Turkish **Number of items:** 12 items (each item consists of two sections) self-administered tool. The first section comprises urinary symptoms questions based on a 5-point Likert scale (0 = never; 4 = always **Description of the item:** 5-point Likert scale with three domains: filling symptoms (four items, 0–15); voiding symptoms (three items, 0–12); and incontinence symptoms (five items, 0–20. The second section enquires about the degree to which the symptoms of overactive bladder hurt and bother individuals with overactive bladder. **Scoring scheme:** Zero scores indicate no symptom, while 10 signifies extreme bothersome. The higher the score, the more severe the diagnosis	**Duration to complete:** 10–15 min. **Cost of the outcome measure:** Available free online	**Strengths:** - useful for intervention and research among people with lower urinary tract symptoms. **Limitations:** validation is limited by the invasiveness and cost of the urodynamic test for the Bristol Female Lower Urinary Tract Symptoms instrument and International Consultation on Incontinence Questionnaire Overactive Bladder **Population tested:** Females with lower urinary tract symptoms.
Danish Prostatic Symptom Score -1 [313-315]	**Language of instruction:** Danish, Turkish **Number of items:** comprises 12 lower urinary tract symptoms-related questions on bladder symptoms two weeks preceding period—each question composed of Part A and B. In Part A, questions on frequency and severity (symptom score) of the overactive bladder symptoms were asked, while in Part B, questions on the symptoms impact daily life (bother score) on individuals with overactive bladder were requested. **Description of the item:** 4-ranked scale ranging from zero to three scores, with zero scores indicating the absence of symptoms/daily life impact while three scores indicate maximum symptom. Questions 1-4 covered voiding symptoms, 5-8 were designed on storage symptoms, and the last four reflected miscellaneous symptoms. The lower the score, the better the symptoms **Scoring scheme:** The total score is equivalent to the multiplication of symptom and bother scores, which range from 0 to 9. A zero score in symptom and bother signifies the absence of the score.	**Duration to complete:** average of 5 minutes **Cost of the outcome measure:** Available free online	**Strengths:** -a common and validated tool for evaluating overactive bladder symptoms among people with stroke. **Limitations:** self-administration of the tool could be complicated among stroke survivors with a more severe deficit. **Population tested:** stroke survivors
International Consultation on Incontinence Questionnaires Bladder Diary [350]	**Language of instruction:** English, Chinese **Number of items:** 7 items 4-point Likert scale (1-4). The International Consultation on Incontinence Questionnaires bladder diary is a 3-day diary consisting of urinary frequency, volume voided and fluid intake (amount time and type), bladder sensation, and pad use. **Scoring scheme:** The lower the score, the better the symptoms.	**Duration to complete:** 3 days **Cost of the outcome measure:** Available free online	**Strengths:** credible evaluation tool recommended for use for over three days bladder diary. **Limitations:** More bladder pain scores could be added in the future. **Population tested:** women with overactive bladder /lower urinary tract symptoms.

International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms [331, 349]	**Language of instruction:** Polish, Chinese **Number of items:** 12 items 5-point Likert scale (0-4). **Description of the item:** it measures the females' symptoms of lower urinary tract symptoms and associated bother symptoms. Self-completed by people with overactive bladder. **Scoring scheme**: 0 to 16 fillings, 0 to 12 voidings, and 0 to 20 incontinence symptoms subscales. The lower the score, the better the symptoms.	**Duration to complete:** 4 to 5 minutes **Cost of the outcome measure:** Available free online	**Strengths: the** rigorous process of validation (cultural and translation). **Limitations:** Questions were not designed to detect changes in overactive bladder status. **Population tested:** females with overactive bladder.
ICIQ-MLUTS: International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms [335, 339, 340]	**Language of instruction:** Persian, Turkish **Number of items:** 23 items with two sections. Section A has 20 items, while Section B has three items. 5-point Likert scale (0-4). **Description of the item:** measures the females' symptoms of lower urinary tract symptoms and associated bother symptoms. Self-completed by people with overactive bladder. **Scoring scheme**: 1 to 84 filling. The lower the score, the better the symptoms. The lower the score, the better the symptoms	**Duration to complete:** 4 to 5 minutes **Cost of the outcome measure:** Available free online	**Strengths:** -Valid tool for evaluation of overactive bladder symptoms in Males. **Limitations:** there is the addition of extra intensity on the tool scores of evaluations **Population tested:** Males with overactive bladder.
International Consultation on Incontinence Questionnaire Overactive Bladder Module [342]	**Language of instruction:** Polish, Chinese **Number of items:** 4 items with eight questions. 5-point Likert scale (0-4). **Description of the item:** evaluates symptoms of overactive bladder and their effects on treatment outcomes. Self-completed by people with overactive bladder. **Scoring scheme**: 0 to 16 overall score. The lower the score, the better the symptoms.	**Duration to complete:** 3 to 8 minutes **Cost of the outcome measure:** Available free online	**Strengths:** concise, brief, and strong tool **Limitations:** people below 16 and above 50 were excluded which could benefit from the tool evaluation. **Population tested**: Males and females with overactive bladder.
Indevus Urgency Severity Scale [336]	**Language of instruction:** English **Number of items: 4**-point Likert scale (0 to 3), none ranging to severe **Description of the item:** developed to document the severity of urgency incontinence per void during the course of the condition. **Scoring scheme:** completing the seven-day micturition diary. Each question on the OAB symptoms is scored from zero to five. The higher the scores, the worse the symptom severity.	**Duration to complete:** 7-day micturition diary **Cost of the outcome measure:** Available free online	**Strengths:** - measures the events of severity urgency. **Limitations:** it is a single-item measure that needs around 14 days to evaluate the test-retest reliability. **Population tested:** Males and females with overactive bladder.
Neurogenic Bladder Symptom Score [316-318, 347, 348]	**Language of instruction:** Turkish, Polish, Brazilian Portuguese **Number of items:** 24-items **Description of the item:** evaluates bladder symptoms in the component of urinary incontinence (scored 0–29), storage/voiding (scored 0–22), and consequences (scored 0–23) with associated single general urinary symptoms question on health-related quality of life, which is scored from zero (pleased) to four (unhappy). **Scoring scheme**: ranging from 0 (absence of symptoms) to 74 (Maximal symptoms). Higher scores, worse symptoms	**Duration to complete:** median of 6 minutes **Cost of the outcome measure:** Available free online	**Population tested:** Adult diagnosed with spinal cord injury or multiple sclerosis. **Strengths:** A pioneer, versatile, comprehensive, and all-in-one instrument for people with neurogenic lower urinary tract disorders. **Limitations:** The participants were evaluated as a single group. Although the spinal cord injury and multiple sclerosis were not equally distributed**.**
Overactive Bladder-Bladder Assessment Tool [321]	**Language of instruction:** English **Number of items:** 17 items **Description of the item:** consists of urinary frequency, symptom bother, impact, and intervention satisfaction. The Overactive Bladder-Bladder Assessment Tool is usually completed on a weekly basis, starting on day one. **Scoring scheme:** scored on five-, six-, or seven-point scales, with seven days of recall. The Higher score indicates less severity	**Duration to complete:** 7-day period **Cost of the outcome measure:** No charge for academic and clinical use	**Strengths:** -developed with validation from multiple stages and brevity and simplicity. **Limitations:** Further evaluation of bladder dairy voided volumes is warranted. **Population tested:** Males and females with overactive bladder
Overactive bladder -V8 [319]	**Language of instruction:** English **Number of items:** 8 items with a six-point Likert scale (0 to 5). **Description of the item:** The tool is a self-administered questionnaire that evaluates the degree of overactive bladder burden, bother symptoms and severity.	**Duration to complete:** 4 to 5 minutes **Cost of the outcome measure:** No charge for academic and clinical use	**Strengths:** -Brief and useful tool for overactive bladder burden and severity evaluation. **Limitations:** re-retest reliability could not be investigated because the participants received intervention in the study.

	Scoring scheme: ranging from 0 (absence of symptoms) to 40 (Maximal symptoms). 0 to 8=low; 8 to 16= medium; 16 to 24=high. Higher scores, worse symptoms		**Population tested:** women with overactive bladder
Overactive Bladder Questionnaire [312, 324-327, 334, 338]	**Language of instruction:** English, Korean **Number of items:** 33 items with a six-point Likert scale (0 to 5) **Description of the item:** The tool is composed of an 8-item symptom Bother scale and 25 items of health-related quality of life that comprises the coping, concern, sleep, and social interaction scales. **Scoring scheme**: total score ranged from 0 to 100, with higher scores signifying worse symptoms	**Duration to complete:** 5 to 7 minutes **Cost of the outcome measure:** No charge for academic and clinical use	**Strengths:** -simple and easy for application captures both continent and incontinent people with overactive bladder. **Limitations:** 8-item symptom Bother scale and 25 items of health-related quality of life. **Population tested:** Males and females with overactive bladder
Overactive Bladder Satisfaction with Treatment Questionnaire [333]	**Language of instruction:** English **Number of items:** 11 items with a six-point Likert scale (0 to 5) **Description of the item:** developed to evaluate the satisfaction of individuals with overactive bladder in a clinical setting. The items include effectiveness, reference for treatment, convenience, willingness to re-treatment, side effects, and an evaluation of global satisfaction. **Scoring scheme**: total higher score indicative of less severity	**Duration to complete:** 5 minutes **Cost of the outcome measure:** No charge for academic and clinical use.	**Strengths:** -good psychometric properties and useful tool. **Limitations:** further research is needed for the validation of psychometric properties. **Population tested:** women with overactive bladder.
Overactive Bladder Symptom Score [322, 323, 328-330, 332, 343-346]	**Language of instruction:** English, Korean, Turkish, Japanese, Thai, Indonesian, Arab, Cantonese, Chinese **Number of items:** 4 items with a 5-point Likert scale (0 to 5) **Description of the item:** The tool involves a five-point Likert rating scale with a maximum score of 2, 3, 4, and 5, respectively. **Scoring scheme:** The total score of the tool ranges from zero to 15. Score of <5= mild, 6 to 11=moderate, while 12>=severe. The higher the scores, the worse the symptom severity.	**Duration to complete:** 5 to 10 minutes **Cost of the outcome measure:** No charge for academic and clinical use.	**Strengths:** Inclusion of both sexes with different symptom presentations and age differences. **Limitations:** generalisation could be affected by the language disparity unless a translated version is available. **Population tested:** Males and females with overactive bladder.
Patient Perception of Intensity of Urgency Scale [337]	**Language of instruction:** English **Number of items:** 5-point Likert scale (0 to 5) **Description of the item: T**he daily micturition diary tool is completed thrice weekly. **Scoring scheme:**" Each question of the symptoms of the overactive bladder is scored using a range from zero to 5. The higher the scores, the worse the symptom severity	**Duration to complete:** 3 days to record micturition diary. **Cost of the outcome measure:** No charge for academic and clinical use	**Strengths:** -an objective measure of overactive bladder symptoms . **Limitations:** This could not be generalised to male participants. Only 18% of the participants are males, while the target is usually 30% males. Urgency and incontinence are not fully explored. **Population tested:** Males and females with overactive bladder.

3.4.4 The psychometric properties of the outcome measures in the included studies

Reliability and validity were the most commonly tested psychometric properties, whereas responsiveness was the least commonly tested psychometric property. While the Cronbach's alpha, representing internal consistency, reported by most of the included studies reflected good to excellent correlation, only a few were within the acceptable threshold ($\alpha = 0.70$) [322, 328, 331, 332, 335, 339, 347]. The intraclass correlation coefficients (ICCs) for test-retest reliability were within the acceptable threshold ($\alpha = 0.70$) for most of the included studies [314, 318, 319, 328, 335, 341, 342]. Among the identified clinical tools, OABSS, OAB-q and NBSS tended to have good to excellent internal consistency, test-retest reliability, validity and responsiveness. Regarding concurrent validity, OABSS was strongly correlated with OAB-V8 and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), while OAB-q was moderately correlated with Short Form-36. Regarding discriminant validity, OABSS and OAB-q differed significantly from the International Prostate Symptom Score (IPSS) and Patient Perception of Bladder Condition (PPBC) questionnaires, respectively.

Structural and criterion validities were not reported for the OABSS or OAB-q, and only the OAB-BAT was evaluated for structural validity. Among the psychometric properties examined for OABSS in the included studies, test-retest reliability was rated as very good in six of the eight studies in which it was examined (75%), internal consistency was rated as very good in five of the seven studies (71%), validity was rated as very good in seven of the eight studies (82%), and responsiveness was rated as very good in two of three studies (67%). The psychometric properties assessed for the identified clinical tools used in the included studies are summarised in Table 3.3.

Table 3.3: Psychometric properties of the identified outcome measures

Outcome measures	Reliability	Validity	Responsiveness
Actionable Bladder Symptom Screening Tool [311, 320]	**Internal Consistency**: Cronbach's scores of 0.90 range from 0.88 to 0.91 [320]. **Test-retest reliability**: Intra-class correlation coefficient scores of 0.803 and 0.805 between the subscale of the items [311].	**Criterion validity:** higher correlations were observed for Overactive Bladder Questionnaire subscales (0.83; −0.88; p<0.001), while moderate correlations were noted for urinary symptoms and self-reported history (0.63; p<0.00) [320]. **Predictive validity**: it demonstrates a robust total score to determine individuals requiring referral to a urologist [320]. **Known-group validity**: statistically significant pairwise comparisons were observed (p<0.0001)—similarly statistically significant dependent t-test comparisons (p<0.0001) were found between participants [320].	**Sensitivity:** 79.1 % [320] and 85.7% [311].
Bristol Female Lower Urinary Tract Symptoms instrument [341]	**Internal consistency:** Cronbach's alpha was 0.83 and 0.89, respectively [341]. **Test-retest reliability:** Intra-class correlation coefficient score: 0.77 [341].	**Content/face validity:** All the items were clear without confusion and ambiguity. However, only 0.5% of the items were missing [341]. **Construct/Criterion validity:** The correlation coefficient was 0.77 ($r = 0.77$, $p < 0.001$) [341].	None
Danish Prostatic Symptom Score -1 [313-315]	**Internal consistency**: Cronbach alpha scores were 0.83 to 0.97 [314] and 0.97 for all subdomains, and the overall score [315]. **Test-retest reliability**: weighted kappa coefficient scores were 0.43 to 0.75 [314]. Intra-class correlation coefficient scores were 0.990, 0.953, and 0.987 for the symptom, bother, and overall scores, respectively [315].	**Face validity:** No suggestion by experts for omission or improvement of items [313]. **Construct validity:** the correlation between the Barthel Index and International Consultation on Incontinence Questionnaires -short form and all the sub-scores of Danish Prostatic Symptom Score -1 ($p < 0.05$) were significantly negative [315]. **Content validity:** Item-Content Validity Index of 75% of the symptoms and bother items was>0.78 (range 0.94–1.00) [313]. All experts agreed the Danish Prostatic Symptom Score -1 has a Scale-Content Validity Index= 1.00 [313].	None
International Consultation on Incontinence Questionnaires Bladder Diary [350]	**Test-retest reliability:** Spearman's rank-order correlation coefficients: 0.582 [350].	**Content validity/Face validity:** the tool was reported to be easy to complete and understandable [350]. **Construct validity:** established in the study hypothesis [350]. **Criterion validity:** A strong correlation between nocturia and reasonable agreement was reported, but a weak correlation between incontinence and urgency. ($k = 0.730$; 0.828; $P < 0.001$), and a reasonable association for urination frequency was demonstrated ($k = 0.468$, $P < 0.001$) [350].	None
International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms [331, 349]	**Internal consistency**: Cronbach's alpha coefficient >0.70 [331]; 0.89 [349]. **Test-retest reliability**: The kappa values 0.72-0.93 (P<0.001) [331]; intra-class correlation coefficient score = 0.92 [349].	**Content/face validity:** missing data were all less than 2%, indicating all items were well interpreted [331]. All the participants found the instruments clear, understandable, and quick to fill [349]. **Criterion validity:** A weak correlation was identified between the total scores of lower urinary tract symptoms and the control group [349].	None
ICIQ-MLUTS: International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms [335, 339, 340]	**Internal consistency:** Cronbach alpha value= 0.798 [335]; 0.757 [339]; 0.819 [340]. **Test-retest reliability:** The mean correlation value= 0.741 [335]; Intra-	**Content validity:** easy to understand by interviewees [339].	None

	class correlation coefficient= 0.901 [339]; 0.971 [340].		
International Consultation on Incontinence Questionnaire Overactive Bladder Module [342]	**Internal consistency:** Cronbach alpha value= 0.919 [342]. **Test-retest reliability:** Intra-class correlation coefficient= 0.789 [342].	**None**	None
Indevus Urgency Severity Scale [336]	**Test-retest reliability:** The intra-class correlation coefficient was found to be 0.8 compared to baseline days 2 and 5 [336].	**Content validity:** a good measure of magnitude and severity of discomfort of urgency incontinence associated with OAB [336].	**Responsiveness:** detect changes in a reduction in patient toilet voids and moderate urge incontinence from 24 hours to 7 days and 24 hours to zero, respectively (effect size: 0.97; 0.81) [336]. It detects changes below and above median figures of toilet voids and urgency incontinence episodes per 24 hours (effect size 1.26) [336].
Neurogenic Bladder Symptom Score [316-318, 347, 348]	**Internal consistency**: Cronbach α value = 0.81 [316], 0.893 to 0.910 [317]. 0.81 and 0.83 for MS and SCI respectively [318]. 0.86 [348]; 0,95, 0.78 and 0.73 [347]. **Test-retest reliability:** Intraclass correlation coefficient = 0.852 [0.24-0.875] [347]; >0.7 [318] and 0.86 [0.76-0.92] ($p < 0.0001$) for the overall score [316]. An intra-class correlation value of 0.91 (95% CI 0.87–0.94, $p<0.001$ [317]. 0.91 [348].	**Face/Content validity:** The experts confirmed that the questionnaire covers the relevant aspect of the patient's condition [316]. The questionnaire is clear, easy to understand, and fast to complete [318]. All items are simple, unambiguous, and relevant and achieved the acceptable value of the content validity index [347]. **Concurrent/criterion validity:** A significant moderate positive correlation was revealed in the total scores of the Turkish version of the NBSS and the subdomains King Health Questionnaire ($p<0.001$) [317]. **Ceiling effect:** 3%-7% of multiple sclerosis and 0%-2% spinal cord injry [318]. **Construct validity:** a moderate correlation NBSS with the Qualiveen-SF was revealed using Pearson Correlation 0.66 ([0.40-0.82]; $p < 0.0001$) [316].	None
Overactive Bladder-Bladder Assessment Tool [321]	**Internal consistency:** excellent Cronbach alpha value= 0.918 [321]. **Test-retest reliability:** Intra-class correlation coefficient value=0.81, 95% CI, 0.77–0.85 [321].	**Convergent/divergent validity:** A strong correlation was observed in most values $r > 0.8$ [321]. **Known-group validity**: Summaries for continence and sex status correlated between constituent groups [321].	None
Overactive Bladder Satisfaction with Treatment Questionnaire [333]	**Internal consistency:** excellent for the subscales: 0.84, 0.87 and 0.95 [333].	**Concurrent validity:** small to moderate correlations were observed in the symptom bother and Overactive Bladder Questionnaire subscales scores = -0.27 to -0.44; 0.10–0.38; $p < 0.05$ [333]. **Discriminant validity:** significantly discriminated between with and without improvement $p<0.05$ [333].	None
Overactive bladder -V8 [319]	**Internal consistency:** Cronbach's α test ranged from 0.911 to 0.919 [319]. **Test-retest reliability**: inter-domain correlations= 0.657 to 0.789 [319].	**Discriminatory validity:** 5.3 for the control group while 24.2 for the intervention group with a p-value < 0.001 [319].	None
Overactive Bladder Questionnaire [312, 324-327, 334, 338]	**Internal consistency**: The Cronbach's α test is quite good, with scores greater than 0.85 across all items for all subscales [326]; 0.89 to 0.96 [324], while an excellent Cronbach's alpha coefficient (>0.82) was also reported [338].	**Concurrent validity**: A moderate correlation was observed at baseline, while it was moderate to strong at week 12. The strongest correlation was reported in the symptoms of bother, coping, concern, and health-related quality of life.[326] There was a moderate correlation between the Overactive Bladder Questionnaire and Short-Form-36 subscales (0.16 to 0.52) [324]. **Discriminant validity**: The patient Perception of Intensity of Urgency Scale was used to evaluate the discriminant validity. Significant differences were observed in the mean Overactive Bladder Questionnaire scores and Patient Perception of Intensity of Urgency	**Responsiveness:** moderate to large effect sizes were observed in multiple assessments with responsive changes (Study 1: 0.73–1.53; Study 2: 0.44–1.17; Study 3:0.55– 1.31) [326]. Another study also observed significant responsive change in the Overactive Bladder Questionnaire ($P<0.001$) with the exception of the social domain and Overactive

	Test-retest reliability: Each item and the subscale scores have good test-retest reliability with reproducible results [338]. Overactive bladder questionnaire subscales and Short Form Intra-class correlation scores: 0.55 to 0.77 (P<0.001) [338], item range (0.69–0.89); total scale (0.88).[338] There is a strong correlation in the Overactive bladder questionnaire scores (visits 1 and 2). Intra-class correlation coefficient scores: 0.83 to 0.95; Spearman's correlations: 0.80 to 0.94 (p<0.001) [334].	Scale responses [341] with p < 0:0001 for the Overactive Bladder Questionnaire subscales among continent and incontinent patients [324]. Significant differences were observed in the Overactive Bladder Questionnaire and Overactive Bladder Questionnaire Short Form subscales p<0.001 [338]. **Convergent validity:** High correlation coefficients p<0.05 [338].	Bladder Questionnaire Short Form [338]. Significant differences were observed in all the King Health Questionnaire scores (except personal relationships scores) p<0.05[338] and between the Overactive bladder Questionnaire change scores and bladder diary (micturition frequency) changes from baseline to week 12 p < 0.001 (0.13 to 0.35) with small to moderate change in magnitude [326, 327].
Overactive Bladder Symptom Score [322, 323, 328-330, 332, 343-346]	**Internal consistency**: Cronbach's alpha scores: 0.674 [323]; 0.71 [322]; 0.75 [332]; 0.736 [328], 0.56 [330], 0.92 [345]. **Test-retest reliability:** Intra-class correlation coefficient: 0.88 [322]; 0.82 [332, 346]; 0.74 [328]; 0.83 [344]; 0.95 [337]. Weighted kappa coefficient: 0.515-0.721;[323] 0.635-0.831 [328]; 0.55-0.84 [330]; 0.55–0.66 [344]. **Spearman's rank-order correlation coefficients**: 0.65-0.84 (P < 0.001) [345].	**Content /Face validity:** the questions have a clear meaning, are relevant to the urinary symptoms, and have an easy understanding of the questions in 88% of patients, and are easily completed in 82% of the patients within 5 minutes [332]. **Construct validity:** A strong correlation was observed in the number of incontinence episodes at first visit (r=0.406; p<0.05) and second visit (r=0.576; P<0.001) compared to bladder diary and Patient Perception of Bladder Condition scores of first visit (r=0.516; P<0.001) and second visit (r=0.499; P<0.001 [346]. Moderate to high correlation was observed in the diary, and the IPSS total scores for the number of micturition and urgency episodes [346]. Low correlations were reported in the nocturia episodes, voided volumes, and pads utilised [346]. **Concurrent validity:** A strong correlation was found between the Overactive bladder symptom score and Overactive bladder -V8 and International Consultation on Incontinence Questionnaire-Short Form using the Spearman correlation coefficient: 0.715, p = 0.001; 0.714, p = 0.001)[328] respectively. A moderate to strong degree correlation was observed in the Overactive bladder symptom score total scores compared to the gold standard (Patient Perception of Bladder Condition, Overactive Bladder Questionnaire symptom bother, International Prostate Symptom Score total) [330]. **Discriminant validity**: A significant correlation was observed in the OABSS total score compared to the IPSS-storage score (r = 0.34–0.68) and not with the International Prostate Symptom Score-voiding score (r = -0.07–0.40) [332]. A significant difference was observed in all diagnostic groups' responses at first or second (p < 0.001) [345]. **Convergent validity**: Moderately positive correlation was observed in the International Prostate Symptom Score selected items compared to the 3-day Bladder diary variables except for International Prostate Symptom Score Q2-frequency (Spearman correlation coefficient: 0.43 and 0.57) [332] . .	**Responsiveness:** Significant correlation (p<-0.001) in the night-time frequency with the smallest effect sizes (Overactive bladder symptom score:-0.369 and bladder diary:-0.271) and urgency with the largest effect sizes (Overactive Bladder Symptom Score:-1.485 and bladder diary: -0.970) [329]. All effect sizes of the Overactive bladder symptom score scales were considered large except the night-time frequency (-1.485 to -0.936) [329]. The Overactive bladder symptom score score decreased from 10.2 to 6.0 (p < 0.001) following the patient's treatment from baseline to 3 months.[323] Moderate responsiveness to treatment was also observed through each Overactive bladder symptom score item score with effect sizes, Guyatt responsiveness index, and standardised response means (-0.5 to -1.1) [332]. **Minimally important difference:** 95% CI: -3.15 for the upper limit with mean change: -3.67 in the urgency assessment, while minor improvement: -2.49 at the lower limit of 95% CI -3.03 [329].
Patient Perception of Intensity of Urgency Scale [337]	**Test-retest reliability**: excellent test-retest reliability was found based on an intraclass correlation coefficient of 0.97 and Spearman's correlation of 0.89 (p < 0.0001) [337].	**Content validity:** a general agreement was observed among the participants in explaining the meaning of the urgency ratings and expressing their experiences [337].	None

3.4.5 The COSMIN findings for the outcome measures in the included studies

Ten studies [322, 323, 328-330, 332, 343-346] had reported the psychometric properties of the OABSS, which had been tested for test-retest reliability [322, 323, 328, 330, 332, 343-346], internal consistency [322, 323, 328, 330, 332, 343, 345] and responsiveness [323, 329, 332] among individuals with OAB. Seven studies had reported the psychometric properties of the OAB-q [312, 324-327, 334, 338, 346], which had been tested for test-retest reliability [334, 338], internal consistency [312, 324, 338] and responsiveness [312, 325-327, 338]. Three studies had reported the psychometric properties of the NBSS [316-318], which had been tested for test-retest reliability [334, 338] and internal consistency [316-318]. The methodological quality of the psychometric properties of the OABSS, OAB-q and NBSS ranged from very good to doubtful. The COSMIN findings of the outcome measures in the included studies are detailed in Table 3.4.

Table 3.4: COSMIN findings of the identified outcome measures

Outcome Measures	Reliability		Validity							Responsiveness
	Internal consistency	Test-retest reliability	Structural validity	Content validity	Criterion validity	Convergent validity	Concurrent validity	Discriminant validity	Known-group validity	
Actionable Bladder Symptom Screening Tool [311, 320]	Very good [311, 320]	Doubtful [311]	-	-	Very good [311, 320]	-	-	-	Very good [320]	-
Bristol Female Lower Urinary Tract Symptoms Instrument [341]	-	Adequate [341]	-	Very good [341]	Very good [341]	-	-	-	-	-
Danish Prostatic Symptom Score -1 [313-315]	Very good [315]	Very good [314] Adequate [315]	-	Doubtful [313]	-	Very good [315]	-	-	-	-
International Consultation on Incontinence Questionnaires Bladder Diary [350]	Doubtful [342]	Adequate [342]	-	-	-	-	-	-	-	-
International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms [331, 349]	-	Adequate [350]	-	Very good [350]	Inadequate [350]	-	-	-	-	Very good [350]
ICIQ-MLUTS: International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms [335, 339, 340]	Very good [331, 349]	Very good [331] [349]	-	Very good [349] Doubtful [331]	Very good [349]	-	-	-	-	-
International Consultation on Incontinence Questionnaire Overactive Bladder Module [342]	Very good [335, 339, 340]	Adequate [335, 339] Doubtful [340]	-	Doubtful [339, 340]	Very good [339]	-	-	-	-	-
Indevus Urgency Severity Scale [336]	-	Adequate [336]	-	Adequate [336]	-	-	-	-	-	Very good [336]
Neurogenic Bladder Symptom Score [316-318, 347, 348]	Very good [316-318]	Adequate [318] Very good [317]	-	Adequate [318], Doubtful [316]	Very good [318]	-	Very good [317]	-	-	-
Overactive Bladder-Bladder Assessment Tool [321]	Very good [321]	Very good [321]	Adequate [321]	-	-	Very good [321]	-	-	Very good [321]	-
Overactive Bladder -V8 [319]	Very good [312, 324, 338]	Adequate [334] Very good [338]	-	Adequate [338]	-	Very good [338]	Very good [312, 324]	Very good [312, 324, 338]	-	Very good [312, 325-327, 338]
Overactive Bladder Questionnaire [312, 324-327, 334, 338]	Very good [333]	-	-	-	-	-	Very good [333]	Very good [333]	-	-
Overactive Bladder Satisfaction with Treatment Questionnaire [333]	Very good [319]	Doubtful [319]	-	-	-	-	-	Adequate [319]	-	-

Overactive Bladder Symptom Score [322, 323, 328-330, 332, 343-346]	Very good [322, 323, 330, 332, 345], Doubtful [328, 343]	Very good [323, 328, 330, 344-346], Adequate [322, 332] Doubtful [343]	-	Doubtful [332]	-	Very good [332, 346]	Very good [328, 330]	Very good [332, 345], Adequate [343]	Adequate [330]	Very good [329, 332] Adequate [323]
Patient Perception of Intensity of Urgency Scale [337]	-	Very good [337]	-	Very good [337]	-	-	-	-	-	-

3.4.6 GRADE findings for the psychometric properties of the outcome measures in the included studies

Table 3.5 presents the GRADE findings for the evidence quality of the outcome measures in the included studies. The psychometric scores were pooled to obtain the GRADE findings of each included outcome measure. The pooling was conducted for internal consistency, test-retest reliability (ICC/weighted kappa), validity and responsiveness. The quality of evidence of the evaluated outcome measures ranged from low to high, with 33%, 53%, and 13% being of high, moderate, and low quality, respectively. DAN-PSS-1, IUSS, NBSS, OAB-q and OABSS had high quality; BFLUTS, ICIQ-FLUTS, ICIQ-MLUTS, ICIQ-OAB, OAB-BAT, OAB-SAT-q, OAB-V8 and PPIUS had moderate quality; and ABSST and ICIQ-BD had low quality. Almost all outcome measures were found to have sufficient overall quality of evidence (93%), with only one (ICIQ-BD) found to have insufficient overall quality of evidence.

Table 3.5: Summary of evidence, overall rating and grading of the quality of evidence using GRADE Assessment

Outcome measures	Summary or pooled result	Overall rating	Quality of evidence
Actionable Bladder Symptom Screening Tool [311, 320]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.88-0.91 **Test re-test reliability (ICC score)**: 0.803-0.806 **Total sample size**: 72	Sufficient	Very low (due to risk of bias and imprecision)
Bristol Female Lower Urinary Tract Symptoms instrument [341]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.83-0.89 **Test-retest reliability (ICC scores)**: 0.77 **Total sample size**: 114	Sufficient	Moderate (due to risk of bias)
Danish Prostatic Symptom Score -1 [313-315]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.83-0.97. **Test-retest reliability (ICC scores)**: 0.953-0.990 **Total sample size**: 573	Sufficient	Low (due to risk of bias)
International Consultation on Incontinence Questionnaires Bladder Diary [350]	**Test-retest reliability (Spearman's rank order correlation coefficients):** 0.582-0.940 **Total sample size**: 354 **Responsiveness**: The result is in accordance with the hypothesis	Insufficient	Low (due to risk of bias and imprecision)
International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms [331, 349]	**Internal consistency (Summarised Cronbach's alpha coefficient)**: >0.70; 0.89 **Kappa coefficient scores** = 0.72-0.93. **Test-retest reliability (ICC scores)**: 0.92 **Total sample size**: 300	Sufficient	Moderate (due to risk of bias)
ICIQ-MLUTS: International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms [335, 339, 340]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.757-0.819 **Test-retest reliability (ICC scores)** = 0.90; 0.971 **Total sample size**: 354	Sufficient	Moderate (due to risk of bias)
International Consultation on Incontinence Questionnaire Overactive Bladder Module [342]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.919. **Test-retest reliability (ICC scores)**: 0.789 **Total sample size**: 50	Sufficient	Moderate (due to imprecision)
Indevus Urgency Severity Scale [336]	**Test-retest reliability (ICC scores):** 0.8 **Total sample size**: 658 **Responsiveness**: The result is in accordance with the hypothesis	insufficient	High
Neurogenic Bladder Symptom Score [316-318, 347, 348]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.81-0.910 (MS); 0.81-0.83 (SCI). **Test-retest reliability (ICC scores):** 0.76-0.92 **Total sample size:** 380	Sufficient	High
Overactive Bladder-Bladder Assessment Tool [321]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.918. **Test-retest reliability (ICC scores):** 0.77–0.85 **Total sample size:** 92	Sufficient	Moderate (due to imprecision)
Overactive Bladder -V8 [319]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.95 **Total sample size:** 375	Sufficient	Moderate (due to risk of bias)
Overactive Bladder Questionnaire [312, 324-327, 334, 338]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.911-0.919 **Test-retest reliability (ICC scores):** 0.657-0.789 **Total sample size:** 104	Sufficient	Moderate (due to risk of bias)
Overactive Bladder Satisfaction with Treatment Questionnaire [333]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.82-0.96 **Test-retest reliability (ICC scores):** 0.55-0.95 **Spearman's correlation coefficient:** 0.80-0.94 **Responsiveness**: The result is in accordance with the hypothesis	Sufficient	High

	Total sample size: 5466		
Overactive Bladder Symptom Score [322, 323, 328-330, 332, 343-346]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.56-0.92 **Test-retest reliability (ICC scores):** 0.74-0.95 **Weighted kappa coefficient:** 0.515-0.84. **Spearman's correlation coefficient**: 0.65-0.84 **Responsiveness**: The result is in accordance with the hypothesis **Total sample size:** 757	Sufficient	High
Patient Perception of Intensity of Urgency Scale [337]	**Test-retest reliability (ICC scores):** 0.97 **Spearman's correlation coefficient**: 0.89 **Total sample size:** 51	Sufficient	Moderate (due to imprecision)

ICC: Intra-class correlation coefficient

3.5 Discussion

This review investigated the psychometric properties of clinical tools used to evaluate OAB symptoms. It included 40 studies reporting 15 clinical tools, including seven original scales and eight modified versions. The most extensively tested clinical tools were OABSS, OAB-q and NBSS among the original scales and OAB-BAT, ICIQ-FLUTS, ICIQ-MLUTS and ICIQ-BD among the modified scales. Among the psychometric properties examined for OABSS in the included studies, test-retest reliability was rated as very good in six of the eight studies in which it was examined (75%), internal consistency was rated as very good in five of the seven studies (71%), validity was rated as very good in seven of the eight studies (82%), and responsiveness was rated as very good in two of the three studies (67%). The OABSS and OAB-q were assessed as having similar GRADE-based evidence quality for diverse validation measures and similar COSMIN qualities. However, the OABSS appeared to be the most diverse and flexible clinical tool across different study settings.

The OABSS is a highly responsive self-administered questionnaire with a single total score. It was developed to address the concerns of a therapist providing interventions to those with OAB by quantifying OAB symptoms and grading responses for urgency [330]. It is a simple to administer and reliable questionnaire that contains four questions evaluating night-time frequency, daytime frequency, urinary urgency and UUI with a maximum score of 2, 3, 5, and 5, respectively, totalling an overall possible score of 15, with higher scores indicating worse symptoms [329]. The Cronbach's alpha, ICCs, weighted kappa coefficients, Spearman's correlation coefficients, and responsiveness summarised in our study revealed the optimality and effectiveness of the OABSS in evaluating the severity of OAB symptoms. This finding is consistent with a 2017 review by Narang et al., which reported that the OABSS was an easily

administered, clinically relevant adjunct to the bladder diary that efficiently characterised the symptom burden of individuals with OAB [352]. Our review found that the structural and criterion validities of the OABSS were yet to be determined as part of its psychometric properties. However, strong criterion validity has been reported previously [330, 353], which is necessary to ascertain how much the outcome measure coincides with the gold standard [354]. In the included studies, the OABSS was used to evaluate OAB symptoms; similarly, other studies have reported OABSS as a primary outcome measure for assessing the symptoms of OAB due to stroke [355], multiple sclerosis [356] and spinal cord injury [357].

The OAB-q is a valid, reliable and responsive self-administered psychometric questionnaire developed to evaluate OAB symptoms through focus group discussions with men and women, therapist opinions and a detailed literature review [324]. Its overall subscale scores range from 0 to 100, with higher scores indicating worse symptoms. A previous 2007 review by Avery et al. demonstrated that OAB-q achieved sound, adequate, and very good internal consistency, test-retest reliability, validity and responsiveness [358]. Future studies should investigate the structural, criterion and known-group validities of the OAB-q to address the evident gap in the included studies.

The NBSS is a valid and reliable condition-specific self-administered questionnaire for evaluating OAB symptoms and their consequences in men and women [317]. Its possible scores range from 0 to 74, with higher scores indicating greater symptom severity [317]. It is composed of questions covering incontinence (eight questions), voiding symptoms, storage (seven questions) and urinary complications (seven questions) arising from neurogenic bladder dysfunction; bladder emptying method (one question); and quality of life impact (one question)

[317]. While our systematic review revealed an acceptable and reliable summary of Cronbach's alpha and ICCs, only concurrent validity was reported by the included studies.

Our study found that the OABSS and OAB-q had the best responsiveness ratings across the identified clinical tools, suggesting that they can be highly sensitive clinical tools that can easily detect treatment-related changes in patients' symptoms. To achieve the clinical benefits of responsiveness, the International Continence Society suggests using responsive condition-specific clinical measures in clinical practice and research to accurately detect and monitor patients' symptoms [359]. Our study found that both the OABSS and the OAB-q are supported by high-quality evidence (GRADE). However, the OABSS focuses only on OAB symptoms, whereas the OAB-q evaluates the quality of life and bother symptoms. Integrating quality of life and bother symptoms into a single clinical tool could affect its efficacy parameters [360]. By excluding bother symptoms, the OABSS may offer a more objective view of symptoms. For example, patients who experience similar levels of incontinence have varied bother symptoms. Moreover, unlike the OABSS, the OAB-q does not quantify OAB symptoms [360].

The applicability of clinical measures depends on their quality, which must be validated. A sound and validated measure offers an appropriate, feasible, valid and reproducible evaluation of patients' concerns and can be used to monitor their recovery [361]. Clinical tools are recommended for use in clinical practice based on the clarity, simplicity, number, quality and strength of psychometric properties [361]. To receive a 'highly recommended' status from the International Continence Society, the psychometric properties of an evaluated instrument, such as validity, reliability and responsiveness, must display established rigour and soundness [359]. The OABSS, which is widely used across culturally diverse populations [322, 323, 328-330,

332, 343-346, 360, 362-365], demonstrated higher ratings for most of the tested psychometric properties than the other identified clinical tools. In addition, our study found that the OABSS provides a better assessment of overactive symptoms than both the OAB-q and the NBSS, which focus more on evaluating how OAB impacts and burdens daily life [353]. Blaivas et al. reported that the OABSS is a valid tool that evaluates all aspects of OAB symptoms and may be used as a symptom score [360].

3.6 Strengths and limitations

Our review used a sound, systematic, comprehensive search strategy, using relevant search terms to identify studies validating clinical tools used to assess OAB symptom severity. The COSMIN risk of bias and modified GRADE approaches were used to assess the methodological and evidence quality of the clinical tools examined in the included studies. However, our review also had some limitations. Firstly, it may be subject to language bias due to the exclusion of studies not published in English. Secondly, it may be subject to publication bias due to the exclusion of conference abstracts, grey literature and unpublished reports, which may result in potentially vital information being overlooked. Thirdly, no study had investigated the structural validity of the OABSS, and only one had its content validity, which was rated as doubtful.

3.7 Conclusions

Our review found that the OABSS, OAB-q and NBSS are the most widely validated clinical measures across several countries with sound psychometric properties. Among the identified clinical measures, the OABSS was the most culturally diverse and psychometrically sound clinical tool supported by studies of good methodological quality and high evidence quality

among individuals with UUI due to OAB. The OABSS might be adopted as a single clinical tool capable of assessing OAB symptoms in clinical practice and research settings because it specifically evaluates all OAB symptoms. However, no included study had investigated the structural validity of the OABSS, and only one had investigated its content validity, which was rated as doubtful. Further studies investigating the content and structural validities of the OABSS are required.

3.8 Clinical messages

1. The OABSS exhibits sound, cross-cultural suitability with robust psychometric findings across diverse cultural backgrounds.
2. The OABSS can be used to evaluate OAB symptoms.
3. The OAB-q possesses robust psychometric properties but is less culturally diverse.
4. The OAB-q can also be used to evaluate neurogenic OAB symptoms. However, clinicians should be aware that the OABSS provides a more specific and detailed assessment of the neurogenic OAB symptoms.

Chapter 4

Measures of the quality of life of individuals with neurogenic overactive bladder: A systematic review of their psychometric properties

4.1 Commentary

This chapter presents the background, methodology, findings, discussions and conclusions of the systematic review on the psychometric properties of clinical tools measuring the quality of life of individuals with neurogenic overactive bladder (OAB). This systematic review aimed to identify the most psychometrically sound clinical tool for evaluating the quality of life of individuals with OAB.

4.2 Introduction

OAB is a devastating and distressing condition associated with severe adverse consequences, such as restricted participation, social isolation and depression [366]. Its symptoms can include urinary urgency, either with or without urgency urinary incontinence [UUI], increased urinary frequency (voiding at least eight times within 24 hours) or nocturia (voiding two or more times during the night) [367]. The International Continence Society suggests that OAB is likely caused by lower urinary tract dysfunction with neurological origins (neurogenic OAB) when no evidence indicates infection or other apparent pathological aetiology, such as neoplasms or metabolic dysfunction [367]. The symptoms associated with neurogenic OAB have been

implicated in impaired quality of life, with considerably negative impacts on physical and psychosocial functioning, depression and anxiety [117, 368]. The degree of quality of life impairment increases with symptom severity among affected individuals [369]. The number of voiding episodes reported during the day and night is considered a predictor of quality of life among individuals with OAB [370].

Neurogenic OAB symptoms have been associated with impaired quality of life, with considerable negative effects on physical and psychosocial functioning, depression and anxiety [117, 368]. Patients' neurogenic OAB symptom severity correlates negatively with their quality of life scores [371]. The decrease in quality of life scores varies based on patients' awareness of their symptom severity [369]. Quality of life scores were consistently lower among individuals with neurogenic OAB than their continent peers [372, 373]. Those with UUI symptoms of neurogenic OAB are reported to experience a deteriorated quality of life compared to their peers with stress incontinence [374]. The rates of voids per day and night were considered predictors of quality of life among those with OAB [370].

Outcome measures for evaluating quality of life are being increasingly applied during clinical assessments [361], leading to the development, application, and validation of new quality-of-life measures to provide evidence-based evaluations of clinical outcomes and monitor interventions [361]. In clinical settings, health status measures can be used to screen for functional problems, monitor disease progression and therapeutic response, and assess the quality of care [375]. Outcome measures must have robust psychometric properties, such as validity, reliability and responsiveness, to be relevant in both clinical practice and research settings [376]. The International Continence Society recommends using validated quality-of-

life measures when assessing therapeutic interventions for managing urinary incontinence and clinical decision-making [377].

Previous systematic reviews have assessed the application of distinct health-related quality-of-life measures for evaluating the impacts of interventions on quality of life among those with stress urinary incontinence [378, 379]. While multiple quality-of-life measures exist for assessing those with urinary incontinence [380-382], previous reviews have not indicated which quality-of-life measure is the most suitable for use among those with UUI due to neurogenic OAB. The lack of quality-of-life measures explicitly designed for those with neurogenic OAB has limited researchers and clinicians to measures of generic quality-of-life or those developed for specific patient populations [383]. A previous systematic review of the quality-of-life measures by Wuytack et al. [300] focused primarily on applying disease-specific and generic quality-of-life measures in women with stress urinary incontinence without considering neurogenic OAB. Focusing on quality-of-life measurement instruments applied to populations with neurogenic OAB is crucial for understanding their psychometric strengths among those with OAB. Therefore, this systematic review was conducted to identify the psychometrically sound quality of life measure(s) for evaluating those with neurogenic OAB and make clinical practice and research recommendations for monitoring their quality of life.

4.3 Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [231] and prospectively

registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42021267409).

4.3.1 Search strategy and study screening

An author (MUA) conducted the database searches. The following electronic databases were searched from inception to 6 January 2023: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), MEDLINE, Scopus and Web of Science. Three themes were developed for the search terms: psychometric properties, outcome measures and OAB. The search strategy developed for the MEDLINE database is described in detail in Appendix 4.1. The reference lists of all included studies and relevant systematic reviews were manually searched to identify other potentially relevant studies. Because we retrieved and analysed data from published studies that obtained informed consent, no ethical approval was required for this systematic review [384].

4.3.2 Study selection

This systematic review selected studies according to the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework [252]. The studies included in this systematic review were selected based on the following criteria: (1) evaluating quality of life among those with OAB of both sexes aged ≥18 years; (2) testing the psychometric properties of OAB-specific quality of life measures; and (3) assessing one or more of the following psychometric properties: internal consistency, intra-rater reliability, inter-rater reliability, test-retest reliability, measurement error, cross-cultural validity, content validity, face validity, structural validity, criterion validity, hypothesis testing and responsiveness. The exclusion criteria were (1) published in languages other than English; (2) systematic reviews or meta-analyses; (3)

commentaries or editorials; (4) unpublished theses; (5) conference proceedings, abstracts, or event annals; and (6) inaccessible full-text. The reasons for exclusion can be found in Appendix 4.2.

The articles were comprehensively screened by first exporting the database search results to the citation manager EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). Next, duplicate studies were identified and removed. Then, one author (MUA and Umar Muhammad Bello) screened the titles and abstracts for inclusion according to the predefined criteria. Two authors (MUA and Dauda Salihu) then independently screened the full texts, with disagreements reconciled through discussion. Irreconcilable differences during the screening process were mediated by a third author (Priya Kannan) until a consensus was reached.

4.3.3 Data extraction

Two authors (MUA and DS) independently extracted the data from the included studies, and all discrepancies were addressed through discussion. A third author (PK) was consulted to address unresolved discrepancies during data extraction. The following data were extracted from each included study: first author, publication year, country of origin, participant characteristics (the mean and standard deviation of participants' age and the sample size of each group), population, outcome measure(s), psychometric property tested, and authors' conclusions.

4.3.4 Quality appraisal

The COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) risk of bias (RoB) checklist [305] and the modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [235] were used to evaluate the methodological and evidence quality, respectively, of each included study. The COSMIN RoB checklist evaluates the RoB for each included study regarding eight psychometric properties: reliability (relative measures including test-retest, inter-rater and intra-rater reliability), internal consistency, measurement error, content validity (including face validity), hypotheses testing, structural validity, criterion validity, cross-cultural validity and responsiveness [305]. The methodological quality of each psychometric property in each included study was graded using a four-point rating scale as 'very good', 'adequate', 'doubtful', or 'inadequate'. The overall methodological quality score for each tested psychometric property was considered the lowest or worst score for any item on the checklist [305]. After completing this step, the identified outcome measures were rated as sufficient (+), insufficient (−), inconsistent (±) or indeterminate (?) based on the pooled results for the included studies [305]. An outcome measure was considered to be of sufficient overall quality (+) if most (>50%) of the included studies were graded as sufficient [305]. Two independent authors (MUA and PK) evaluated the psychometric methodological quality of the included outcome measures. A third reviewer (SJW) assisted with addressing any unresolved discrepancies.

A COSMIN-modified GRADE assessment was performed to evaluate the quality of evidence for each psychometric property of the identified outcome measures [306]. The outcomes of each included study were evaluated against the proposed revised GRADE criteria [306, 309] for good psychometric properties to determine a cumulative modified GRADE score. The

pooled psychometric properties included internal consistency, test-retest reliability (intraclass correlation coefficient [ICC]/weighted kappa), validity and responsiveness. In this modified GRADE approach, each property's evidence quality was graded as high, moderate, low or very low [308, 385]. The grading of the identified outcome measures starts with the assumption that the evidence quality is high, and the quality rating is then downgraded by up to three levels depending on the RoB, inconsistency, indirectness and imprecision of the evidence [307, 308].

For example, the Urinary Distress Inventory (UDI) was used in five studies with sufficient psychometric findings. While six of the seven psychometric properties were identified as of very good quality, the internal consistency was doubtful in two studies, indicating potential RoB and requiring the downgrading of quality from high to low. However, the internal consistency of the UDI was identified as sufficient, indicating no need to downgrade the quality rating for inconsistency. The total sample size of the included studies was 826, which is more than 100, indicating no need to downgrade quality for imprecision. The study populations in which UDI was assessed were homogeneous, indicating no need to downgrade quality for indirectness.

Two authors (MUA and PK) independently evaluated the GRADE score for each included outcome measure. A third reviewer (SJW) was consulted for unresolved disagreements. The International Continence Society stated that for a tool to receive a 'highly recommended' grade, its psychometric properties, such as validity, reliability and responsiveness, must have an established rigour and soundness [377]. High-quality scores for appropriateness, feasibility, interpretability, acceptability, judgment, clarity, simplicity and accessibility are also considered when determining recommendations for applying outcome measures [361].

4.4 Results

4.4.1 Study selection

This systematic review identified 6,937 potentially relevant articles from electronic database searches and manual searches of the reference lists of relevant articles. After the search results were exported to the EndNote citation manager, 1025 duplicate records were removed. Of the remaining studies, 47 [288, 312, 324-327, 334, 338, 370, 386-424] met the eligibility criteria for this systematic review. The reasons for study exclusion at the full-text screening stage are provided in Appendix 4.1. A PRISMA flowchart illustrating the screening process is presented in Figure 4.1.

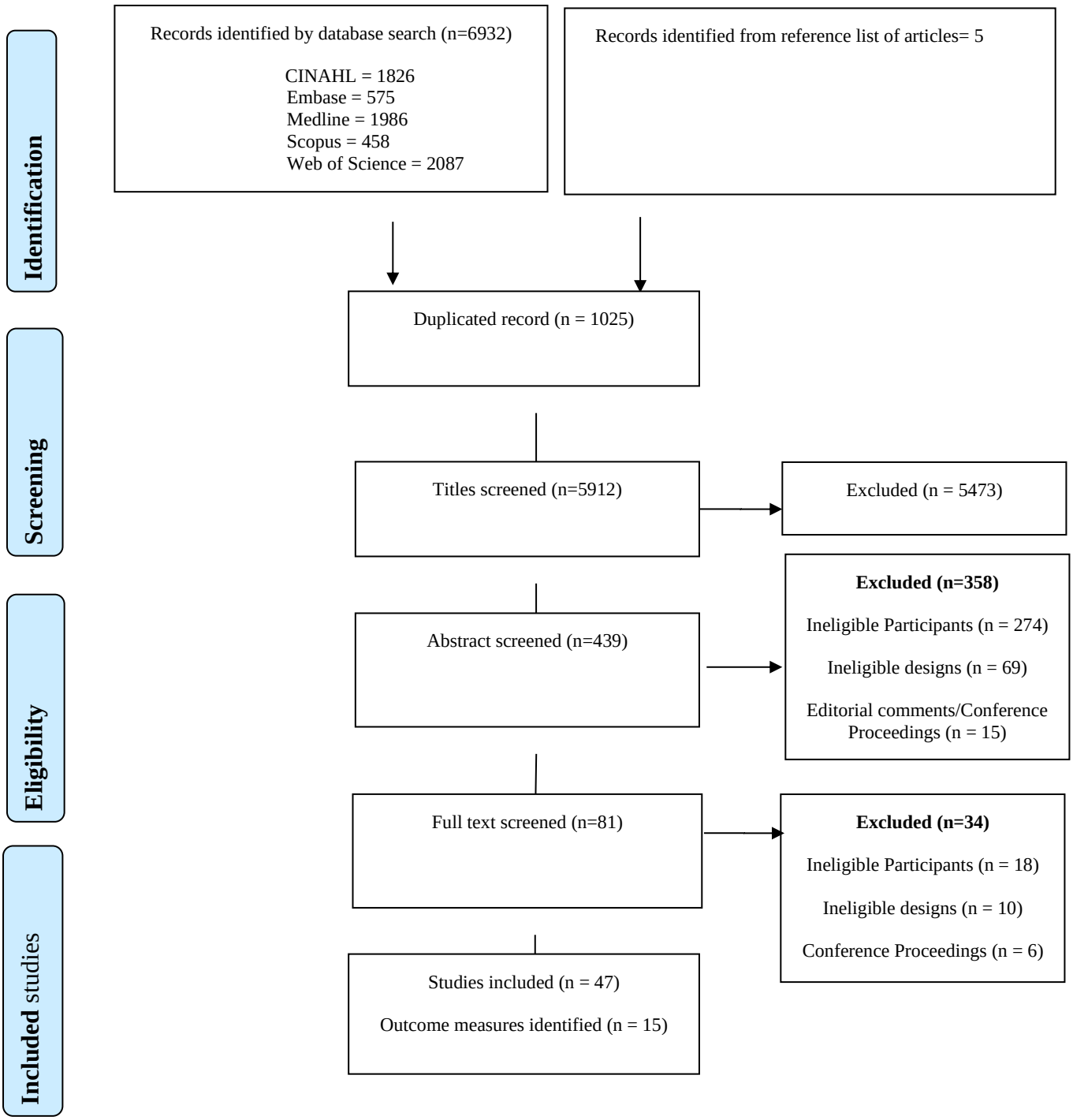

Figure 4.1: Flowchart of screened studies

4.4.2 Study characteristics of the included studies

This systematic review included 47 studies involving 19,994 participants, with the sample size ranging from 22 [421] to 1831 [416] (mean = 425). The participants were aged 18–89 years. The included studies were published between 1997 [420] and 2021 [408], with 26 published within the last decade (2011–2021). Nine of the included studies recruited subjects with OAB secondary to specific health conditions, including multiple sclerosis only (n = 5) [396, 402, 403, 407-409]; spinal cord injury only (n = 1) [408]; multiple sclerosis and spinal cord injury (n = 2) [405, 406]; or multiple sclerosis, spinal cord injury and myelomeningocele (n = 1) [404]. The remaining 38 studies reported recruiting patients with neurological conditions without focusing on specific health conditions [288, 312, 325-327, 334, 338, 370, 386-395, 397-401, 410-424]. The characteristics of the included studies are presented in Table 4.1.

Table 4.1: Characteristics of included studies (n =47)

First author, year, country of study	Participant characteristics (mean age of participants (SD); Sample size of each group)	Population	Outcome measure(s)	Psychometric property tested	Author's Conclusion of each included study
Multiple Sclerosis/Spinal cord injuries/Myelomeningocele					
Bonniaud et al., 2008 [403] Canada	Exp: 58.45±15.9 Con: 62.05±19.9 n = 121	Multiple sclerosis	Qualiveen	Test-retest reliability Criterion validity Construct validity Responsiveness	Qualiveen possesses excellent psychometric properties in clinical and research settings similar to the long version.
D'Ancona et al., 2008 [404] Brazil	36.33±12.20 n = 51	Spinal cord injury Multiple sclerosis Myelomeningocele	Brazilian Portuguese version Qualiveen	Internal consistency Test-retest reliability Construct validity	The Portuguese version of Qualiveen indicated a good validation psychometric property for investigating the quality of life among people with urinary symptoms due to neurological conditions.
Konstantinidis et al., 2020 [405] Greece	Paraplegia: 50.69±13.78 Tetraplegia: 51.06±10.47 MS: 51.15±13.32 n = 124	Spinal cord injury Multiple sclerosis	Greek version Qualiveen	Internal consistency Test-retest reliability Structural validity Criterion validity	This Greek version of Qualiveen indicates good reliability and validity following well-established psychometric assessment guidelines.
Milinis et al., 2017 [402] United Kingdom	50.8±11.8 n = 258	Multiple sclerosis	Qualiveen	Structural validity	Qualiveen demonstrates good validity in assessing the impact of urinary symptoms among people with multiple sclerosis.
Nikfallah et al., 2015 [406] Iran	35.3±9.8 n = 154	Spinal cord injury Multiple sclerosis	Persian version Qualiveen	Test-retest reliability Internal consistency Convergent validity Discriminant validity	The Persian version of Qualiveen is a reliable and valid measure for evaluating the quality of life among people with spinal cord injuries or multiple sclerosis.
Philippova et al., 2020 [407] Russia	37.9±9.16 n = 60	Multiple sclerosis	Russian version Qualiveen	Internal consistency Test-retest reliability Criterion validity	The Russian Qualiveen demonstrated good reliability and validity for evaluating the impact of urinary symptoms on incontinence-related quality of life among people with multiple sclerosis.
Przydacz et al., 2020 [409] Poland	47.3±15.6 n = 189	Multiple sclerosis	Polish versions Qualiveen	Test-retest reliability Internal consistency Content validity Criterion validity	The Polish Qualiveen demonstrate strong reliability and validity for evaluating the impact of urinary symptoms on incontinence-related quality of life among Polish in clinical practice and research.
Przydacz et al., 2021 [408] Poland	46 (32–59) n = 178	Spinal cord injury	Polish versions Qualiveen	Internal consistency Test-retest reliability Content validity Criterion validity	The Polish versions of Qualiveen demonstrate acceptable validity and reliability for evaluating the impact of urinary symptoms on incontinence-related quality of life in Poland.
Stievano et al., 2014 [396] Brazil	Con: 40.99±14.85 MS: 41.26±12.24 n = 211	Multiple sclerosis	Brazilian version IIQ-7 and UDI-6	Internal consistency Test-retest reliability Criterion validity	Brazilian versions IIQ-7 and UDI-6 demonstrated good applicability, sensitivity, specificity, and stability among people with multiple sclerosis.

				Responsiveness	
Overactive bladder					
Brown et al., 1999 [393] United States	63.8 ± 11.6 n = 83	Overactive bladder	IIQ UDI	Test-retest reliability Internal consistency Face validity Construct validity Convergent validity Divergent validity	The IIQ and UDI demonstrated good reliability and validity in a diverse population.
Cam et al., 2007 [394] Turkey	47.9 ± 11.0 n = 302	Overactive bladder	SF-IIQ-7. UDI-6	Internal consistency Test-retest reliability	The Turkish versions of IIQ-7 and UDI-6 could be reliable and valid measures for evaluating the impact and severity of symptom severity on quality of life among Turkish women with urinary incontinence.
Castejón et al., 2015 [398] Spain	60.4 (18-90) n = 970	Overactive bladder	IUI	Test-retest reliability Criterion validity Convergent validity Responsiveness	The IUI possesses good measurement properties for valuing the impact and evaluating the urological symptoms of people with idiopathic OAB.
Chattrakulchai et al., 2020 [288] Thailand	Exp: 65.08± 11.68 Con: 55.25 ± 12.76 n = 283	Overactive bladder	Thai version ICIQ-FLUTS	Test-retest reliability Internal consistency Content validity Construct validity Known-group validity	The Thai ICIQ-FLUTS has excellent internal consistency, test-retest reliability, content, and construct validity in evaluating LUTS among Thai women.
Chiu et al., 2013 [417] Taiwan	65.0 ± 11.8 65.0 ± 11.8 n = 346	Overactive bladder	Traditional Chinese version KHQ	Internal consistency Discriminant validity	The traditional Chinese version of KHQ indicated adequate validity and reliability in evaluating symptoms of OAB among the Taiwanese.
Choi et al., 2015 [388] Hong Kong	64.4 ± 11.2 n = 133	Overactive bladder	ICIQ-UI SF	Test-retest reliability	The test-retest reliability of the ICIQ-UI SF measure was better in females than the male gender.
Coyne et al., 2002 [370] United Kingdom	58.5 ± 16.6 n = 990	Overactive bladder	OAB-q	Internal consistency Concurrent validity Discriminant validity	The OAB-q is a valid and reliable measure that discriminates between health and clinically diagnosed incontinence and continent people with OAB.
Coyne et al., 2005 United States [327]	61.0±14.7 n = 865	Overactive bladder	OAB-q	Responsiveness	The tool appears useful with high responsiveness in urinary urgency, frequency, and urge incontinence symptoms.
Coyne et al. 2006 United States [326]	58.7±13.2 58.8±13.8 n1 = 548 n2 = 520	Overactive bladder	OAB-q	Minimally important difference	The tool may provide a sound, minimally important difference and reasonable interpretation of OAB symptoms.
Coyne et al., 2007 [325] United States	Study 1: Continent: 58.8 ± 16.2 Incontinent: 62.5 ± 14.1 ITC: 60.9 ± 13.7 n = 865 Study 2: Continent: 53.8 ± 15.1 Incontinent: 61.0 ± 13.1 ITC: 58.0 ± 12.3 n = 520	Overactive bladder	OAB-q	Responsiveness	The OAB-q is a valid and highly responsive measure of the continent and incontinent people with OAB.

Coyne et al., 2011 United States [312]	59.6±13.6 59.4±13.5 59.9±13.3 n = 516 n = 441 n = 882	Overactive bladder	OAB-q	Internal consistency Discriminant validity Responsiveness	The tool has good reliability, validity, and responsiveness. It has psychometric equivalence to the four-week recall version, and the validation offers an additional option for using the OAB-q for researchers and clinicians.
Coyne et al., 2015 [416] United States	Study 1: 61.0 ± 14.7 n=865 Study 2: 52.1 ± 16.3 n =523 C-OAB: 54.3 ± 16.7 n=228 I-OAB: 60.0 ± 15.1 n=168 Study 3: 66.0 ± 12.9 n=47	Overactive bladder	OAB-q	Internal reliability Convergent validity Discriminant validity Responsiveness	The OAB-q SF indicates good reliability, validity, and responsiveness. It is less time-consuming to complete and evaluate the full spectrum of OAB Symptom Bother and HRQOL impact.
Coyne et al., 2015 [401] United States	Study 1: 48.9±13.0 n=974 Study 2: 58.0±14.0 n=163 Study 3: 66.0±12.9 n=47	Overactive bladder	UQ	Internal consistency Convergent validity Discriminant validity Responsiveness	The results provide quantitative evidence that urinary urgency, as assessed by the UQ, is a pathological sensation distinctive from the usual urge to void and suggest that the UQ might be a reliable, valid, and responsive instrument for evaluating the severity and HRQL impact of urinary urgency in OAB.
Gotoh et al., 2009 [389] Japan	Study 1: 62(53-70) n=122 Study 2: 71(62-76) n=58	Overactive bladder	Japanese version ICIQ-SF	Test-retest reliability Concurrent validity Discriminant validity Responsiveness	The Japanese version of the ICIQ-SF indicates good reliability, validity, and responsiveness in evaluating the urinary quality of life symptoms in people with overactive bladders.
Groenendijk et al., 2019 [400] Netherlands	Exp: 64.0±13.0 Con: 41.0±15.0 n = 103	Overactive bladder	OAB-q SF	Internal consistency Test-retest reliability Content validity Criterion validity Convergent validity	The Dutch OAB-q SF possesses good reliability and validity in evaluating symptom bother and incontinence-related quality of life among people with OAB.
Hashim et al., 2016 [390] United Kingdom	Exp 1: 45.7(19-77) Exp 2: 37.8(18-73) Exp 3: 37.7(17-73) Exp 4: 37.2(16-73) n = 306	Overactive bladder	ICIQUI-SF	Test-retest reliability Internal consistency Content validity Discriminant validity Responsiveness	The Arabic version of the ICIQ-SF demonstrates good reliability, validity, and responsiveness. The psychometric property remains uniform through the validation process and conforms to the UK-English ICIQ-SF.
Homma and Uemura, 2003 [418] Japan	Male: 65.6±11.7 Female: 61.7±11.2 n=293	Overactive bladder	SF-KHQ	Internal consistency Structural validity Responsiveness	The SF-KHQ's psychometric properties and clinical value appear sound for evaluating the incontinence-related quality of life instrument.
Kang, 2015 [410] South Korea	51.1±10.7 n = 176	Overactive bladder	Korean version I-QOL	Internal consistency Construct validity Convergent validity Discriminant validity	The Korean version of the I-QOL questionnaire is valuable in assessing different domains of incontinence-related quality of life among people with urinary incontinence.
Kelleher et al., 1997 [420] United Kingdom	51.4 (17-85) n = 285	Overactive bladder	KHQ	Internal consistency Test-retest reliability Face validity Content validity Criterion validity	The KHQ is a valid and reliable measure for evaluating the quality of life and rapid appraisal among women with urinary incontinence across different clinical settings.
Lubeck et al., 1999 [424] United States	59.6±13.9 n = 257	Overactive bladder	U-IIQ U-UDI	Internal consistency Test-retest reliability Discriminant validity	The U-IIQ and U-UDI are valid, reliable, and responsive measures that evaluate relevant and distinct domains of incontinence-related QOL.

Matza et al., 2005 [334] United States	66.0 66.8 63.8 n = 47 n = 35 n = 12	Overactive bladder	OAB-q	Test-retest reliability	The tools demonstrated reasonable test-retest reliability as outcome measures for OAB treatments.
Margolis et al., 2011 [421] United States	59.0±11.1 n = 24	Overactive bladder	KHQ	Content validity	The KHQ indicated excellent content validity with relevance and appropriateness in evaluating the impact of incontinence-related quality of life among people with overactive bladder.
Monteiro et al., 2020 [391] Brazil	42.46±17.47 n = 118	Overactive bladder	Brazilian Portuguese version ICIQ-OABqol	Internal consistency Test-retest reliability Construct validity	The Brazilian Portuguese version of ICIQ-OABqol demonstrated satisfactory measurement properties in evaluating people with overactive bladder quality of life.
Nusee et al., 2016 [392] Malaysia	55.0±13.5 n = 91	Overactive bladder	UDI-6 IIQ-7	Internal consistency Test-retest reliability Criterion validity	UDI-6 and IIQ-7 demonstrate appropriate test-retest reliability and internal consistency with good application in clinical settings.
Oh et al., 2012 [338] Korea	n = 58	Overactive bladder	Korean version OAB-q	Test-retest reliability Internal consistency Face and content validity Discriminant validity Convergent validity Responsiveness	The tool has an excellent, valid, and reliable measure of outcomes in Korean individuals with OAB.
Okamura et al., 2009 [419] Japan	Men Sample A: 70.0±9.0 Sample B: 67.0±9.0 Women Sample A: 70.0±8.0 Sample B: 68.0±9.0 n = 1002	Overactive bladder	KHQ	Internal consistency Test-retest reliability Convergent validity Discriminant validity Construct validity	The KHQ is a reliable and valid measure for evaluating the incontinence-related quality of life of people with lower urinary tract symptoms.
Otmani et al., 2020 [411] Morocco	57.6±12.7 n = 100	Overactive bladder	Moroccan version I-QOL	Test-retest reliability Inter-rater reliability Discriminant validity Structural validity	The Moroccan version of the I-QOL has acceptable validity and reliability in assessing the symptoms of urinary incontinence on incontinence-related quality of life among Moroccans.
Patrick et al., 1999 [412] United States	Age range: (18-76) n = 259	Overactive bladder	French, Spanish, Swedish, and German versions of I-QOL	Internal consistency Test-retest reliability Discriminant validity	The I-QOL demonstrated good cross-sectional psychometric validity across the four European countries in evaluating the impact of urinary incontinence on incontinence-related quality of life.
Patrick et al., 2013 [414] United States	Age range: (18-76) n = 313	Overactive bladder	I-QOL	Internal consistency Test-retest reliability Convergent validity Discriminant validity Responsiveness	The I-QOL indicated good reliability and validity in evaluating symptoms of overactive bladder on incontinence-related quality of life.
Peterson et al., 2018 [399] Canada	59.0±16.6 n = 1128	Overactive bladder	OAB-v8	Internal consistency Validity	OAB-v8 proved to be highly valid and reliable and could be appropriate for a wide range of overactive bladder conditions.

Possavino et al., 2013 [413] Italy	Continent: 62.2 (9.6) Incontinent: 60.2 (11.3) UI: 63.4 (9.2) Clinically incontinent: 55.9 (10.8) n = 298	Overactive bladder	Italian version I-QOL	Convergent validity Test-retest reliability Internal consistency	The Italian version of the I-QOL demonstrated strong reliability and validity for evaluating symptoms of overactive bladder on incontinence-related quality of life among Italian women.
Pourmomeny et al., 2017 [386] Iran	48.8±5.0 n = 114	Overactive bladder	Persian version BFLUTS	Internal consistency Test-retest reliability Content/face validity Construct validity	The Persian version of the BFLUTS measure indicated good internal consistency test-retest reliability and content validity.
Resee et al., 2003 [422] United Kingdom	60.9±14.2 n = 1284	Overactive bladder	KHQ	Reliability Validity Responsiveness	KHQ demonstrated good reliability and validity in assessing symptoms of overactive bladder on incontinence-related quality of life.
Robinson and Shea, 2002 [395] United States	Phase I: 70 (50.1+18.3) Phase II: 65 (30-90) n = 139	Overactive bladder	UDI IIQ	Internal consistency Content validity Concurrent validity Construct validity	The UDI and IIQ provided good validity and reliability for evaluating the effects of urinary incontinence symptoms on incontinence-related quality of life.
Sahai et al., 2014 [387] United Kingdom	62 (19–101) n=50	Overactive bladder	B-SAQ	Test-retest reliability Discriminant validity	The B-SAQ is a valid measure in evaluating people with overactive bladder.
Schurch et al., 2007 [415] Switzerland	41.2 (20-72) n = 59	Overactive bladder	I-QOL	Internal consistency Convergent validity Concurrent validity Responsiveness	I-QOL demonstrated strong validity, reliability, and responsiveness of incontinence-related quality of life among people with overactive bladder.
Twiss et al., 2009 [397] United States	1st cohort: 59.1±0.9 2nd cohort: 59.8±0.7 3rd cohort: 63.3±1.4 n = 345	Overactive bladder	ISS	Test-retest reliability Internal consistency Concurrent validity	The ISS is reliable and valid for evaluating female urinary incontinence across clinical and research settings.
Uemura and Homma, 2004 [423] Japan	Male: 65.6 ±11.70 Female: 61.7±11.20 n = 293	Overactive bladder	Japanese version KHQ	Internal consistency Convergent validity Discriminant validity Construct validity	The Japanese version of KHQ indicates acceptable reliability and validity for evaluating symptoms of overactive bladder on incontinence-related quality of life.

ICIQ-FLUTS: International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; SF-Qualiveen: Short form Qualiveen; IIQ-7: SF-Incontinence Impact Questionnaire; UDI-6: Urogenital Distress Inventory; IUI: Incontinence Utility Index; KHQ: Kings' Health Questionnaire; OAB-q: The Overactive Bladder Questionnaire; UQ: Urgency Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire- Short Form; OAB-q SF: The overactive bladder quality of life short-form questionnaire; SF-KHQ: short version of the King's Health Questionnaire; ICIQ-UI-SF: Arabic version International Consultation on Incontinence short-form questionnaire; I-QOL: Incontinence Quality of Life Questionnaire; U-IIQ: Urge-Incontinence Impact Questionnaire; U-UDI: Urge-Urinary Distress Inventory; ICIQ-OABqol: International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; UDI-6: Urogenital Distress Inventory; IIQ-7: Incontinence Impact Quality of Life; OAB-V8: Overactive bladder questionnaire; B-SAQ: Bladder Control Self-Assessment Questionnaire; ISS: The Incontinence Symptom Severity Index; PFLUTS: Persian Female Lower Urinary Tract Symptoms instrument

4.4.3 The outcome measures evaluated by the included studies

The 47 included studies tested the psychometric properties of 15 outcome measures evaluating the quality of life of individuals with OAB due to multiple sclerosis (*n* = 2), spinal cord injury (*n* = 1), myelomeningocele (*n* = 1) and other OAB conditions with no specified cause (*n* = 13). Their characteristics are presented in Table 4.2. All outcome measures were self-reported and disease-specific measures that are available free of charge, although some are only free when used for clinical and research purposes. Eight studies had evaluated the Qualiveen [402-409] and King Health Questionnaire (KHQ) [417-423]; seven had evaluated the Overactive Bladder Questionnaire (OAB-q) [312, 324-327, 334, 338, 400, 401]; six had evaluated the Incontinence Quality of Life Questionnaire (I-QOL) [410-415]; five had evaluated the Incontinence Impact Questionnaire (IIQ-7) [392-396, 424] and UDI [392-396, 424]; three had evaluated the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) [388-390]; and one had evaluated the Persian Female Lower Urinary Tract Symptoms (PFLUTS) [386], Bladder Control Self-Assessment Questionnaire (B-SAQ) [387], International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) [288], International Consultation on Incontinence Questionnaire-Overactive Bladder Quality of Life (ICIQ-OABqol) [288, 391], Incontinence Symptom Severity (ISS) [397], Incontinence Utility Index (IUI) [398], Overactive Bladder-Validated 8-question Screener (OAB-V8) [399] and Urgency Questionnaire (UQ) [416].

Among the 47 included studies examining the quality of life of patients with neurogenic OAB, 22 developed or tested the psychometric properties of the original outcome measures [325, 370, 387, 390, 393, 395, 397, 399, 401-403, 414, 416, 420, 422, 424-427], whereas 25 conducted cross-cultural validations of the original outcome measures [288, 386, 388, 389, 391, 392, 394,

396, 398, 400, 404-411, 413, 415, 417-419, 423, 428, 429]. Among the studies performing cross-cultural validations, the outcome measures were assessed in versions adapted to the following languages: Japanese (*n* = 4) [389, 418, 419, 423], Brazilian Portuguese (*n* = 3) [391, 396, 404], Polish (*n* = 2) [408, 409], Persian (*n* = 2) [408, 409], Arabic (*n* = 2) [386, 406], Spanish (*n* = 2) [390, 411], Turkish (*n* = 1) [394], Thai (*n* = 1) [288], Malay (*n* = 1) [392], Korean (*n* = 1) [410], Romansh (*n* = 1) [383], Italian (*n* = 1) [413], Belgian (*n* = 1) [383], French (*n* = 1) [412], German (*n* = 1) [412], Chinese (*n* = 1) [417], Chinese-Taiwanese (*n* = 1) [417], Chinese-Cantonese (*n* = 1) [388], Greek (*n* = 1) [405] and Russian (*n* = 1) [407].

Table 4.2: Description of the identified outcome measures

Outcome measures Number of studies Reference	Language of instruction Number of items Description of the item Scoring scheme	Duration to complete Cost of the OM: Free/licensed/ need to purchase	Strengths and limitations of the Outcome measures Population tested
PFLUTS [386]	**Language of instruction:** Persian **Number of items:** 12 Items **Description of the items:** A measure is a self-administered tool with two sections in clinical and research settings. The first section concerns symptoms and is evaluated using a 5-point Likert scale (0=never; 4=always) with three domains: Filling symptoms (four items, 0 to 15); voiding symptoms (three items, 0 to 12), and incontinence symptoms (five items, 0 to 20). The second section evaluates the extent of hurts and bothers. **Scoring Scheme:** Higher scores denote worse symptoms	**Duration to complete:** average of 5.33 minutes **Cost of the OM:** Available free online	**Strengths:** Brief and helpful questionnaire, easy-to-use items, and facilitates communication between medical practitioners and people with Urinary incontinence due to multiple sclerosis. **Limitations:** Educational level disparity could affect the generalisation of their counterparts. **Population tested:** Females with overactive bladder.
B-SAQ [387]	**Language of instruction:** English **Number of items:** 8-items **Description of the items:** Four-point Likert scales were developed by a European expert panel through a standardised multistep method, such as expert panel discussion, questionnaire piloting, focused group discussions, and direct patient involvement. The questions are simple to understand, select, and modify through piloting. If the symptom score is ≥4 and the bother score is greater than 1, the patient is recommended to seek medical attention. **Scoring scheme:** The severity of symptoms and bother are graded as none (zero), mild (1 to 3), moderate (4 to 6), severe (7 to 9), and very severe (10 to 12). Higher scores denote worse symptoms.	**Duration to complete:** in less than 5 minutes. **Cost of the OM:** Available free online	**Strengths:** The closed format of the measure design enabled a subjective and qualitative evaluation of lower urinary tract symptoms. **Limitations:** some of the items could be irrelevant and confusing. **Population tested:** Males and females with lower urinary tract symptoms.
ICIQ-FLUTS [288]	**Language of instruction:** Thai **Number of items:** 12-item 5-point Likert scale (0-4). **Description of the items:** ICIQ-FLUTS measures the females' symptoms of LUTS and associated bother symptoms. Self-completed by people with OAB **Scoring scheme**: 0 to 16 filling, 0 to 12 voidings, and 0 to 20 incontinence symptoms subscales. The lower the score, the better the symptoms.	**Duration to complete:** 3 to 5 minutes **Cost of the OM:** Available free online	**Strengths: the** rigorous process of validation (cultural and translation). **Limitations:** Questions were not designed to detect changes in OAB status. **Population tested:** females with OAB.
ICIQ-UI-SF [388-390]	**Language of instruction:** Japanese, Arabic. **Number of items:** four-item **Description of the items:** a disease-specific measure that evaluates QOL and symptoms with urinary incontinence. It consists of four questions: 1. frequency (0 to 5), 2. amount of leakage (0 to 6), 3, QOL (0 to 10), and 4. perceived cause of leakage. Likert scale is used to grade the first three questions, ranging with maximum scores possible of 5, 6, and 10, respectively. In the final question, the people with urinary incontinence were evaluated on the circumstances under which urinary leakage results. **Scoring scheme:** The total score was derived from the summation of the scores of the first three questions (range: 0 to 21). Higher scores denote worse symptoms.	**Duration to complete:** less than five minutes **Cost of the OM:** Available free online for clinical use. Permission is required for research purposes.	**Strengths:** sound psychometric properties (reliability, validity, and responsiveness) throughout the adaptation process. **Limitations:** cultural diversity is not sufficient **Population tested:** men and women with urinary incontinence.
ICIQ-OABqol [391]	**Language of instruction:** Brazilian **Number of items:** 28 items	**Duration to complete:** 10-15 minutes.	**Strengths:** brief and psychometrically robust self-administered measure for assessing the

	Description of the items: The measure is a self-administered measure with a grade A recommendation due to its psychometric robustness in investigating the QOL of people with symptoms of overactive bladder. It has four domains consisting of 28 questions: sleep, concern, social interaction, and symptoms coping. **Scoring scheme:** Six alternative answers were available for the first 27 questions (none of the time: one; a little of the time: two; some of the time: three; a good bit of the time: four; most of the time: five; all of the time: six), while question 28 evaluated the effect of urinary symptoms on the individual's daily activities, grading it on a scale of zero (no effect) to 10 (severe effect).	**Cost of the OM:** Available free online for clinical use. Permission is required for research purposes.	incontinence-related QOL of people with symptoms of overactive bladder in both sexes in clinical and research settings. **Limitations**: lack of homogeneity of the studied population **Population tested:** Males and females with overactive bladder
IIQ [392-396, 424]	**Language of instruction:** English, Brazilian, Turkish, Malay **Number of items:** 7 items **Description of the items:** consists of 7 items, which are subdivided into four domains: relationships, emotional health, travel, and physical activity. The Likert scale of each measure item ranges from slight to moderate and moderate to great. **Scoring Scheme:** Higher scores indicate the reduced incontinence-related QOL and severity of symptoms.	**Duration to complete:** 5 minutes **Cost of the OM:** Administrative fees are required to use the measure.	**Strengths:** The measure is predictive for urodynamic diagnosis **Limitations:** Low response rate of the respondents. **Population tested:** men and women with urinary incontinence.
ISS [397]	**Language of instruction:** Spanish **Number of items:** 8 items **Description of the items:** This is a self-administered measure on a four-point Likert scale (0 to 3) for evaluating eight domains: incomplete emptying, the sensation of urgency, nocturia, daytime urinary frequency, stress incontinence, urge incontinence, leakage with activity, and pad use. **Scoring scheme:** Each item score is evaluated as an independent domain without score summation.	**Duration to complete:** 5 minutes **Cost of the OM:** Available free online	**Strengths:** a useful measure for evaluating female voiding symptoms severity and incontinence in clinical and research settings. **Limitations:** Lack of focus group discussion or consensus expert opinion in the tool development. **Population tested:** Females with urinary incontinence.
IUI [398]	**Language of instruction:** Spanish **Number of items:** 5 items **Description of the items:** 5 items with three different levels from each of the items of the attribute. **Scoring Scheme:** Higher scores indicate the reduced incontinence-related QOL and severity of symptoms.	**Duration to complete**: less than 5 minutes **Cost of the OM:** Available free online	**Strengths:** Derived from I-QOL and neurogenic modules **Limitations:** Anchoring of the measure was anticipated **Population tested:** men and women with overactive bladder
I-QOL [410-415]	**Language of instruction:** Korean, Moroccan, Romansh, English, Italian, Belgium, French, Spanish, Swedish, and German **Number of items:** 22 items **Description of the items:** The measure evaluates the QOL of people with urinary incontinence and consists of 22 items on a 5-point Likert scale from 1 (extreme) to 5 (not at all). The items are divided into three domains: avoidance and limiting behaviour, psychosocial impact, and social embarrassment. **Scoring Scheme:** A total score is obtained by summing the individual scores of all items (0–100). Higher scores indicate better urinary incontinence-related QOL.	**Duration to complete:** 5 minutes **Cost of the OM:** It is copyrighted and can be purchased for $500 for commercial purposes. It is freely available for clinical and academic purposes.	**Strengths:** The measure evaluates the broader impact of urinary incontinence on incontinence-related QOL. **Limitations:** Content validity is not well assessed. **Population tested:** males and females with urinary incontinence.
KHQ [417-423]	**Language of instruction:** English, Chinese, Japanese **Number of items:** 21 items **Description of the items:** This is a disease-specific self-administered measure of the incontinence-related QOL of people with urinary incontinence. Twenty-one items are subdivided into eight domains: urinary symptom severity, role limitations, physical functioning, social functioning, emotional problems, personal relationships, sleep disturbance, and general health.	**Duration to complete:** 5 minutes **Cost of the OM:** Available free online	**Strengths:** responsive to clinically meaningful changes. **Limitations:** Limited generalisability due to racial homogeneity. **Population tested:** men and women with overactive bladder.

	Scoring scheme: scored on a 4-point Likert scale ranging from 0 (best) to 100 (worst).		
OAB-V8 [399]	**Language of instruction:** English **Number of items:** 8-items with a six-point Likert scale (0 to 5) **Description of the items:** The tool is a self-administered questionnaire that evaluates the degree of OAB burden, bother symptoms and severity. **Scoring scheme**: ranging from 0 (absence of symptoms) to 40 (Maximal symptoms). 0 to 8 = low; 8 to 16 = medium; 16 to 24 = high. Higher scores indicate worse symptoms.	**Duration to complete:** 4 to 5 minutes **Cost of the OM:** No charge for academic and clinical use.	**Strengths:** -Brief and useful tool for OAB burden and severity evaluation. **Limitations:** re-retest reliability could not be investigated because the participants received intervention in the study. **Population tested:** women with OAB.
OAB-q [312, 324-327, 334, 338, 400, 401]	**Language of instruction:** English **Number of items:** 33-item six-point Likert scale (0 to 5) **Description of the items:** The tool is composed of an 8-item symptom Bother scale and 25-item HRQOL that comprises the coping, concern, sleep, and social interaction scales **Scoring scheme**: total score ranged from 0 to 100, with higher scores signifying worse symptoms	**Duration to complete:** 5 to 7 minutes **Cost of the OM:** No charge for academic and clinical use	**Strengths:** -simple and easy for application to capture both continent and incontinent people with OAB. **Limitations:** 8-item symptom Bother scale and 25-item health related quality of life **Population tested:** Males and females with OAB
Qualiveen [402-409]	**Language of instruction:** English, Brazilian Portuguese, Greek, Persian, Russian, Polish, Slavic **Number of items: 30 items** **Description of the items:** The original Qualiveen has 30 items focusing on four aspects of patients' daily lives: 9 items with limitations, eight items- with frequency of limitations, eight items with fears, and five items- with feelings. **Scoring scheme:** scored on a 5-point Likert-type scale with zero (0) indicating absence of urinary symptoms impact HRQOL while four (4) indicate high urinary symptoms impact HRQOL.	**Duration to complete:** 5 minutes **Cost of the OM:** No charge for academic and clinical use	**Strengths:** Patients evaluated in this measure represent a highly selected cohort. **Limitations:** floor and ceiling effect not observed. **Population tested:** men and women with overactive bladder.
UDI [392-396, 424]	**Language of instruction:** Brazilian, Turkish, English **Number of items:** 6 items **Description of the items:** It is a six-item measure subdivided into three subscales: stress, discomfort/obstructive, and irritative symptoms. **Scoring scheme:** the items of the measure are scored from zero to four, with higher scores signifying the worst symptoms.	**Duration to complete:** less than 5 minutes **Cost of the OM:** Available free online	**Strengths:** responsive to clinically meaningful changes **Limitations:** Low response rate of the respondents. **Population tested:** men and women with urinary incontinence.
UQ [416]	**Language of instruction:** English **Number of items:** 15-point Likert scale items **Description of the items:** The measure consists of a 15-point Likert scale of items measured into five responses from ‘’never’’ to ‘’all the time’’, which is subdivided into four domains: impact on daily activities, nocturia, time to control urgency, and fear of incontinence. **Scoring Scheme:** Higher scores signify the worst symptoms.	**Duration to complete:** 5 minutes **Cost of the OM:** Available free online	**Strengths:** it provides a quantitative, clear perceptual discrepancy between urge and urgency. **Limitations:** cultural diversity lacks **Population tested:** Men and women with overactive bladder.

ICIQ-FLUTS: International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; SF-Qualiveen: Short form Qualiveen; IIQ-7: SF-Incontinence Impact Questionnaire; UDI-6: Urogenital Distress Inventory; IUI: Incontinence Utility Index; KHQ: Kings' Health Questionnaire; OAB-q: The Overactive Bladder Questionnaire; UQ: Urgency Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire- Short Form; OAB-q SF: The overactive bladder quality of life short-form questionnaire; SF-KHQ: short version of the King's Health Questionnaire; ICIQ-UI-SF: Arabic version International Consultation on Incontinence short-form questionnaire; I-QOL: Incontinence Quality of Life Questionnaire; U-IIQ: Urge-Incontinence Impact Questionnaire; U-UDI: Urge-Urinary Distress Inventory; ICIQ-OABqol: International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; UDI-6: Urogenital Distress Inventory; IIQ-7: Incontinence Impact Quality of Life; OAB-V8: Overactive bladder questionnaire; B-SAQ: Bladder Control Self-Assessment Questionnaire; ISS: The Incontinence Symptom Severity Index; PFLUTS: Persian Female Lower Urinary Tract Symptoms instrument

4.4.4 The psychometric properties of the outcome measures assessed in the included studies

A complete list of the psychometric properties investigated for the outcome measures identified in the included studies is provided in Table 4.3. Reliability and validity were the most investigated psychometric properties, whereas responsiveness was the least frequently evaluated. Most included studies (70%) reported acceptable internal consistency, with Cronbach's alpha above 0.70, and 64% reported test-retest reliability using ICCs (0.50–0.75). Cronbach's alpha ranged from 0.79 to 0.99 across six studies (average = 0.92) for the I-QOL, from 0.63 to 0.95 across seven studies (average = 0.81) for the KHQ, from 0.70 to 0.96 across three studies (average = 0.86) for the OAB-q, and from 0.70 to 0.95 across seven studies (average = 0.84) for the Qualiveen questionnaire. A Cronbach's alpha below 0.5 represents unacceptable consistency, from 0.5 to 0.6 indicates poor consistency, from 0.6 to 0.7 indicates questionable consistency, from 0.7 to 0.8 indicates acceptable consistency, from 0.8 to 0.9 indicates good consistency, and greater than 0.9 indicates excellent consistency [430].

The ICCs for test-retest reliability ranged from 0.81 to 0.99 across four studies (average = 0.92) for the I-QOL, from 0.80 to 0.96 across one study (average = 0.88) for the KHQ, from 0.55 to 92 across four studies (average = 0.78) for the OAB-q, and from 0.62 to 0.97 across six studies (average= 0.85) for the Qualiveen questionnaire. ICCs below 0.5 represent poor reliability, from 0.5 to 0.75 indicate moderate reliability, from 0.75 to 0.9 indicate good reliability, and above 0.9 represent excellent reliability [431].

Criterion, discriminant, and convergent validities were the most commonly assessed validity measures for the I-QOL, KHQ, Qualiveen questionnaire, and OAB-q. Strong correlations were observed among the I-QOL, KHQ, Qualiveen questionnaire, OAB-q, International Consultation on Incontinence Questionnaire-Short Form (ICIQ-UI-SF), and 36-Item Short Form Health Survey (SF-36), with spearman's correlation coefficients ranging from 0.68 to 0.88 between I-QOL domains and the other outcome measures and from 0.762 to 0.78 between KHQ domains and the other outcome measures. Responsiveness was strong for individual domains and the total scores of nine identified outcome measures: ICI-UI-SF, IIQ, UDI, IUI, I-QOL, KHQ, OAB-Q, Qualiveen and UQ.

Table 4.3: Psychometric properties of the identified outcome measures

Outcome measures Number of studies Reference	Reliability	Validity	Responsiveness
PFLUTS [386]	**Internal consistency:** First and second sections Cronbach's alpha scores: Good (0.83 and 0.89). Incontinence, voiding and filling subscales Cronbach's scores were Debatable, acceptable and Good (0.87, 0.67, and 0.70, respectively) [386]. **Test-retest reliability:** ICC: Good (0.77) [386]	**Face/Content validity:** All the items were clear [386]. **Criterion validity:** OAB and the Persian FLUTS measures' correlation coefficient was 0.77 ($r = 0.77$, $p < 0.001$) [386].	None
B-SAQ [387]	None	**Criterion validity:** 0.86 to 0.89 for the frequency, urgency, nocturia, urge incontinence[387] is the agreement between the KHQ and the B-SAQ. **Discriminant validity:** AUC 0.85 vs 0.68 for the B-SAQ and OAB-v8 [387].	None
ICIQ-FLUTS [288]	**Internal consistency:** Cronbach's alpha coefficient score: Good (0.849) (95% CI, 0.819-0.864). The Cronbach's alpha scores for each subscale (Filling, voiding and incontinence symptoms): Debatable to acceptable (0.646, 0.709, and 0.792, respectively) [288]. **Test-retest reliability:** >0.75. The subscales' (filling, voiding and incontinence) test-retest correlation coefficients: Good and Excellent (0.925, 0.769 and 0.921, respectively) [288].	**Face/Content validity:** All the items were clear [288]. **Known-group validity:** Statistical differences in the comparison scores were observed among clinical and community women in the filling, voiding, and incontinence subscales ($p<0.001$) [288].	None
ICIQ-UI-SF [388-390]	**Test-retest reliability**: moderate correlation using Kappa statistics (0.66 and 0.67 for items on coughing/sneezing and physically active/exercising, respectively).[388] Kappa scores: High correlation (0.61 and 0.62 and ICC values: 0.90 and 0.91) [389] and Kappa values: 0.83-0.91 ($P<0.0001$) [390]. **Internal consistency:** Cronbach's alpha scores: Acceptable (0.71 [390] and 0.78 [389]).	**Content validity: The** measure covers all the important domains and is well-interpreted [390]. **Concurrent validity:** moderate to high correlation with KHQ subscales was observed (0.74: severity measures; 0.68: physical limitation; 0.59: social limitations; and 0.55: emotions; $p<0.05$) [389]. **Discriminant validity:** a statistically significant difference was observed between males and females among different types of incontinence ($X^2=35.4$; $P<0.0001$) [390].	**Responsiveness:** ICIQ-UI-SF changes were statistically significant (greater than 0.5) with the KHQ subscales [389]. The proportion of patients' symptoms was reported to decrease correlation significantly on all three items ($P<0.0001$ for all the items) [390].
ICIQ-OABqol [391]	**Internal consistency:** Cronbach's alpha coefficient: Good (0.88 [391]). **Test-retest reliability:** ICC: Excellent (0.906-0.933 ($P<0.05$) [391]).	**Construct validity:** Confirmatory factor analysis and Kaiser-Mayer-Olkin test: adequate data adjustment of the domains [391]. **Criterion validity:** The ICIQ-OABqol measure correlated with ICIQ-OAB with r-values (0.53 and 0.59) [391].	None
IIQ [392-396, 424]	**Internal consistency:** Cronbach's alpha score: Acceptable, good and excellent (0.90 [392]; 0.95 [395]; 0.87 [392, 394]; 0.95 [395]; 0.87 [394]; 0.70 [394, 396]; 0.70 [396]). **Test-retest reliability:** ICC: Excellent (0.95 [392]; 0.85 [393] Spearman's rho: 0.99 [394]; Pearson's correlation coefficient: 0.9431 [394, 396]; Pearson's correlation coefficient: 0.9431 [396]; Pearson's correlation coefficient: 0.9431 [396]).	**Content validity:** Percentage agreement scores of the three rounds of testing ranged from 67% to 100% for item fit while 100% for item clarity [395]. **Criterion validity:** A positive correlation was observed between nocturia and emotional subscales and physical activity [392]. **Concurrent validity**: The disattenuated correlation was 0.64, while Pearson's correlation coefficient between MUDI and MUSIQ was 0.95 ($P<0.001$) [395]. **Construct validity:** The mean measure scores varied urine leakage, desire for socialisation, and depression [395].	**Responsiveness**: significant changes were observed ($p<0.0001$) for the IIQ-7 for the control and MS group with and without urinary incontinence [396].

		Convergent validity: moderate correlation (0.50-0.80) was observed within the domains: travel, feelings, physical activities, and relationships.[393] **Divergent validity:** A weak correlation (≤0.10) was seen in the domain of sexual function [393]. No significant correlation with the sexual dysfunction domains of disability status expanded scale scores [396].	
ISS [397]	**Test-retest reliability**: Statistically significant correlation was observed using Spearman's correlation coefficients for all the eight items (p<0.0001) [397]. **Internal consistency:** Cronbach's alpha coefficient scores: Debatable (0.69 [397]).	**Concurrent validity:** Statistically significant correlations were observed between similar items of the ISS and both PFDI and UDI, respectively (p<0.0001) [397].	None
IUI [398]	**Test-retest reliability:** ICC: Excellent (0.900) (CI 95% 0.886-0.912) and Excellent (0.944) (CI 95%: 0.936-0.950) for the base and week 12 of the abbreviated version and original version of the I-QOL (p<0.001) [398].	**Convergent validity:** Rasch analysis reveals statistically relevant differential items among the domains functioning of the urinary symptoms' aetiology (neurogenic vs idiopathic) [398]. **Criterion validity:** after 12 weeks of interventions, a statistically significant difference was observed for the IUI scores across perceived levels, I-QOL scores, and abbreviated health state descriptive system (p<0.001) [398].	**Responsiveness:** large differences were observed in the utility values between IUI, KHQ and SF-12 (p<0.001) using the Bland-Altman methods [398].
I-QOL [410-415]	**Internal consistency:** The Cronbach's alpha coefficient scores: Acceptable, Good and Excellent (0.96 [410]; 0.99 [411]; 0.92-0.95 [412]; 0.86 [414]; 0.88-0.96 [413]; 0.79-0.93 [413, 415]; 0.79-0.93 [415]; 0.79-0.93 [415]). **Test-retest reliability**: ICC: Good and excellent (0.99 [411]; 0.87-0.93 [412]; 0.81 [414]; 0.99 [413]).	**Convergent validity:** the items were strongly correlated with the original subscale: avoidance and limiting behaviour (r: 0.71-0.80), social embarrassment (r: 0.76-0.86) and psychosocial impacts (r:0.67-0.88) [410]. A strong correlation was observed between the I-QOL total scores and KHQ symptom score[414]. Moderate to strong correlations were observed between the I-QOL subscales items and most SF-36 domains [413, 415]Moderate to strong correlations were observed between the I-QOL subscales items and most SF-36 domains [413, 415]Moderate to strong correlations were observed between the I-QOL subscales items and most SF-36 domains [413, 415]. **Discriminant validity**: Low correlation of items to other subscales other than their own subscales was observed [410, 414]. The measure differentiates between different self-reported severity levels with significant differences in the I-QOL scores by incontinence-related medical visits number (p<0.0001) [411-413]The measure differentiates between different self-reported severity levels with significant differences in the I-QOL scores by incontinence-related medical visits number (p<0.0001) [411-413]The measure differentiates between different self-reported severity levels with significant differences in the I-QOL scores by incontinence-related medical visits number (p<0.0001) [411-413]. **Construct validity:** all the items of the measure accounted for 54.85% (total variance) loaded into 0.51-0.88 [410]. The comparative fit index and standardised root mean square residual were satisfying, while the indices Tucker-Lewis index and root mean square error of approximation were not [411].	**Responsiveness:** The cumulative distribution function indicates differentiation between intervention groups[414]. Responsiveness was observed to be strong for individual domains and total scores [415]Responsiveness was observed to be strong for individual domains and total scores [415]Responsiveness was observed to be strong for individual domains and total scores [415].
KHQ [417-423]	**Internal consistency:** Cronbach's alpha coefficient scores: Acceptable, Good and Excellent (0.948 [417]; 0.83-0.86 [418]; 0.725-0.892 [420]; 0.721-0.898 and 0.780-0.915 in men and women respectively[419]; 0.70-091 [422]; 0.63 [423]).	**Content validity:** acceptable and understandable [421]. **Discriminant validity:** significantly higher scores were observed on all KHQ subscores in comparison with the control group (p<0.0001) [417].	**Responsiveness:** a statistically significant change in the clinical efficacy variables and self-perception of bladder condition across all domains [418].

	Test-retest reliability: ICC: Good and Excellent (0.80-0.96 [420]).	**Structural validity**: using exploratory factor analysis (promax rotation), two factors limitation of daily activities, social and travel, tired and depressed [418]. **Criterion validity:** highly significant correlations were observed between the common domains of the KHQ and the SF-36 [420, 422]. **Convergent validity:** high correlation coefficients (0.762-0.784 and 0.722-0.752 in men and women, respectively) [419] (0.65-0.75 in males and 0.61-69 in females) [423] were observed in the physical limitations, social limitations and role limitations. **Divergent validity:** low correlation coefficients 0.333 (LUT impact), 0.476 (role limitations) and 0.464 (sleep/energy) in men and 0.493 (LUTS impact) and 0.533 (emotions) in women [419] and 0.32 (coping severity), 0.29 (symptom severity scale) in males and 0.27 (symptom severity scale), 0.28 (role limitation) and 0.29 (coping severity scale) [423] were observed in the personal relationships with other domains.	
OAB-V8 [399]	**Internal consistency:** Cronbach's alpha coefficient scores: Good and Excellent (0.891-0.910 [399]) **Test-retest reliability:** ICC: Excellent (0.93 through local item dependence [399]).	**Discriminant validity:** indicates good item-level characteristics and is not sensitive to missing data estimates [399].	None
OAB-q [312, 324-327, 334, 338, 400, 401]	**Internal consistency:** Cronbach's alpha scores: Acceptable, Good and Excellent (0.70-0.95 [400]). The Cronbach's α test is quite good, with scores greater than 0.85 across all items for all subscales [326]: Good and Excellent (0.89 to 0.96 [324]), while an excellent Cronbach's alpha coefficient: Good (>0.82) was also reported [338]. **Test-retest reliability:** ICC: Moderate (>0.7[400]); Good (0.81-0.92 [401]). Spearman's correlation coefficient: Good (0.83-0.93 (p<0.001) [401]. Each item and the subscale scores have good test-retest reliability with reproducible results [338]. OAB-q subscales and SF ICC scores: Poor and Acceptable (0.55 to 0.77 (P<0.001) [338]. item range Debatable, acceptable and Good (0.69–0.89); total scale, Good (0.88) [338]. There is a strong correlation in the OAB-q scores (visits 1 and 2). ICCs scores: 0.83 to 0.95; Spearman's correlations: Good (0.80 to 0.94 (p<0.001) [334].	**Content validity:** clear, understandable and easy to complete [400]. **Criterion validity**: a moderate to strong correlation was observed between the measure symptom bother and HRQOL with the UDI-6 and ICIQ-Q [400]. Statistically significant correlations were observed between OAB-q SF items and CES-D, SF-36 domains [401]. **Construct validity:** The control group possesses higher OAB-q SF HRQOL and lower OAB-q SF symptom bother scores than the patient group [401]. **Concurrent validity**: a moderate correlation was observed at baseline, while at week 12, it is moderate to strong. The strongest correlation was reported in the symptoms of bother, coping, concern and HRQOL [326]. There was a moderate correlation between OAB-q and SF-36 subscales (0.16 to 0.52) [324]. **Discriminant validity**: PPUS was used to evaluate the discriminant validity. Significant differences were observed in the mean OAB-q scores and PPUS responses[326] with p < 0:0001 for the OAB-q subscales among continent and incontinent patients[324]. Significant differences were observed in the OAB-q and OAB-q SF subscales p<0.001 [338]. **Convergent validity:** High correlation coefficients p<0.05 [338]	**Responsiveness:** consistently, the greatest OAB-q change scores were observed for the incontinent at baseline and continent at week 12 [325]. Both the HRQOL scales and symptom bother are differentiated between control, C-OAB and I-OAB patients (p<0.0001) [401]. Moderate to large effect sizes were observed in multiple assessments with responsive changes (Study 1: 0.73–1.53; Study 2: 0.44–1.17; Study 3:0.55– 1.31) [326]. Another study also observed significant responsive change in the OAB-q (P<0.001) with the exception of social domain and OAB-q SF [338]. Significant differences were observed in all the KHQ scores (except personal relationships scores) p<0.05 [338] and between the OAB-q change scores and bladder diary (micturition frequency) changes from baseline to week 12 p < 0.001 (0.13 to 0.35) with small to moderate change in magnitude [326, 327].
Qualiveen [402-409]	**Internal consistency:** Cronbach's alpha scores: Acceptable (0.75-0.90[404]); Acceptable (0.70 [405]); Good (0.88 [402]); Excellent (0.95 [406]); Excellent (0.90 [407]); Good (0.86 and 0.85) [408]; Good (>0.80 [409]). **Test-retest reliability:** ICC: Excellent (0.93 [403]); Moderate and Good (0.62-0.86 [404]); Excellent (0.97 [406]); Good (0.81-0.89 [407]); Good (>0.80 [409]); Good (>0.80 [408]).	**Content validity:** clear, understandable and easy to complete [409]. **Criterion validity**: A high ICC was observed between the Qualiveen original version and the SF-Qualiveen (r: 0.70-0.92).[403] A significant correlation was observed between the majority of the Qualiveen scores and ICIQ-SF domains [404]. The correlation was observed with relevant domains of the KHQ [405]. There is a high correlation between the SF-Qualiveen with the NBSS [407]. Positive correlation was noted in the Qualiveen/SF-Qualiveen and ICIQ-SF total scores (Qualiveen: r = 0.693 and p<0.001; SF-Qualiveen: r = 0.611 and p<0.001) [408]. Linear	**Responsiveness:** Similar standardised response mean were consistently observed for the short and long versions of the Qualiveen [403].

		correlation was noted in the Qualiveen/SF-Qualiveen and ICIQ-SF total scores (Qualiveen: r = 0.565 and p<0.001; SF-Qualiveen: r = 0.524 and p<0.001) [409]. **Construct validity:** there is less correlation between the symptom type and incontinence severity of the SF-Qualiveen and the original version [403]. The Qualiveen fitted the Rasch analysis model and was unidimensional [402]. **Convergent validity:** positive correlations were observed between Qualiveen and ICIQ-UI SF (0.57) and SF-12 [406]. **Discriminant validity:** significantly improved incontinent-related QOL was observed among patients with higher education and income [406].	
UDI [392-396, 424]	**Internal consistency:** Cronbach's alpha scores: Acceptable (0.73 [392]); Good (0.89 [395]); Acceptable (0.74 [392, 394]); Good (0.89 [395]); Acceptable (0.74 [394]); Acceptable (0.70 [393]). **Test-retest reliability:** ICC: Good (0.85 [392]); 0.59 [393];. Spearman's rho: Excellent (0.99[394]); Pearson's correlation coefficient: Excellent (0.933 [394, 396]).	**Content validity:** Percentage agreement score of the three rounds ranged from 79% to 100% for item fit while 89% to 100% for item clarity [395]. **Criterion validity**: a good connection was observed between daytime voiding incidence and nocturia and irritable and obstructive symptoms [392]. **Concurrent validity**: The disattenuated correlation was 0.64, while Pearson's correlation coefficient between MUDI and MUSIQ was 0.95 (P<0.001) [395]. **Construct validity:** The measure mean scores varied for mobility, urine leakage, desire for socialisation, diabetes mellitus and prostate enlargement [395]. **Divergent validity:** negative correlation in the urge symptoms of the QOL [393]. No significant correlation with the sexual dysfunction domains of disability status expanded scale scores[393, 396].	**Responsiveness**: significant changes were observed (p<0.0001) for the control and MS group with and without urinary incontinence [396].
UQ [416]	**Internal consistency:** Cronbach's alpha score: Acceptable, Good and Excellent (0.79-0.94 [416]). **Test-retest reliability:** ICC: Good and Excellent (0.80-0.94 [325]) and Spearman's correlations: Moderate, Good and Excellent (0.69-0.92 (p<0.001) [325]).	**Convergent validity:** statistically significant correlations were observed between the micturition diary variables and VAS with the UQ item scores [416]. **Discriminant validity:** discrimination between the symptom severity levels of subscale and VAS scores of the UQ [416].	**Responsiveness**: All the UQ subscale and VAS scores were sensitive to change [416].

ICIQ-FLUTS: International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; SF-Qualiveen: Short form Qualiveen; SF-IIQ-7: Short Form-Incontinence Impact Questionnaire; UDI-6: Urogenital Distress Inventory; IUI: Incontinence Utility Index; KHQ: Kings' Health Questionnaire; OAB-q: The Overactive Bladder Questionnaire; UQ: Urgency Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire- Short Form; OAB-q SF: The overactive bladder quality of life short-form questionnaire; SF-KHQ: short version of the King's Health Questionnaire; Arabic version International Consultation on Incontinence short-form questionnaire; I-QOL: Incontinence-quality of life; U-IIQ: Urge-Incontinence Impact Questionnaire; U-UDI: Urge-Urinary Distress Inventory; ICIQ-OABqol: International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; UDI-6: Urogenital Distress Inventory; IIQ-7: Incontinence Impact Quality of Life; OAB-V8: Overactive bladder questionnaire:; B-SAQ-Bladder Control Self-Assessment Questionnaire; ISS: The Incontinence Symptom Severity Index; PFLUTS: Persian Female Lower Urinary Tract Symptoms instrument; MUDI: Male Urinary Distress Inventory: MUSIQ: Male Urinary Symptom Impact Questionnaire; VAS: Visual Analogue Scale; PFDI: Pelvic Floor Distress Inventory

4.4.5 COSMIN-based methodological quality of the included studies

Six studies reported the psychometric properties of the I-QOL [410-415]. Among individuals with OAB, the I-QOL has been evaluated for internal consistency [410-415], test-retest reliability [412-414], convergent validity [410, 413-415], discriminant validity [410-412, 414], structural validity [410, 411] and responsiveness [414, 415]. The I-QOL was reported to have very good internal consistency in six studies [410-415] and very good test-retest reliability in three studies [410-415]. The I-QOL was also reported to have very good convergent [410, 413-415] and discriminant [412, 414] validity, with two studies [410, 411] reporting only adequate discriminant validity.

Seven studies evaluated the psychometric properties of the KHQ [417-423], including internal consistency [417-420, 422, 423], test-retest reliability [420], convergent validity [419, 422, 423], discriminant validity [417, 419, 422, 423], structural validity [418] and responsiveness [418, 422]. The KHQ was reported to have very good internal consistency in five studies [417-420, 422, 423], with only one study reporting adequate test-retest reliability [420].

Nine studies evaluated the psychometric properties of the OAB-q [312, 324-327, 334, 338, 400, 401], including internal consistency [312, 324, 338, 400, 401], test-retest reliability [312, 325-327, 334, 338, 400, 401], content validity [338, 400], convergent validity [338, 400, 401], discriminant validity [312, 324, 338, 401], concurrent validity [312, 324] and responsiveness [312, 325-327, 338, 401]. The OAB-q was reported to have very good internal consistency in five studies [312, 324, 338, 400, 401] and adequate test-retest reliability in eight studies [312, 325-327, 334, 338, 400, 401].

Eight studies evaluated the psychometric properties of the Qualiveen questionnaire [402-409], including internal consistency [403-409], test-retest reliability [404-409], structural validity [402, 405], content validity [408, 409], criterion validity [403-405, 407-409], convergent validity [403, 406], discriminant validity [406] and responsiveness [403]. The Qualiveen questionnaire was reported to have very good internal consistency in five studies [404, 406-409] and very good test-retest reliability in two studies [404, 409]. Table 4.4 details the COSMIN findings for each outcome measure assessed in the included studies.

Table 4.4: COSMIN findings of the identified outcome measures

Outcome Measures Number of studies Reference	Reliability		Validity							Responsiveness
	Internal consistency	Test-retest reliability	Structural validity	Content validity	Criterion validity	Convergent validity	Concurrent validity	Discriminant validity	Known-group validity	
PFLUTS [386]	Very good [386]	Very good [386]	-	Adequate [386]	Very good [386]	-	-	-	-	-
B-SAQ [387]	-	-	-	Very good [387]	-	-	-	Adequate [387]	-	-
ICIQ-FLUTS [288]	Very good [288]	Adequate [288]	-	Doubtful [288]	-	-	-	-	Adequate [288]	-
ICIQ-UI-SF [388-390]	Very good [390]	Very good [388-390]	-	Very good [390]	-	-	Very good [389]	Very good [390]	-	Very good [389, 390]
ICIQ-OABqol [391]	Very good [391]	Adequate [391]	-		Very good [391]	-		-	-	Very good [391]
IIQ [392-396, 424]	Very good [392-394] Doubtful [395, 396]	Adequate [392-394, 396]	-	Adequate [393, 395]	Very good [392, 395, 396]	Very good [393]	-	Very good [393]	-	Very good [395, 396]
ISS [397]	Very good [397]	Adequate [397]	-	-	-	-	Very good [397]	-	-	-
IUI [398]	-	Adequate [398]	-	-	Very good [398]	Adequate [398]	-	-	-	Very good [398]
I-QOL [410-415]	Very good [410-415]	Very good [412-414] Adequate [411]	Very good [411] Adequate [410]	-	Very good [415]	Very good [410, 413-415]	-	Very good [412, 414] Adequate [410, 411]	-	Very good [414, 415]
KHQ [417-423]	Very good [417, 419, 420, 422, 423] Doubtful [418]	Adequate [420]	Adequate [418]	Very good [421]	Very good [420]	Very good [419, 422, 423]	-	Very good [417, 419, 423] Doubtful [422]	-	Very good [418, 422]
OAB-V8 [399]	Very good [399]	-	-	-	-	-	-	-	-	-
OAB-q [312, 324-327, 334, 338, 400, 401]	Very good [312, 324, 338, 400, 401]	Adequate [312, 325-327, 338, 400, 401] Very good [338]	-	Very good [400] Adequate [338]	Very good [400]	Very good [338, 400, 401]	Very good [312, 324]	Adequate [401]	-	Very good [312, 325-327, 338, 401]
Qualiveen [402-409]	Very good [404, 406-409] Adequate [403] Doubtful	Very good [404, 409] Adequate [406-408] Doubtful	Very good [402, 405]	Adequate [408, 409]	Very good [403-405, 407-409]	Very good [403, 406]	-	Very good [406]	-	Very good [403]

	[405]	[405]								
UDI [392-396, 424]	Very good [392-394] Doubtful [395, 396]	Adequate [392-394, 396]	-	Adequate [393, 395]	Very good [392, 395, 396]	Very good [393]	-	Very good [393]	-	Very good [395, 396]
UQ [416]	Very good [416]	-	-	-	-	Very good [416]	-	Very good [416]	-	-

ICIQ-FLUTS: International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; SF-Qualiveen: Short form Qualiveen; SF-IIQ-7: Short Form-Incontinence Impact Questionnaire; UDI-6: Urogenital Distress Inventory; IUI: Incontinence Utility Index; KHQ: Kings' Health Questionnaire; OAB-q: The Overactive Bladder Questionnaire; UQ: Urgency Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire- Short Form; OAB-q SF: The overactive bladder quality of life short-form questionnaire; SF-KHQ: short version of the King's Health Questionnaire; Arabic version International Consultation on Incontinence short-form questionnaire; I-QOL: Incontinence-quality of life; U-IIQ: Urge-Incontinence Impact Questionnaire; U-UDI: Urge-Urinary Distress Inventory; ICIQ-OABqol: International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; UDI-6: Urogenital Distress Inventory; IIQ-7: Incontinence Impact Quality of Life; OAB-V8: Overactive bladder questionnaire:; B-SAQ-Bladder Control Self-Assessment Questionnaire; ISS: The Incontinence Symptom Severity Index; PFLUTS: Persian Female Lower Urinary Tract Symptoms instrument; MUDI: Male Urinary Distress Inventory: MUSIQ: Male Urinary Symptom Impact Questionnaire; VAS: Visual Analogue Scale; PFDI: Pelvic Floor Distress Inventory

4.4.6 GRADE findings for the psychometric properties of the outcome measures assessed in the included studies

The modified GRADE tool was used to evaluate the quality of evidence for each of the 15 outcome measures based on pooled findings for their validated psychometric properties. According to the modified GRADE tool, the evidence quality for the pooled outcome measures of the included studies was high for 67% of the assessments and moderate for 33%. The outcome measures supported by high-quality evidence were PFLUTS, ICIQ-FLUTS, ICIQ-UI-SF, ICIQ-OABqol, IUI, I-QOL, KHQ, OAB-q, Qualiveen questionnaire, and UQ. In contrast, B-SAQ, IIQ, ISS, OAB-V8, and UDI were supported by moderate-quality evidence. The GRADE findings for each outcome measure are summarised in Table 4.5.

Table 4.5: Summary of evidence, overall rating, and grading of the quality of evidence using GRADE Assessment

Outcome measures	Summary or pooled result	Overall rating	Quality of evidence
PFLUTS [386]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Debatable, acceptable and good (0.67-0.89) **Test re-test reliability (ICC score)**: Good (0.77) **Criterion validity**: 0.77 **Total sample size**: 114	Sufficient	High
B-SAQ [387]	**Criterion validity**: 0.86-0.89 **Total sample size**: 50	Sufficient	Moderate (due to the risk of imprecision)
ICIQ-FLUTS [288]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Debatable, Acceptable and good (0.646-0.864) **Test-retest reliability (ICC scores)**: 0.769-0.925 **Total sample size**: 283	Sufficient	High
ICIQ-UI-SF [388-390]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Acceptable **(**0.71-0.78) **Test-retest reliability (ICC):** Moderate, good and excellent (0.61-0.91) **Criterion validity**: 0.55-0.74 **Responsiveness**: The result is in accordance with the hypothesis **Total sample size**: 619	Sufficient	High
ICIQ-OABqol [391]	**Internal consistency (Summarised Cronbach's alpha coefficient)**: Good (0.88) **Test-retest reliability (ICC scores)**: Excellent (0.906-0.933) **Total sample size**: 118	Sufficient	High
IIQ [392-396, 424]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Acceptable, good and excellent (0.70-0.95) **Test-retest reliability (ICC scores)** = Good and excellent 0.85; 0.95 **Test-retest reliability (Spearman's rho): Excellent (**0.99) **Test-retest reliability (Pearson's correlation)**: Excellent (0.9431) **Total sample size**: 826	Sufficient	Moderate (due to the risk of indirectness)
ISS [397]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Debatable (0.69) **Test-retest reliability (ICC scores)**: Moderate (0.69) **Total sample size**: 345	Sufficient	Moderate (due to the risk of bias)
IUI [398]	**Test-retest reliability (ICC scores):** Excellent (0.90) **Responsiveness**: The result is in accordance with the hypothesis **Total sample size**: 658	Sufficient	High
I-QOL [410-415]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Acceptable, good and excellent (0.79-0.99). **Test-retest reliability (ICC scores):** Good and excellent (0.81-0.99) **Criterion validity**: 0.76-0.86 **Responsiveness**: The result is in accordance with the hypothesis **Total sample size:** 1205	Sufficient	High

KHQ [417-423]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Debatable, acceptable, good and excellent **(**0.63-0.948) **Test-retest reliability (ICC scores):** Good and excellent (0.80-0.96) **Criterion validity**: 0.722-0.784 **Responsiveness**: The result is in accordance with the hypothesis **Total sample size:** 3527	Sufficient	High
OAB-V8 [399]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Good and excellent (0.891-0.910) **Test-retest reliability (ICC scores):** Excellent (0.93) **Total sample size:** 1128	Sufficient	Moderate (due to the risk of bias)
OAB-q [312, 324-327, 334, 338, 400, 401]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Acceptable, good and excellent (0.70-0.95) **Test-retest reliability (ICC scores):** Moderate, good and excellent **(**0.70-092) **Responsiveness**: The result is in accordance with the hypothesis **Total sample size:** 1807	Sufficient	High
Qualiveen [402-409]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Acceptable, good and excellent (0.70-0.95) **Test-retest reliability (ICC scores):** Moderate, good and excellent (0.62-0.97) **Criterion validity**: 0.70-0.92 **Responsiveness**: The result is in accordance with the hypothesis **Total sample size:** 1135	Sufficient	High
UDI [392-396, 424]	**Internal consistency (Summarised Cronbach's alpha coefficient):** 0.70-0.89 **Test-retest reliability (ICC scores):** Moderate (0.59); Good (0.85) **Pearson's correlations:** 0.933 **Spearman's correlation coefficient**: 0.99 **Responsiveness**: The result is in accordance with the hypothesis **Total sample size:** 826	Sufficient	Moderate (due to the risk of indirectness)
UQ [416]	**Internal consistency (Summarised Cronbach's alpha coefficient):** Acceptable, good and excellent (0.79-0.94) **Test-retest reliability (ICC scores):** Good and excellent **(**0.80-0.94) **Spearman's correlation coefficient**: 0.69-0.92 **Total sample size:** 1388	Sufficient	High

ICIQ-FLUTS: International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; SF-Qualiveen: Short form Qualiveen; SF-IIQ-7: Short Form-Incontinence Impact Questionnaire; UDI-6: Urogenital Distress Inventory; IUI: Incontinence Utility Index; KHQ: Kings' Health Questionnaire; OAB-q: The Overactive Bladder Questionnaire; UQ: Urgency Questionnaire; ICIQ-SF: International Consultation on Incontinence Questionnaire- Short Form; OAB-q SF: The overactive bladder quality of life short-form questionnaire; SF-KHQ: short version of the King's Health Questionnaire; Arabic version International Consultation on Incontinence short-form questionnaire; I-QOL: Incontinence-quality of life; U-IIQ: Urge-Incontinence Impact Questionnaire; U-UDI: Urge-Urinary Distress Inventory; ICIQ-OABqol: International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; UDI-6: Urogenital Distress Inventory; IIQ-7: Incontinence Impact Quality of Life; OAB-V8: Overactive bladder questionnaire:; B-SAQ-Bladder Control Self-Assessment Questionnaire; ISS: The Incontinence Symptom Severity Index; PFLUTS: Persian Female Lower Urinary Tract Symptoms instrument; MUDI: Male Urinary Distress Inventory: MUSIQ: Male Urinary Symptom Impact Questionnaire; VAS: Visual Analogue Scale; PFDI: Pelvic Floor Distress Inventory

4.5 Discussion

This systematic review investigated the psychometric properties of the outcome measures used to evaluate the quality of life of individuals with neurogenic OAB in 47 studies that met the eligibility criteria. Among the included studies, neurogenic OAB was attributed to multiple sclerosis only (*n* = 5); spinal cord injury only (*n* = 1); multiple sclerosis and spinal cord injury (*n* = 2); multiple sclerosis, spinal cord injury and myelomeningocele (*n*=1); or no specific underlying cause (*n* = 38). They used 15 outcome measures to evaluate the quality of life of individuals with neurogenic OAB. The GRADE tool indicated that the quality of evidence for the pooled outcome measures ranged from high (67%) to moderate (33%). The I-QOL, KHQ, OAB-q and Qualiveen questionnaires were the most extensively validated outcome measures for validity, reliability and responsiveness. The ICI-UI-SF, IIQ, UDI, IUI and UQ were also validated for responsiveness, whereas the PFLUTS, B-SAQ, ICIQ-FLUTS, ICIQ-OABqol, ISS and OAB-V8 were not evaluated for responsiveness.

Our systematic review found that the I-QOL was the most psychometrically robust and culturally diverse measure tested in several countries [432]. Based on our findings, the I-QOL demonstrates excellent internal consistency (Cronbach's alpha = 0.92) and test-retest reliability (ICC = 0.92); very good criterion, convergent, and discriminant validities; and very good responsiveness. The pooled psychometric findings were assessed using the COSMIN and GRADE approaches, which indicated sound methodological quality and high evidence quality in the studies using the I-QOL to evaluate the quality of life of individuals with neurogenic OAB. The studies included in this systematic review had translated the I-QOL for use in more than 10 countries. Based on our findings, the I-QOL represents a widely used and highly translated outcome measure [410-415] with highly rated psychometric properties that has been

applied in Africa, America, Asia, and Europe. These findings corroborate the findings of previous systematic reviews by Wuytack et al. [433] and Ross et al. [434], in which the I-QOL was identified as the most widely translated measure with sound overall psychometric quality and available in many languages.

While our study included individuals of both sexes with UUI due to neurogenic OAB, its findings were consistent with those of previous reviews [433, 434] conducted specifically in women with UUI due to OAB. A 50% reduction in incontinence episode frequency, as evaluated by the I-QOL, is recognised as the minimal clinically important difference among patients [435].

Our systematic review identified that the KHQ has acceptable internal consistency (Cronbach's alpha = 0.721–0.948), test-retest reliability (ICC = 0.80–0.96), and responsiveness. The COSMIN evaluation revealed very good methodological quality for most of the psychometric properties examined in the included studies, and the GRADE findings found sufficient overall evidence quality, with some studies identified as having high-quality evidence. The KHQ has been validated and translated into three languages [417-423] and applied to large cohorts of individuals with UUI due to OAB, indicating that it is broadly applied for evaluating OAB in clinical practice and demonstrating its acceptance and benefits.

The methodological quality of the included studies evaluating the OAB-q ranged from very good to adequate, with an overall COSMIN rating of sufficient. The GRADE evaluation identified high-quality evidence supporting the OAB-q. A previous review by Avery et al.

[358] reported a high level of psychometric strength (sound, adequate and very good levels of evidence for internal consistency, test-retest reliability, validity and responsiveness) and scientific rigour for the OAB-q.

According to the GRADE tool, the Qualiveen questionnaire was found to have a sufficient overall COSMIN rating and high-quality evidence. The Qualiveen questionnaire is reported to be a useful outcome measure for clinical trials directed at improving urinary-specific health-related quality of life [299].

The cost, feasibility and clinical relevance of outcome measures are barriers to their recommendation and routine utilisation by clinicians and researchers [375]. In addition to criteria such as validity, appropriateness, reliability, responsiveness and interpretability [436], clinically useful outcome measures must be easy to use, easily understood, quick to complete, easy to score and provide useful clinical data [436]. Based on our findings, we recommend the I-QOL as the first-choice outcome measure when evaluating the quality of life of individuals with neurogenic OAB. The I-QOL evaluates the broad impacts of urinary incontinence on incontinence-related quality of life in both men and women with UUI due to neurogenic OAB. It can be completed within five minutes, has been applied in both community studies and clinical trials regardless of the OAB classifications or severity, and demonstrates suitable generalisability across different international settings and conditions [437-440].

4.6 Strengths and limitations

This systematic review had several strengths. Firstly, the COSMIN and GRADE guidelines were adopted to assess, summarise and compare methodological quality and evidence quality of studies using the identified outcome measures. Secondly, a robust, transparent and comprehensive search strategy was employed, using relevant search themes and terms to identify studies validating the outcome measures used to assess the quality of life of those with OAB.

However, this systematic review also had some limitations. Firstly, some of the requirements of COSMIN checklists involve subjective judgments, which might influence the overall scores for these instruments [441]. Secondly, excluding studies not published in English introduces potential language bias, which may impair the external validity of our findings. Thirdly, excluding conference abstracts, grey literature and unpublished reports may result in potentially vital information being overlooked, leading to publication bias. Fourthly, while none of the included studies included those with stroke, Parkinson's disease or multiple sclerosis, considering the broad application of the I-QOL in several multicenter studies, it could be generalised in the evaluation of such individuals [442-445]. The exclusion of the underreported outcome measures in the discussion section might result in an incomplete interpretation of these measures and a failure to reveal their full scope. We felt that including them might not add any detail or alter the final outcome, since they are fully represented in the COSMIN and GRADE analyses.

4.7 Conclusion and recommendations

Our systematic review identified the I-QOL as the most psychometrically robust, cross-culturally diverse and easily administered outcome measure based on studies with good methodological quality and high evidence quality. It supports using the I-QOL to evaluate the quality of life of individuals with neurogenic OAB due to stroke, Parkinson's disease, multiple sclerosis or spinal cord injuries. However, the included studies did not evaluate the content, concurrent and known-group validities of the I-QOL among individuals with neurogenic OAB. Therefore, further investigations of these psychometric properties could broaden these recommendations and support the routine utilisation of the I-QOL among individuals with neurogenic OAB in clinical practice.

Chapter 5

Clinical effectiveness and cost-effectiveness of repetitive transcranial magnetic stimulation for managing neurogenic overactive bladder in stroke survivors: Introduction and methods of a randomised controlled trial

5.1 Introduction

Overactive bladder (OAB) imposes a significant multidimensional burden on stroke survivors, placing psychosocial distress and financial strain on them and their caregivers [80]. These issues are exacerbated by inadequate management, potentially leading to urinary tract complications, heightened social isolation, psychological morbidities such as anxiety and depression, frequent hospitalisations, long-term disability, and higher mortality risk [195].

Treatment approaches include pharmacological, surgical, and physiotherapeutic interventions. Pharmacotherapy involving anticholinergics, alpha-adrenergic blockers, and 5-alpha-reductase inhibitors [151] is complicated by adverse effects, including blurred vision, constipation, and impaired renal function, which can hinder patient adherence and long-term management [151]. While behavioural therapies and invasive or semi-invasive procedures (intermittent urethral catheterisation, indwelling, suprapubic catheters, open retropubic colposuspension, laparoscopic colposuspension, periurethral injections, and bladder neck needle suspension) have demonstrated effectiveness [152], they are often accompanied by discomfort, high costs, and potential long-term adverse effects [152].

Pelvic floor muscle training (PFMT), with or without adjuncts such as electromyography (EMG) biofeedback or electrical stimulation, constitutes a key physiotherapy approach [128-131]. However, standardised PFMT protocols are lacking [446], and invasive techniques such as EMG biofeedback with vaginal or anal probes are often avoided due to their discomfort and invasiveness [132, 199], particularly for stroke survivors with functional impairments. Therefore, a systematic review and meta-analysis were conducted on the effectiveness of nonsurgical minimally- or non-invasive therapies for managing urgency urinary incontinence (UUI) due to neurogenic OAB (Chapter 2). The systematic review and meta-analysis were conducted to determine the effects of nonsurgical, minimally or non-invasive therapies on UUI symptoms and quality of life of individuals with neurogenic OAB. Our meta-analyses revealed a significant effect of electrical stimulation on UUI symptoms due to multiple sclerosis ($p = 0.003$) and stroke ($p = 0.000$). The pooled analyses of transcutaneous tibial nerve stimulation ($p = 0.000$) and behavioural therapy ($p = 0.002$) revealed significant effects of these interventions on quality of life in people with Parkinson's disease. However, meta-analyses revealed nonsignificant effects for pelvic floor muscle training ($p = 0.380$) and behavioural therapy ($p = 0.085$) on UUI due to Parkinson's disease [130]. Our systematic review [130] found no RCTs evaluating the effects of rTMS for managing neurogenic OAB symptoms in stroke survivors. Given the lack of empirical evidence for the effectiveness of rTMS for managing neurogenic OAB symptom severity in stroke survivors, a well-planned RCT of high methodological rigour to determine its efficacy was needed.

rTMS non-invasively delivers magnetic pulses to stimulate neural activity in bladder control-related brain regions, promoting sustained effects and facilitating neuroplastic changes [154,

155, 158], offering a promising direction for future management strategies. This study aimed to evaluate the efficacy of active rTMS compared to sham rTMS in alleviating neurogenic OAB symptoms, improving quality of life and resilience among stroke survivors. Evaluating neurogenic OAB symptoms, quality of life and resilience is pivotal in understanding the severity of the neurogenic OAB symptoms and ascertaining an accurate intervention outcome [292]. We aimed to analyse whether active rTMS achieves better health benefits and outcomes with lower intervention costs than sham rTMS. Therefore, a cost-effectiveness (expressed as the cost-utility) analysis was included to evaluate the active rTMS compared to sham rTMS for alleviating neurogenic OAB symptoms following the rTMS interventions. To explore the experiences and opinions of stroke survivors with neurogenic OAB toward the rTMS intervention and their views regarding its impact on their urinary symptoms and well-being, a qualitative study was included. Real-life experiences and the meanings individuals attribute to them were explored to reveal important insights about patients' perceptions of the therapeutic interventions [447].

Neurogenic OAB symptoms severity and quality of life evaluation relied on outcome measures that had undergone rigorous validation, ensuring they were psychometrically sound for both clinical and research contexts [293]. The core attributes of these measures – validity, reliability, and responsiveness [294] – are critical for facilitating rigorous evaluations that integrate evidence-based practice [295]. The use of validated and standardised outcome measures also ensured the accuracy and comparability of the study results, allowing for meaningful interpretations and implications for clinical practice and future research [448-450]. The accuracy of the symptom and quality of life evaluations is directly linked to the psychometric robustness of the clinical tools used [296]. Consequently, to ensure the reliability and validity of our assessments, we conducted two systematic reviews on the psychometric properties of

commonly used instruments (Chapters 3 and 4), thereby grounding our study in the most robust and psychometrically accepted clinical measures for assessing neurogenic OAB symptoms and quality of life. The psychometric systematic review on the neurogenic OAB symptoms among people with neurological conditions [112] identified the Overactive Bladder Symptom Score (OABSS), Overactive Bladder Questionnaire (OAB-q), and Neurogenic Bladder Symptoms Score as the most widely validated clinical measures with sound psychometric properties across several countries. Among the identified clinical tools for neurogenic OAB symptoms, the OABSS was the most culturally diverse and psychometrically sound clinical measure among individuals with UUI due to OAB, supported by studies with good methodological quality and high evidence quality according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The psychometric systematic review on the quality of life of people with neurogenic OAB [111] found that the Incontinence Quality of Life Questionnaire (I-QOL), King Health Questionnaire, OAB-q, and Qualiveen questionnaire were the most psychometrically sound clinical tools. However, assessing their psychometric robustness and cross-cultural diversity identified the I-QOL as the most suitable for evaluating the quality of life of individuals with neurogenic OAB. The I-QOL is an easily administered and readily available outcome measure with good methodological quality and high evidence quality for clinicians and researchers. It evaluates the broad impacts of urinary incontinence on incontinence-related quality of life in both men and women with UUI due to neurogenic OAB.

5.2 Aims

The aim of this study is to evaluate the effectiveness of active rTMS compared to sham rTMS in managing neurogenic OAB symptoms of stroke survivors.

The objectives of this study are to:

1. evaluate the clinical effectiveness of active rTMS compared to sham rTMS in managing neurogenic OAB symptoms severity among stroke survivors.
2. To evaluate the effectiveness of active rTMS compared to sham rTMS in improving the quality of life and resilience of stroke survivors with neurogenic OAB.
3. In addition to evaluating the two primary objectives listed above, we will also conduct a series of secondary analyses to: (1) evaluate the longer-term (8 weeks after randomisation) effects of the active treatment on neurogenic OAB symptoms; (2) determine the immediate and longer-term effects of the active treatment on secondary outcome variables, quality of life and resilience; (3) estimate the cost of active rTMS compared to sham rTMS in treating neurogenic OAB among stroke survivors; and (4) explore stroke survivors' experiences and perspectives about using rTMS to treat neurogenic OAB symptoms among stroke survivors.

5.3 Hypotheses:

1. Stroke survivors with neurogenic OAB randomly assigned to receive active rTMS for 4 weeks will evidence a significantly greater reduction in neurogenic OAB symptoms than stroke survivors with neurogenic OAB randomly assigned to receive sham rTMS 4 weeks after randomisation (primary endpoint).

2. Stroke survivors with neurogenic OAB randomly assigned to receive active rTMS for 4 weeks will evidence a significantly improved quality of life and resilience than stroke survivors with neurogenic OAB randomly assigned to receive sham rTMS 4 weeks after randomisation.

3. Stroke survivors with neurogenic OAB receiving active rTMS for 4 weeks will evidence a lower estimate of cost than stroke survivors with neurogenic OAB randomly assigned to receive sham rTMS 4 weeks after randomisation.
4. Stroke survivors with neurogenic OAB randomly assigned to receive active rTMS for 4 weeks will demonstrate a positive experience and perception of the 4-week rTMS intervention.

5.4 Methods

5.4.1 Research design and study setting

A prospective, double-blinded, two-arm randomised, sham-controlled trial with embedded cost-effective study (expressed as cost-utility) and qualitative study was conducted in Hong Kong between January and December 2023. A mixed-method approach (RCT combined with cost estimation and qualitative studies) was adopted to enhance the comprehensiveness of the research evidence by integrating the strengths of both quantitative and qualitative methods [451]. This approach allows researchers to explore social phenomena, generate hypotheses, and provide rich, detailed descriptions of the research context while testing hypotheses, establishing causal relationships, and generalising to larger populations [452, 453]. Study interventions of the RCT were provided at the Neuro-modulatory Laboratory in the Department of Rehabilitation Sciences of The Hong Kong Polytechnic University. The methods of the qualitative study are presented in Chapter 7.

5.4.2 Ethical approval

Ethics approval to conduct this RCT was obtained from the Institutional Review Board of the Hong Kong Polytechnic University (Reference number.: HSEARS20210913002) before enrolling the first participant (Appendix 5.1). All study procedures involving stroke survivors with neurogenic OAB were conducted according to the principles of the 1964 Declaration of Helsinki, as amended by the sixty-fourth World Medical Association General Assembly in 2013, and relevant ethical guidelines. The study protocol was prospectively registered in ClinicalTrials.gov (NCT05557175). Written informed consent was obtained from all participants before their enrolment in this study. Participants were also given copies of the signed information sheets (Appendix 5.2) and consent forms (Appendix 5.3) for their records. Anonymity was ensured by using unique codes instead of real names to allow the researchers to identify participants' data without knowing the participants' identities. The anonymity will ensure confidentiality and protect participant information within a relationship of trust unless consistent with the original purpose of the disclosure [454]. Participants' records were safeguarded against disclosure outside the research setting or to unauthorised persons. The researchers safeguarded all the data obtained from the participants on password-protected personal computers. The hard copies of data will be safeguarded in locked office cabinets for three years after the research project's completion and then discarded in accordance with Hong Kong Polytechnic University's research regulations.

5.4.3 Sample size

The sample size for this RCT was calculated using the G*Power program (version 3.1.0; Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany), considering a power of 80%, a significance level of 5% [455], and an effect size of 0.40, which was chosen based on a previous

pilot RCT that focused on the same primary outcome, OABSS, and a similar population (stroke) [355]. Eight additional participants were recruited to account for an anticipated 15% attrition rate, resulting in a total sample size of 60 participants (30 per group) [53]. An attrition rate of 15% is considered acceptable for this RCT, given the nature of its intervention and the potential for participants to experience mild headaches and the 12 sessions of the intervention during the treatment course [456]. However, it is not a fixed standard compared to the 20% attrition rate but rather a comparative benchmark. Lower attrition is generally preferred since it helps maintain the statistical power and validity of the trial results [456]. The sample size determination using the G*Power program helped ensure that the RCT had sufficient statistical power to detect a significant effect of the intervention [457].

5.4.4 Participant recruitment

Participants were recruited for the RCT using snowball sampling and through self-help organisations such as the Hong Kong Stroke Society. Snowball sampling is a non-probability method where existing participants recommend potential participants who refer others, creating a ‘snowball’ effect [458]. This approach is useful when the population of interest is hard to reach or a sampling frame is lacking [458]. In this study, snowball sampling was used to recruit stroke survivors with neurogenic OAB symptoms who may not have been identified through traditional recruitment methods. The snowball sampling approach allowed for the recruitment of participants who may have been more engaged in their clinical appointments, are unaware of ongoing research projects and are interested in participating in research projects. Recruitment was also performed using fliers conspicuously posted across The Hong Kong Polytechnic University notice boards (at each University core building, canteens, and food

court) (Appendix 5.4). Fliers were also posted to the stroke community's WhatsApp groups for participation.

5.4.5 Participants

The eligibility of potential participants was assessed according to the following inclusion and exclusion criteria. Volunteers with stroke were considered eligible to participate if they: (1) were aged 18–80 years [459] and having neurogenic OAB symptoms; (2) were experiencing moderate (scoring 6-11 points on the OABSS) to severe neurogenic OAB (scoring $12 \geq$ points on the OABSS) [460]; (3) obtained a Mini-Mental State Examination (MMSE) score of $\geq$ 24 (implies normal cognitive function) [461]; and (4) expressed willingness to be randomised. Volunteers with stroke were excluded if they: (1) have contraindications to rTMS as per the 13-question safety questionnaire (Appendix 5.5) [462]; (2) indicated evidence of the presence of metals in the cranium, intracardiac lines, increased intracranial pressure, heart diseases, cardiac pacemaker, or use of sacral neuromodulation [463]; (3) were pregnant or in the postpartum stage of less than six months at the time of study participation; (4) had a family history of epilepsy or seizures; (5) were using tricyclic antidepressants or neuroleptics at the time of the study participation [463]; (6) were participating in other urinary incontinence-related research projects [463]; (7) were contraindicated to magnetic resonance imaging; (8) presented with urologic cancer, prostatic pathology, or severe pelvic pain; (9) were within six weeks post-surgery; and (10) were diagnosed with a non-neurogenic bladder [464].

The aforementioned eligibility criteria were used to ensure that the study participants were appropriate for the rTMS intervention and that any potential confounding factors (such as

rTMS contraindications and urinary incontinence-related studies' participation) were eliminated as much as possible [465]. Selecting participants diagnosed with neurogenic OAB and normal cognitive function ensured that the rTMS intervention was targeted at those that fulfil the eligibility criteria [466].

5.4.6 Randomisation and blinding

After the participants read the information sheets, signed the informed consent form, and underwent the baseline assessments, they were randomly allocated to the active or sham rTMS group. The use of two groups of active and sham rTMS groups only was based on Equipoise. Equipoise exists when there is genuine uncertainty about the relative therapeutic merits of the treatments being compared [467]. In this state, it is ethical to randomize participants to different treatment arms, including a sham or placebo arm, because it is not known which treatment is superior. If equipoise exists, it can justify the use of a sham control group. Secondly it was based on a lack of established effective treatments, If there are no established effective treatments for the condition being studied, or if existing treatments have significant limitations, the use of a sham control group may be justified [468]. In this case, the active rTMS intervention being investigated could potentially fill an unmet medical need. Thirdly, methodological rigour, the use of a sham control group can strengthen the methodological rigour of the study by reducing the risk of bias [469]. This can increase confidence in the study's findings and contribute to more robust and reliable scientific knowledge.

The randomisation was performed by a research assistant not involved in the rTMS intervention using a computer-generated randomisation schedule [470, 471]. Randomisation is a crucial aspect of clinical trials since it helps to minimise bias and ensure that any observed differences between the study groups are due to the intervention being investigated. The effects of

confounding factors, such as attending urinary incontinence-related research and other neuromodulation interventions are identified and excluded.[470, 472, 473]. Using a computer-generated randomisation procedure and a minimisation method (balancing age and sex) helps ensure that the allocation of participants is truly random and that potential confounding factors are balanced between the study groups [470, 474, 475]. In a population of the stroke survivors, the age distribution is not disproportionately spread as their age are usually well-defined. We used a computer-generated randomisation process and a minimisation method to ensure a balance of age and gender in the study groups. As each new participant is enrolled, the minimisation algorithm assesses the age and gender distribution across the study groups. It then assigns the new participant to the group that would best minimise any imbalance in age and gender distribution across the study groups. The therapist and the participants were blinded to the recruitment, randomisation, and treatment allocation [470]. Sixty sealed, opaque envelopes were used for allocation concealment. This approach helps to ensure that the allocation process is unbiased and that the study results are not influenced by the researchers' expectations or preferences [470, 472, 473]. The outcome assessments and statistical analyses were blinded, with the groups coded 'Group A' and 'Group B'. These group codes were revealed only after completing all analyses [470, 476].

5.4.7 Procedure

Volunteers who contacted the research personnel via phone were invited to The Hong Kong Polytechnic University for eligibility screening (Appendix 5.6), obtaining written informed consent, and conducting the baseline assessments. During their initial visit, those who provided written informed consent completed the OABSS, Incontinence Quality of Life questionnaire (I-QOL), Brief Resilience Scale (BRS), client service recipient inventory (CSRI), EuroQol

five-dimension five-level questionnaire (EQ-5D-5L), and MMSE to determine eligibility and baseline (week 0) scores. Subsequently, all eligible participants completed the study's outcome questionnaires post-intervention (week 4) and at the follow-up assessment (week 8). The baseline assessments allowed for comparing outcomes between the active and sham rTMS groups, controlling for potential confounding factors by balancing age and sex and excluding participation in urinary incontinence research, ensuring the validity and reliability of the study findings.

5.4.8 Interventions

5.4.6.1 Active rTMS

The participants in the active rTMS group received low-frequency rTMS stimulation using a standard 70 mm figure-of-eight air-cooled coil (MagPro), targeting the sensorimotor cortex hot spot anterior-medially on the contralesional primary motor cortex (M1) [477-479]. The motor hotspot was identified as the site with the greatest motor-evoked potential (MEP) [480]. At this hotspot, the motor threshold was determined as the lowest intensity of single-pulse TMS necessary to elicit an MEP of >50 μV in more than 5 out of 10 consecutive trials [481]. Identifying the motor hotspot and determining the resting motor threshold (RMT) are crucial for ensuring the safety and efficacy of the TMS procedures [482, 483]. By targeting the appropriate brain region and adjusting the stimulation intensity to the individual's RMT, TMS can be delivered safely and effectively, with minimal discomfort and risk of adverse effects [484, 485].

The MEP was measured using EMG, specifically recording from the first dorsal interosseous (FDI) muscle according to the recommendations of the International Federation of Clinical Neurophysiology [485]. Activating the FDI muscle significantly increases the activity in the medial wall of the precentral gyrus [486]. FDI muscle activation increases gluteus maximus and pelvic floor muscle activation [486]. To locate the vertex of the skull, the midway between the nasion-inion and between the pre-auricular points of both tragus was identified [482]. The coil was placed with its centre approximately 5 cm lateral and 2 cm anterior in a parasagittal plane from the vertex [482, 487], which will be approximately in line with the tragus-to-tragus skull mid-point. The coil was positioned tangentially at approximately a 45° angle from the midline on the scalp over the hand area of the M1 [488] to identify the hot spot, which is the location on the scalp where stimulation of the lowest threshold intensity elicited the largest MEP in the FDI muscle [485, 489]. Beginning with low intensity (30%–35%), single pulse stimulation was commenced with the pulses every 3–5 seconds. The coil was slowly moved around the estimated location of the M1, applying 1 or 2 pulses at each site [487]. Starting at a low intensity is important to relax the study participants during the procedure and avoid discomfort [482]. If no movement or twitch was observed in the contralateral hand, the RMT for that participant is higher than the current TMS output setting. In this case, the output was incrementally increased by 5%, with the response tested at several site/scalp locations at each step. If the hand and/or twitch movement was observed, the applied intensity was close to the RMT. Responses were tested at several scalp sites, and the one that appeared to produce the greatest motor response was marked. The intensity was increased gradually if the observed movement was not produced on each pulse. The coil was gently moved in 0.5–1.0 cm increments laterally and medially of the marked point to determine the optimal stimulation site in the lateral/medial plane [482]. Stimulation was provided at the optimal location with pulses of approximately 0.2 Hz no more than once every five seconds.

After identifying the hot spot, the RMT was determined using the lowest stimulus intensity to produce an MEP of >50 μV peak to peak amplitude in 5 out of 10 consecutive trials [482]. The MEP was obtained during hot spot calculation in the contralesional M1 [482]. The participants in the active rTMS group received 1 Hz inhibitory low-frequency rTMS, delivering one pulse per second, totalling 1,200 pulses at 80% of the active motor threshold [463, 478]. Each stimulation session lasted 20 minutes and was conducted three times a week over four weeks (12 sessions in total) [463, 478]. The stimulation parameters were selected according to the safety guidelines for rTMS. Therefore, the participants in the active rTMS group received stimulation at a subthreshold intensity sufficient to induce muscle contraction without causing painful peripheral sensations.

5.4.6.2 Sham rTMS

The participants in the sham rTMS group received low-frequency stimulation at 20% of the RMT [490]. This sham stimulation was delivered using the same coil as the active rTMS and placed to target the M1, with 20% RMT chosen to significantly reduce the TMS-induced electrical fields in the cortex [490, 491]. Sham stimulation aimed to control for potential placebo effects and ensure that any observed effects were due to the active rTMS intervention [492, 493]. Using sham rTMS that mimics the sensory experience of active rTMS but without the same physiological effects enables the direct comparison of the outcomes between the active and sham rTMS groups to determine if the intervention had a significant effect [494]. Sham stimulation is commonly used in TMS research to control for the non-specific effects of the intervention [495]. By reducing the TMS-induced electrical fields in the cortex, the sham rTMS is unlikely to have the same physiological effects as the active rTMS, making it an

appropriate control condition [496]. Using sham rTMS in this RCT helped ensure the validity of its results by controlling for potential confounding factors and allowing for a more accurate assessment of the effects of active rTMS on neurogenic OAB symptoms in stroke survivors.

5.4.7 Outcome measures

All primary and secondary outcome assessments of the RCT were evaluated at baseline (week 0), post-intervention (week 4) and at follow-up (week 8). The EQ-5D-5L was evaluated at baseline (week 0), post-intervention (week 4), and at the follow-up (week 8), while the CSRI was assessed at the follow-up (week 8) to evaluate the cost utilisation.

Demographics and clinical characteristics: Demographic and clinical information such as age, sex, occupation, education, employment, side and stroke duration was elicited.

5.4.7.1 Primary measure

OAB symptoms severity: OABSS was used to assess the severity of OAB symptoms. The OABSS is a clinical measure developed in 2006 among the Japanese population to identify patients with OAB and evaluate the severity of neurogenic OAB symptoms and treatment outcomes (Appendix 5.7) [353, 497]. Our systematic review of the psychometric properties identified the OABSS as the most psychometrically robust clinical tool for evaluating neurogenic OAB symptoms [112]. It was found to have high internal consistency and test-retest reliability of 0.92 and 0.95, respectively [112]. Its construct, concurrent, discriminant, and convergent validities were robust and significantly related to the bladder diary, international

incontinence questionnaire, International Prostate Symptom Score (IPSS) voiding subscore, and the IPSS, respectively [112]. OABSS comprises four questions on OAB symptoms with maximum domain scores ranging from two to five: daytime frequency (two points), night-time frequency (three points), urgency (four points), and UUI (five points) [498]. The OABSS values range from 0 to 15, with higher scores indicating greater symptom severity [498].

The OABSS is considered a reliable and valid questionnaire for quantitatively assessing OAB symptoms in the Hong Kong population (intraclass correlation coefficient [ICC] = 0.82) [499]. OAB severity evaluated by OABSS is classified as mild (3–5 points), moderate (6–11 points), or severe (≥12 points) [460]. Given the robust psychometrics of the OABSS in evaluating neurogenic OAB symptoms, using the OABSS in this study will allow for an accurate assessment of the effectiveness of rTMS on neurogenic OAB symptom severity among stroke survivors. The OABSS was evaluated at baseline (week 0), post-intervention (week 4) and follow-up (week 8).

5.4.7.2 Secondary measures

OAB-related quality of life: The I-QOL was used to evaluate OAB-related quality of life (Appendix 5.8) [111]. Our systematic review of the psychometric properties identified the I-QOL as a culturally diverse measure with robust reliability, validity, and responsiveness for assessing quality of life among individuals with neurogenic OAB [111]. It comprises 22 items subdivided into three subscales. Its total score ranges from 0 to 100, where 0 represents the worst quality of life, and 100 indicates the complete absence of OAB-related issues [433]. The I-QOL has been reported to demonstrate high internal consistency (Cronbach's $\alpha = 0.99$) [411], excellent test-retest reliability (ICC = 0.99) [413], and strong convergent validity with the King

Health Questionnaire (KHQ; r = 0.76–0.88). The I-QOL's discriminant validity demonstrates a low correlation of items to subscales other than their own [410, 414]. Its construct validity shows that all its items accounted for 54.85% of the total variance, loaded into 0.51–0.88 [410]. The I-QOL has demonstrated a sensitivity of 18.4% and a specificity of 90.4% [500]. Using the I-QOL in this study provided a valid, reliable, and responsive measure of neurogenic OAB-related quality of life among stroke survivors. A Chinese-Cantonese I-QOL clinical measure was employed for evaluating the OAB-related quality of life of the Chinese-speaking population. The I-QOL was evaluated at baseline (week 0), post-intervention (week 4) and follow-up (week 8).

Resilience: The BRS was used to measure resilience, which is defined as resistance to illness, adaptation, and thriving, the ability to bounce back or recover from stress [501]. The BRS has been reported to provide unique and critical information regarding people coping with health-related stressors [501]. It comprises both positively worded (items 1, 3, and 5) and negatively worded (items 2, 4, and 6) statements (Appendix 5.9). Resilience is a coping strategy for individuals facing stressful environments and adverse life events [502]. Notably, resilience is often lower in individuals with urinary incontinence of all ages [502]. Therefore, assessing resilience in individuals with neurogenic OAB is crucial for understanding their coping abilities and identifying potential targets for intervention. The BRS has been reported to demonstrate good internal consistency (Cronbach's alpha = 0.80–0.91) and acceptable test-retest reliability (ICC = 0.69) [503]. Regarding convergent validity, the BRS correlated positively with resilience measures, optimism, and purpose in life and negatively with pessimism and alexithymia [503]. Regarding discriminant validity, the BRS demonstrated partial correlations, revealing that the 'resilience' measures strongly correlated in the expected direction with the outcomes, except that ego resiliency was only marginally related to less negative effects [503].

The BRS was evaluated at baseline (week 0), post-intervention (week 4) and follow-up (week 8).

Adherence: Adherence to the active and sham rTMS interventions was measured by calculating the percentage of prescribed rTMS sessions each participant attended. The number of sessions attended was divided by the total number of sessions prescribed and multiplied by 100. The reasons for missing any sessions were also recorded. This information is crucial for understanding potential barriers to treatment adherence and identifying strategies to improve adherence in future studies. Measuring adherence to the intervention is essential for evaluating the effectiveness of rTMS in managing neurogenic OAB symptoms. Poor adherence can lead to an underestimation of the treatment effect and may impact the generalisability of the study findings. Therefore, assessing adherence and identifying factors that may affect adherence is crucial for interpreting the study results and informing clinical practice. The adherence rate of rTMS intervention among stroke survivors is 98%, with participants' subjective reports indicating positive responses [504]. Combining therapeutic approaches: rTMS and aerobic exercise in post-stroke depression: a case series [504]. The researcher of the presence study places calls or WhatsApp messages reminders to participants a day before the rTMS session.

5.4.8 Economic evaluation

The economic evaluation was conducted to determine the estimated costs in active rTMS and sham rTMS for managing neurogenic OAB symptoms among stroke survivors. The cost estimation analysis was conducted from a societal perspective of Hong Kong. It considered direct and indirect costs associated with the intervention, including healthcare service

utilisation, medications, and transportation [505, 506]. Direct costs included those incurred by utilising the health system, the society, individual patients, and their families. These cost items include medical care expenditures for diagnosis, treatment, rehabilitation, medical professional services, drugs, and other medical supplies. Indirect costs refer to loss of productivity due to morbidity and mortality; and these costs are borne by the patient or his/her family. The CSRI developed by Beecham and Knapp [507] was used to evaluate the health and social care resources and service utilisation in the last six months (Appendix 5.10) [508]. The CSRI is a versatile tool commonly tailored to accommodate the unique requirements of individual studies [509]. This adaptation process ensures that the CSRI effectively captures the relevant information about the services received, costs, and resources utilised by participants, aligning seamlessly with the study's objectives and context [509]. The CSRI has been validated in Hong Kong with an overall ICC of 0.69 and acceptable criterion concurrent validity [510]. It generates an accurate inventory of cost data, allowing costs associated with the intervention to be calculated [508]. The CSRI was administered at baseline (week 0) and follow-up (week 8) timepoints. The EuroQol Research Foundation developed the EQ-5D-5L as an enhanced version of the original EQ-5D, introduced to provide a more refined assessment of health status [511, 512] (Appendix 5.11). The EQ-5D-5L, a preference-based health status measure, was used to evaluate the treatment effect of an intervention on generic quality of life, offering better discrimination capability and lower ceiling effects [513]. While it maintains the same five core domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – it significantly increases the level of detail by offering five response options for each domain (no problems, slight problems, moderate problems, severe problems, and unable to do/unbearable) [511, 514]. This updated EQ-5D-5L, which was introduced later than the initial creation of the EQ-5D in the 1980s, provides a better understanding of an individual's health status, leading to a more accurate reflection of health-related quality of life [515]. Since its development, the

EQ-5D-5L's widespread adoption is a testament to its improved sensitivity in capturing health changes, making it a preferred tool in health outcomes research and economic evaluations in healthcare [511]. The EQ-5D-5L is highly regarded for its strong psychometric properties, which include reliability, validity, and responsiveness [516]. The EQ-5D-5L domain responses and utility scores demonstrated good test-retest reliability (ICC = 0.777; agreement = 76.4%–98.1%) in the Hong Kong population [517]. The EQ-5D-5L utility score showed good internal consistency (Cronbach's α = 0.78) [517] and sensitivity to detect differences among participants receiving different intervention modalities and across time points [517].

5.4.9 Safety and adverse events

rTMS is generally a well-tolerated, safe, non-invasive modality with no significant side effects or safety concerns [518]. While systematic reviews [519, 520] have reported that rTMS may induce transient mild headaches, it is broadly characterised as an efficacious and safe intervention for managing stroke survivors with motor and cognitive impairments. The safety profile of rTMS is one of its main advantages over other brain stimulation techniques, such as deep brain or vagus nerve stimulation, which require surgical implantation of electrodes and are associated with a higher risk of complications [521, 522].

The participants were informed about the possibility of experiencing mild, transient headaches, neck pain, or local scalp pain at the stimulation site, which could be effectively managed with paracetamol analgesics [518, 523, 524]. In order to prevent any potential adverse effects from the intervention, rTMS contraindications were strictly adhered to, and participants underwent thorough screening against inclusion and exclusion criteria [523], including assessing for any

rTMS contraindications, such as metals in the cranium, intracardiac lines, increased intracranial pressure, heart diseases, cardiac pacemakers, or use of sacral neuromodulation. Potential participants with a family history of epilepsy or seizures or currently using tricyclic antidepressants or neuroleptics were also excluded [523]. Any side effects that occur, such as mild headaches, typically subside after the first few days of starting the rTMS treatment [524]. The participants were observed for adverse effects during and after each treatment session. All the reported adverse events that occurred were recorded and retrieved using the adverse effect form (Appendix 5.12).

5.4.10 Statistical analyses

Statistical analyses were conducted using SPSS software (version 28.0; IBM, Armonk, NY, USA). Missing data can affect a study's statistical power and efficiency, leading to biased impact estimates of findings [525]. Motivation to comply with the rTMS and follow-up phone call reminders were used to reduce missing data. Missing data due to early dropouts was not considered random since it was not evenly distributed within the study groups. All the statistical analyses were conducted on an intention-to-treat basis using the last observation carried forward approach for handling missing data [526-528]. Repeated measure analysis of covariance (ANCOVA) was used to compare changes in the primary outcome (OABSS) and secondary outcomes (I-QOL and BRS) over time between the active and sham rTMS groups. The analysis model was constructed with group allocation as the independent variable, the primary outcomes (OABSS), and the secondary outcomes (I-QOL, BRS). Age and sex were included as covariates [529]. Sociodemographic variables are reported as the mean and standard deviation for continuous variables and frequency and percentage for categorical variables. A p-value of <0.05 was considered statistically significant. The normality of the data

was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The p-values were Bonferroni corrected to reduce the probability of type I errors from multiple comparisons [530, 531].

Descriptive statistics were used to estimate the costs incurred in both groups in managing neurogenic OAB symptoms among stroke survivors. An estimate of the mean cost per patient was determined by dividing the total cost in each group by the total number of stroke survivors with neurogenic OAB. The unadjusted mean and differences in total and disaggregated costs (urology clinic: consultation and medications, physiotherapy; alternative medicine: acupuncture, yoga, massage; medical devices/consumables: diapers, liners, mattress covers, personal care wipes, skincare and washcloths; transportation: mass transit railway [MTR], taxi, bus, or rehab bus) were calculated for the active and sham rTMS groups [532].

Chapter 6

Clinical and cost-effectiveness of repetitive transcranial magnetic stimulation (rTMS) for treating neurogenic overactive bladder in stroke survivors: results and discussion of the randomised controlled trial

6.1 Introduction

This chapter reports and discusses the findings of the randomised controlled trial (RCT) and cost-effectiveness study that evaluated the clinical and cost-effectiveness (expressed as the cost-utility) of repetitive transcranial magnetic stimulation (rTMS) in managing neurogenic overactive bladder (OAB) in stroke survivors. Chapter 5 introduced the RCT and cost-effectiveness study and described their methodology. The objectives of the RCT, cost-effectiveness study and qualitative study were as follows:

1. To assess the effectiveness of active- compared to sham rTMS in reducing neurogenic OAB symptom severity in stroke survivors.

2. To compare the estimate costs in active and sham rTMS groups in managing neurogenic OAB symptom severity in stroke survivors.

3. To explore the experiences and views of participants receiving rTMS for neurogenic OAB secondary to stroke (the findings of the qualitative study are reported in Chapter 7).

The primary outcome measure of the RCT was the Overactive Bladder Symptom Score (OABSS), which evaluates neurogenic OAB symptom severity. Its secondary outcome measures were the Incontinence Quality of Life Questionnaire (I-QOL), Brief Resilience Scale (BRS), EuroQol five-dimension five-level questionnaire (EQ-5D-5L) and Client Service Recipient Inventory (CSRI), which evaluated OAB-related quality of life, resilience, generic quality of life and service utilisation, respectively. The outcome assessments were completed at three time points: baseline (week 0), post-intervention (week 4; primary time-point) and follow-up (week 8; secondary time-point). The assessments were performed at baseline (week 0) and follow-up (week 8) for the cost-estimation study to account for the estimated cost from the active and sham rTMS groups during the study period.

6.2 Results

6.2.1 The flow of participants through the study

Figure 6.1 presents the flow of participants through the study. One hundred ten stroke survivors were screened for eligibility using a 13-question safety questionnaire (Appendix 5.4) and OABSS (Appendix 5.6), of which 60 with neurogenic OAB met the eligibility criteria and were enrolled in this study. The study participants were randomly allocated to the active (n = 30) and sham (n = 30) rTMS groups.

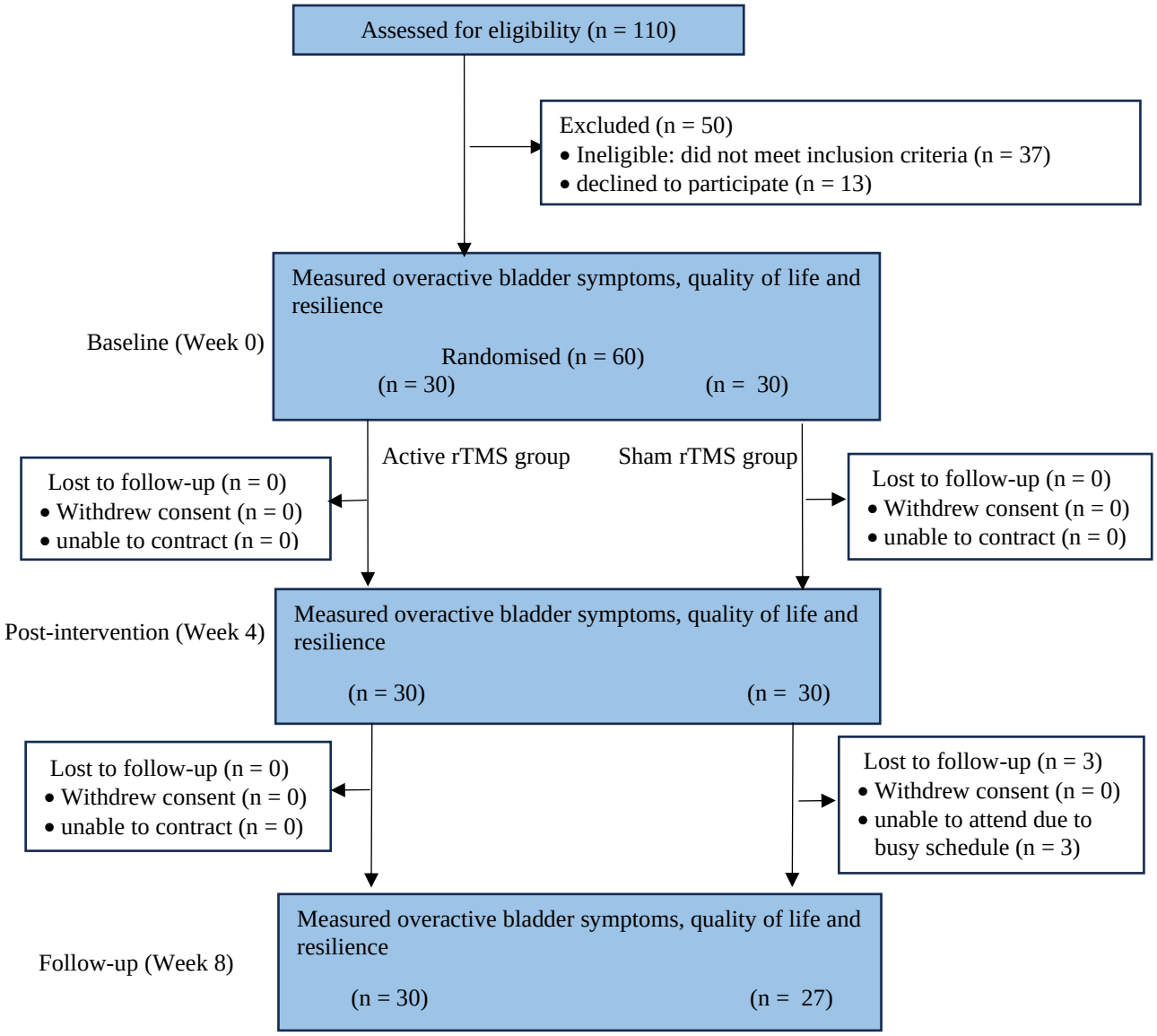

Figure 6.1: Flow of study participants through the trial

rTMS: repetitive Transcranial Magnetic Stimulation

6.2.2 Baseline characteristics of the study participants

The baseline sociodemographic and clinical characteristics of all study participants are shown in Table 6.1. The mean age was 62.10 years (standard deviation [SD] = 9.54) in the active rTMS group and 61.67 years (SD 8.29) in the sham rTMS group, ranging from 37 to 78 years across both groups. In addition, across all study participants, 32 (53.3%) were male, and 28 (46.7%) were female. All study participants belonged to the same Chinese ethnic background. At baseline, sociodemographic and clinical characteristics did not differ significantly between the active and sham rTMS groups. All participants in both groups completed the four-week intervention protocol. However, three in the sham rTMS group were lost to follow-up due to their busy and conflicting schedules.

Table 6.1: Baseline characteristics of the study participants

Characteristic	**Active rTMS group (n = 30)**	**Sham rTMS group (n = 30)**	***p*-value**
Age, Mean ± SD	62.10 ± 9.54	61.67 ± 8.29	0.908*
Gender, *n* (%)			0.121†
Male	13 (43.3%)	19 (63.3%)	
Female	17 (56.7%)	11 (36.7%)	
Side of hemiplegia *n* (%)			0.071†
Right	18 (60%)	11 (36.7%)	
Left	12 (40%)	19 (63.3%)	
Marital status n (%)			0.634†
Married	19 (63.3%)	22 (73.3%)	
Divorced	8 (26.7%)	5 (16.7%)	
Single	3 (10%)	3 (10%)	
Level of Education, *n* (%)			0.601†
Degree	3 (10%)	2 (6.7%)	
College Diploma	5 (16.7%)	2 (6.7%)	
High School	19 (63.3%)	23 (76.7%)	
Primary school	3 (10%)	3 (10%)	
Baseline assessments, Mean ± SD			
OABSS score	7.53 ± 1.72	8.13 ± 2.56	0.290*
I-QOL score	48.32 ± 8.92	46.52 ± 5.32	0.348*
BRS score,	3.13±0.41	2.93±0.42	0.076*
Time since stroke (months)	43.70 ± 28.92	48.18 ± 34.52	0.605*

rTMS: repetitive transcranial magnetic stimulation; OABSS: overactive bladder symptom score; I-QOL: incontinence quality of life questionnaire

*Independent sample t-test

†Fisher exact test.

6.2.3 Safety of rTMS for stroke survivors

The rTMS intervention was generally well-tolerated by participants in both groups. Mild headache was the only adverse reaction reported by the study participants. Two participants (3.3%) in the active rTMS group and one (1.6%) in the sham rTMS group reported mild headaches post-treatment. Nonetheless, all of these participants reported that the headache had resolved before the next treatment visit. No study participants reported any adverse effects during the week-8 follow-up assessments. Notably, none of the participants in either group reported rTMS-induced seizures throughout the study period. Figures 6.2, 6.3 and 6.4 present images of participants receiving the rTMS intervention, the right primary motor cortex (M1) connected to the TMS machine during the intervention, and representations of the stimulation induced by electrical fields generated by active and sham rTMS, respectively.

Figure 6.2: Participant from the active rTMS group receiving Repetitive Transcranial Magnetic Stimulation Intervention

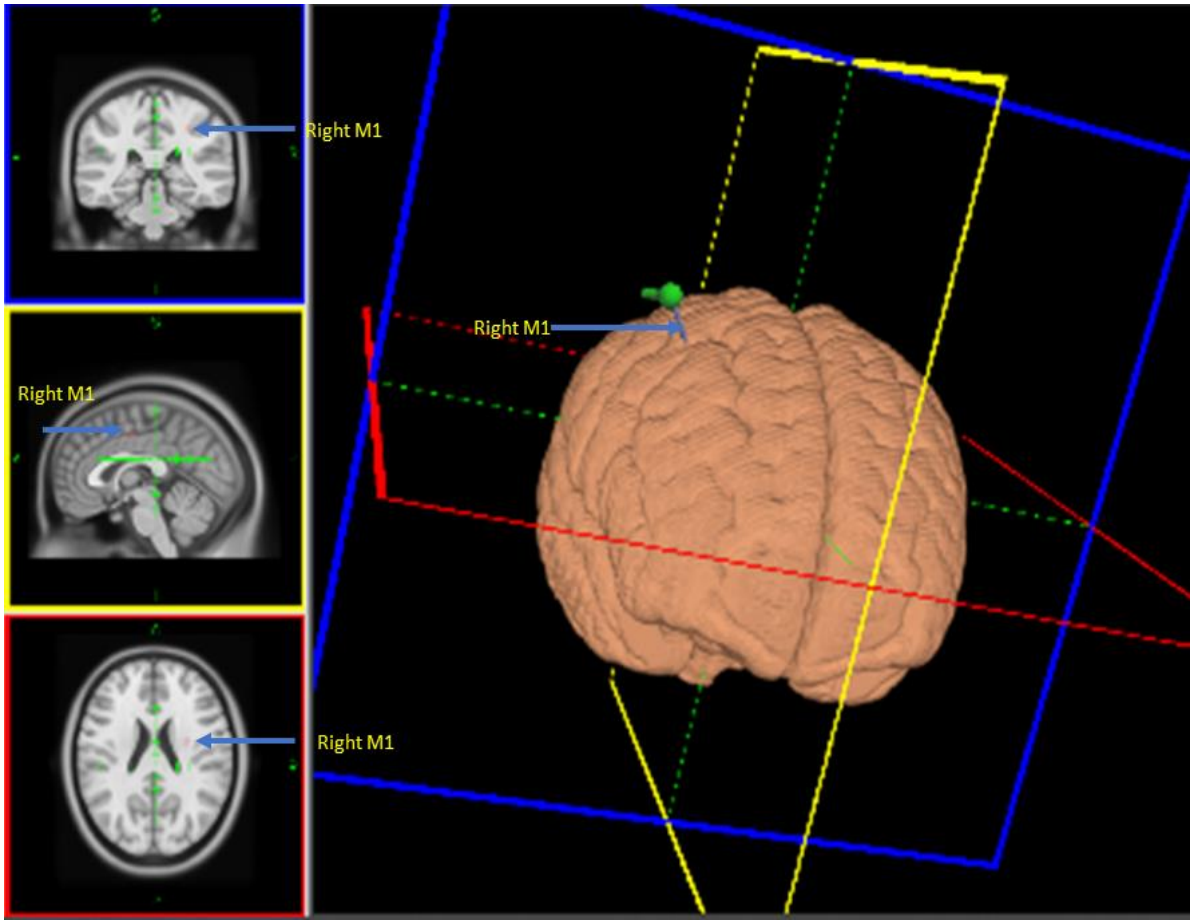

Figure 6.3: Right M1 depicted by Transcranial Magnetic Stimulation Machine during Intervention (MagVenture A/S, Tonica Elektronik A/S Lucernemarken 15 DK-3520 Farum, Denmark)

Note: M1: primary motor cortex

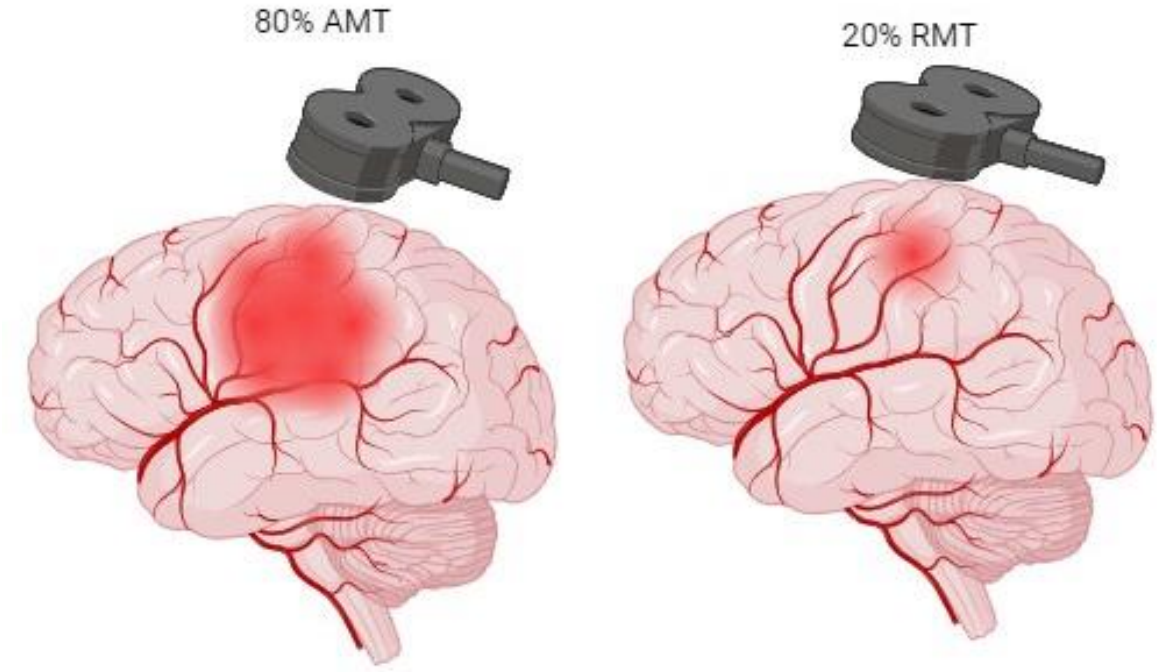

Figure 6.4: Simulation representations of electrical field induced by active-rTMS (80% AMT: represented by large red shedding indicating increased TMS-induced electrical field) and sham-rTMS (20% RMT: represented by small red shedding indicating reduced TMS-induced electrical field)

Note: AMT: Active motor threshold stimulation; RMT: Active motor threshold stimulation; rTMS: repetitive Transcranial magnetic stimulation

6.2.4 Descriptive findings of the outcome measures

The descriptive findings of the primary and secondary outcome measures are presented in Table 6.2.

6.2.4.1 OAB symptom severity using the OABSS

In the active rTMS group, the mean OABSS was 7.5 ± 1.7 at baseline (week 0), progressively decreasing to 2.9 ± 1.2 at the post-intervention (week 4) assessment and 2.6 ± 1.1 at the follow-up (week 8) assessment. These findings indicate a substantial reduction in the severity of neurogenic OAB symptoms after the rTMS intervention (week 4), which was maintained at the follow-up visit (week 8). In the sham rTMS group, the mean OABSS was 8.1 ± 2.6 at baseline (week 0), marginally higher than the mean OABSS in the active rTMS group, although the difference was not statistically significant, and decreased slightly to 7.6 ± 2.7 at the post-intervention (week 4) assessment and 7.5 ± 2.4 at the follow-up (week 8) assessment (Figure 6.5).

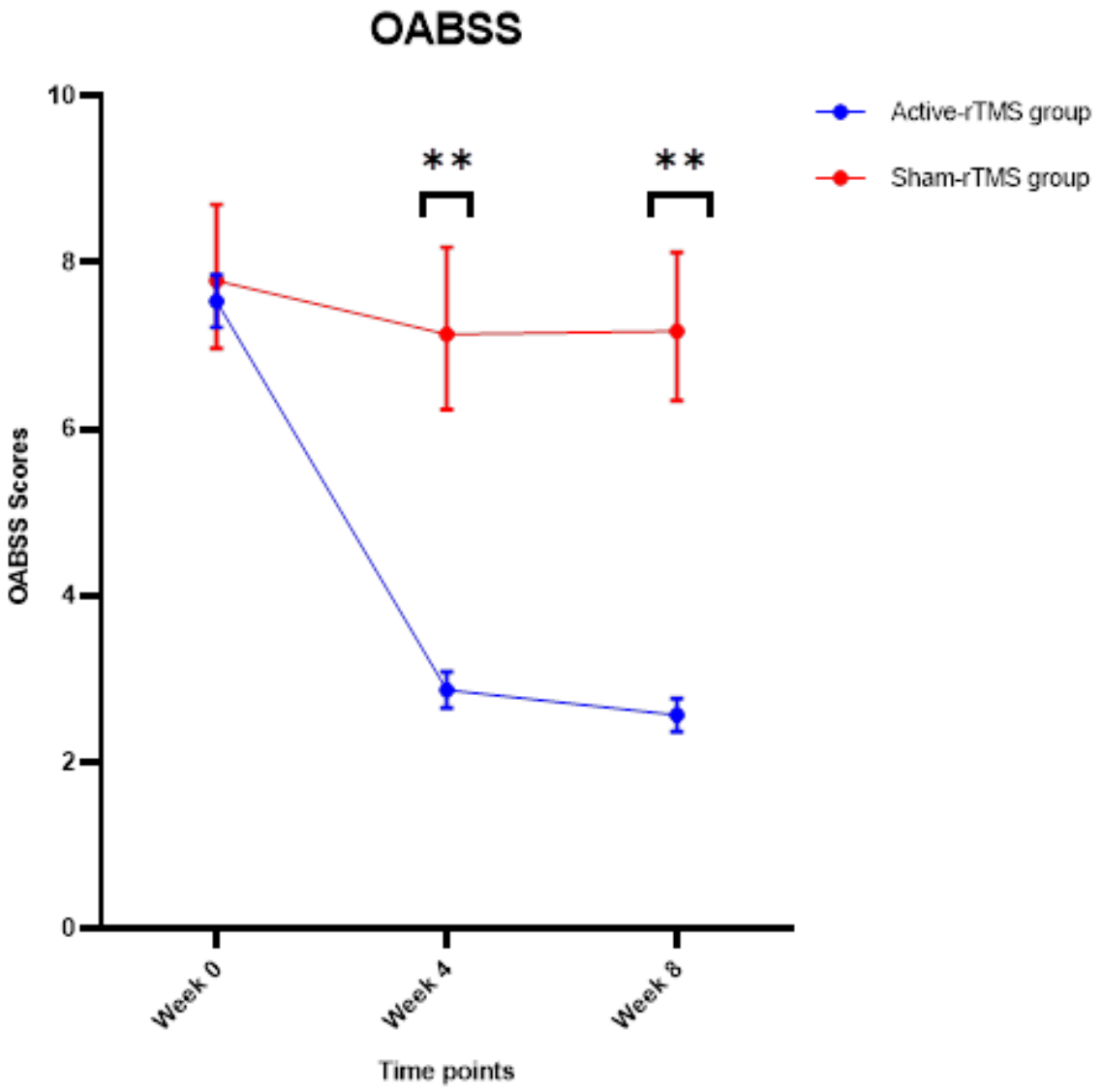

Figure 6.5: Mean overactive bladder symptom score (OABSS) for overactive bladder symptoms from baseline (week 0), post-intervention (week 4) to follow-up (week 8). The OABSS scores in the active repetitive transcranial magnetic stimulation (rTMS) group were significantly lower than in the sham-rTMS at week 4 and week 8 (** = $p<0.001$). OABSS scores range from 0 to 15, with higher scores indicating more severe symptoms.

6.2.4.2 OAB-related Quality of Life using the I-QOL

In the active rTMS group, the mean I-QOL score was 48.3 ± 8.9 at baseline (week 0), increasing to 76.6 ± 11.4 at the post-intervention (week 4) assessment and 79.0 ± 13.9 at the follow-up (week 8) assessment. These findings suggest a remarkable improvement in OAB-related quality of life in the active rTMS group. In the sham rTMS group, the mean I-QOL score was 46.5 ± 5.3 at baseline (week 0), lower than the mean I-QOL score in the active rTMS group, although the difference was not statistically significant, and increased marginally to 50.7 ± 4.6 at the post-intervention (week 4) assessment before decreasing slightly to 50.3 ± 5.3 at the follow-up (week 8) assessment (Figure 6.6).

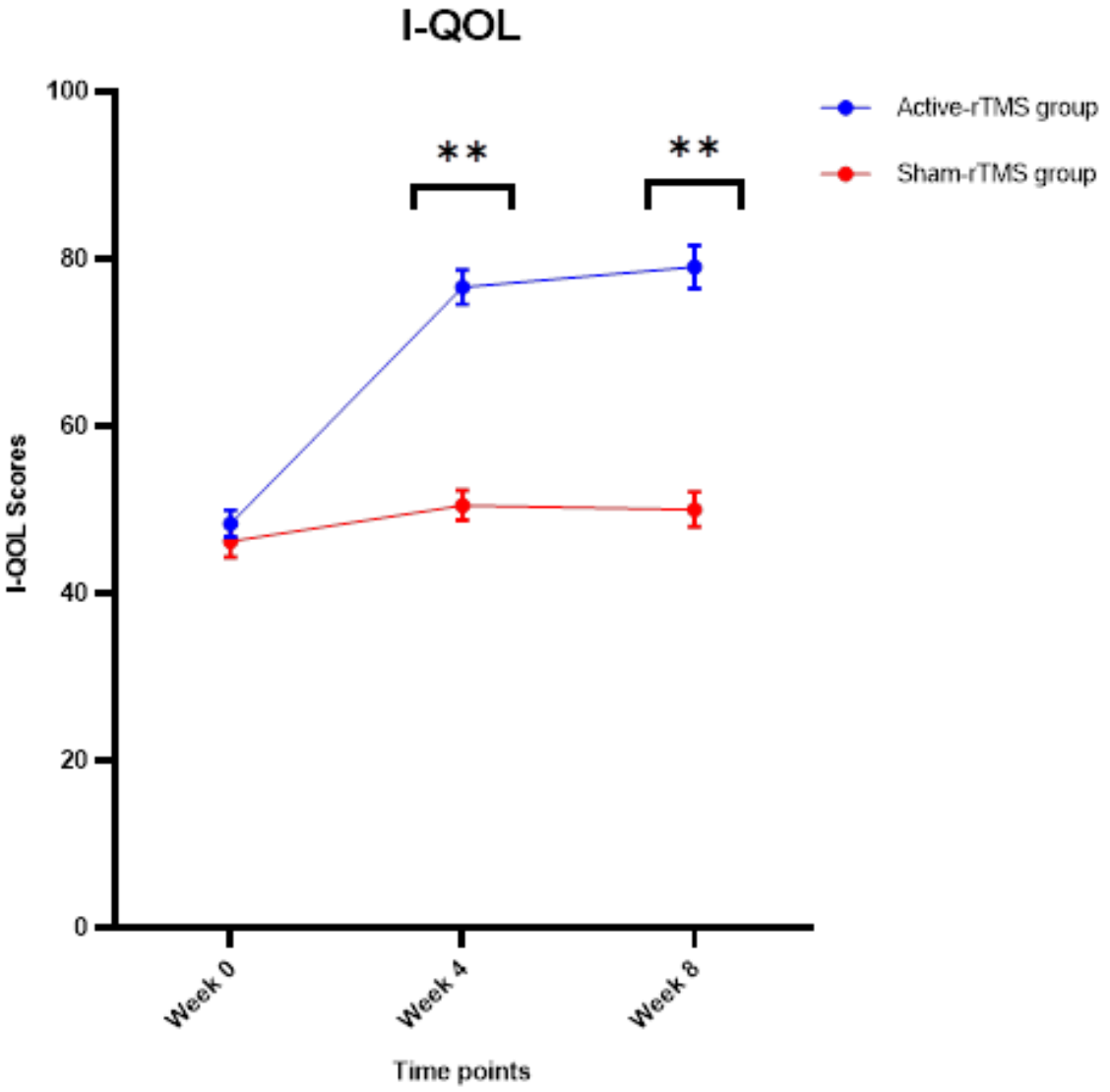

Figure 6.6: The mean Incontinence Quality of Life (I-QOL) for OAB-related quality of life from baseline (week 0), post-intervention (week 4) and follow-up (week 8). The active repetitive transcranial magnetic stimulation (rTMS) group demonstrated a significantly greater improvement in the quality of life compared to the sham-rTMS group from week 4, and week 8. The I-QOL scores range from 0 to 100, with higher scores indicating greater improvement in quality of life.

6.2.4.3 Resilience using BRS

In the active rTMS group, the mean BRS score was 3.3 ± 0.4 at baseline (week 0), increasing marginally to 3.3 ± 0.5 at the post-intervention (week 4) assessment and remaining largely unchanged at 3.4 ± 0.6 at the follow-up (week 8) assessment. These findings indicate a mild improvement in the OAB-related resilience in the active rTMS group. In the sham rTMS group, the mean BRS score was 2.9 ± 0.4 at baseline (week 0), lower than the mean BRS score in the active rTMS group, although the difference was not statistically significant, and increased to 3.0 ± 0.5 at the post-intervention (week 4) assessment and 3.1 ± 0.7 at the follow-up (week 8) assessment (Figure 6.7).

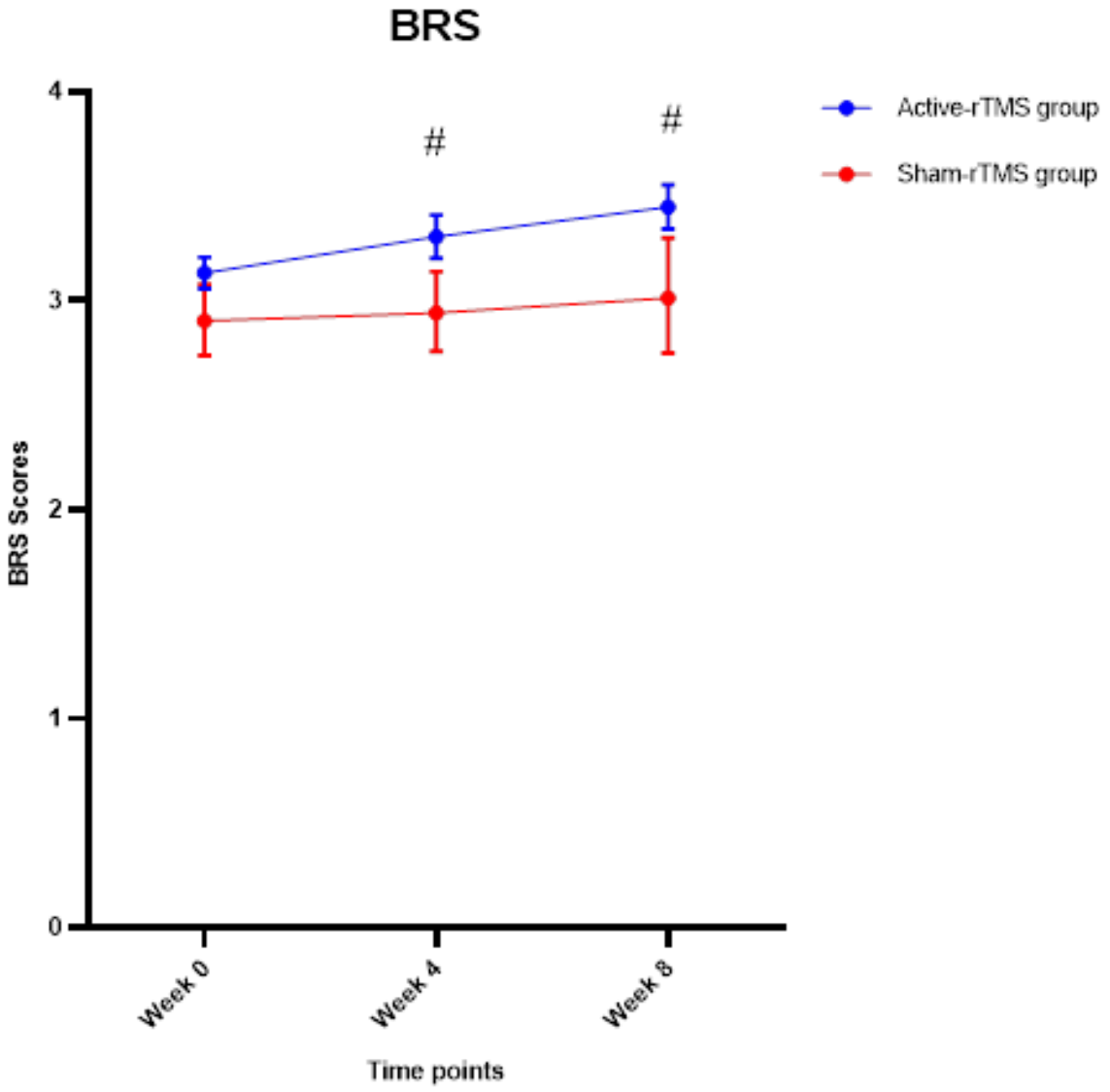

Figure 6.7: Mean brief resilience scale (BRS) scores for resilience from baseline (week 0), post-intervention (week 4) and follow-up (week 8). The BRS scores within the active repetitive transcranial magnetic stimulation (rTMS) group show a statistically significant difference in week 4 and week 8. The BRS scores range from 0 to 6, with higher scores indicating greater improvement in resilience.

Table 6.2: Descriptive statistics for the primary and secondary outcome measure across the different time points

Statistics	**Active rTMS**			**Sham rTMS**		
	Baseline (Week 0)	Post-intervention (Week 4)	Follow-up (Week 8)	Baseline (Week 0)	Post-intervention (Week 4)	Follow-up (Week 8)
OABSS (0 to 15)						
Mean ± SD	7.5 ± 1.7	2.9 ± 1.2	2.6 ± 1.1	8.1 ± 2.6	7.6 ± 2.7	7.5 ± 2.4
95% CI	6.9, 8.2	2.4, 3.3	2.2, 3.0	7.2, 8.4	6.6, 8.6	6.6, 8.5
Range	6-12	1-6	0-5	6-14	1-13	4-13
I-QOL (0 to 100)						
Mean ± SD	48.3 ± 8.9	76.6 ± 11.4	79.0 ± 13.9	46.5 ± 5.3	50.7 ± 4.6	50.3 ± 5.3
95% CI	45.0, 51.6	72.4, 80.8	73.8, 84.2	44.6, 48.5	49.9, 52.5	48.3, 52.4
Range	32.7-75.5	53.3-96.4	56.4-98.2	38.2-60.0	37.3-58.2	37.3-62.2
BRS (0 to 6)						
Mean ± SD	3.3 ± 0.4	3.3 ± 0.5	3.4 ± 0.6	2.9 ± 0.4	3.0 ± 0.5	3.1 ± 0.7
95% CI	3.0, 3.3	3.1, 3.5	3.2, 3.7	2.8, 3.1	2.8, 3.1	2.8, 3.4
Range	2.2-4.0	2.3-4.7	2.3-4.5	1.8-4.0	1.8-3.8	1.7-5.0

OABSS: Overactive Bladder Symptom Scores; I-QOL: Incontinence Quality of Life Questionnaire; BRS: Brief Resilience Score; CI: Confidence Interval; SD: Standard Deviation

6.2.5 Adherence to the rTMS intervention

Adherence to the study interventions is reported in Table 6.3. Both the active and sham rTMS groups demonstrated high adherence to the rTMS intervention protocol, successfully completing all 12 intervention sessions during the four-week rTMS treatment period. However, three participants (5% of all study participants) could not attend the follow-up (week 8) assessment due to their conflicting commitments and busy schedules (Figure 6.8).

Table 6.3: Adherence to study interventions

Time points	Active rTMS group (N = 30)	Sham rTMS group (N = 30)
Baseline (Week 0)	30 participants (100%)	30 participants (100%)
Post-intervention (Week 4)	30 participants (100%)	30 participants (100%)
Follow-up (Week 8)	30 participants (100%)	27 participants (95%)

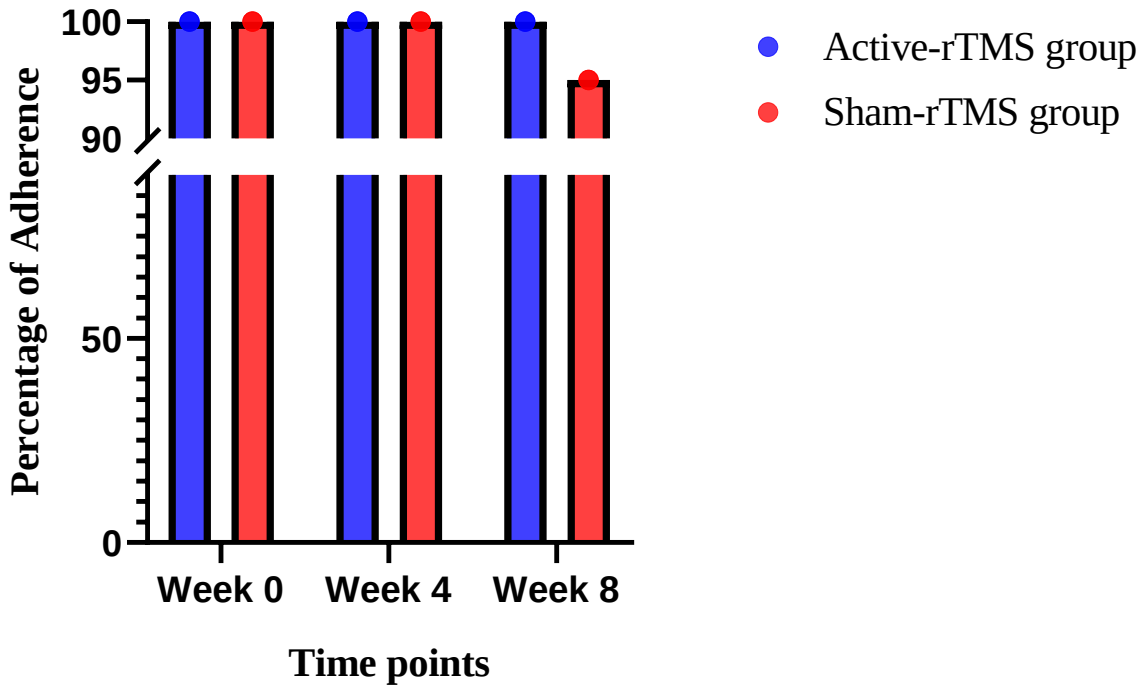

Figure 6.8: Trial adherence of the study participants

6.2.6 Effectiveness of interventions

Table 6.4 presents the within- and between-group differences of the active and sham rTMS groups at the primary and secondary endpoints of the study clinical tools.

6.2.6.1 OABSS

The within-group analysis of OABSS revealed a statistically significant effect for active rTMS from baseline to weeks 4 (primary endpoint; mean difference [MD] = 4.00, 95% confidence interval [CI] = 3.39–4.61, $p < 0.010$) and 8 (secondary endpoint; MD = 4.31, 95% CI = 3.39–4.61, $p < 0.010$). However, OABSS did not differ significantly between week 4 and week 8 (MD = 0.31, 95% CI = −0.11–0.72, $p = 0.140$). The effect sizes in the active rTMS group at the primary and secondary endpoints were 0.68 and 0.75, respectively. Similarly, the within-group analysis of OABSS revealed a statistically significant effect for sham rTMS from baseline to weeks 4 (MD = 0.68, 95% CI = 0.05–1.33, $p = 0.030$) and 8 (MD = 0.69, 95% CI = 0.13–1.25, $p = 0.020$). However, OABSS did not differ significantly between week 4 and week 8 (MD = 0.01, 95% CI = −0.42–0.44, $p = 0.969$).

OABSS differed significantly between the active and sham rTMS groups at the primary (MD = 1.66, 95% CI = 1.22–2.10, $p <0.001$) and secondary (MD = 1.81, 95% CI = 1.42–2.20, $p < 0.001$) endpoints. However, they did not differ significantly from week 4 to week 8 (MD = 0.15, 95% CI = −0.15–0.45, $p = 0.316$). The between-group effect size was medium (0.62).

6.2.6.2 I-QOL

The within-group analysis of I-QOL scores revealed a statistically significant effect for active rTMS from baseline to week 4 (MD = 28.28, 95% CI = 24.4–32.10, $p < 0.010$) and 8 (MD = 30.80, 95% CI = 26.20–35.40, $p < 0.010$). However, I-QOL scores did not differ significantly from week 4 to week 8 (MD = 2.52, 95% CI = −0.90–5.96, $p = 0.147$). Similarly, the within-group analysis of OABSS revealed a statistically significant effect for sham rTMS from baseline to weeks 4 (MD = 4.73, 95% CI = 0.73–8.73, $p = 0.021$) and 8 (MD = 4.17, 95% CI = −0.59–8.93, $p = 0.080$). However, I-QOL scores did not differ significantly between week 4 and week 8 (MD = 0.56, 95% CI = −2.99–4.12, $p = 0.750$). The effect sizes in the active rTMS group at the primary and secondary endpoints were 0.57 and 0.55, respectively.

I-QOL scores differed significantly between the active and sham rTMS groups at the primary (MD = 16.5, 95% CI = 13.73–19.28, $p < 0.001$) and secondary (MD 17.48 = 95% CI = 14.18–20.79, $p < 0.001$) endpoints. However, I-QOL scores did not differ significantly from week 4 to week 8 (MD = 0.98, 95% CI = −1.49–3.45, $p = 0.430$). The between-group effect size was medium (0.74).

6.2.6.3 BRS

The within-group analysis of BRS scores revealed a statistically significant effect for active rTMS from baseline to weeks 4 (MD = 0.20, 95% CI = 0.05–0.34, $p = 0.009$) and 8 (MD = 0.35, 95% CI = 0.12–0.58, $p = 0.004$). However, BRS scores did not differ significantly from week 4 to week 8 (MD = 0.15, 95% CI = −0.03–0.34, $p = 0.108$). The effect sizes in the active rTMS group at the primary and secondary endpoints were 0.14 and 0.23, respectively.

Similarly, the within-group analysis of BRS scores revealed a statistically significant effect for sham rTMS from baseline to weeks 4 (MD = 0.05, 95% CI = −0.09–0.19, p = 0.497) and 8 (MD = 0.16, 95% CI = −0.06–0.38, p = 0.156). However, BRS scores did not differ significantly between week 4 and week 8 (MD = 0.11, 95% CI = −0.07–0.29, p = 0.217).

BRS scores differed significantly between the active and sham rTMS groups at the primary (MD = 0.12, 95% CI = 0.20–0.22, p = 0.018) and secondary (MD = 0.25, 95% CI = 0.09–0.41, p = 0.002) endpoints. However, BRS scores did not differ significantly from week 4 to week 8 (MD = 0.13, 95% CI = −0.003–0.26, p = 0.050). The between-group effect size was small (0.10).

In the multivariable logistic regression analysis, higher baseline symptom severity of the OABSS (Odd Ratio = 1.2, 95% CI: 1.1-1.4, p = 0.01) and younger age (OR = 0.95, 95% CI: 0.92-0.98, p = 0.002) were significant independent predictors of treatment response in the active rTMS group. No significant predictors were identified in the sham group. There was no significant interaction between treatment group and predictors.

Table 6.2: Comparison of the primary and secondary outcome measures

Measures	Time points	Within-group difference (mean difference [95% CI], *p* value)		Within-group effect size (Active rTMS)	Between-group difference (Mean Difference [95% CI] *p* value)	Overall between-group difference (Mean Difference [95% CI] *p* value)	Between-group Effect size
		Active rTMS (n = 30)	Sham rTMS (n = 30)				
Primary outcome measure							
OABSS	T0-T1	4.00 (3.39 to 4.61), <0.001*	0.68 (0.05 to 1.31), 0.03*	0.68	1.66 (1.22 to 2.10), <0.001*	3.22 (2.43 to 4.02), <0.001*	0.62
	T0-T2	4.31 (3.77 to 4.85), <0.001*	0.69 (0.13 to 1.25), 0.02*	0.75	1.81 (1.42 to 2.20), <0.001*		
	T1-T2	0.31 (-0.11 to 0.72), 0.140	0.01 (-0.42 to 0.44), 0.969	-	0.15 (-0.15 to 0.45), 0.316		
Secondary outcome measures							
I-QOL	T0-T1	28.28 (24.4 to 32.10), <0.001*	4.73 (0.73 to 8.73), 0.021*	0.57	16.50 (13.73 to 19.28), <0.001*	18.92 (15.51 to 22.34), <0.001*	0.74
	T0-T2	30.80 (26.20 to 35.40), <0.001*	4.17 (-0.59 to 8.93), 0.08	0.55	17.48 (14.18 to 20.79), <0.001*		
	T1-T2	2.52 (-0.9 to 5.96), 0.147	0.56 (-2.99 to 4.12), 0.75	-	0.98 (-1.49 to 3.45), 0.430		
BRS	T0-T1	0.20 (0.05 to 0.34), 0.009*	0.05 (-0.09 to 0.19), 0.497	0.14	0.12 (0.2 to 0.22), 0.018*	0.28 (0.04 to 0.52), 0.022*	0.10
	T0-T2	0.35 (0.12 to 0.58), 0.004*	0.16 (-0.06 to 0.38), 0.156	0.23	0.25 (0.09 to 0.41), 0.002*		
	T1-T2	0.15 (-0.03 to 0.34), 0.108	0.11 (-0.07 to 0.29), 0.217	-	0.13 (-0.003 to 0.26), 0.05		

rTMS: repetitive transcranial magnetic stimulation; OABSS: overactive bladder symptom score; I-QOL: incontinence quality of life questionnaire; BRS: brief resilience score; CI: confidence interval; T0: Baseline (Week 0); T1: Post-intervention (Week 4); T2: Follow-up (Week 8)

6.2.7 Socioeconomic characteristics

Table 6.5 presents the socioeconomic and demographic characteristics of the participants in the active and sham rTMS groups and the services and support they received. Most participants in both groups had 1–2 children and resided in public or subsidised housing. Regarding living arrangements, most participants in both groups cohabited with a spouse or child/children, while smaller proportions lived independently or with a relative/friend or resided in a residential home/school residence. Home modification was common in both groups, with handrails being the most common. About 63% (n = 38) of all participants received care from unpaid caregivers, with spouses (50%) being the most frequent caregivers. About 82% (n = 49) of all participants had a monthly income of less than $20,000, and 95% ($n$ = 57) received some form of government social support, such as disability or old age allowance. About 58% (n = 35) of all participants received assistance from a non-governmental organisation (NGO), with therapeutic training being the most utilised service.

Table 6.3: Socio-economic characteristics of stroke survivors with neurogenic OAB

	Active rTMS group (n = 30)	Sham rTMS group (n = 30)
Number of Children, *n* (%)		
0	5 (16.7%)	6 (20%)
1	9 (30%)	9 (30%)
2	9 (30%)	12 (40%)
3	6 (20%)	3 (10%)
4	1 (3.3%)	0 (0%)
Types of Residence, *n* (%)		
Public Housing	7 (23.3%)	7 (23.3%)
Bought Subsidised Home Ownership	11 (36.7%)	12 (40%)
Rented Subsidized Home Ownership	4 (13.3%)	4 (13.3%)
Bought Private Housing Flat	5 (16.7%)	6 (20%)
Rented Private Housing Flat	2 (6.7%)	0 (0%)
Rented Subdivided Flat	1 (3.3%)	1 (3.3%)
Living partner, *n* (%)		
Living alone	1 (3.3%)	5 (16.7%)
Both parents	4 (13.3%)	4 (13.3%)
Single parent	1 (3.3%)	2 (6.7%)
Spouse	12 (40%)	15 (50%)
Child/Children	6 (20%)	2 (6.7%)
Relative/Friend	5 (16.7%)	2 (6.7%)
Residential Home/School residence	1 (3.3%)	0 (0%)
Home Modification, *n* (%)		
Handrails	13 (43.3%)	14 (46.7%)
Patient Hoist	5 (16.7%)	3 (10%)
Shower Chair	5 (16.7%)	5 (16.7%)
No	7 (23.3%)	8 (26.6%)
Receiving Care from Unpaid Carers, *n* (%)		
Mother	3 (13.3%)	4 (13.3%)
Father	1 (3.3%)	2 (6.7%)
Spouse	9 (30%)	10 (33.3%)
Child/Children	4 (13.3)	2 (6.7%)
Relative/Friend	1 (3.3%)	2 (6.7%)
No	12 (36.8%)	10 (33.3%)
Monthly Income *n* (%)		
Less than $10,000	11 (36.7%)	15 (50%)
10,001 to 20,000	12 (40%)	11 (36.7%)
20,001 to 30,000	7 (23.3%)	2 (6.7%)
60,001 to 70,000	0 (0%)	1 (3.3%)
70,001 to 80,000	0 (0%)	1 (3.3%)
Social Support from Government *n* (%)		
CSSA	2 (6.7%)	1 (3.3%)
Normal Disability Allowance	19 (63.3%)	21 (70%)
Higher Disability Allowance	4 (13.3%)	4 (13.3%)
Old Age Allowance	3 (10%)	1 (3.3%)
Community Care Fund	0 (0%)	2 (6.7%)
No	2 (6.7%)	1 (3.3%)
Utilisation of NGO *n* (%)		
Homework guidance	3 (10%)	4 (13.3%)
Therapeutic training	9 (30%)	9 (30%)
Counselling	1 (3.3%)	3 (10%)
Recreation services	3 (10%)	3 (10%)
No	14 (46.7%)	11 (36.7%)

rTMS: repetitive transcranial magnetic stimulation; OABSS: Overactive Bladder Symptom Score; I-QOL: Incontinence Quality of Life Questionnaire; CSSA: Comprehensive Social Security Assistance; NGO: Non-Governmental Organisation

6.2.8 Costs estimation incurred in the active and sham rTMS groups

Table 6.6 presents the incurred cost categories estimated for the participants in the active and sham rTMS groups: urology clinic (consultations and medications), alternative medicine (e.g. acupuncture, yoga and massage), medical devices/consumables (e.g. diapers, liners, mattress covers, personal care wipes, skincare and washcloths), and transportation (e.g. mass transit railway [MTR], taxi, bus or rehab bus). The mean total cost utilised per patient was HK$1267.3 (95% CI = 1148.2–1386.5) in the active rTMS group and HK$ 1839.0 (95% CI = 1654.2–2023.8) in the sham rTMS group, suggesting that the estimated mean costs per patient were lower in the active rTMS group than in the sham rTMS group.

Table 6.4: Costs associated with active rTMS and sham rTMS groups

Cost category, ***Mean (95% CI)***	**Active rTMS group (N= 30)**	**Sham rTMS group (N=30)**
Urology Clinic (Consultation and medications)	221.0 (146.9 to 295.1)	336.7 (248.8 to 424.5)
Physiotherapy	278.3 (237.4 to 319.3)	408.3 (347.9 to 468.8)
Alternative Medicine (Acupuncture, Yoga, Massage)	370 (335.5 to 404.5)	438.3 (396.5 to 433.3)
Medical devices/ Consumables (Diapers, liners, mattress covers, personal care wipes, skincare and washcloths)	181.7 (135.6 to 227.7)	315.7 (254.1 to 377.3)
Transportation (MTR, Taxi, Bus or Rehab bus)	216.3 (181.0 to 251.6)	340.0 (294.2 to 385.8)
Total cost per participant	1267.3 (1148.2 to 1386.5)	1839.0 (1654.2 to 2023.8)
Incremental cost gain	HK$571.7 (-500 to 637.3)	

rTMS, Repetitive Transcranial Magnetic Stimulation; MTR: mass transit railway. The costs for all resources are denominated in Hong Kong Dollars (HKD) for the year 2023.

6.3 Discussion

6.3.1 Key findings

This RCT is the first to investigate the clinical effectiveness of low-frequency rTMS in managing neurogenic OAB symptom severity among stroke survivors. It also included an economic evaluation that compared the estimated costs of the active and sham rTMS as an intervention for managing neurogenic OAB symptom severity in stroke survivors. Sixty stroke survivors with neurogenic OAB who met the eligibility criteria were enrolled in the RCT and participated in the baseline (week 0), post-intervention (week 4), and follow-up (week 8) assessments. Sociodemographic and clinical characteristics did not differ significantly between the active and sham rTMS groups at baseline (week 0).

The within-group analysis demonstrated significant effects of the active rTMS intervention on OABSS, I-QOL and BRS scores at the primary (week 4) and secondary (week 8) endpoints but non-significant effects from week 4 to week 8. The within-group analysis also demonstrated a significant effect of the sham rTMS intervention on OABSS at the primary and secondary endpoints. Additionally, the within-group analysis revealed significant effects of the sham rTMS intervention on I-QOL scores only at the primary endpoint (week 4). However, the within-group analysis showed no significant effect of the rTMS intervention on BRS scores at the primary and secondary endpoints. The within-group effect sizes of the active rTMS intervention at the primary and secondary endpoints were 0.68 and 0.75 (medium) for OABSS, 0.57 and 0.55 (medium) for the I-QOL, and 0.14 and 0.23 (small) for the BRS.

The between-group analysis of the active and sham rTMS interventions revealed significant effects on OABSS, I-QOL and BRS scores at the primary (week 4) and secondary (week 8) endpoints. However, the between-group analysis indicated that the post-intervention effects of the active and sham rTMS interventions on OABSS, I-QOL and BRS scores did not differ significantly between the primary (week 4) and secondary (week 8) endpoints. The between-group effect sizes of active rTMS compared to sham rTMS for OABSS, I-QOL and BRS scores were 0.62 (medium), 0.74 (medium) and 0.10 (small), respectively.

The total mean costs of the study participants revealed that the mean cost per patient was HK$1267.3 (95% CI = 1148.2–1386.5) in the active rTMS group and HK$1839.0 (95% CI = 1654.2–2023.8) in the sham rTMS group. These findings indicate that the mean cost per patient was higher in the sham rTMS group than in the active rTMS group.

6.3.2 Interpretation of RCT results

The RCT found that the active rTMS intervention had a significant and clinically meaningful impact on OAB symptom severity, quality of life and resilience among stroke survivors with neurogenic OAB. The between-group MD in OABSS at the primary and secondary endpoints were 1.66 (95% CI 1.22 to 2.10, $p < 0.001$) and 1.81 (95% CI 1.42 to 2.20, $p < 0.001$), respectively, with overall between-group difference as 3.22 (95% CI 2.43 to 4.02, $p < 0.001$) exceeding the suggested minimal clinically important difference (MCID) of 3 points, indicating a clinically meaningful difference between the active and sham rTMS interventions [497]. This finding suggests that the active rTMS intervention substantially affects OAB symptom severity, exceeding the threshold for clinical relevance. It also demonstrate that the

significant improvement achieved at primary endpoint is sustained at the secondary endpoint. These results imply that the active rTMS intervention had a significant and worthwhile effect on OABSS compared to the sham rTMS intervention both pots-intervention and follow-up assessment timepoints, which is important for clinical decision-making and patient care. Similarly, the between-group MD in I-QOL scores at the primary and secondary endpoints were 16.50 (95% CI 13.73 to 19.28, $p < 0.001$) and 17.48 (95% CI 14.18 to 20.79, $p < 0.001$), respectively, with overall between-group difference as 18.92 (95% CI 15.51 to 22.34, $p < 0.001$), demonstrating improvement in OAB-related quality of life with a moderate between-group effect size of 0.7 and MD is well above the MCID of 6.8 points for the I-QOL instrument [533]. It also reveals that the significant improvement demonstrated at the primary endpoint is sustained at the secondary endpoint. These findings indicate that the active rTMS intervention has a clinically meaningful and worthwhile effect on I-QOL, suggesting that it effectively improves the quality of life of stroke survivors with neurogenic OAB at the post-intervention and follow-up assessment timepoints [533].

The findings of this RCT are consistent with Bruso et al. [179], who investigated the effects of low-frequency rTMS on individuals with OAB symptoms due to Parkinson's disease and found it enhanced bladder capacity. Neurogenic OAB symptoms are common in individuals with Parkinson's disease due to detrusor overactivity [534, 535]. A case report on neurogenic OAB in stroke by Qian et al. found that continuous theta burst stimulation, a form of rTMS [536], decreased urinary frequency and anxiety and improved quality of life. Both of these studies demonstrated the potential effects of rTMS on the M1 region in improving neurogenic OAB symptom severity.

The similar pathophysiological presentation of neurogenic overactivity among stroke survivors and those with Parkinson's disease informed the comparison of the current RCT findings to Bruso et al. [179]. The participants in Bruso et al. [179] reported enhanced bladder capacity and the first sensation of the filling phase after low-frequency rTMS [179]. This improvement is presumed to be related to the induction of cortical inhibition, which suppresses neural overactivity in the descending projections, ultimately reversing OAB symptom severity by increasing pelvic floor tonicity and reducing detrusor overactivity. However, the outcome measures and the Parkinson's disease population used in Bruso et al. [179] differ from the stroke survivors and outcome measures used in our study. However, these disparities in study populations and outcome measures may not hinder direct comparisons between our findings and those of Bruso et al. [196], given the similar pathophysiology and treatment outcomes achieved.

Stroke and Parkinson's disease can cause neurogenic OAB symptoms, which are primarily due to involuntary detrusor overactivity during the storage phase [46]. Therefore, inhibitory rTMS may have induced an opposite modulation in the descending corticospinal tract output targeting the detrusor muscle, reducing bladder overactivity [537]. The rTMS intervention may also increase motor cortical output, resulting in enhanced modulation of the motor emotional system and improved control over the pontine micturition centre [538]. This explanation provides a potential mechanism for the observed effects of inhibitory rTMS on bladder function in individuals with detrusor overactivity, offering insights into the specific neural pathways and mechanisms involved in modulating neurogenic OAB symptom severity among stroke survivors [179].

Several studies have found that applying low-frequency rTMS to the contralateral M1 of stroke survivors, as our study did, effectively decreased the resting motor threshold and increased the motor-evoked potential [189, 539, 540]. The finding that low-frequency rTMS is effective in managing neurogenic OAB symptom severity among stroke survivors is supported by the precept that the representation of the pelvic floor muscles is located in the M1 [69, 175, 176, 178, 477, 541]. A TMS study by Yani et al. examining the distributed representation of pelvic floor muscles in the human motor cortex among healthy individuals reported that pelvic floor muscles are broadly represented in the M1 [541]. Previous studies have demonstrated strong activation of the M1 in response to the contraction and synergies of pelvic floor muscles via cortico-spinal projections in both men and women [486, 542, 543]. M1 regions, such as the superolateral and superomedial precentral gyri, have been reported as critical structures for the voluntary control of the pelvic floor muscles [542, 544], suggesting that modulating M1 activity through rTMS may directly impact the function of the pelvic floor muscles and related bladder control. Targeting the M1 with low-frequency rTMS makes it possible to modulate the neural circuits involved in pelvic floor muscle function, potentially leading to improvements in neurogenic OAB symptom severity [179]. This rationale is supported by the observed effectiveness of low-frequency rTMS in our study and provides a neurophysiological basis for its therapeutic potential in managing neurogenic OAB.

6.3.3 Interpretation of cost estimation results

The average estimated costs for each participant with neurogenic OAB due to stroke was lower in the active rTMS group than in the the sham rTMS group. intervention, reducing the costs incurred from urology consultations, medications, physiotherapy services for urinary incontinence management (e.g. electrical stimulation and pelvic floor muscle exercises),

alternative therapies (e.g. yoga, taichi and massage), medical devices/consumables (e.g. disposable diapers and underpads), and travel expenses. Our findings suggest that the active rTMS intervention has lower cost estimate than the sham rTMS intervention, resulting in lower expenses and higher QALYs. The lower costs observed in the active rTMS group than in the sham rTMS group indicate that the active rTMS intervention was both efficacious with lower estimated cost of the intervention. The estimated lower cost estimate will allow decision-makers to assess the value of different treatment strategies and make informed choices about resource allocation within the healthcare system [545]. This estimated cost can guide healthcare policy and resource allocation decisions, helping to prioritise interventions that offer the greatest health benefits relative to their costs [546]. It also provides a clear standard for determining the cost estimation analyses of healthcare strategies [547], including the potential adoption of rTMS for managing neurogenic OAB in Hong Kong. Given the relatively high GDP per capita in Hong Kong, there may be greater capacity within the healthcare system to invest in innovative interventions such as rTMS with low estimated cost of management.

Brusa et al. [179] revealed that rTMS can effectively reduce urinary frequency and urgency in individuals with neurogenic OAB due to Parkinson's disease. Our findings also revealed that rTMS is a clinically efficacious, well-tolerated intervention with no significant adverse effects. Additionally, neuromodulation, such as rTMS, is a non-invasive and safe procedure [520, 548-550], which may result in lower healthcare costs than more invasive or high-risk treatments [551-553]. Given its observed effectiveness in our study, clinically implementing rTMS may lead to cost savings by reducing the expenses for other treatments such as medications, catheterisation or surgery. From the societal perspective in Hong Kong, cost estimation includes detailed direct medical costs [554], such as physiotherapy, alternative medicine, medical devices/consumables and the transportation associated with managing neurogenic

OAB. It also accounts for not only the clinical burden on the healthcare system but also the economic burden on patients, caregivers and the broader community, which can inform healthcare policy, resource allocation and decision-making [555]. However, it is important to note that the cost estimate of rTMS for neurogenic OAB may vary depending on factors such as the frequency and duration of treatment, the availability of rTMS facilities and individual patient responses.

6.4 Clinical Implications

Our results suggest that low-frequency rTMS could be an effective and safe treatment option for managing neurogenic OAB symptom severity in stroke survivors. They showed that the active rTMS intervention was associated with significant improvements in neurogenic OAB symptom severity, quality of life, and resilience compared to the sham rTMS intervention. The observed effect sizes were above the suggested MCID, indicating that the improvements were clinically meaningful. Our study also found that the effects of the active rTMS intervention were maintained at the follow-up (week 8) assessment. These findings provide valuable insights into the potential clinical benefits of rTMS as a non-invasive therapeutic option for stroke survivors with neurogenic OAB.

The results of our RCT and cost estimation study provide valuable information for physiotherapists specialising in stroke rehabilitation. The RCT suggests that a low-frequency rTMS intervention is an effective and safe procedure [520, 548-550] for managing neurogenic OAB symptom severity in stroke survivors. Physiotherapists and other healthcare providers can consider incorporating this intervention into their treatment plans for stroke survivors with

neurogenic OAB symptoms. Additionally, our study highlights the importance of considering the cost estimation of interventions in stroke rehabilitation since it can help guide decision-making and resource allocation. Our findings may provide clinicians with clinically useful findings, such as reduced urinary frequency, urinary frequency and urgency incontinence, cost estimation and positive patient experiences, which can be incorporated into their rehabilitation programs to address neurogenic OAB symptom severity and improve the overall quality of life of stroke survivors.

Our findings could also positively impact the well-being and daily functioning of stroke survivors with neurogenic OAB, given the non-invasiveness and convenience of rTMS. The rTMS intervention may also contribute to reducing the burden on healthcare systems by providing an estimated lower-cost and patient-friendly intervention for neurogenic OAB management. Overall, our findings can potentially inform clinical practice and guide future research in neurogenic OAB management, ultimately contributing to the development of more effective and cost-efficient interventions for individuals with neurological bladder issues.

6.5 Strengths and limitations

This RCT is the first to investigate the effectiveness of rTMS in alleviating the neurogenic OAB symptom severity, quality of life and resilience of individuals with neurogenic OAB due to stroke. Our findings revealed positive effects of the rTMS intervention in managing the severity of OAB symptoms, improving the quality of life and resilience of individuals with neurogenic OAB due to stroke. Our study also demonstrated that the active rTMS intervention

has an estimated lower cost in managing the neurogenic OAB symptom severity compared to the sham rTMS intervention.

Our study treated a relatively large sample size with the rTMS intervention and had a high treatment completion rate (100%) of the 12 rTMS treatment sessions and a high follow-up rate (95%), indicating a high level of adherence to the treatment protocol [556]. This high adherence rate indicates the participants' commitment to the treatment and willingness to participate in the follow-up assessments [556]. High adherence rates in clinical interventions are important since they can contribute to the reliability and validity of the study results and provide valuable insights into the effectiveness and tolerability of the treatment [557]. Our study followed allocation concealment and analysis on an intention-to-treat basis to minimise the influence of bias, enhance the validity of the results, and strengthen the overall quality of the research findings [558].

Our study suggests that rTMS could be a non-invasive and more comfortable option for managing neurogenic OAB in stroke survivors than other treatments such as percutaneous tibial nerve stimulation, augmentation cystoplasty, botulinum toxin type A, sacral neuromodulation and bladder reconstruction surgery. Since rTMS intervention has been shown to be effective in relieving OAB symptom severity, individuals with neurogenic OAB due to stroke may not need to consider invasive interventions that involve the insertion of vaginal or anal probes.

1. Our RCT had some limitations that should be acknowledged. Firstly, the four-week follow-up duration could be a potential limitation since it is relatively short and may not capture the long-term effects of the rTMS intervention on neurogenic OAB symptom severity among stroke survivors. Secondly, our findings may be limited to stroke survivors with neurogenic OAB and not generalise to OAB caused by other neurological conditions. Thirdly, cost estimation analyses may not capture the full spectrum of costs and benefits since they typically focus on direct medical costs and health outcomes and may not account for indirect costs such as productivity losses, caregiver burden or long-term societal impacts. Additionally, the lack of baseline mobility assessment among stroke survivors with neurogenic OAB rTMS could have confounded the findings. To mitigate these issues, future studies should include a baseline mobility assessment using validated tools, such as the De Morton Mobility Index (DEMMI) or the Clinical Frailty Scale (CFS) to classify participants' functional status at baseline. This would allow for better control of confounding variables, more accurate interpretation of results, and improved generalizability of the findings. Neglecting to assess bowel dysfunction could have led to overlooking potential improvements that participants might have experienced from rTMS interventions. Because bowel dysfunction commonly co-exists with bladder symptoms. The bladder and bowel share common neurological pathways. Symptoms of bladder and bowel dysfunction can overlap, and treating one may impact the other.

6.6 Conclusions

Our study found that the active rTMS intervention significantly improved OABSS, I-QOL and BRS scores at the primary and secondary endpoints. In contrast, the sham rTMS intervention

only significantly improved OABSS at the primary and secondary endpoints and I-QOL scores at the primary endpoint and did not significantly affect BRS scores. Our study also demonstrated significantly better OABSS, I-QOL and BRS scores in the active rTMS group compared to the sham rTMS group at the primary and secondary endpoints. The overall between-group findings demonstrated that the rTMS intervention significantly improved the OABSS, I-QOL and BRS scores of stroke survivors with neurogenic OAB with effect sizes of 0.62, 0.74 and 0.10, respectively. Between-group MDs for the OABSS and I-QOL instruments exceeded their MCID, indicating a clinically meaningful difference between the active and sham rTMS interventions. This observation suggests that the rTMS intervention is effective, clinically worthwhile and meaningful in improving the OAB symptom severity, quality of life and resilience in stroke survivors with neurogenic OAB. Our study also found a lower cost and higher QALY in the active rTMS group than in the sham rTMS group, indicating that the active rTMS intervention was associated with an estimated lower cost and greater quality of life and efficacy. Baseline neurogenic OAB symptom severity and age could be used to identify stroke survivors who are more likely to benefit from rTMS intervention. Our findings suggest that low-frequency rTMS may be a promising treatment option for stroke survivors experiencing neurogenic OAB symptoms. They provide valuable insights into the potential of low-frequency rTMS as a non-invasive and effective therapeutic approach for addressing neurogenic OAB symptom severity in stroke survivors. The realistic use of rTMS as a novel therapy in routine rehabilitation for stroke survivors with neurogenic OAB requires careful consideration of feasibility, cost-effectiveness, patient selection, and integration into multidisciplinary rehabilitation programs. By addressing these factors and continuously gathering evidence, rTMS can be effectively incorporated into routine care to improve patient outcomes. rTMS as a stand-alone therapy could be appealing to patients with neurogenic OAB who prefer to avoid medications or invasive procedures. While as an adjunctive effects, rTMS when administered

in combination with other interventions such as medications, pelvic floor muscle training, or lifestyle modification, rTMS might enhance overall therapeutic outcomes. It could help reduce symptoms more effectively compared to single therapy. Generally, decisions regarding the use of rTMS, whether as a stand-alone or adjunctive therapy, should be made on a case-by-case basis, considering the patient's specific condition, treatment history, and goals.

6.7 Recommendations for future research

Further RCTs with longer follow-up periods are warranted to evaluate the long-term effects of the rTMS intervention and the sustainability of clinical outcomes. These RCTs could provide more robust data on the sustainability of our clinical and cost estimation findings for the rTMS intervention for neurogenic OAB due to stroke.

Further research is necessary to decipher the precise mechanisms by which low-frequency repetitive rTMS affects neurogenic OAB. Utilizing TMS with electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) could provide a deeper understanding of the neural activity and connectivity associated with rTMS treatment [559] for neurogenic OAB. Concurrent TMS-EEG studies can offer real-time insights into the effects of rTMS on cortical excitability, network dynamics, and oscillatory activity in the brain. By combining TMS with EEG, researchers can directly observe and analyse the immediate neural responses to rTMS, providing valuable information about how rTMS modulates neural circuits related to bladder control [560]. Additionally, concurrent TMS-fMRI studies can help identify changes in brain activity and connectivity patterns induced by rTMS [561]. fMRI can provide spatial information about the regions of the brain that are influenced by rTMS, as well as the functional

connectivity between these regions [562]. This approach can offer a comprehensive view of the neural effects of rTMS on the cortical regions and its potential impact on neurogenic OAB.

Future research should focus on conducting comprehensive cost-effectiveness analyses, incorporating patient perspectives, and combining rTMS with physiotherapy interventions such as electrical stimulations and pelvic floor muscle exercises to provide a more accurate assessment of its value in managing neurogenic OAB to determine the economic impact of using the rTMS intervention. However, it would still be important to conduct specific cost-effectiveness studies to determine the financial implications of implementing rTMS for neurogenic OAB within the Hong Kong healthcare system. Future research should consider a broader societal perspective to capture the full economic impact of rTMS for neurogenic OAB.

Chapter 7

Experiences and Perception of Repetitive Transcranial Magnetic Stimulation (rTMS) Among Individuals with Neurogenic Overactive Bladder due to Stroke: A Qualitative Study

7.1 Commentary

This thesis included a systematic review and meta-analysis on the effectiveness of non-surgical, minimally or non-invasive therapies for managing urgency urinary incontinence (UUI) due to neurogenic overactive bladder (OAB). The meta-analysis revealed that electrical stimulations such as intravaginal and neuromuscular electrical stimulations are effective in decreasing UUI symptoms among individuals with neurogenic OAB due to stroke and multiple sclerosis. This evidence had moderate to high methodological quality and moderate overall quality. The findings of the meta-analysis revealed the absence of randomised controlled trials (RCTs) investigating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in alleviating neurogenic OAB symptoms, identifying a research gap and laying the foundation for undertaking this thesis (see Chapter 2).

Additionally, a systematic review of psychometric properties was conducted to identify the most psychometrically sound clinical instrument for evaluating neurogenic OAB symptoms. This review of the psychometric properties of outcome measures identified the Overactive Bladder Symptom Score (OABSS), Overactive Bladder Questionnaire (OAB-q) and Neurogenic Bladder Symptoms Score as the most widely validated clinical measures across

several countries with sound psychometric properties. Among the identified clinical measures, the OABSS was the most culturally diverse and psychometrically sound clinical instrument supported by studies with good methodological quality and high Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) evidence quality among individuals with UUI incontinence due to OAB (see Chapter 3).

Furthermore, a systematic review of psychometric properties was also conducted to identify the most psychometrically sound clinical instrument for evaluating the quality of life of individuals with neurogenic OAB. It identified the Incontinence Quality of Life Questionnaire (I-QOL), King's Health Questionnaire, OAB-q and Qualiveen as the most psychometrically sound clinical instruments. However, due to the rating of psychometric robustness and cross-cultural diversity, the I-QOL was identified as the most suitable tool for evaluating the quality of life of individuals with neurogenic OAB (see Chapter 4).

Following these findings, an RCT combined with cost estimation and qualitative studies was conducted to investigate the effectiveness of rTMS on neurogenic OAB symptoms among stroke survivors. The active rTMS intervention significantly improved OABSS, I-QOL, and Brief Resilience Scale (BRS) scores at the primary and secondary endpoints compared to the sham rTMS intervention, with between-group effect sizes of 0.62, 0.74 and 0.10, respectively. Higher mean differences exceeding the suggested minimal clinically important difference (MCID) for the OABSS and I-QOL clinical instruments were observed, indicating a clinically meaningful difference between the active and sham rTMS interventions. This finding suggests that the rTMS intervention is effective, clinically worthwhile and meaningful in improving the neurogenic OAB symptom severity and quality of life of stroke survivors. Our study also

identified an estimated lower cost in the active rTMS group compared to the sham rTMS group. Therefore, a qualitative study among the participants in the RCT is warranted to explore their views and experiences regarding the rTMS intervention. Consequently, this chapter presents the findings of the qualitative study exploring the experiences and views of stroke survivors with neurogenic OAB regarding the rTMS intervention.

7.2 Introduction

Neurogenic OAB is a multifaceted condition with far-reaching consequences for stroke survivors [563]. The relationship between neurogenic OAB and stroke outcomes is a subject of increasing interest within the medical field due to its implications for patient recovery and long-term care [564]. Neurogenic OAB has been identified as a significant predictor of morbidity, a critical indicator of poor functional outcomes, and a strong prognostic factor of stroke recovery and mortality [56, 565]. Neurogenic OAB is a condition that significantly impacts social functioning and daily living activities, often leading to embarrassment and considerable inconvenience for stroke survivors [566]. This significant impact of neurogenic OAB on stroke survivors results in reduced quality of life and possibly impacts physical and cognitive performance [566]. Neurogenic OAB is associated with a significant risk of being admitted into institutional care [567] due to the increased burden of care, the risk of complications such as urinary tract infections, and the psychosocial sequelae of this condition, which can affect overall health and recovery. The psychosocial distress caused by neurogenic OAB can lead to social withdrawal, depression, and anxiety, all of which can hinder recovery and rehabilitation efforts [568].

Given the broad physical, social, and psychological complications and adverse effects of OAB, an intervention that improves OAB symptoms with a high safety profile is crucial. An RCT with an embedded qualitative study is essential to investigate the efficacy of non-invasive brain stimulation such as rTMS and explore patients' perspectives of the rTMS intervention. rTMS is a safe, painless, non-invasive method that activates cortical neuron fibres by delivering intense and brief magnetic fields [182]. Low-frequency rTMS (<1 Hz) can modulate neurons, inhibit cortical activity and is considered relatively safe [569].

In the past two decades, the scientific and medical communities have studied the safety profile of TMS and rTMS through research and clinical applications [194, 485, 570]. The application of conventional TMS has increased significantly over this time, and new rTMS methods have been developed [194, 485, 570]. Technical advancements have also led to the creation of new devices and the integration of TMS with other imaging techniques [194, 485, 570]. Consequently, thousands of healthy individuals (research studies) and patients with various neurological and psychiatric conditions (clinical studies) have undergone TMS, allowing a better understanding of the potential risks associated with this treatment [194, 485, 570].

While rTMS is generally considered safe, as with any medical intervention, there are potential risks and side effects associated with its use, including headaches, scalp discomfort, and, in rare cases, seizures [571]. Several systematic reviews have assessed the safety of rTMS among stroke survivors [519, 550, 572-578]. Reviews have investigated the efficacy and safety profile of rTMS among stroke survivors regarding aphasia [572], spasticity [573] and post-stroke depression [574], impairment [550], motor function [575-577], memory disorder [519] and sleep disorder [578]. These reviews have generally found rTMS to be safe and well-tolerated,

with few adverse events reported, ranging from scalp pain and mild headaches to rare seizures [194, 485, 570]. However, it is crucial to note that the safety profile of rTMS may vary depending on the specific condition being treated and the individual patient.

While scientific evidence supports the safety and efficacy of rTMS in stroke rehabilitation [519, 550, 571-578], it remains uncertain whether stroke survivors with neurogenic OAB would engage with the novel rTMS treatment in a clinical setting. Whether the rTMS effects on neurogenic OAB are clinically meaningful must also be further elucidated through qualitative studies such as focus group discussions. Focus group discussion has recently gained widespread recognition and usage due to several strengths, including its convenience, economic advantages, high face validity and rapid results [579]. Focus group discussion is also advantageous because it purposefully uses social interaction to gather qualitative data [580]. This emphasis on social interaction sets focus group discussion apart from other qualitative research methodologies [581]. Focus-group interviews are characterised by their unique group dynamics, which often lead to the generation of deeper and richer data through the participants' social interaction [582, 583]. Unlike one-to-one interviews, the group setting can stimulate diverse perspectives, interactions and discussions that may uncover broader insights and experiences [582, 583]. Focus groups can potentially yield insights into individuals' diverse ideas and emotions regarding specific issues [582]. They can also shed light on the divergent perspectives among different groups of individuals [582].

Critical information about the convenience, safety, effectiveness, satisfaction and suitability of rTMS could be gained from understanding the participants' views and experiences after the rTMS intervention [584-586]. Exploring patients' experiences and perceptions of an

intervention can provide valuable insights into how it impacts their symptoms and well-being [587]. Patient input is essential in healthcare and clinical research to ensure that treatments are safe, effective and aligned with patients' values and preferences [588]. Gaining insights from patients' viewpoints can help researchers and healthcare providers identify significant issues for patients undergoing treatment, which may enhance the design of future clinical trials and their implementation in clinical practice [589].

Moreover, patients' expectations can be crucial predictors of treatment compliance and outcomes [590, 591]. Patients' perspectives can provide valuable information about their experiences, concerns and priorities, which can help researchers and healthcare providers identify potential barriers to treatment adherence and engagement [592]. For example, patients may have concerns about the safety, efficacy or side effects of a new treatment or practical concerns about the treatment burden, such as time commitment, cost or accessibility. By understanding patients' perspectives, researchers and healthcare providers can identify areas for improvement and tailor their services to meet patients' needs and expectations [593, 594]. This understanding could improve patient satisfaction, health outcomes and the efficient use of healthcare resources [595, 596].

By identifying these clinical benefits, researchers and healthcare providers may also be guided to design clinical trials that address these concerns and implement strategies to improve treatment adherence and engagement [597]. Patients with positive expectations about treatment are more likely to adhere to it and experience better outcomes than those with negative expectations [598]. Therefore, understanding patients' expectations and addressing any misconceptions or concerns they may have before initiating treatment is essential. It can help

ensure that patients have realistic expectations and are more likely to adhere to the treatment, leading to better outcomes. Therefore, this qualitative study aimed to explore patients' experiences and perceptions of the rTMS intervention to elicit valuable insights into the impact of rTMS on their neurogenic OAB symptoms and well-being.

7.3 Methods

This qualitative study is reported according to the Consolidated Criteria for Reporting Qualitative Research guidelines [599].

7.3.1 Research design

The qualitative study embedded within the RCT used a semi-structured focus group discussion approach to explore the experiences and views of stroke survivors with neurogenic OAB given the rTMS intervention. A focus group discussion design was chosen because it can elicit responses and generate insights that may not be obtained through individual interviews [600]. The interactive nature of focus groups enables the exploration of complex issues and the emergence of new perspectives, which can provide a more comprehensive understanding of the studied topic [601]. This study used a phenomenological approach to gain a comprehensive understanding of the lived experiences [602, 603] of its participating stroke survivors with neurogenic OAB and explore their perspectives on the active rTMS intervention. The phenomenological approach is well-suited to exploring individuals' real-life experiences and the meanings they attribute to them [602]. By exploring the lived experiences of individuals, this approach offers a rich and in-depth understanding of patient perceptions regarding rTMS

interventions [604]. This understanding can be particularly valuable in healthcare research since it allows for a broader exploration of how individuals make sense of their experiences and the impact of interventions on their lives [605].

7.3.2 Sampling and recruitment

This study used convenience sampling, a technique where potential participants fulfilling the eligibility criteria participate at their discretion, to recruit the study participants [606]. After completing the follow-up assessment (week 8), the participants in the active rTMS group who were willing to discuss their experiences and views were invited to participate in the focus group discussions by telephone or WhatsApp. Interested participants were asked to express their interest in participation to the researcher via telephone. Twelve participants expressed their willingness to participate and were placed into three separate focus groups. This approach allowed for a more manageable and efficient way to gather participant feedback and insights since each group could be facilitated and moderated individually. Dividing the participants into smaller groups may have also encouraged more active participation and engagement from each individual since they would have greater opportunities to share their thoughts and opinions in an informative and productive way. The focus group discussions lasted 45–60 minutes for the three focus groups. Homogeneity within the group was established through all participants having similar sociodemographic characteristics.

7.3.3 Ethics approval

This study was ethically approved by the Institutional Review Board of The Hong Kong Polytechnic University (Ref No.: HSEARS20210913002), and the mixed method study

protocol (RCT and cost-estimation and qualitative studies) was prospectively registered at ClinicalTrials.gov (NCT05557175). Written informed consent was obtained from all participants, who were provided copies of the signed information sheets and informed consent forms for their records (Appendix 5.2 and 5.3).

7.3.4 Study setting

The focus group discussions were conducted in a private room at The Hong Kong Polytechnic University, Hong Kong.

7.3.5 Participants

Eligible participants were those assigned to the active rTMS group in the RCT (Chapter 6). All participants provided written informed consent to participate in the focus groups. The inclusion criteria for the participants in this qualitative study on stroke survivors with neurogenic OAB were completing the rTMS intervention as part of the RCT study, being allocated to the active rTMS group, willingness to participate and ability to provide informed consent and participate in the focus group discussions. The exclusion criteria were cognitive impairments, participation in a previous focus group discussion on rTMS and inability to communicate fluently in Chinese or English.

7.3.6 Sample size

Data saturation is a critical principle in qualitative research that helps determine when data collection is sufficient and no new information or themes emerge from additional participants

[607]. In this study, we recruited 12 participants from the active rTMS group who were grouped into three focus groups. After conducting three focus group discussions, similar responses emerged from the participants, indicating that data saturation had been reached. Therefore, data collection was suspended. The decision to suspend data collection once data saturation is presumed to have been reached is important in qualitative research since it helps ensure that the sample size is sufficient to capture the range of experiences and perspectives relevant to the research question [608]. In this study, the researcher compared the total sample size of previous qualitative studies on rTMS and determined that the focus group discussions were sufficient to achieve data saturation [591, 609, 610]. This approach helps ensure that the study results are reliable and representative of stroke survivors with neurogenic OAB.

Data collection ended once data saturation was achieved, which was agreed upon by the research team through ongoing analysis of the three focus group discussions. Data saturation is important for ensuring the rigour and trustworthiness of qualitative research findings because it is essential to establish credibility, transferability, dependability, and confirmability [611]. By incorporating data saturation into the qualitative study, the researchers can demonstrate that they have collected and analysed sufficient data to support the research objectives [612].

7.3.7 Development of the focus group discussion questions

Developing questions for focus group discussions is an important step in conducting a focus group study [580] since they will help guide the conversation and ensure that the topics of interest are covered [613]. Focus group questions are designed to guide the discussion and elicit information from participants about their participation in a research project [614]. When

formulating appropriate focus group discussion questions, it is imperative to prioritise several critical factors, including clarity to mitigate ambiguity, relevance to the research subject matter, promotion of open-ended responses, probing to elicit comprehensive insights and avoidance of leading questions to prevent prejudiced outcomes [580, 613, 614]. These considerations facilitate thorough and substantive discourse within the focus group setting.

The following questions were used to guide the focus group discussions:

- What benefits did you experience while participating in the rTMS intervention?
- Did you encounter any safety concerns or issues during the treatment sessions or with the rTMS equipment?
- What factors aided or motivated you to complete the treatment sessions?
- Can you please share your overall experiences and satisfaction with the recovery process?
- Would you feel comfortable recommending the rTMS intervention to your friends?

A semi-structured focus group discussion approach was used to discuss and elicit information on these predetermined questions related to the rTMS intervention experiences. This approach allowed for a straightforward, detailed exploration of participants' opinions, perspectives and experiences, thereby generating an in-depth and comprehensive understanding of their rTMS exposure.

7.3.8 Data collection

All focus group discussion sessions were audio recorded using a voice recorder, and student helpers took additional notes. Audio recording and note-taking are commonly used to capture the information and insights shared during focus group discussions [580]. Audio recordings provide an accurate and detailed record of the discussions, which were transcribed into text for further analysis [615]. Transcripts can be used to identify themes, patterns, and trends in the data and to compare and contrast the views and experiences of different participants [616]. Note-taking is also important for capturing additional information that may not have been recorded, such as nonverbal cues, body language and other contextual information [617]. Notes can be used to supplement the audio recordings and provide a more complete picture of the discussion [618].

7.3.9 Data analysis

The focus group discussion was transcribed verbatim by an independent transcription service. In addition to the focus group discussion transcripts, interview summaries and team debriefing notes were included as data in this study. These data sources were uploaded into NVivo [599], a qualitative analysis software program, to facilitate coding and analysis. The accuracy of the data was ensured by comparing the transcripts with the recordings [618].

The Braun and Clarke guidelines were adopted for analysing the data transcripts according to the six phases of inductive thematic analysis [619]. In Phase 1, two investigators (MUA and PK) independently read and re-read the transcribed data to familiarise themselves with it [619]. In Phase 2, the investigators (PK and CK) identified quotations that answered the research

questions and assigned appropriate codes to them. This process involved discussions between the investigators until a consensus was reached [620]. In Phase 3, the identified codes were independently collated based on data relevancy into potential themes [620]. In Phase 4, these themes underwent a two-level review. Level 1 focused on establishing a coherent pattern within the collated themes by examining how well they aligned with the coded data extracts [620]. Level 2 extended this examination to ascertain the working pattern of these themes within the entire dataset and verify each theme's accuracy and significance [620]. In Phase 5, these themes were defined and named based on their content. Finally, in Phase 6, a review was conducted to confirm that the final set of themes was comprehensive and coherently represented the data.

7.4 Results

7.4.1 Participants' characteristics

The focus group participants' demographic and clinical characteristics are presented in Table 7.1. Twelve of the 15 stroke survivors with neurogenic OAB in the active rTMS group participated in the focus group discussions. Their age ranged from 43 to 69 years, with a mean of 60.12 ±7.22 years. Seven of the 12 participants were male (58.3%), and eight had left-sided hemiparesis (66.7%). The 12 participants were divided into three focus groups with differing numbers of participants: Groups 1 and 2 each had five participants, and Group 3 had only two participants. The three participants who could not attend the focus group discussions stated a clash of appointments with doctors and prior commitments on the planned date as the reason for non-participation. The participants in the focus group discussions had completed all rTMS intervention sessions and follow-up assessments without reporting any adverse effects.

Table 7.1: Characteristics of the Participants in the Focus Group Discussion

Focus group (n = 12)	
Mean age in years ± SD	60.12 ± 7.22
Sex, n (%)	
Male	7 (58.3)
Female	5 (41.7)
Side of hemiplegia, n (%)	
Right	4 (33.3)
Left	8 (66.7)
Marital Status, n (%)	
Married	7 (58.3)
Divorced	1 (8.3)
Single	4 (33.3)
Educational Qualification, n (%)	
Post-graduation	1 (8.3)
University Degree	1 (8.3)
High School	8 (66.7)
Primary School	2 (16.7)
Duration of stroke, Mean ± SD	
Time since stroke (months)	43.70 ± 28.92

7.4.2 Themes generated from the focus group discussions

The themes generated from the focus group discussions are presented in Table 7.2. The focus group discussions emphasised the experiences and views of stroke survivors with neurogenic OAB after the rTMS intervention. The four themes generated from the focus group discussions were perceived neurogenic OAB symptom improvement, the safety profile of the intervention, the sense of fulfilment derived from the intervention, and the social benefits experienced by the participants. The result sections below delve into each theme and provide insights into the participants' experiences. The participants reported improvement and satisfaction with the rTMS intervention in reducing the severity of neurogenic OAB symptoms. They described how their symptoms have changed, such as reduced urgency, fewer incontinence episodes or improved bladder control. All participants were satisfied with the treatment and improvement after the rTMS intervention. They also reported satisfaction with the rTMS intervention, indicating they perceived the treatment as beneficial and worthwhile. Moreover, the participants expressed the reasons behind their satisfaction, such as improved urinary frequency, UUI, executing activities of daily living or reduced anxiety related to neurogenic OAB symptoms. This high level of satisfaction suggests that rTMS may positively impact the severity of specific neurogenic OAB symptoms and the overall quality of life and well-being of individuals undergoing this treatment.

Table 7.2: Overview of themes and subthemes generated from participants' experiences with the rTMS intervention

Key themes	***Subthemes***	***Category***	***Sub-category***	***Illustrative quotations***
Perceived neurogenic OAB symptom improvement	Improvement in nocturia	Physical	Frequency of nocturia	*'I used the restroom frequently both during the day and at night, especially after the initial few sessions of rTMS treatment. However, I did not notice any improvement until after a week. There was a slight improvement, particularly at night, as I went one less time, from three times before not using it to only two times after using it.'* (P1)
	Improvement in urinary urgency		Frequency of urinary urgency	
	Decreased urinary frequency		Gradual decreases in urinary frequency	
	Decreased UUI		Frequency of UUI	
Safety profile of the intervention	High safety	Preventive	Mild or no side effects	*'The rTMS treatment session is very fine; everything goes well, there are no side effects after the treatment session.'* (P11) *'Yes, the rTMS treatment session does no harm.'* (P9)
	No pain or discomfort		No concerns about the discomfort or potential pain associated with the rTMS intervention	
	Highly convenient		The treatment sessions were relatively short	
Sense of fulfilment derived from the intervention	Improved confidence	Psychological	Improved confidence	*'It used to be very worried. Every time I went out with someone, I had to check the time before going home because I was afraid of suddenly losing control. Women are the most troublesome, they have to bring some diapers from the beginning. Now, I don't*
	Improved motivation		All participants expressed motivation to undergo the rTMS intervention	

	Improved satisfaction		High levels of satisfaction	*need them anymore, I'm very confident. I can go to church with friends for two or three hours.'* (P8)
Social benefits experienced by the participants	Positive impact on daily life	Societal	Able to participate in social activities	*'After completing rTMS sessions, it changed my life a lot. Now I can go out on the street or to other places without worrying too much.'* (P2) *'When I feel the urge, I have to go, but now I can hold it until I finish watching the movie.'* (P12) *'I am now capable of going without using the restroom for two to three hours, which is a typical frequency for most individuals. I only need to use the restroom once every two to three hours, which represents a significant improvement from my previous condition. I believe the treatment has been particularly effective during the night, as I used to have to go to the restroom three times at night, but now I no longer do.'* (P10)
	Sense of empowerment		Feeling powerful enough to discharge personal needs and expectation	

OAB: Overactive bladder; rTMS: repetitive transcranial magnetic stimulation; UUI: urgency urinary incontinence.

7.4.3 Overview of the themes generated from participants' experiences with the rTMS intervention

7.4.3.1 Theme 1: Perceived benefits of the neurogenic OAB treatment

The experiences regarding neurogenic OAB symptom improvement varied among the participating stroke survivors. Seven of the 12 (58%) participants experienced significant relief from their urinary frequency, urgency and nocturia symptoms, while the remaining five (42%) reported more modest improvements. Factors such as the severity of the condition, duration of symptoms, and individual response to the treatment influenced the degree of improvement. The following are statements from participants related to this theme:

'After completing the first week of treatment, I improved a lot in the whole month.' (P2)

'There was no improvement after a week of rTMS intervention. There was a slight improvement, especially at night; I went one less time, from three times before not doing it to two only after doing it.' (P4)

Nine of the 12 (75%) participants reported that symptom improvement was not immediate but gradual during the rTMS intervention. They reported reduced urinary urgency, frequency, nocturia and incontinence episodes after the first five rTMS sessions. The gradual improvement was perceived as a positive sign and provided optimism for further improvement in neurogenic OAB symptoms. The following is a statement from a participant related to this theme:

'I used the restroom frequently both during the day and at night, especially after the initial few sessions of rTMS treatment. However, I did not notice any improvement after using it until after a week. There was a slight improvement, particularly at night, as I went one less time, from three times before not using it to only two times after using it. After that, the frequency decreased by an average of one time during the day. Once I completed the rTMS treatment sessions, the interval between urination increased, and the number of times I needed to use the restroom decreased. This is how the improvement occurred.' (P1)

Nine of the 12 (75%) participants highlighted the long-term benefits of the rTMS intervention. They reported that the improvements in symptoms were sustained even after the completion of the treatment. This long-lasting effect was considered a significant advantage since it provided them with continued relief from their neurogenic OAB symptoms. One (8.3%) participant mentioned that rTMS improved their urgency incontinence. The following is a statement from a participant related to this theme:

'Before, I couldn't hold it, but now I can hold it a little bit and slowly walk to the toilet.' (P3)

'When I feel the urge, I have to go, but now I can hold it until I finish watching the movie.' (P14)

Ten of the 12 (83%) participants emphasised that their experiences with neurogenic OAB symptom improvement were unique to their circumstances, implying that the effectiveness of the rTMS intervention may vary among participants and help determine the extent of symptom improvement. Five of the 12 (42%) participants experienced greater improvement in specific symptoms, such as urgency, while seven (58%) noticed greater improvement in frequency or incontinence. This personalised experience highlighted the importance of tailoring the rTMS intervention to address individual needs and symptom patterns. The following are statements from participants related to this theme:

'After completing rTMS sessions, it changed my life a lot. Now I can go out on the street or to other places without worrying too much. I don't have to go to a specific place to find a washroom because now I feel that when I need to go there, it's not suddenly urgent; it's slowly urgent. So, you have time to find a bathroom. This thing is okay. So far, I have been able to do it. So maybe everyone is different.' (P7)

'The amount has decreased, and it's less frequent.' (P8)

The participants were often considering long-term goals when undergoing the rTMS intervention. They envisioned a future where they could engage in activities, they previously avoided due to bladder symptoms, such as going to the cinema to watch movies. These goals served as a source of motivation throughout the treatment, as the participants remained focused

on the potential long-term benefits of the intervention. The following is a statement from a participant related to this theme:

'After completing rTMS sessions, it improved my life a lot. Now I can go out on the street or to other places without worrying too much.' (P13)

The participants who experienced positive outcomes in neurogenic OAB symptoms with the rTMS intervention may be more inclined to recommend it to others. Those participants who achieved significant improvements in the neurogenic OAB symptoms and quality of life may feel confident in suggesting the rTMS intervention to other stroke survivors with neurogenic OAB symptoms [621]. Their firsthand experiences and the benefits they have gained can make them advocates for the rTMS intervention, especially if they have tried other treatments without success [621]. The following is a statement from a participant related to this theme:

'Overall, I am confident in recommending rTMS to my friends who may be dealing with neurogenic overactive bladder. It has the potential to provide them with relief from their symptoms and improve their overall well-being.' (P7)

7.4.3.2 Theme: Safety profile of the intervention

All participants (100%) perceived the rTMS intervention as safe. They reported minimal side effects, such as mild headaches that disappeared before the subsequent treatment sessions. They appreciated the non-invasive nature of the intervention since it did not involve any surgical incisions or medications with potential side effects. The following are statements from participants related to this theme:

'The rTMS treatment session is very fine; everything goes well, there are no side effects after the treatment session.' (P11)

'Yes, the rTMS treatment session does no harm compared to surgery.' (P9)

During the first three sessions, four of the 12 (33%) participants had concerns about the discomfort or potential pain associated with the rTMS intervention. However, as they gained familiarity with the procedure and underwent the treatment sessions, their concerns were frequently mitigated before subsequent treatment sessions. Four (33%) of the participants found that the discomfort was manageable and outweighed by the potential benefits of symptom improvement. The following are statements from participants related to this theme:

'I don't think there's any problem because I think it's relatively safe.' (P2)

'No, there is no physical discomfort, but there might be some psychological concerns because the rTMS coil is always facing the brain.' (P5)

Ten of the 12 (83%) participants highlighted their convenience with the rTMS intervention in neurogenic OAB management. The treatment sessions were relatively short, typically lasting 20 minutes. The participants appreciated that the treatment did not require any hospitalisation or extensive preparation, allowing them to continue their regular activities without significant disruption. The following is a statement from a participant related to this theme:

'To me, it's very useful. I'm very comfortable coming from home, not in the hospital. The rTMS treatment chair is convenient when I'm sitting down in the chair. I feel relaxed, and sometimes I talk to you about funny things, and when I concentrate, I feel very silenced.' (P8)

7.4.3.3 Theme: Sense of fulfilment derived from the intervention

The experiences of participating stroke survivors regarding confidence, motivation and satisfaction with the rTMS intervention for neurogenic OAB were generally positive. Nine of the 12 (75%) participants reported increased confidence due to improvements in neurogenic OAB symptoms after the rTMS intervention. The improvement in neurogenic OAB symptoms, such as reduced urgency and incontinence, allowed them to feel more in control of their bladder

and less anxious about potential accidents. This increased confidence positively impacted their daily activities, social interactions and overall well-being. The following are statements from participants related to this theme:

'Before, I was afraid because I couldn't go to the bathroom at once, and my urine may leak out. Now, I can hold my urine better. I feel more relaxed, happier, it's good.' (P4)

'It used to be very worried. Every time I went out with someone, I had to check the time before going home because I was afraid of suddenly losing control. Women are the most troublesome, they have to bring some diapers from the beginning. Now, I don't need them anymore, I'm very confident. I can go to church with friends for two or three hours.' (P8)

All the participants expressed motivation to undergo the rTMS intervention due to the potential for symptom improvement. They were motivated by the prospect of regaining control over their bladder and improving their personal and societal quality of life. The desire to alleviate the burden of bladder symptoms and the hope for a better future served as strong motivators throughout the treatment process. The following is a statement from a participant related to this theme:

'It's really hard when you're in such a hurry. You can't help but hold it in. It's embarrassing. It becomes a desire to improve, so you have to feel that the whole treatment process must be completed to be effective. So, this is what drives me to complete the treatment sessions.' (P10)

All the participants expressed positive feedback regarding symptom improvement, confidence and motivation. As they experienced improvements in their neurogenic OAB symptoms, their confidence increased, leading to greater motivation to sustain the treatment sessions. This motivation, in turn, strengthened their commitment to the intervention and adherence to the treatment protocol. The following is a statement from a participant related to this theme:

'It's all about wanting to improve, and when I started doing it, I found that I really improved, and the improvement was quite obvious. So that's the main reason why I participated.' (P12)

Ten of the 12 (83%) participants expressed high satisfaction with the symptom improvement they experienced through the rTMS intervention. They appreciated its non-invasive nature and positive impact on their quality of life. They felt that the symptom improvement justified their decision to undergo the rTMS intervention and were grateful for the relief it provided. The following is a statement from a participant related to this theme:

"I can now go without using the restroom for two to three hours, which is a typical frequency for most individuals. I only need to use the restroom once every two to three hours, which significantly improves my condition. I believe the treatment has been particularly effective during the night, as I used to have to go to the restroom three times at night, but now I no longer do.' (P10)

7.4.3.4 Theme 4: Social benefits experienced by the participants

Seven of the 12 (58%) participants expressed how the symptom improvement positively impacted their daily lives. They reported engaging in social activities without constantly worrying about urgency or incontinence. They felt more confident and comfortable in social situations since they had better control over their neurogenic OAB symptoms. The reduction in neurogenic OAB symptoms also improved sleep quality, allowing them to feel more relaxed and energised. The following is a statement from participants related to this theme:

'After completing rTMS sessions, it changed my life a lot. Now I can go out on the street or to other places without worrying too much.' (P6)

'When I feel the urge, I have to go, but now I can hold it until I finish watching the movie.' (P12)

Ten of the 12 (83%) participants felt empowered by the rTMS intervention. They appreciated being actively involved in their treatment and having a non-invasive option to manage their neurogenic OAB symptoms. The ability to take control of their bladder symptoms and improve their quality of life through the rTMS intervention instilled a sense of empowerment and self-efficacy. The following is a statement from a participant related to this theme:

'I am extremely pleased to be able to go about my activities uninterrupted for two hours without having to visit the restroom. I am very grateful to him.' (P6)

7.5 Discussion

This qualitative study is the first to qualitatively explore the experiences and opinions about an rTMS intervention among individuals with neurogenic OAB due to stroke. It aimed to understand the perceived efficacy of rTMS in treating neurogenic OAB and its impact on the symptoms and well-being of stroke survivors with this condition. It conducted three focus group discussions encompassing 12 stroke survivors with neurogenic OAB who were part of the active rTMS group of the RCT reported in Chapter 6. Several thematic categories emerged from the analysis of the focus group discussions: the perceived neurogenic OAB symptom improvement, the safety profile of the intervention, the sense of fulfilment derived from the intervention, and the social benefits experienced by the participants. The participants reported that the rTMS intervention was effective in improving their neurogenic OAB symptoms, such

as reduced urinary frequency, urinary urgency, nocturia and UUI. All participants felt the rTMS treatment was safe, worthwhile and satisfactory in improving their social and community engagement. These perceived benefits may have positively impacted not only the neurogenic OAB symptoms but also the overall quality of life and well-being of individuals who received the rTMS intervention.

The participants reported various clinical benefits such as reduced urinary frequency, urinary urgency, urgency incontinence, improved quality of life and confidence associated with the rTMS intervention for neurogenic OAB. Seven of the 12 participants (58%) reported significant improvement in neurogenic OAB symptoms after the rTMS intervention, with only five (42%) indicating modest improvements in OAB symptoms. They reported improved bladder control and a decreased need for medication or invasive procedures. These findings suggest that rTMS could potentially reduce reliance on pharmacological treatments, which often have adverse effects, or on more invasive interventions, such as bladder augmentation, which can be associated with higher risks and longer recovery times. The participants also highlighted an enhanced quality of life, including improved sleep patterns, increased social confidence and a greater sense of freedom. Neurogenic OAB can be a debilitating condition that affects not only physical health but also mental well-being and social interactions [96].

The participating stroke survivors with neurogenic OAB expressed satisfaction after the rTMS intervention. The high level of satisfaction expressed by the participants emanated from the

multifaceted benefits offered by rTMS, particularly in addressing neurogenic OAB symptoms that significantly impact the quality of life. Moreover, it could have significantly influenced their motivation and confidence to complete the treatment sessions. Patient satisfaction is an essential aspect of healthcare and can substantially impact treatment adherence and outcomes [622]. When patients are satisfied with their treatment, they are more likely to comply with the recommended treatment plan, attend follow-up appointments and continue with the treatment sessions.

Regarding rTMS for neurogenic OAB symptoms severity, completing the full course of treatment is crucial for achieving optimal outcomes. Therefore, the satisfaction expressed by the participants could have contributed to their adherence to the treatment plan and their ability to complete all the sessions. Moreover, satisfaction with treatment can enhance patients' confidence in their ability to manage their symptoms and improve their quality of life [623]. For stroke survivors with neurogenic OAB symptoms, achieving symptom relief and improved bladder control could significantly enhance their confidence and independence, enabling them to participate in social activities and perform daily tasks with greater ease.

The participants' experiences regarding safety concerns, such as pain and discomfort, associated with rTMS intervention and the convenience of the rTMS procedure were generally positive. No serious adverse events were reported during the treatment sessions, and the participants tolerated the treatment well. While some reported mild side effects, such as

headaches and scalp discomfort, that disappeared before subsequent treatment sessions, these were generally mild and transient and did not interfere with their ability to complete the treatment sessions. Numerous systematic reviews [519, 520, 548-550, 571-578] have reported that while rTMS can cause transient mild headaches, it is generally an effective and safe procedure for managing neurogenic OAB symptoms in stroke survivors. The safety profile of rTMS is one of its main advantages over other brain stimulation techniques, such as deep brain stimulation or vagus nerve stimulation, which require the surgical implantation of electrodes and are associated with a higher risk of complications [521, 522].

At the outset, some participants were apprehensive about discomfort or possible pain during the rTMS sessions. However, such concerns typically lessened as the participants grew accustomed to the procedure. The concerns about discomfort or pain during rTMS sessions are mainly due to the use of a magnetic coil placed on the scalp to deliver brief pulses of magnetic energy to specific areas of the brain [182]. Participants also appreciated the flexibility of undergoing rTMS sessions without being admitted to the hospital since it permitted them to continue their daily activities without significant disruption.

Participants expressed feeling more confident and comfortable in social situations since they had better control over their neurogenic OAB symptoms. The improvement in neurogenic OAB symptoms was associated with a significant reduction in anxiety and stress associated with the constant worry of UUI accidents or the need to locate restrooms frequently [624, 625]. The

frequent trips to the bathroom, urgency, and other symptoms associated with neurogenic OAB can elicit negative reactions from others, such as awkwardness, embarrassment, or avoidance, which could result in social isolation, anxiety, and decreased quality of life for those with neurogenic OAB [625]. Furthermore, the reduction in neurogenic OAB symptoms after the rTMS intervention could engender frequent participation in more social activities and community engagement.

7.6 Strengths and limitations

This study used a rigorous approach to conduct a focus group discussion and analysis, using NVivo for coding and theme generation. It adopted a focus group discussion methodology [580] to elicit an in-depth, rich, open discussion and probe experiences to uncover the participants' feelings and views about using rTMS to manage neurogenic OAB due to stroke.

This qualitative study was conducted after the follow-ups of the main study's RCT, which might risk introducing a form of recall and cognitive bias among some participants [591]. In addition, most participants were male (58%), which could introduce gender bias into these findings [603]. Moreover, this study may be subject to participation bias [603] since only participants who were confident in discussing their experiences and views about the rTMS intervention for managing neurogenic OAB volunteered. We excluded participants from the sham rTMS group. To address this limitation, future studies should consider including participants from both the active and sham TMS groups in focus group discussions. This

inclusive approach can provide a more comprehensive understanding of the treatment experience and its broader implications. We used data saturation to determine the sample size of the focus group discussion. When the data saturation was assumed prematurely, the data collection might have stopped before capturing the full range of participants' perspectives. This can lead to bias because it excludes potentially important voices and viewpoints from the analysis.

7.7 Conclusions

The participating stroke survivors' experiences and views about the rTMS intervention for neurogenic OAB were generally positive. Seven of the 12 (58%) participants experienced significant relief from their neurogenic OAB symptoms of urinary frequency, urgency and nocturia, while five (42%) reported more modest improvements. The participants reported increased confidence and long-term benefits in urinary frequency, urinary urgency, nocturia and UUI as a result of the rTMS intervention. They also highlighted the convenience of the rTMS intervention and appreciated its non-invasive nature since it did not involve any surgical incisions or medications with potential side effects.

7.8 Clinical implications

Focus group discussions can provide valuable insights into the lived experiences, challenges and preferences of the rTMS intervention among individuals with neurogenic OAB symptoms. This information can help physiotherapists and other clinicians managing patients with neurogenic OAB consider satisfaction, convenience and safety to achieve maximum clinical benefit and better meet patients' needs, expectations and priorities, promoting patient-centred care. Clinicians managing patients with neurogenic OAB due to stroke should focus not only on the physical symptoms of neurogenic OAB but also its psychosocial impact on patients' lives, which may include addressing issues related to stigma, social isolation and reduced quality of life. The findings obtained by exploring the experiences of participants might yield information about the acceptability of the treatment options to facilitate the use of the rTMS intervention for stroke survivors with neurogenic OAB symptoms in clinical practice. This study might identify the participants' expectations and needs to achieve maximum therapeutic benefits and satisfaction regarding the rTMS intervention.

7.9 Recommendations for future research

We excluded sham rTMS grom from the focus group discussion, further qualitative studies exploring the opinions and views of caregivers of stroke survivors with neurogenic OAB symptoms receiving both active and sham rTMS interventions are needed, which would help determine the actual effects of the active rTMS compared to sham rTMS. This inclusive

approach can provide a more comprehensive understanding of the treatment experience and its broader implications.

Further qualitative studies exploring the economic implications of the rTMS intervention on the improvement of stroke survivors' neurogenic OAB symptoms are also required. They could provide valuable insights into the patients' views and opinions about the cost estimation of the rTMS intervention and its potential impact on their quality of life. Exploring the rTMS intervention's economic implications can help understand its potential benefits and limitations and inform future decision-making about its use in clinical practice. By considering the economic implications of the intervention, decision-makers can make more informed choices about whether to adopt the intervention in clinical practice and how to allocate resources to achieve this, which can ultimately lead to more efficient and effective use of resources in healthcare and improve patient outcomes. This information can also help stakeholders understand the potential return on investment for the rTMS intervention, which can be useful for making funding decisions.

Further qualitative studies investigating the effects of stigma on patients' attitudes towards management and well-being are needed. Stigma can profoundly impact individuals' psychological, social and physical well-being and affect their help-seeking behaviours, treatment adherence and overall quality of life [626]. In-depth qualitative studies on stroke survivors with neurogenic OAB can help to understand how stigma affects their experiences

and perceptions of their condition. This information can be used to develop interventions to reduce stigma and improve the well-being of stroke survivors with neurogenic OAB. Additionally, qualitative studies can help identify the specific factors contributing to stigma and inform the development of targeted interventions to address them.

Chapter 8

General Discussion, Clinical Implications, Recommendations for Future Research and Conclusions

8.1 Commentary

This chapter presents a general discussion of the systematic review and meta-analysis, systematic reviews of psychometric properties, randomised controlled trial (RCT), cost estimation analysis, and qualitative study reported in this thesis. It also discusses the strengths, limitations and clinical implications of the findings and provides recommendations for future research that is needed to improve patient outcomes.

8.2 General discussion of the thesis

This thesis aimed to investigate the clinical effectiveness and cost estimation of repetitive transcranial magnetic stimulation (rTMS) in reducing the severity of neurogenic overactive bladder (OAB) symptoms in stroke survivors. A series of studies were systematically conducted to achieve this aim. First, a systematic review and meta-analysis were conducted on the effectiveness of nonsurgical, minimally or non-invasive therapies for managing urgency urinary incontinence (UUI) due to neurogenic OAB (Chapter 2). These findings not only

identified a research gap but also laid the foundation for conducting the main study of this thesis: there were no studies, specifically RCTs, evaluating the effectiveness of rTMS for managing neurogenic OAB symptoms in stroke survivors. Neurogenic OAB is a common and debilitating condition that affects several stroke survivors, and there is a need for non-invasive, clinically efficacious with estimated lower cost and higher safety profiles. The lack of RCTs on rTMS for managing the severity of neurogenic OAB symptoms in stroke survivors means that there is limited evidence to support its use, and further research is needed to determine its efficacy and safety. Therefore, the systematic review and meta-analysis justified the rationale for conducting the main study that would address this research gap by investigating the effectiveness of rTMS in treating neurogenic OAB symptoms severity among stroke survivors using an RCT design.

Next, systematic reviews of psychometric properties (Chapters 3 and 4) were conducted to identify the most robust outcome measures for evaluating the neurogenic OAB symptoms and quality of life of individuals with neurogenic OAB symptoms in the main RCT. Their findings provided the scientific evidence needed to make an informed decision about the most psychometrically sound outcome measures.

Then, the methods used to conduct the main study of the thesis were described, highlighting the steps taken to investigate the clinical effectiveness and cost estimation of rTMS through an RCT, cost estimation analysis and qualitative study (Chapter 5). The results of the RCT and

cost estimation and qualitative studies of using the rTMS intervention to treat stroke survivors with neurogenic OAB symptoms are presented and discussed in Chapters 6 and 7.

This thesis provides invaluable insights into the therapeutic effectiveness of rTMS as a non-invasive therapy for reducing the severity of neurogenic OAB symptoms due to stroke. The meta-analysis, psychometric review of neurogenic OAB symptoms, psychometric review of neurogenic OAB-related quality of life, RCT and cost estimation analysis and qualitative studies were reported in Chapters 2, 3, 4, 6 and 7 of this thesis, respectively.

8.3 Discussion of the systematic review and meta-analysis findings (Chapter 2)

A meta-analysis of RCTs was conducted to determine the effectiveness of non-invasive therapies for managing UUI due to neurogenic OAB (last database search: September 2021, updated 15 May 2024). The findings of the meta-analysis revealed that electrical stimulation (intravaginal and neuromuscular) is effective in decreasing UUI symptoms in individuals with neurogenic OAB due to stroke or multiple sclerosis. The methodological quality of electrical stimulation was moderate to high (Physiotherapy Evidence Database [PEDro] scale), and the quality of evidence was moderate (Grading of Recommendations, Assessment, Development and Evaluation [GRADE]). Furthermore, the meta-analysis demonstrated that transcutaneous tibial nerve stimulation and behavioural therapy could improve the quality of life of individuals with neurogenic OAB due to Parkinson's disease [130]. These findings were based on RCTs with moderate to high methodological quality and low to moderate evidence quality. However,

the specific effects of pelvic floor muscle training (PFMT) and behavioural therapy on UUI due to neurogenic OAB remained uncertain due to limited evidence.

Nonetheless, PFMT has been extensively studied and is recognised as an effective first-line treatment for neurogenic OAB [130, 134, 201, 627, 628]. Studies have demonstrated that regular PFMT can significantly improve neurogenic OAB symptoms, making it a valuable non-invasive and low-risk treatment option, especially compared to no treatment or inactive therapies [629-631]. A meta-analysis [202] revealed moderate evidence quality (GRADE) supporting the superiority of electrical stimulation over PFMT with or without biofeedback in improving neurogenic OAB symptoms with low evidence quality (GRADE). The adverse effects (pain and discomfort) are reported, given the enormous clinical benefits of PFMT and electrical stimulation. Individuals with neurogenic OAB found electrical stimulation/PFMT with electromyography (EMG) biofeedback to cause pain and discomfort due to its invasiveness (intra-anal [men] or intravaginal [women] probe) [132, 632, 633]. Amid these reported clinical benefits, adverse effects related to the electrical stimulation, particularly intravaginal stimulation (such as vaginal irritation, occasional pain, vaginal infection, and urinary tract infection), have been reported. This discomfort and pain hinder patients' compliance with the treatment regimen and overall treatment outcomes [132]. Therefore, less invasive interventions are needed to improve compliance and treatment outcomes in managing neurogenic OAB in stroke survivors, such as rTMS.

8.2.1 Updated database search for the systematic review and meta-analysis

The electronic database and reference list searches were updated in May 2024 to identify any recently published RCTs on the effectiveness of non-invasive and nonsurgical therapies for individuals with neurogenic OAB symptoms that meet the eligibility criteria [130]. This update was important in ensuring the meta-analysis includes the most up-to-date and relevant evidence. Conductors of systematic reviews need to be aware that new evidence relevant to clinical decision-making may emerge within a year of the last search date [634]. Therefore, it is recommended that they search for more recent RCTs on the same topic to identify new evidence that could affect a particular systematic review's findings [634].

Repeating the database searches for the period January 2022 to May 2024 identified 1293 potentially relevant articles, of which one RCT [635] met the eligibility criteria following title, abstract and full-text screening. Potentially relevant studies were excluded during the screening processes due to ineligible participants (women and older adults with stress urinary incontinence), ineligible study designs (non-RCTs and protocols) and editorial comments or conference proceedings. The RCT [635] identified by the updated search found that applying transcutaneous electrical nerve stimulation (TENS) over the sacral region for 90 days improved neurogenic OAB symptoms due to stroke, Parkinson's disease, spinal cord injury or diabetes. These findings are consistent with the results of the meta-analysis presented in this thesis (Chapter 2) [130], which also found that non-invasive therapies such as TENS could effectively manage the severity of neurogenic OAB symptoms in stroke survivors.

Several systematic reviews [144, 636, 637] have indicated that TENS might be beneficial for managing symptoms related to neurogenic OAB, particularly in individuals with stroke, spinal cord injuries and multiple sclerosis. However, they [144, 636, 637] have indicated that the TENS intervention is not yet sufficiently robust to establish it as a standard therapy due to small sample sizes and a lack of high-quality RCTs. A recent meta-analysis [638] investigated the effectiveness of conservative management, such as PFMT and electrical stimulations, for neurogenic OAB symptoms due to stroke, Parkinson's disease, multiple sclerosis or spinal cord injuries. Recent systematic reviews needed to be identified to assess their consistency with the original meta-analysis (Chapter 2) and update its findings if required. The findings of that meta-analysis [638] revealed that individuals with neurogenic OAB could benefit from conservative interventions such as PFMT and electrical stimulations that improve their neurogenic OAB symptoms and quality of life. Its findings [638] are consistent with those of the meta-analysis in this thesis (Chapter 2). Both found that electrical stimulations and PFMT were effective in managing neurogenic OAB symptoms in individuals with stroke or Parkinson's disease. However, the quality of evidence for PFMT was moderate in that meta-analysis [638], while it was low in the meta-analysis in this thesis (Chapter 2). Nonetheless, both consistently support the effectiveness of these interventions for neurogenic OAB symptoms. The fact that these reviews [144, 636-638] noted small sample sizes and a dearth of high-quality RCTs underscores the importance of further research to confirm the efficacy of non-invasive therapies and to establish it as a standard clinical intervention. This information is crucial for healthcare professionals to make informed decisions about treatment options and for patients to have access to therapies with proven effectiveness and safety profiles.

8.3 Discussion of Chapters 3 and 4 findings

Systematic reviews of psychometric properties were conducted to identify psychometrically sound measures for evaluating neurogenic OAB symptoms and quality of life. The Overactive Bladder Symptom Score (OABSS) and Incontinence Quality of Life questionnaire (I-QOL) were identified as the most psychometrically sound measures for evaluating neurogenic OAB symptoms and quality of life, respectively. These measures (OABSS and I-QOL) were chosen for the main study based on criteria established by the International Consultation on Incontinence Society, which included factors such as clarity of the measures, simplicity of the measures, number of studies, quality of the evidence, and strength of psychometric properties [361]. The strength of a measure's psychometric properties depends on its validity, reliability, and responsiveness, which must be established through rigorous and thorough methodology [359]. To be considered 'highly recommended', a measure must demonstrate strong psychometric properties, including validity, reliability, and responsiveness [361]. Using a valid and reliable measure makes it possible to assess patients' outcomes accurately and monitor their recovery process [361].

8.3.1 Updated database search for the psychometric reviews

Update searches of databases were conducted for the two systematic reviews of the psychometric properties of outcome measures evaluating neurogenic OAB symptoms and quality of life (Chapters 3 and 4, respectively). The update searches were conducted to identify any recently published potentially relevant studies evaluating the psychometric properties of

outcome measures that meet the eligibility criteria. An updated database search for the period February 2023 to May 2024 identified 792 potentially relevant articles. After screening the titles, abstracts and full texts, only one study [639] met the psychometric systematic review eligibility criteria of the quality of life measures (Chapter 4) for assessing individuals with neurogenic OAB symptoms. This study [639] identified the short form (SF)-Qualiveen as a reliable and valid clinical measure for evaluating quality of life with excellent internal consistency (Cronbach's alpha = 0.90). Regarding construct validity, it also found a strong association between SF-Qualiveen and neurogenic OAB symptom scores ($r = 0.82$, $p = 0.003$). Its findings were also consistent with the psychometric systematic review of the quality of life measures (Study III) in this thesis (Chapter 4), demonstrating that SF-Qualiveen (one of the clinical tools identified in Study III) was a reliable and valid clinical tool appropriate for Arabic-speaking patients with spinal cord injuries in both research and clinical practices.

Moreover, the database searches for the psychometric systematic review of the outcome measures for neurogenic OAB symptoms were repeated for the period September 2023 to May 2024. After the title, abstract and full-text screenings, no new studies were identified that met the eligibility criteria. Therefore, no new updates exist to the articles discussed in Chapter 3.

The findings of the systematic reviews of the psychometric properties of clinical tools for assessing neurogenic OAB symptoms and quality of life informed the clinical measures used to evaluate the neurogenic OAB symptoms and quality of life of stroke survivors. The

systematic reviews of the psychometric properties identified the OABSS and I-QOL as psychometrically sound measures for evaluating neurogenic OAB symptoms and quality of life, respectively. Applying these measures in the RCT was significant in providing more valid, reliable and responsive findings for evaluating the neurogenic OAB symptoms and quality of life of stroke survivors with neurogenic OAB. RCTs are considered the 'gold standard' in clinical research for yielding reliable and valid findings through compliance with study designs that reduce bias to inform evidence-based making in healthcare [640, 641].

8.4 Discussion of Chapters 6 and 7 findings

The RCT evaluated the clinical effectiveness of low-frequency rTMS in managing neurogenic OAB symptom severity among stroke survivors. Its findings demonstrated significant differences in OABSS, I-QOL, and Brief Resilience Scale (BRS) scores between active and sham rTMS groups at the primary and secondary endpoints. This observable difference implies that the active rTMS intervention had a significant and clinically meaningful impact on OAB symptom severity, quality of life and resilience among stroke survivors with neurogenic OAB. The between-group mean difference in OABSS and I-QOL scores at the primary and secondary endpoints exceeded the suggested minimal clinically important difference (MCID) of −3 and 6.8 points, indicating a clinically meaningful difference between the active and sham rTMS interventions [497]. This finding suggests that the active rTMS intervention substantially impacts the severity of OAB symptoms and quality of life, exceeding the threshold for clinical relevance. These results imply that the active rTMS intervention had a significant and

worthwhile effect on OABSS and I-QOL scores compared to the sham rTMS intervention, which is important for clinical decision-making and patient care.

The effect sizes of active rTMS compared to sham rTMS for OABSS, I-QOL, and BRS scores were statistically significant: 0.62 (medium), 0.74 (medium) and 0.10 (small), respectively. These effect sizes indicate that the active rTMS intervention had a significantly greater effect on OABSS and I-QOL scores than the sham rTMS intervention, while it only had a small effect on BRS scores. This study provides novel evidence that active rTMS can effectively reduce the severity of neurogenic OAB symptoms and improve the quality of life of stroke survivors, as evaluated by OABSS, I-QOL, and BRS scores. Its novelty lies in providing empirical evidence that rTMS could significantly improve neurogenic OAB symptoms, a relatively unexplored area in stroke rehabilitation.

The findings of this RCT on the effectiveness of rTMS in reducing neurogenic OAB symptoms in stroke survivors are consistent with the clinical outcomes of previous low-frequency rTMS studies by Bruso et al. [179] and Qian et al. [536] on individuals with neurogenic OAB symptoms due to Parkinson's disease or stroke, respectively. Bruso et al. [2] investigated the effects of low-frequency rTMS on individuals with OAB symptoms due to Parkinson's disease and found it enhanced bladder capacity. Similarly, a case report by Qian et al. [536] evaluated how continuous theta burst stimulation, a form of rTMS, affected neurogenic OAB symptoms in stroke survivors and observed decreased urinary frequency and anxiety and improved quality

of life. Both studies demonstrated the potential effects of rTMS on the primary motor cortex (M1) in improving the severity of neurogenic OAB symptoms.

Our RCT findings were compared to those of Bruso et al. [179] and Qian et al. [536] because of the similar pathophysiological presentation of neurogenic overactivity in stroke survivors and individuals with Parkinson's disease. Stroke survivors and individuals with Parkinson's disease present with reduced cortical inhibition and induced uninhibited bladder contractions, resulting in detrusor overactivity and reduced bladder filling volumes [642]. The pelvic floor muscle representation in the brain is believed to be located in the M1, more precisely within its superolateral and superomedial precentral gyri [542, 544]. Several previous studies found that applying low-frequency rTMS to the contralateral M1 of stroke survivors effectively reduced the resting motor threshold and increased the motor-evoked potential [10-12]. Targeting the M1 with low-frequency rTMS makes it possible to modulate the neural circuits involved in pelvic floor muscle function, potentially leading to improvements in neurogenic OAB symptom severity [179].

The cost-estimation analysis revealed that the active rTMS intervention has an estimated lower cost than the sham rTMS intervention in reducing the severity of neurogenic OAB symptoms in stroke survivors. The average estimated costs for each participant with neurogenic OAB due to stroke were lower in the active rTMS group than in the sham rTMS group. The estimated lower cost was observed in the urology consultations, medications, physiotherapy services for

urinary incontinence management (e.g. electrical stimulation and pelvic floor muscle exercises), alternative therapies (e.g. yoga, taichi and massage), medical devices/consumables (e.g. disposable diapers and underpads), and travel expenses. Moreover, the reduction in neurogenic OAB symptoms with active rTMS not only improves patients' quality of life but also potentially reduces the long-term burden on the healthcare system. The reduced cost and improved quality of life could include decreased medication needs, fewer hospital visits and improved satisfaction [643]. The fact that active rTMS achieves better outcomes at a potentially lower estimated cost suggests that it could be a preferred treatment option from both clinical and economic perspectives. It reduces the economic burden on both the healthcare system and patients while enhancing patient well-being [644, 645]. This kind of findings are crucial for decision-makers in healthcare since it helps guide resource allocation towards interventions that provide the greatest health benefits for the least cost [646, 647]. It also underscores the importance of considering the long-term health outcomes and costs associated with different treatment options [648-650], especially for chronic conditions such as neurogenic OAB in stroke survivors.

The findings of the qualitative study revealed that stroke survivors with neurogenic OAB symptoms experienced the rTMS intervention positively. Participants reported improvements in neurogenic OAB symptoms such as urinary urgency, frequency, nocturia and incontinence, with seven of the 12 (58%) experiencing significant relief and five (42%) reporting moderate improvements. The rTMS intervention may reduce reliance on pharmacological treatments or invasive procedures, and participants expressed high satisfaction, which could impact

treatment adherence and outcomes [622]. The rTMS intervention also enhanced quality of life, including improved sleep patterns, social confidence and freedom. Neurogenic OAB can affect physical and mental well-being and social interactions, making the positive outcomes of rTMS intervention particularly significant [96].

8.5 Strengths and limitations of the thesis

8.5.1 Study I (systematic and meta-analysis)

The systematic review and meta-analysis included a relatively small number of RCTs for conditions such as stroke, Parkinson's disease and multiple sclerosis (studies for pooled meta-analysis), which may impact the generalisability of its findings. The possibility of language bias cannot be eliminated in the meta-analysis and systematic review of RCTs. We only considered studies published in English and Chinese, potentially excluding relevant studies in other languages, which may limit the external validity of our study. In addition, it may be subject to publication bias due to the exclusion of conference abstracts, grey literature, and unpublished reports, which may result in potentially vital data being overlooked in the meta-analysis.

8.5.2 Studies II and III (systematic reviews of psychometric properties)

In the systematic reviews of the psychometric properties of outcome measures evaluating neurologic OAB symptoms and quality of life, no study investigated the structural validity, and

only one study examined the content validity of the OABSS, which was rated as doubtful. The lack of a structural validity study means it may inadvertently measure unrelated or distinct constructs and lose precision [651]. Subjective bias could also affect the COnsensus-based Standards for selecting health status Measurement Instruments (COSMIN) evaluation since the COSMIN checklist involves subjective judgment, which might influence the overall scoring of these instruments [441].

8.5.3 Study IV (RCT and cost estimation study)

The main study in this thesis was the first RCT investigating the effectiveness of rTMS in reducing the severity of neurogenic OAB symptoms due to stroke. There were high rates of completing the 12 rTMS treatment sessions (100%) and follow-up (95%), indicating a high level of adherence to the treatment protocol [556]. This high adherence shows the participants' commitment to the treatment and willingness to participate in the follow-up assessments [556]. High adherence rates for clinical interventions are significant since they can contribute to the reliability and validity of the study findings and provide valuable insights into the effectiveness and tolerability of the treatment [557]. The RCT used allocation concealment and analysis on an intention-to-treat basis to minimise the influence of bias, enhance the validity of its results [652] and strengthen the overall quality of its findings [558]. However, the follow-up period of four weeks was relatively short and may not capture the long-term effects of the rTMS intervention on neurologic OAB symptoms in stroke survivors. Moreover, the generalisability of the findings may be limited to stroke survivors with neurogenic OAB symptoms.

Cost estimation analyses typically focus on direct medical costs and health outcomes but may not fully capture indirect costs, such as productivity losses, caregiver burden or long-term societal impacts. Many Cost estimation analyses and qualitative studies may focus on short-term outcomes, but the long-term effects and sustainability of rTMS for neurogenic OAB are also crucial.

8.5.4 Study V (qualitative study)

The qualitative study used a rigorous approach to collect and analyse data from focus group discussions using NVivo for coding and theme generation. It adopted a focus group discussion to elicit an in-depth, open discussion and probe experiences to uncover participants' feelings and views regarding using rTMS to manage neurogenic OAB due to stroke. The focus group discussions were conducted after the follow-ups, which might risk introducing a form of recall bias among some participants [591]. Recall bias occurs when the accuracy of recall regarding reporting experiences and events changes with the time since the intervention. In addition, most participants were male (58%), which could introduce gender bias in the results [603]. Moreover, this study may have been subject to participation bias [603] since only those participants who were confident in discussing their experiences and views regarding the rTMS intervention for managing neurogenic OAB volunteered.

8.6 Clinical implications

1. Electrical stimulation has the greatest effects, although it may not be preferred by all patients. Electrical stimulation is superior to PFMT.

2. The OABSS is characterised by sound, cross-cultural suitability with robust psychometric findings across diverse cultural backgrounds. It can be used to evaluate the severity of neurogenic OAB symptoms.

3. The I-QOL is the most psychometrically robust, cross-culturally diverse, and easily administered outcome measure.

4. The RCT results suggest that low-frequency rTMS could be an effective treatment option for managing the severity of neurogenic OAB symptoms in stroke survivors. It found that active rTMS was associated with significant improvements in neurogenic OAB symptom severity, quality of life, and resilience compared to sham rTMS. The observed effect sizes were above the suggested MCID, indicating that these improvements were clinically meaningful. It also found that the effects of active rTMS were sustained at the week-8 follow-up assessment. These findings provide valuable insights into the potential clinical benefits of rTMS as a non-invasive therapeutic option for stroke survivors with neurogenic OAB. They may provide clinicians with clinically useful findings such as reduced urinary frequency, urinary urgency and urgency incontinence, which can be incorporated into their rehabilitation programs to reduce the severity of neurogenic OAB symptoms and improve the overall quality of life of stroke survivors.

5. The RCT also suggests that low-frequency rTMS intervention is an effective and safe procedure [520, 548-550] for managing neurogenic OAB symptoms severity in stroke survivors. Physiotherapists and other clinicians can consider incorporating this intervention into their treatment plans for stroke survivors with neurogenic OAB symptoms, given the positive clinical outcomes on efficacy and safety. This approach aligns with minimising the risks associated with invasive therapies while providing effective management of neurogenic OAB symptoms in stroke survivors.

6. The cost estimation study highlights the importance of considering the estimate of the cost of interventions in stroke rehabilitation, as it can help guide policymakers and stakeholders in decision-making and resource allocation. The rTMS intervention may also contribute to reducing the burden on healthcare systems by providing a low cost estimate and patient-friendly intervention for neurogenic OAB management. The findings of this study can potentially inform clinical practice and guide future research in neurogenic OAB management, ultimately contributing to the development of more clinically effective and cost-efficient interventions for stroke survivors with neurogenic OAB symptoms.

7. The focus group discussions provide valuable insights into the lived experiences, challenges and preferences of rTMS intervention of stroke survivors with neurogenic OAB symptoms. This information can help physiotherapists and other clinicians managing patients with neurogenic OAB consider satisfaction, convenience and safety to achieve maximum clinical benefit and better meet patients' needs, expectations and priorities, promoting patient-centred care. Clinicians managing individuals with

neurogenic OAB due to stroke should focus not only on its physical symptoms but also on its psychosocial impact on patients' lives, including addressing issues related to stigma, social isolation and reduced quality of life. Exploring participants' experiences can yield information about their acceptance of treatment options to facilitate using the rTMS intervention to treat stroke survivors with neurogenic OAB symptoms in clinical practice, which might identify their expectations and needs to maximise therapeutic benefits and satisfaction regarding the rTMS intervention. The study's findings could positively impact the well-being and daily functioning of stroke survivors with neurogenic OAB symptoms, given the reported qualitative clinical benefits of non-invasiveness, social benefits and a sense of fulfilment.

8. The study findings can potentially inform clinical practice and guide future research in neurogenic OAB management, ultimately contributing to developing healthcare policies that could help reduce cost and improve the effectiveness of neurogenic OAB symptom management in stroke survivors.

8.7 Recommendations for future research

1. Future RCTs with adequate power are warranted to investigate the effectiveness of PFMT, behavioural therapy, rTMS and other interventions that have received less attention in treating neurogenic OAB symptoms in stroke survivors.

2. Further studies are required to investigate the content and structural validity of the OABSS, Overactive Bladder Questionnaire (OAB-q) and NGSS, given the role of

content and structural validity in ensuring that the instrument accurately reflects the theoretical components of the construct in question [653]. The content and structural validities are critical in developing and evaluating any instrument or assessment [654]. Assessing these validities is a critical and complex step in developing instruments frequently used to measure complex constructs [655].

3. Our studies investigating the quality of life of stroke survivors with neurogenic OAB did not test content, concurrent and known-group validity, which are critical for developing, assessing and applying clinical tools across fields [656]. The psychometric properties provide evidence that an instrument can accurately measure a construct and distinguish between relevant groups as expected, ensuring its relevance and applicability in real-world settings [657, 658]. Therefore, further investigations of these psychometric properties could broaden these recommendations and support the routine use of the I-QOL for individuals with neurogenic OAB in clinical practice.

4. Further RCTs with longer follow-up periods are warranted to evaluate the long-term effect of the rTMS intervention and the sustainability of its clinical outcomes. These RCTs could provide more robust data on the sustainability of the clinical- and cost estimation analyses of the rTMS intervention for neurogenic OAB due to stroke.

5. Future research should focus on standardising rTMS parameters for managing the severity of neurogenic OAB symptoms in stroke survivors. Establishing standardised parameters for rTMS protocols for neurogenic OAB will ensure consistency, comparability and reproducibility across research studies and clinical applications [659]. Key parameters that should be standardised include the stimulation site,

frequency, intensity, duration and the total number of sessions [182]. Additionally, appropriate patient populations, clinical tools, and outcome criteria should be standardised to facilitate meaningful comparisons and the accumulation of robust evidence [485]. By standardising rTMS parameters, researchers and clinicians can more effectively evaluate the efficacy, safety and optimal application of rTMS for managing neurogenic OAB symptoms. These standardised parameters could also enable the development of evidence-based guidelines and best practices for using rTMS. Furthermore, standardised rTMS parameters will support the reproducibility of findings and facilitate the translation of research outcomes into clinical practice, ultimately benefiting patients by ensuring consistent and effective treatment approaches [660].

6. Future research should adopt individualised rTMS parameters for managing neurogenic OAB, which are crucial for optimising neuromodulation's benefits [661]. Tailoring rTMS parameters to each patient's specific needs and characteristics can optimise the effectiveness and safety of this non-invasive therapy [662]. Individualised parameters may include the precise localisation of stimulation based on neuroimaging or neurophysiological assessments, personalised stimulation intensity and frequency, and considering each patient's unique neurogenic OAB symptoms and underlying neurological condition [663]. By individualising rTMS parameters, researchers and clinicians can better account for the heterogeneity of neurogenic OAB presentations and optimise treatment outcomes for each patient. This personalised approach may lead to more targeted and effective modulation of neural pathways related to bladder control, potentially improving symptom management and overall patient satisfaction [62].

Furthermore, individualised rTMS parameters can help identify potential predictors of treatment response and guide the development of personalised treatment plans for neurogenic OAB in stroke survivors and other affected individuals [664].

7. Future research should incorporate neuro-navigation to confirm coil position, which could significantly enhance applying rTMS in managing neurogenic OAB [466]. Neuronavigation systems can provide real-time guidance to ensure accurate and precise coil placement over the targeted brain regions, improving the reliability and reproducibility of rTMS interventions [665]. This technology can help researchers and clinicians confirm the optimal positioning of the stimulation coil, leading to more consistent and effective treatment delivery [666].

8. Further research is needed to decipher the precise mechanisms by which low-frequency repetitive rTMS reduced the severity of neurogenic OAB symptoms. Monitoring the rTMS intervention using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) could provide a deeper understanding of its associated neural activity and connectivity [559] in reducing neurogenic OAB symptom severity. Concurrent TMS-EEG studies can offer real-time insights into the effects of the rTMS intervention on cortical excitability, neural network dynamics and oscillatory activity in the brain [560]. Additionally, concurrent TMS-EEG studies could directly observe and analyse the immediate neural responses to the rTMS intervention, providing valuable information about how it modulates neural circuits related to bladder control [560]. Moreover, concurrent TMS-fMRI studies could help identify changes in brain activity and connectivity patterns induced by the rTMS intervention [561] since fMRI

can provide spatial information about the brain regions influenced by rTMS and the functional connectivity between them [562]. This approach could offer a comprehensive view of the neural effects of rTMS intervention on the cortical regions and its potential impact on reducing the severity of neurogenic OAB symptoms.

9. Future research should focus on conducting comprehensive cost-effectiveness analyses incorporating patient perspectives and combining rTMS with physiotherapy interventions such as electrical stimulation and pelvic floor muscle exercises to better assess its economic value in managing neurogenic OAB. However, conducting specific cost-effectiveness studies to determine the financial implications of implementing rTMS for neurogenic OAB in Hong Kong and worldwide would still be important. Cost estimation analyses typically focus on direct medical costs and health outcomes and may not fully capture indirect costs, such as productivity losses, caregiver burden or long-term societal impacts, which could help provide a holistic perspective on individuals with neurogenic OAB by estimating humanistic burdens such as depression and anxiety and humanistic cost by evaluating the decrease in health-related quality of life. Future research should consider a broader societal perspective to capture the full economic impact of the rTMS intervention in reducing the severity of neurogenic OAB symptoms.

10. Further qualitative studies exploring the opinions and views of caregivers of stroke survivors with neurogenic OAB symptoms receiving both active and sham rTMS interventions are needed, which would help determine the actual effects of active rTMS compared to sham rTMS.

11. Further qualitative studies exploring the economic implications of the rTMS intervention on improvements in stroke survivors' neurogenic OAB symptoms are required. They could provide valuable insights into the patients' views and opinions on the cost estimation of the rTMS intervention and its potential impact on their quality of life. Exploring the rTMS intervention's economic implications can help to better understand its potential benefits and limitations and inform future decision-making regarding its application in clinical practice. By considering the rTMS intervention's economic implications, decision-makers can make more informed choices about whether to adopt the rTMS intervention in clinical practice and how to allocate resources for its implementation, which could ultimately lead to more effective utilisation of resources in healthcare and improve patient outcomes. This information can also help stakeholders understand the potential return on investment for the rTMS intervention, which can be helpful for making funding decisions.

12. Further qualitative studies investigating the effects of stigma on patients' attitudes towards management and well-being are needed. Stigma can profoundly impact individuals' psychological, social and physical well-being and affect their help-seeking behaviours, treatment adherence and overall quality of life [626]. In-depth qualitative studies on stroke survivors with neurogenic OAB could help to understand how stigma affects their experiences and perceptions of their condition. This information could be used to develop interventions to reduce stigma and improve the well-being of stroke survivors with neurogenic OAB. Additionally, qualitative studies can help identify the

specific factors contributing to stigma and inform the development of targeted interventions to address them.

8.8 Conclusion

Our meta-analysis found that electrical stimulation (IVES and NMES) is effective in reducing symptoms of UUI among individuals with multiple sclerosis. Electrical stimulation (NMES and TENS) was also found to be beneficial for reducing UUI symptoms among individuals with stroke. OABSS was the most culturally diverse and psychometrically sound clinical tool supported by studies of good methodological quality and high evidence quality among individuals with UUI due to OAB. Our systematic review identified the I-QOL as the most psychometrically robust, cross-culturally diverse and easily administered outcome measure based on studies with good methodological quality and high evidence quality. Our study also demonstrated statistically significant improvement in OABSS, I-QOL and BRS scores in the active rTMS group compared to the sham rTMS group at the primary and secondary endpoints. Our study also found a lower cost and higher QALY in the active rTMS group than in the sham rTMS group, indicating that the active rTMS intervention was associated with lower costs and greater quality of life and efficacy. The participants reported increased confidence and long-term benefits in urinary frequency, urinary urgency, nocturia and UUI as a result of the rTMS intervention. Our findings suggest that low-frequency rTMS may be a promising treatment option for stroke survivors experiencing neurogenic OAB symptoms. They provide valuable insights into the potential of low-frequency rTMS as a non-invasive and effective therapeutic approach for addressing neurogenic OAB symptom severity in stroke survivors.

Appendix 2.1: Search strategy of systematic review and meta-analysis

Neurogenic Overactive Bladder	***Conservative interventions***	***Study design***
Neurogenic Urinary Bladder Urgency urinary incontinence Mixed urinary incontinence Urge incontinence Overactive bladder Neurogenic Bladder Uninhibited Neurogenic Bladder Neurogenic lower urinary tract dysfunction Urinary incontinence	Transcranial magnetic stimulation TMS Repetitive Transcranial magnetic stimulation rTMS Transcranial direct current stimulation tDCS Repetitive Transcranial direct current stimulation rtDCS Transcutaneous electrical nerve stimulation TENS Magnetic stimulation Magnetic therapy Electrical stimulation Biofeedback Vaginal electrical stimulation Pelvic floor muscle exercise Cognitive Behavioral training CBT Bladder training Bladder retraining	Randomised Control Trails Randomized Control Trials Randomised Controlled Trails Randomized Controlled Trials RCT Random allocation Randomized controlled clinical trials

	Vaginal cones Vaginal weights	

Appendix 2.2 Embase search strategy

	Examples of Keywords
# 1	('urinary incontinence'/exp OR 'urinary incontinence' OR (urinary AND ('incontinence'/exp OR incontinence)) OR 'neurogenic urinary bladder'/exp OR 'neurogenic urinary bladder' OR (neurogenic AND urinary AND ('bladder'/exp OR bladder)) OR 'urgency urinary incontinence'/exp OR 'urgency urinary incontinence' OR (('urgency'/exp OR urgency) AND urinary AND ('incontinence'/exp OR incontinence)) OR 'mixed urinary incontinence'/exp OR 'mixed urinary incontinence' OR (mixed AND urinary AND ('incontinence'/exp OR incontinence)) OR 'urge incontinence'/exp OR 'urge incontinence' OR (urge AND ('incontinence'/exp OR incontinence)) OR 'overactive bladder'/exp OR 'overactive bladder' OR (overactive AND ('bladder'/exp OR bladder)) OR 'neurogenic bladder'/exp OR 'neurogenic bladder' OR (neurogenic AND ('bladder'/exp OR bladder)) OR 'uninhibited neurogenic bladder' OR (uninhibited AND neurogenic AND ('bladder'/exp OR bladder)) OR 'neurogenic lower urinary tract dysfunction'/exp OR 'neurogenic lower urinary tract dysfunction' OR (neurogenic AND lower AND urinary AND ('tract'/exp OR tract) AND dysfunction

#2	('randomised control trails' OR (randomised AND ('control'/exp OR control) AND trails) OR 'randomized control trials' OR (randomized AND ('control'/exp OR control) AND trials) OR 'randomised controlled trails' OR (randomised AND controlled AND trails) OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR (randomized AND controlled AND trials) OR rct OR 'random allocation'/exp OR 'random allocation' OR (random AND allocation) OR 'randomized controlled clinical trials' OR (randomized AND controlled AND ('clinical'/exp OR clinical) AND trials))
#3	('transcranial magnetic stimulation'/exp OR 'transcranial magnetic stimulation' OR (transcranial AND magnetic AND ('stimulation'/exp OR stimulation)) OR 'tms'/exp OR tms OR 'repetitive transcranial magnetic stimulation'/exp OR 'repetitive transcranial magnetic stimulation' OR (repetitive AND transcranial AND magnetic AND ('stimulation'/exp OR stimulation)) OR rtms OR 'transcranial direct current stimulation'/exp OR 'transcranial direct current stimulation' OR (transcranial AND direct AND current AND ('stimulation'/exp OR stimulation)) OR tdcs OR 'repetitive transcranial direct current stimulation' OR (repetitive AND transcranial AND direct AND current AND ('stimulation'/exp OR stimulation)) OR rtdcs OR

	'transcutaneous electrical nerve stimulation'/exp OR 'transcutaneous electrical nerve stimulation' OR (transcutaneous AND electrical AND ('nerve'/exp OR nerve) AND ('stimulation'/exp OR stimulation)) OR tens OR 'magnetic stimulation'/exp OR 'magnetic stimulation' OR (magnetic AND ('stimulation'/exp OR stimulation)) OR 'magnetic therapy'/exp OR 'magnetic therapy' OR (magnetic AND ('therapy'/exp OR therapy)) OR 'electrical stimulation'/exp OR 'electrical stimulation' OR (electrical AND ('stimulation'/exp OR stimulation)) OR 'biofeedback'/exp OR biofeedback OR 'vaginal electrical stimulation' OR (vaginal AND electrical AND ('stimulation'/exp OR stimulation)) OR 'pelvic floor muscle exercise'/exp OR 'pelvic floor muscle exercise' OR (('pelvic'/exp OR pelvic) AND floor AND ('muscle'/exp OR muscle) AND ('exercise'/exp OR exercise)) OR 'cognitive behavioral training' OR (cognitive AND behavioral AND ('training'/exp OR training)) OR cbt OR 'bladder training'/exp OR 'bladder training' OR (('bladder'/exp OR bladder) AND ('training'/exp OR training)) OR 'bladder retraining' OR (('bladder'/exp OR bladder) AND ('retraining'/exp OR retraining)) OR 'vaginal cones' OR (vaginal AND cones) OR 'vaginal weights' OR (vaginal AND weights)
#4	#1AND#2AND#3

Appendix 3.1: Themes

Neurogenic overactive bladder	Outcome measures	Psychometric properties
Neurogenic Urinary Bladder OR Urgency urinary incontinence OR Mixed urinary incontinence OR Urge incontinence OR Overactive bladder OR Neurogenic Bladder OR Uninhibited Neurogenic OR Bladder Neurogenic lower urinary tract dysfunction OR Urinary incontinence	Actionable Bladder Symptom Screening Tool OR Bristol Female Lower Urinary Tract Symptoms instrument OR Danish Prostate Symptom Score Questionnaire OR International Consultation on Incontinence Questionnaire Bladder Diary OR International Consultation on Incontinence Questionnaire- Female lower urinary tract symptoms OR International	Psychometric property OR Psychometric assessment OR Psychometric measurement OR Psychometric evaluation OR Psychometric testing OR Psychometrics OR Clinometric properties OR Clinometric testing OR Validity OR Reliability OR Responsiveness OR Outcome measures OR Assessment tools OR Scale OR Measure

	Consultation on Incontinence Questionnaire- males lower urinary tract symptoms OR International Consultation on Incontinence questionnaire in overactive bladder OR Indevus Urgency Severity Scale OR Neurogenic bladder symptom score questionnaire OR Overactive Bladder-Bladder Assessment Tool OR Overactive bladder satisfaction with treatment questionnaire OR Overactive bladder questionnaire OR	

	Overactive bladder questionnaire OR Overactive Bladder Symptom Scores Questionnaire OR Patient perception of intensity of urgency scale	

Appendix 3.2: Medline Search Strategy

	Examples of Keywords
# 1	Neurogenic Urinary Bladder OR Urgency urinary incontinence OR Mixed urinary incontinence OR Urge incontinence OR Overactive bladder OR Neurogenic Bladder OR Uninhibited Neurogenic OR Bladder Neurogenic lower urinary tract dysfunction OR Urinary incontinence
#2	Psychometric property OR Psychometric assessment OR Psychometric measurement OR Psychometric evaluation OR Psychometric testing OR Psychometrics OR Clinometric properties OR Clinometric testing OR Validity OR Reliability OR Responsiveness OR Outcome measures OR Assessment tools OR Scale OR Measure
#3	tools or instruments or scales or questionnaires
#4	#1AND#2AND#3

Appendix 3.3: **Reasons for exclusion of studies**

Ineligible Participants
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Appendix 4.1: Medline Search Strategy

	Examples of Keywords
#1	Neurogenic Urinary Bladder OR Urgency urinary incontinence OR Mixed urinary incontinence OR Urge incontinence OR Overactive bladder OR Neurogenic Bladder OR Uninhibited Neurogenic OR Bladder Neurogenic lower urinary tract dysfunction OR Urinary incontinence
#2	Qualiveen Questionnaire OR King Health questionnaire OR Overactive Bladder –V8 Questionnaire OR OAB-V8 OR International Consultation on Incontinence Questionnaire OR ICIQ OR Overactive bladder questionnaire OR UI Overactive Bladder OR Incontinence Impact Questionnaire OR IIQ OR Urogenital Distress Inventory OR UDI OR Danish Prostate Symptom Score OR DAN-PSS-1 OR Incontinence-Quality of Life OR I-QoL OR ICIQ-UI-SF OR ICIQ-UI-OAB OR OABSS OR ICIQ-OAB OR ICI-QOL OR OABQ-SF OR ICIQ-SF OR LUTS (OABQ-SF) OR ICIQ-SF OR Bristol Female Lower Urinary Tract Symptom questionnaire OR ICIQ-OAB OR
#3	Psychometric property OR Psychometric assessment OR Psychometric measurement OR Psychometric evaluation OR Psychometric testing OR Psychometrics OR Clinometric properties OR

	Clinometric testing OR Validity OR Reliability OR Responsiveness OR Outcome measures OR Assessment tools OR Scale OR Measure
#4	#1AND#2AND#3

Appendix 4.2: Reasons for exclusion of studies

Ineligible Participants
1. Hendriks, E. J., Bernards, A. T., Berghmans, B. C., & de Bie, R. A. (2007). The psychometric properties of the PRAFAB-questionnaire: A brief assessment questionnaire to evaluate severity of urinary incontinence in women. *Neurourology and Urodynamics: Official Journal of the International Continence Society*, *26*(7), 998-1007. 2. Bjelic-Radisic, V., Dorfer, M., Tamussino, K., & Greimel, E. (2005). Psychometric properties and validation of the German-language King's Health Questionnaire in women with stress urinary incontinence. *Neurourology and Urodynamics: Official Journal of the International Continence Society*, *24*(1), 63-68. 3. Bjelic-Radisic, V., Dorfer, M., Tamussino, K., & Greimel, E. (2005). Psychometric properties and validation of the German-language King's Health Questionnaire in women with stress urinary incontinence. *Neurourology and Urodynamics: Official Journal of the International Continence Society*, *24*(1), 63-68. 4. Bent, A. E., Gousse, A. E., Hendrix, S. L., Klutke, C. G., Monga, A. K., Yuen, C. K., ... & Muram, D. (2005). Validation of a two-item quantitative questionnaire for the triage of women with urinary incontinence. *Obstetrics & Gynecology*, *106*(4), 767-773.

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Ineligible Design

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Appendix 5.1: Ethical approval

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To Priya-kannan (Department of Rehabilitation Sciences)

From Pang Marco Yiu Chung, Chair, PolyU Institutional Review Board
Email

marco.pang@ Date 18-Nov-2022

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 02-Nov-2022 to 04-Oct-2023:

Project Title:	A mixed-methods evaluation of the clinical and costeffectiveness of repetitive transcranial magnetic stimulation (rTMS) on neurogenic overactive bladder in stroke
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Priya-kannan
Project Start Date:	02-Nov-2022
Project type:	Human subjects (clinical)
Review type:	Full Review
Reference Number:	HSEARS20210913002

You will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In case the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the PolyU Institutional Review Board in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

Pang Marco Yiu Chung

Chair

PolyU Institutional Review Board

Appendix 5.2: <u>Information Sheet</u>

A mixed-method evaluation of the clinical and cost effectiveness of repetitive transcranial magnetic stimulation (rTMS) on neurogenic overactive bladder in stroke

Mohammed Usman Ali,

Department of Rehabilitation Sciences,

The Hong Kong Polytechnic University,

5935

m-usman.ali@

You are invited to participate in the above project conducted by Mr. Mohammed Usman Ali, who is a PhD candidate in the Department of Rehabilitation Sciences at The Hong Kong Polytechnic University (PolyU). The project has been approved by the PolyU Institutional Review Board (PolyU IRB) (or its Delegate) (Reference Number: HSEARS20210913002)

Why is this study conducted?

The findings of this study may contribute to a better understanding of neurogenic overactive bladder (OAB) so that better treatment can be developed. The findings of the proposed study will be useful for reducing healthcare-related costs associated with neurogenic OAB. Therefore, providing an effective treatment approach to reduce neurogenic OAB among stroke

survivors may also reduce socioeconomic burdens. Researchers and clinicians will receive new insights into the efficacy of rTMS in managing neurogenic OAB through the findings of this study. The findings of the proposed study will also benefit the community of stroke survivors with neurogenic OAB, thus reducing the level of discomfort associated with the insertion of a vaginal or anal probe. Physiotherapists in the field of stroke rehabilitation could benefit from the findings of the proposed study since they may provide new insight into the management of neurogenic OAB among stroke survivors.

The aims/objectives

1. To investigate the effects of active-rTMS and sham-rTMS groups on treating neurogenic OAB among stroke survivors.
2. To explore the experiences and perceptions of participants regarding rTMS interventions.
3. To estimate the cost of intervention in the active-rTMS and sham-rTMS groups for managing neurogenic OAB among stroke survivors.

When does the study start and when does it end? What are the sources of funding for this study?

The study will start on 2 November 2022 and be completed on 4 October 2023.

The study is funded by The Hong Kong Polytechnic University (Dean's Reserve, Faculty of Health and Social Sciences (Department of Rehabilitation Sciences). Ref No. ZVSV.

What will my participation in this study involve?

Participants who fulfill the following inclusion criteria will be eligible to be recruited in the: (1) stroke survivors aged between 18–80 years diagnosed with neurogenic OAB; (2) experience moderate (OABSS scores: 6-11 points) to severe neurogenic OAB (OABSS scores: 12 points and above); (3) obtain a Mini-Mental State Examination (MMSE) score of ≥ 24; and (4) be willing to be randomised.

The volunteers who contact the research personnel via phone or email will be requested to come over to the PolyU for eligibility screening, written informed consent, and baseline assessments. On the first day of contact, eligible participants who provide written informed consent will complete a set of questionnaires to establish the baseline severity of urinary incontinence, quality of life, and resilience. Following this, you will be randomly assigned to one of the following two groups where you have equal chances of belonging to either group: active-rTMS and sham-rTMS groups. The active-rTMS group will receive real rTMS intervention and participation in a semi-structured interview of focus group discussion. Similarly, the sham rTMS group will receive an rTMS intervention with a sham coil, presuming it is a true rTMS coil for the intervention.

During the treatment, you will be required not to move or sleep. There will be a baseline outcomes assessment before the commencement of the interventions, a post-intervention outcomes assessment at the end of the four weeks, and a follow-up assessment at the end of 8

weeks following your entry into the study. The duration of the rTMS intervention will last 20 minutes, while the duration of the first assessment and subsequent assessments, including the follow-up assessment, will take 1 hour and 45 minutes. The assessments will involve the administration of a self-reported overactive bladder symptom score (OABSS), Incontinence Quality-of-Life Questionnaire (I-QoL) and Brief Resilience Scale, as well as evaluation of intervention adherence.

In the focus group discussion, 15 participants from the active-rTMS group will be recruited and grouped into three groups of five participants each. The focus group discussion will be used to discuss and elicit information on some predetermined and open-ended questions, but not limited to the questions. The following questions will be included for discussion during the focus groups. (1) Which incontinence symptom (urge frequency, nocturnal frequency, urge accidents) would you most like further relief? (2) How did you find your experience with rTMS? (3) What differences did you experience in incontinence during your study participation? (4) Would you recommend rTMS to your family and friends with neurogenic urinary incontinence? (5) How do you get yourself motivated to be social? (6) In your opinion, what can help you improve and strengthen your resilience? In all focus group discussions, notes will be taken.

Risks and benefits of participating

The rTMS is a well-tolerated and safe non-invasive modality. Participation in this study might result in mild transitory headache, neck pain or mild local scalp pain at the stimulation site that can be resolved by the administration of analgesics such as paracetamol. Although, in a large proportion of patients, rTMS can be administered safely when assessment and monitoring are conducted properly. To avoid such incidences, the contraindications to using rTMS will be well observed, and participants will be adequately screened to avoid the incidence of any undesirable adverse effects associated with the intervention. Some individuals might experience mild tiredness during the therapeutic interventions, or they might feel headaches and scalp pain after rTMS – both of which tend to subside after the first few days of treatment.

Participants will be observed for adverse effects during and after each treatment session. At the end of each treatment day, participants will be assessed for adverse effects with open-ended questions. A follow-up phone interview will be completed four weeks after the participant's week of rTMS treatment. During this follow-up interview, participants will be directly asked about migraine and headaches, dizziness, concentration, memory, vision, speech, hearing ailment, and emotional instability during and after the rTMS treatments. If any symptom occurs, the participants will be asked about the symptom's onset, duration, and severity. – Emergency department personnel will be contacted in case of an adverse event. The Principal Investigator will report any serious adverse event to the Institutional Review Board (IRB) committee (Ms. Cherrie MOK, tel. no.: 27666378, cherrie.mok@) within 48 hours of the incident.

Each participant will be offered HKD 100 following each assessment to cover any transport expenses incurred for participation in the study. As you will be undergoing assessments at 3 time points (baseline, 4, and 8 weeks), you will receive a total amount of HKD 300. Participants allocated to the intervention group and involved in the focus group discussion will receive HKD 100 to cover transport expenses for participation in the focus group study.

The information you provide as part of the project is the research data. Any research data from which you can be identified is known as personal data. Personal data does not include data where the identity has been removed (anonymous data). We will minimise our use of personal data in the study as much as possible. The researcher and his team, and supervisors will have access to personal data and research data for the purposes of the study. Confidentiality of the participants' personal, health information and collected raw data will be provided and assured. Participants' identities will be kept anonymous via the assignment of ID numbers. The principal investigator and team members will safeguard all the obtained participants' data on password-protected personal computers. The hard copies of data will be kept safe in office-locked cabinets three years after the research project's completion and discarded based on the Hong Kong Polytechnic University research regulations. The research team members will take appropriate measures and be responsible for safeguarding the patients' data. The obtained findings after the completion of the study will be published in scientific journals. Names or photographers of the participants will not be displayed in any publication from the findings of the study.

What are my rights as a participant in this study?

The confidentiality of the participants will be provided and explained thoroughly to the participants. Anonymity will be used to maintain confidentiality and safeguard the information that the participants have disclosed in a relationship of trust and with the expectation that it will not be disclosed to others without permission, except in ways consistent with the original disclosure. The participants' records will remain protected from disclosure outside the research setting or to unauthorised persons. The participants have every right to withdraw from the study before or during the treatment without penalty of any kind. Written informed consent will be sought and obtained before their enrolment in the study. Copies of the signed consent form and information sheets will be given to the individual participants for their records.

If you have any questions, you may ask for our help now or later, even after the study has started.

You may contact Dr. Priya Kannan (tel. no.: 3400 3277 / email: priya.kannan@) or Dr. Georg S Kranz (tel. no.: 27664838 / email: georg.kranz@) or Prof Kenneth Fong (tel. no.: 27666716 / email: kenneth.fong@) of PolyU under the following situations:

a. if you have any other questions in relation to the study.

b. if, under very rare conditions, you become injured as a result of your participation in the study; or

c. if you want to get access to/or change your personal data before.

In the event you have any complaints about the conduct of this research study, you may contact the Secretary, PolyU Institutional Review Board in writing (Ms Cherrie MOK, tel. no.: 27666378, cherrie.mok@) stating clearly the responsible person and department of this study as well as the Reference Number.

Thank you for your interest in participating in this study.

Mohammed Usman Ali

Telephone number: 5935

Email address: m-usman.ali@

Information Sheet (Chinese-Cantonese Version)

附錄：研究資料

研究資料

重複性經顱磁刺激（rTMS）對中風人士神經性膀胱過動症的臨床和成本效益的混合方法評估

主要研究員

Mohammed Usman Ali，康復治療科學系

香港理工大學

5935

m-usman.ali@

我們邀請您參與由香港理工大學康復治療科學系研究生 Mohammed Usman Ali 先生負責的上述項目。本項目已獲香港理工大學機構審查委員會（理大 IRB）（或其代表）（參考編號：HSEARS20210913002）批准。

為什麼要進行這項研究？

本研究的結果可能有助於更好地了解神經性膀胱過動症（OAB），以便更好地進行治療並有助於降低 NOAB 的治療成本。以此，提供一種有效的治療方法來減少中風人士患 NOAB 的機會，也可以減輕社會經濟負擔。通過這項研究的結果，研究人員和臨床醫生將獲得有關 rTMS 對 OAB 的功效的新見解。此研究的結果還將使患有 NOAB 的中風人士受益，因可減少使用插入陰道或肛門探針以降低不適程度。從事中風康復的物理治療師亦可以從本研究的結果中受益，因本研究可以為治療患 NOAB 的中風人士提供新的見解。

宗旨/目標

1. 探討有效 rTMS 組和假 rTMS 組對中風人士治療 NOAB 的影響。
2. 探索參與者對 rTMS 的看法和態度。
3. 比較有效 rTMS 和假 rTMS 組治療 OAB 的成本效益。

研究何時開始，何時結束？這項研究的資金來源是什麼？

該研究將於 2022 年 11 月 2 日開始，並於 2023 年 10 月 4 日完成。

該研究由香港理工大學（醫療及社會科學院（康復科學系）院長儲備）資助。參考編號 ZVSV。

我參與這項研究將涉及什麼？

符合以下參加標準的參與者將有資格參加研究：（1）被診斷患有 NOAB 的 18-80 歲的中風人士； (2)有中度（OABSS 評分：6-11 分）至重度 OAB（OABSS 評分：12 分及以上）； (3) 在簡易精神狀態檢查 (MMSE) 得到 24 分或以上； (4) 願意被隨機分到任何一組實驗組。

研究人員將通過電話或電子郵件聯繫志願者並邀請到香港理工大學（理大）進行資格篩選，簽署書面同意書和初次評估。 在第一天，提供書面同意書並合資格的參與者將完成一組問卷，以評估尿失禁的嚴重程度，生活質量和復原力。在此之後，您將被隨機分配到以下兩個組之一，您有平等的機會分配到任何一組：有效 rTMS 和假 rTMS 組。有效 rTMS 組將接受真正的 rTMS，並參與焦點小組討論的半結構性訪談。同樣地，假 rTMS 組將接受帶有假線圈 rTMS，假定為真正 rTMS 治療。

在治療期間，您需要保持沉默，減少動作。在研究開始之前將進行基礎評估，並在研究結束時進行最終評估。後續結果評估也將在最後一次評估的四周後進行。rTMS 的時間將持續 20 分鐘，而第一次評估和後續評估的時間將為 1 小時 45 分鐘。評估將包括自我報告的膀胱過度活躍徵狀問卷（OABSS），尿失禁生活品質問卷（I-QoL）和簡要復原力量表以及治療依從性的評估。

在焦點小組討論中，來自有效 rTMS 小組的 15 名參與者將被招募並分為三組，每五名參與者為一個半結構化焦點小組。研究人員將與焦點小組討論的參與者討論和引出有關一些預定和開放式問題的資訊，但不限於這些問題。以下問題將會在焦點小組會議期間進行討論：（1）您最想進一步緩解哪種尿失禁徵狀（急迫頻率，夜間頻率，急迫事故）？（2） 您是如何找到使用 rTMS 的體驗的？（3）在學習過程中，您在尿失禁方面經歷了哪些差異？（4）您會向患有神經性尿失禁的家人和朋友推薦 rTMS 嗎？（5）你如何讓自己有動力去社交？（6）在你看來，什麼可以提高和加強你的復原力？所有焦點小組討論都將以筆記進行記錄。

參與的風險和收益

rTMS 是一種耐受性良好且安全的非侵入性方式，沒有異常副作用和安全問題。參與本研究不會導致任何不適或其他傷害，除了常見的副作用，如輕度暫時性頭痛、頸部疼痛或刺激部位的輕度局部頭皮疼痛，這些在低頻 rTMS 中不太常見。在很大一部分患者中正確進行評估和監測時，rTMS 可以安全地使用。但這些副作用是不常見的嚴重副作用。為了避免此類事件，研究人員將會觀察使用 rTMS 的副作用，並將對參與者進行充分篩查，以避免相關的任何不良反應發生。 有些人可能會在治療期間感到輕微的不適或疲倦，或者他們可能會在 rTMS 後感到頭痛和頭皮不適。這兩者在治療的頭幾天後都會消退。然而，這種不適不會比他們在日常生活中所經歷的更大。

參與者將在每次治療期間和之後觀察不良反應。在每個治療日結束時，參與者將接受開放式問題的不良反應評估。後續電話面試將在參與者接受 rTMS 治療四周後完成。在這次後續訪談中，研究人員將詢問參與者是否有偏頭痛和頭痛、頭暈、注意力、記憶力、視力、言語、聽力疾病、情緒不穩定等副作用以及 rTMS 治療期間和之後的不適。如果出現任何徵狀，參與者將被詢問徵狀的情況，持續時間和嚴重程度。如果參與者感到不舒服，將實施風險管理和應急計劃： - 將聯繫急診科人員，和將記錄事故和緊急情況的救護車號碼和電話號碼 ，，以評估患者的狀態。首席研究員將在事件發生後 48 小時內向機構審查委員會 (IRB)（莫女士，電話：27666378，cherrie.mok@ ）報告任何嚴重不良事件。

參與者將獲得港幣 300 元，以支付初次評估、治療後評估和後續評估的交通費用。如果參與者被隨機分配到焦點小組討論的小組中，他們還將獲得 100 港元的交通費用，每次接受的治療將會是免費的。

您所提供的資訊是研究數據，任何可以識別您身份的研究數據都稱為個人數據。個人數據不包括身份已被刪除的數據（匿名數據）。我們將盡可能減少在研究中對個人數據的使用。研究人員及其團隊以及主管將有權訪問個人數據和研究數據，以用於研究目的。香港理工大學的負責成員會對研究進行監督和/或審計。研究完成後，数据将在

部门数据存储库软件中保留三个 年。将在研究项目上完成数据的硬拷贝三年后安全地保存在办公室上锁的柜子中，然后根据香港理工大学的研究规定丢弃

。與您有關的所有資訊都將保密，並且只有知道代碼的研究人員可以瀏覽。香港理工大學會採取合理的預防措施，以防止您提供的資訊丟失、盜用、未經授權的訪問或破壞。

作為本研究的參與者，我有哪些權利？

研究人員會向參與者提供保密。參與者披露的資訊將以匿名的方式保護並保持機密性，未經許可不會向他人披露，除非以原始披露的方式。參與者的記錄將受到保護，不得在研究環境之外或向未經授權的人員中披露。參與者完全有權在治療之前或期間退出研究，而不會受到任何形式的懲罰。在他們參加研究之前，將尋求並獲得書面同意書。已簽署的同意書及資料表副本將交予個別參與者作記錄。

如果您有任何疑問，您可以立即或稍後詢問我們的研究人員，即使在研究開始後也是如此。

在下列情況下 ，你可聯絡理大的 Priya Kannan 博士（電話：34003277 / 電郵：priya.kannan@ ）或 Georg S Kranz 博士（電話： 27664838 / 電郵： georg.kranz@ ）或方乃權教授（電話： 27666716 / 電郵 ： kenneth.fong@ ）：

a. 如果您有任何其他與研究有關的問題；

b. 如果在極少數情況下，您因參與研究而受傷；或

c. 如果您想在（到期日）之前存取/或更改您的個人資料。

如您對本研究的進行有任何投訴，你可以書面形式聯絡理大構審查委員會秘書（莫女士，電話：27666378 / 電郵： cherrie.mok@ ），並清楚說明本研究的負責人及部門，以及參考編號。

感謝您有興趣參與這項研究。

Mohammed Usman Ali

电话号码：5935

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Appendix 5.3: <u>Consent form</u>

CONSENT TO PARTICIPATE IN RESEARCH

A mixed-method evaluation of the clinical and cost effectiveness of repetitive transcranial magnetic stimulation (rTMS) on neurogenic overactive bladder in stroke

I _____ hereby consent to participate in the captioned research conducted by Mohammed Usman Ali.

I understand that information obtained from this research may be used in future research and published. However, my right to privacy will be retained, i.e. my personal details will not be revealed.

The procedure as set out in the attached information sheet has been fully explained. I understand the benefit and risks involved. My participation in the project is voluntary.

I know that I will undergo assessments at three time points including baseline (prior to the intervention), 4 weeks, and 8 weeks.

I am aware that I can volunteer to participate in focus group discussions to provide my opinion and experience of the intervention.

I am aware that I will be provided HKD 100 following each assessment to cover any travel expenses incurred for my participation in the study. As there are three assessments, in total, I will be receiving HKD 300.

I am also aware that participants assigned to the intervention group and involved in the focus group discussion will receive HKD 100 to cover transport expenses for participation in the focus group study.

I acknowledge that I have the right to question any part of the procedure and can withdraw at any time without penalty of any kind.

Name of participant _____

Signature of participant_____

Name of Parent or Guardian (if applicable) _____

Signature of Parent or Guardian (if applicable) _____

Name of researcher Mohammed Usman Ali

Signature of researcher

Date

<u>Consent form</u> (Chinese-Cantonese Version)

參加研究同意書

重複性經顱磁刺激（rTMS）對中風人士神經性膀胱過動症的臨床和成本效益的混合方法評估

本人 _____ 特此同意參與由 Mohammed Usman Ali 進行的標題研究。

本人瞭解從這項研究中獲得的資訊可能會用於未來的研究並發表。但是，本人的隱私權將被保留，即本人的個人詳細資訊不會被洩露。

所附資訊表中列出的程式已得到充分解釋。本人瞭解所涉及的利益和風險。本人參與這個項目是自願的。

本人知道將被分配接受治療，並在治療開始和結束時以及最後一次評估後四個星期接受評估。

本人知道可能會被分配到一個焦點小組討論訪談中進行半結構化訪談，以獲得本人對治療的意見和經驗。

我明白每次评估后，我将获得港币 100 元，以支付我参与研究所产生的任何差旅费用。由于有三项评估，我将获得港币 300 元。

我也知道分配到干预小组并参与焦点小组讨论的参与者将获得 100 港元，以支付参与焦点小组研究的交通费用。

本人承認本人有權質疑程式的任何部分，並且可以隨時退出而不會受到任何形式的懲罰。

參加者姓名 _____

參與者簽名 _____

父母或監護人姓名（如適用）_____

父母或監護人簽名（如適用）_____

研究員姓名_____

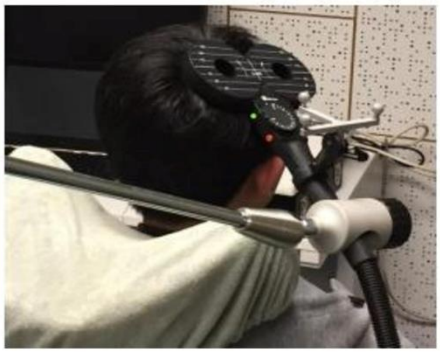
研究員簽名

日期 _____

Appendix 5.4: Recruitment flier

A mixed-methods evaluation of the clinical and cost-effectiveness of repetitive transcranial magnetic stimulation (rTMS) on neurogenic overactive bladder in stroke

Transcranial magnetic stimulation (TMS) is a non-invasive device that painlessly delivers an intense and brief magnetic field to the brain to provide an effective treatment approach to reduce neurogenic overactive bladder (NOAB) symptoms and socioeconomic burdens among stroke survivors and improve bladder capacity and bladder filling.



Male and female stroke survivors (18–80 years) with urinary incontinence.

Experience moderate (OABSS scores: 6-11 points) to severe NOAB (OABSS scores: 12 points and above).

Obtain a Mini-Mental State Examination (MMSE) score of ≥ 24.

*A payment of **HKD 100** will be made at the first and final assessment visit each*

This study will benefit the community of stroke survivors with NOAB, thus reducing the level of discomfort associated with the insertion of a vaginal or anal probe.

*This study will provide 4-weeks (12 visits) intervention sessions. Invitees will visit the Hong Kong Polytechnic University to participate in this research. Interested participant can contact the researcher through this number **5935**[redacted] or email at m-usman.ali@[redacted]*

Recruitment flier (Chinese-Cantonese Version)

THE HONG KONG POLYTECHNIC UNIVERSITY 香港理工大學

康復治療科學系 Department of Rehabilitation Sciences

重複性經顱磁刺激（rTMS）對中風人士神經性膀胱過動症的臨床和成本效益的混合方法評估

經顱磁刺激 (TMS) 是一種無創設備，可無痛地向大腦輸送強烈而短暫的磁場，從而提供有效的治療方法以改善膀胱容量和灌注並減輕中風人士的神經性膀胱過度活動症 (NOAB) 症狀和

患有尿失禁的男性和女性中風人士 (18-80 歲)

經歷中度（膀胱過度活躍徵狀問卷 (OABSS) 分數：6-11 分）到重度神經性膀胱過度活動症（膀胱過度活躍徵狀問卷 (OABSS) 分數：12 分及以上)

獲得≥ 24 的簡易精神狀態檢查 (MMSE) 分數

這項研究將使患有神經性膀胱過度活動症的中風人士受益，從而減少使用插入陰道或肛門探針以降低不適程度。

MU Ali
WhatsApp contact

本研究將提供為期 4 週（12 次）的治療課程。受邀者將前往香港理工大學參與此項研究。有興趣的參與者可以通過電話 5935 [redacted] 或發送電子郵件至 m-usman.ali@[redacted] 與研究人員聯繫。

Appendix 5.5: 13-items Screening Questionnaire for the TMS Candidates

Screening questionnaire for TMS study in adult participants (TASS) (Ref Rossi et al., 2011)

(1) Do you have epilepsy or have you ever had a convulsion or a seizure?

□ Yes □ No

(2) Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?

□ Yes □ No

(3) Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?

□ Yes □ No

(4) Do you have any hearing problems or ringing in your ears?

□ Yes □ No

(5) Do you have cochlear implants?

□ Yes □ No

(6) Are you pregnant or is there any chance that you might be?

□ Yes □ No

(7) Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.

□ Yes □ No

(8) Do you have an implanted neurostimulator (e.g., DBS, epidural/ subdural, VNS)?

□ Yes □ No

(9) Do you have a cardiac pacemaker or intracardiac lines?

□ Yes □ No

(10) Do you have a medication infusion device?

□ Yes □ No

(11) Are you taking any medications? (please list)

□ Yes □ No

(12) Did you ever undergo TMS in the past? If so, were there any problems.

□ Yes □ No

(13) Did you ever undergo MRI in the past? If so, were there any problems

□ Yes □ No

_____	_____
Participant Signature	Date
_____	_____
Assessor Signature	Date

Reference:
Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update. Clin Neurophysiol. 2011 Aug;122(8):1686.

Note: Further explanation of this safety screening form:

1. If the participant selects [Yes] in the questions (1)(2)(3)(5)(6)(7)(8)(9)(10), they cannot participate in the study.
2. If the participant selects [Yes] in the question (4), the participant will be further asked if they have any related diseases. If the participant has an intra-orbital or intracranial disease, for example, auditory neuroma, they cannot participate in this TMS study. For hearing loss only or primary tinnitus, participants will be required to wear earplugs during TMS stimulation to reduce the likelihood of ear discomfort cause by TMS noise. If there is significant discomfort or aggravated tinnitus after receiving TMS, participants may not continue to participate in this TMS study.
3. If the participant selects [Yes] in the question (11), the participant will be asked about the specific medicine used. The participant has taken medicine that may increase the excitability of cortex, such as anti-depressant drugs, drugs that can stimulate the central nervous system, anti-epileptic drugs, etc., may not join in this TMS study.
4. If the participant selects [Yes] in the question (12), the participant will be asked about the specific situation during the previous TMS. If the participant complains of persistent headache, sleeping disorders, emotional changes, etc. after receiving TMS, then the participants will not be able to join in this TMS study.
5. If the participant selects [Yes] in the question (13), the participant will be asked about the specific situation during the previous TMS, such as significant discomfort after long-term MRI scanning, potential metal implants in the body, etc., participants will not be able to join in this TMS study.
6. Participants who have undergone craniotomy before are not eligible to join in this TMS study for safety considerations.

13-items Screening Questionnaire for the TMS Candidates (Chinese-Cantonese Version)

附錄 1

經顱磁刺激 （TMS）禁忌症篩查表（**Rossi et al. 2011**）

(1)您是否曾經有過癲癇或驚厥發作

□ 是 □ 否

(2) 您是否曾經有過短暫性意識喪失或暈厥？如果有，請詳細說明當時的情況?

□ 是 □ 否

(3) 您是否有過腦部外傷，診斷為腦震盪，或出現腦部外傷後的意識喪失?

□ 是 □ 否

(4) 您是否有聽力問題或耳鳴?

□ 是 □ 否

(5) 您是否有人工電子耳蝸?

□ 是 □ 否

(6) 您是否懷孕或準備懷孕？（此條僅針對育齡女性受試者）

□ 是 □ 否 □ 不適用

(7) 您的腦部，頭顱和身體其他部分是否有金屬物品植入？如果有，請說明金屬之種類。

□ 是 □ 否

(8) 您是否有植入神經刺激器（如深部腦部電刺激，蛛網膜外/下刺激器，迷走神經電刺激）？

□ 是 □ 否

(9) 您是否有心臟起搏器或心臟內導線?

□ 是 □ 否

(10) 您是否有植入藥物輸入裝置（藥泵）？

□ 是 □ 否

(11) 您是否在服用任何藥物？（請列舉）

□ 是 □ 否

(12) 您先前是否接受過經顱磁刺激（TMS）？如果有，是否出現任何問題?

□ 是 □ 否問題:

(13) 您先前是否接受過磁力共振檢查（MRI）？如果有，是否出現任何問題?

□ 是 □ 否問題:

__ 簽署 (參與者):_____ 日期:

簽署 (評估者):_____ 日期:

參考文獻:

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update.

Clin Neurophysiol. 2011 Aug;122(8):1686.

本安全篩查表的進一步解釋:

1. 如受試者在條目（1）（2）（3）（5）（6）（7）（8）（9）（10）選擇

[是]，則不可以參與本 TMS 研究。

2. 如受試者在條目（4）選擇[是]，受試者將被進一步詢問是否罹患相關疾病，如受試者患有耳內/顱內疾病，如聽神經瘤，則不可以參與本 TMS 研究。如僅為聽力下降或原發性耳鳴，受試者在接受 TMS 期間將被要求佩戴耳塞，以減少 TMS 刺激噪音引發耳部不適的可能性。如接受 TMS 後，耳部出現明顯不適，如 耳鳴加重，受試者則不可以繼續參與本 TMS 研究。

3 如受試者在條目（11）選擇[是]，受試者將被詢問具體使用的藥物，如受試者 近三個月曾服用可能提高改變神經興奮性閾值之藥物，如抗抑鬱症藥物，中樞神經興奮劑，抗癲癇藥物等，則不可參與本 TMS 研究。

4. 如受試者在條目（12）選擇[是]，受試者將被詢問先前接受 TMS 時的具體情況，如受試者主訴接受 TMS 後出現明顯的持續性頭疼，睡眠困難，情緒變化 等，則受試者將不可以參與本 TMS 研究。 5. 如受試者在條目

（13）選擇[是]，受試者將被詢問先前接受 MRI 時的具體情況，如長時間禁錮后出現明顯不適，體內有潛在金屬植入物等，受試者將不可以 參與本 TMS 研究。

6. 基於安全性考慮，曾經過開顱手術的人群亦不可以參與本 TMS 研究。

Appendix 5.6: Screening questions for neurogenic overactive bladder

Participants who fulfil the following **inclusion criteria** will be eligible to be recruited:

1. Stroke survivors (18–80 years) with Neurogenic overactive bladder (OAB).
2. Experience moderate (OABSS scores: 6-11 points) to severe neurogenic OAB (OABSS scores: 12 points and above).
3. Obtain a Mini-Mental State Examination (MMSE) score of ≥ 24.

Bio-data

Age:

Sex:

Marital status:

Educational Qualification:

Occupational Status:

Side of stroke:

Mini-Mental State Examination (MMSE)

Questions	Maximum	Patient scores
"What is the year? Season? Date? Day? Month?"	5	
"Where are we now? State? County? Town/city? Hospital?	5	
The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The	3	
"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD	5	
"Earlier I told you the names of three things. Can you tell	3	
Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.	2	
"Repeat the phrase: 'No ifs, ands, or buts.'"	1	
"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of	3	
"Please read this and do what it says." (Written instruction	1	
"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)	1	
"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must	1	
TOTAL	**30**	

Overactive Bladder Symptom Score *(*OABSS)

Questions	Score	Frequency
How many times do you typically urinate from waking in the morning until sleeping at night?	0	7 or less
	1	8～14
	2	15 or more
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	3	3 or more
How often do you have a sudden desire to urinate, which is difficult to defer?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2～4 times a day
	5	5 times a day or more
How often do you leak urine, because you cannot defer the sudden desire to urinate?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2～4 times a day
	5	5 times a day or more
TOTAL	**15**	

尿失禁篩查問題

滿足以下**納入標準**的參與者將有資格被招募：

1. 患有神經源性膀胱過動症(NOAB) 的中風人士（18-80 歲）
2. 有尿流動力學檢查結果確診為逼尿肌過動
3. 有中度（OABSS 分數：6-11 分）到重度 NOAB（OABSS 分數：12 分及以上）
4. 獲得 ≥ 24 的簡短智能測驗(MMSE) 分數

基本資料

年齡：

性別：

婚姻狀況：

學歷：

職業狀況：

中風患側：

簡短智能測驗 (MMSE)(Chinese-Cantonese version)

問題	最高分數	患者分數
“依家係乜野日子? ”	5	
“我地依家係邊度? ” (九龍/新界/香港)、(九龍/新界/香港既邊區) 、(邊條街/邊個屋	5	
“依家我會講三樣野既名，講完之後，請你重複一次。 請記住佢地，因為幾分鐘後，我會叫你再講番俾我聽。 〔蘋果〕、〔報紙〕、〔火車〕。依家請你講番呢三樣野俾我	3	
“請你用一百減七，然後再減七，一路減落去，直至我叫你停為止。” (減五次後便停)	5	
“我頭先叫你記住既三樣野係乜野呀? ”	3	
“哩樣係乜野？” (鉛筆)(手錶)	2	
“請你跟我講呢句話。” (姨丈買魚腸)	1	
“依家檯上面有一張紙，用你既右手拿起張紙，用兩隻手一齊將張紙	3	
“請讀出哩張紙上面既字，然後照住去做。” (書面說明是 “拍	1	
“你講任何一句完整既句子俾我聽。”	1	
“哩處有幅圖，請你照住呢畫啦。” (檢查者給患者一張白紙，讓他/她在下面畫出符號。10 個角必須全部存在，並且兩個角必須	1	
總分	**30**	

*膀胱過度活躍徵狀問卷 (***OABSS) (Chinese-Cantonese version)**

問題	得分	頻密程度
由早上起床開始至晚上睡覺為止，大約小便了多少次？	0	7 次或以下
	1	8 至 14 次
	2	15 次或以上
由晚上睡覺至早上起床為止，為了小便而起床的次數大約有多少次？	0	0 次
	1	1 次
	2	2 次
	3	3 次或以上
有沒有試過突然感到尿急，覺得難以忍受？	0	沒有
	1	1 星期少過 1 次
	2	1 星期 1 次或以上
	3	大約 1 日 1 次
	4	1 日 2 至 4 次
	5	1 日 5 次或以上
有沒有試過突然感到尿急而達致漏尿？	0	沒有
	1	1 星期少過 1 次
	2	1 星期 1 次或以上
	3	大約 1 日 1 次
	4	1 日 2 至 4 次
	5	1 日 5 次或以上
總分	**15**	

Appendix 5.7: Overactive Bladder Symptom Score (OABSS)

Questions	Score	Frequency
How many times do you typically urinate from waking in the morning until sleeping at night?	0	7 or less
	1	8～14
	2	15 or more
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	3	3 or more
How often do you have a sudden desire to urinate, which is difficult to defer?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2～4 times a day
	5	5 times a day or more
How often do you leak urine, because you cannot defer the sudden desire to urinate?	0	not at all
	1	less than once a week
	2	once a week or more
	3	about once a day
	4	2～4 times a day
	5	5 times a day or more
TOTAL	**15**	

Overactive Bladder Symptom Score (OABSS) (Chinese-Cantonese Version) ***膀胱過度活躍徵狀問卷*** **(OABSS)**

問題	得分	頻密程度
由早上起床開始至晚上睡覺為止，大約小便了多少次？	0	7 次或以下
	1	8 至 14 次
	2	15 次或以上
由晚上睡覺至早上起床為止，為了小便而起床的次數大約有多少次？	0	0 次
	1	1 次
	2	2 次
	3	3 次或以上
有沒有試過突然感到尿急，覺得難以忍受？	0	沒有
	1	1 星期少過 1 次
	2	1 星期 1 次或以上
	3	大約 1 日 1 次
	4	1 日 2 至 4 次
	5	1 日 5 次或以上
有沒有試過突然感到尿急而達致漏尿？	0	沒有
	1	1 星期少過 1 次
	2	1 星期 1 次或以上
	3	大約 1 日 1 次
	4	1 日 2 至 4 次
	5	1 日 5 次或以上
總分	**15**	

Appendix 5.8: Incontinence Quality of Life Questionnaire

PLEASE WRITE IN TODAY'S DATE: ___ _____ ____
Day Month Year

PARTICIPANT ID:

PLEASE READ THIS CAREFULLY

ON THE FOLLOWING PAGES YOU WILL FIND SOME STATEMENTS THAT HAVE BEEN MADE BY PEOPLE WHO HAVE URINARY INCONTINENCE (LEAKING URINE WHEN YOU DON'T WANT TO).

PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU RIGHT NOW AND CIRCLE THE NUMBER OF YOUR ANSWER.

IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN. **THERE ARE NO RIGHT OR WRONG ANSWERS.**

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT:

Your Feelings

(Please circle the number of your answer)

1. I worry about not being able to get to the toilet on time

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

2. I worry about coughing or sneezing because of my urinary problems or incontinence.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

3. I have to be careful standing up after I've been sitting down because of my urinary problems or incontinence.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

4. I worry about where toilets are in new places.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

5. I feel depressed because of my urinary problems or incontinence.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

(Please circle the number of your answer)

6. Because of my urinary problems or incontinence, I don't feel free to leave my home for long periods of time.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

7. I feel frustrated because my urinary problems or incontinence prevents me from doing what I want.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

8. I worry about others smelling urine on me.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

9. My urinary problems or incontinence is always on my mind.

   1 EXTREMELY
   2 QUITE A BIT
   3 MODERATELY
   4 A LITTLE
   5 NOT AT ALL

10. It's important for me to make frequent trips to the toilet.

    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

(Please circle the number of your answer)

11. Because of my urinary problems or incontinence, it's important to plan every detail in advance.

    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

12. I worry about my urinary problems or incontinence getting worse as I grow older.

    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

13. I have a hard time getting a good night of sleep because of my urinary problems or incontinence.

    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

14. I worry about being embarrassed or humiliated because of my urinary problems or incontinence.

    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

15. My urinary problems or incontinence makes me feel like I'm not a healthy person.

    1 EXTREMELY
    2 QUITE A BIT
    3 MODERATELY
    4 A LITTLE
    5 NOT AT ALL

(Please circle the number of your answer)

16. My urinary problems or incontinence makes me feel helpless.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

17. I get less enjoyment out of life because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

18. I worry about wetting myself.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

19. I feel like I have no control over my bladder.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

20. I have to watch what or how much I drink because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

(Please circle the number of your answer)

21. My urinary problems or incontinence limit my choice of clothing.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

22. I worry about having sex because of my urinary problems or incontinence.

1 EXTREMELY
2 QUITE A BIT
3 MODERATELY
4 A LITTLE
5 NOT AT ALL

About You

A-1 How long have you had urinary problems or incontinence? *(Please write the number below)*

_____ _____
YEARS **MONTHS**

A-2 How many medical appointments have you made in the past year to treat your urinary problems or incontinence? *(Please write the number on the line provided)*

_____ **NUMBER OF APPOINTMENTS IN THE LAST YEAR**

A-3 How would you describe the severity of your urinary problems or incontinence? *(Please circle the number of your answer)*

1 **MILD**

2 **MODERATE**

3 **SEVERE**

A-4 Do you lose urine when you cough, sneeze, run, walk, jump or when you do some other specific activity?

0 **NO**

1 **YES**

A-5 Do you lose control of your bladder before you can get to the bathroom?

0 **NO**

1 **YES**

A-6 Do you lose urine at times not associated with any specific activity or the need to go to the bathroom?

0 NO

1 YES

A-7 In the last month, how many times did you lose urine, even a small amount, when you didn't want to? *(Please write the number on the line provided)*

_____ NUMBER OF TIMES IN THE LAST MONTH

A-8 In the last month, how many times did you lose urine, even a small amount, when you didn't want to?

0 NOT AT ALL IN THE LAST MONTH

1 1 TO 2 TIMES IN THE LAST MONTH

2 4 TIMES (ABOUT ONCE A WEEK)

3 2 TO 3 TIMES PER WEEK

4 ABOUT 1 TIME A DAY

5 ONE OR TWO TIMES A DAY

6 THREE OR FOUR TIMES A DAY

7 FIVE OR MORE TIMES A DAY

Incontinence Quality of Life Questionnaire (Cantonese Version)

請寫下今天的日期: ___ _____ ____

日 月 年

參加者編號:

以下請仔細閱讀

在以下幾頁有一些由患有尿失禁（在您不想的時候漏尿）的人所做的陳述。

請選擇目前最適合您的答案並圈出您的答案編號。

如果您不確定如何回答問題，請盡可能給出最佳答案。**這裡沒有正確或錯誤的答案。**

如果您有任何問題，請聯繫:

你的感受

（請圈出你的答案編號）

1. 我擔心不能按時上洗手間。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

2. 因為泌尿問題或尿失禁，我擔心咳嗽或打噴嚏。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

3. 因為泌尿問題或尿失禁，我坐下後站起來要小心。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

4. 我會擔心新地方的廁所在哪裡。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

（請圈出你的答案編號）

5. 我因為泌尿問題或尿失禁而感到沮喪。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

6. 因為泌尿問題或尿失禁，我不敢長時間離開我的家。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

7. 我因為泌尿問題或尿失禁使我無法做我想做的事而感到沮喪。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

8. 我擔心別人聞到我的尿味。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

9. 我的泌尿問題或尿失禁一直在我的腦海中。
   1 非常
   2 相當多
   3 中等
   4 一點點
   5 完全沒有

（請圈出你的答案編號）

10. 經常上廁所對我來說很重要。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

11. 因為泌尿問題或尿失禁，我覺得提前計劃好每個細節很重要。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

12. 我擔心隨著年齡的增長，我的泌尿問題或尿失禁會越來越嚴重。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

13. 因為我的泌尿問題或尿失禁，我很難睡個好覺。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

14. 因為我的泌尿問題或尿失禁，我擔心尷尬或被羞辱。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

（請圈出你的答案編號）

15. 我的泌尿問題或尿失禁讓我覺得自己不是一個健康的人。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

16. 我的泌尿問題或尿失禁讓我感到無助。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

17. 因為泌尿問題或尿失禁，我的生活樂趣減少了。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

18. 我擔心弄濕自己。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

19. 我覺得我無法控制自己的膀胱。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

（請圈出你的答案編號）

20. 因為泌尿問題或尿失禁，我必須注意喝什麼或喝多少。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

21. 我的泌尿問題或尿失禁限制了我對衣服的選擇。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

22. 因為泌尿問題或尿失禁，我擔心進行性行為。
    1 非常
    2 相當多
    3 中等
    4 一點點
    5 完全沒有

關於您

A-1 您有泌尿問題或尿失禁多久了？（請於以下寫上數字）

_____ _____

年　　月

A-2 在過去的一年中，您進行了多少次醫療預約來治療您的泌尿問題或尿失禁？（請在提供的橫線上寫上號碼）

_____ **過去一年的預約次數**

A-3 您如何描述您的泌尿問題或尿失禁的嚴重程度？（請圈出你的答案編號）

1　輕微

2　中度

3　嚴重

A-4 您是否會在咳嗽、打噴嚏、跑步、走路、跳躍或一些其他特定的活動時漏尿？

0　否

1　是

A-5 在去洗手間之前，您是否會失去對膀胱的控制？

0　否

1　是

A-6 您是否會在與任何特定活動無關或無需要去洗手間的情況下漏尿?

0 否

1 是

A-7 在過去一個月中，您有多少次在您不想的時候漏尿（即使是少量）？（請在提供的橫線寫下號碼）

_____ **過去一個月的次數**

A-8 在過去一個月中，您有多少次在您不想的時候漏尿（即使是少量）？

0 上個月完全沒有

1 上個月一至兩次

2 四次（大約一周一次）

3 每週兩至三次

4 每天大約一次

5 一天一至兩次

6 一天三至四次

7 一天五次或以上

Appendix 5.9: **Brief Resilience Scale**

Respond to each statement below by circling one answer per row		**Strongly Disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
BRS 1	I tend to bounce back quickly after hard times.	1	2	3	4	5
BRS 2	I have a hard time making it through stressful events.	5	4	3	2	1
BRS 3	It does not take me long to recover from a stressful event.	1	2	3	4	5
BRS 4	It is hard for me to snap back when something bad happens.	5	4	3	2	1
BRS 5	I usually come through difficult times with little trouble.	1	2	3	4	5
BRS 6	I tend to take a long time to get over setbacks in my life.	5	4	3	2	1

Brief Resilience Scale (Chinese-Cantonese Version)

簡要韌性量表 (BRS)

通過在每行圈出一個答案來回應下面的每項陳述		**非常不同意**	**不同意**	**中立**	**同意**	**非常同意**
BRS 1	我傾向於在艱難時期後迅速恢復。	1	2	3	4	5
BRS 2	我很難熬過壓力大的事件。	5	4	3	2	1
BRS 3	從壓力大的事件中恢復過來並不需要很長時間。	1	2	3	4	5
BRS 4	當發生不好的事情時，我很難恢復過來。	5	4	3	2	1
BRS 5	我通常能順利度過困難時期。	1	2	3	4	5
BRS 6	我往往需要很長時間才能克服生活中的挫折。	5	4	3	2	1

Appendix 5.10: Client Service Receipt Inventory Form (CSRI)

Client Service Receipt Inventory – RAre disease (CSRI-Ra) in Hong Kong [Patient's version]

Claudia CY Chung, Brian HY Chung, SL Lee, Martin Knapp
Li Ka Shing Faculty of Medicine, The University of Hong Kong &
Personal Social Services Research Unit, The London School of Economics and Political Science

This questionnaire is to be completed by the **rare disease patient**.
The retrospective period over which data sought is **6 months**.
Completion and return of the questionnaire implies consent to participate in the study. All data collected will be **de-identified** and **kept strictly confidential**.

BACKGROUND INFORMATION	
1. Date of questionnaire completion *(dd/mm/yy)*	...../...../.....
2. Gender	☐ Male ☐ Female ☐ Prefer not to answer
3. Date of birth *(dd/mm/yy)*	...../...../.....
4. Ethnicity	☐ Chinese ☐ Others, please specify: .....
5. Marital status	☐ Single/ unmarried ☐ Separated ☐ Married ☐ Cohabitation ☐ Divorced ☐ Not known ☐ Remarried ☐ Widowed
6. Number of children	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Others, please specify: .....
7. What is the rare disease you are suffering from?	.....
If known: a) what is the genetic change?	.....
b) year of diagnosis:	.....
8. Do you have another family member with rare disease?	☐ Yes ☐ No
If yes: a) how many family member(s) are suffering from the rare disease?	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ Others, please specify: .....
b) which rare disease(s) do they have?	.....
HOUSEHOLD & CARER SUPPORT	
9. Type of residence	☐ Public housing ☐ Subsidised Home Ownership: ☐ Bought ☐ Rented ☐ Private housing Flat: ☐ Bought ☐ Rented Subdivided flat/unit: ■ Bought ☐ Rented
10. Who do you live with at the moment? *(you can select more than one)*	☐ Living alone ☐ Both parents ☐ Single parent ☐ Spouse ☐ Child/children ☐ Relative(s)/friend(s) ☐ Residential home/ school residence ☐ Formal foster care ☐ Others, please specify: .....

1

11. Are there any home modifications made to help with your condition?	☐ Yes	☐ No
If yes: a) please select all the modifications made:	☐ Handrails ☐ Shower chair ☐ Others, please specify:	☐ Patient hoist ☐ Personal Emergency Link Device
12. Have you received any care from the following **unpaid carers** in the past **6 months**? *(you can select more than one; write down the number of hours each unpaid carer spends per day on taking care of you e.g. ☑ Spouse, 3 hours)*		Hours per day
	☐ Parents: Mother	.....
	☐ Parents: Father	.....
	☐ Spouse	.....
	☐ Child/children	.....
	☐ Relative(s)/Friend(s)	.....
	☐ Others, please specify:	.....
	☐ Did not receive any care from unpaid carers	
13. Were any of the **unpaid carer(s)'** work/employment opportunity affected due to your condition?	☐ Yes ☐ They are unemployed	☐ No ☐ Did not receive care from unpaid carers
If yes: a) Impact on unpaid carer(s)' employment: *(you can choose more than one; write down the unpaid carer whom employment was affected e.g. ☑ Early retirement: Mother, Spouse)*	☐ Resignation/loss of job: ..... ☐ Early retirement: ..... ☐ Changed from full time to part time employment: ..... ☐ Employment options: ..... ☐ Absence from work: ..... ☐ Changes in working hours: ..... ☐ Others, please specify:	
b) Do they need to reduce their working hour/days to take care of you? Please write down the average number of **working hours reduced per week** and the **number of days absent** in the past **6 months** as a result of your condition.		Working hours reduced per week / Days absent in the past 6 months
	☐ Parents: Mother	..... / .....
	☐ Parents: Father	..... / .....
	☐ Spouse	..... / .....
	☐ Child/children	..... / .....
	☐ Relative(s)/Friend(s)	..... / .....
	☐ Others, please specify:	..... / .....
	☐ Did not reduce their working hours/days	
14. Have you received any care from the following **paid carers** in the past **6 months**? *(you can select more than one; write down the number of carers and the hours each carer spends per day on taking care of you. e.g. ☑ Domestic helper, 2, 10 hours each)*		Number / Hours per day
	☐ Domestic helper	..... / .....
	☐ Hourly-paid home care assistant	..... / .....
	☐ Escort care worker	..... / .....
	☐ Others, please specify:	..... / .....
	☐ Did not hire any paid carer	
15. Monthly **household income** *(total monthly household cash income before taxation; including earnings from all jobs and social security support/governmental allowances) (HKD)*	☐ Less than $10,000 ☐ $20,001 to $30,000 ☐ $40,001 to $50,000 ☐ $60,001 to $70,000 ☐ $80,001 to $90,000 ☐ Others, please specify:	☐ $10,001 to $20,000 ☐ $30,001 to $40,000 ☐ $50,001 to $60,000 ☐ $70,001 to $80,000 ☐ $90,001 to $100,000

COMMUNITY SUPPORT	
16. Are you receiving any social security support offered by the government?	☐ Yes ☐ No
If yes: a) Which scheme/allowance do you receive?	☐ Comprehensive Social Security Assistance (CSSA) ☐ Social Security Allowance: ☐ Normal Disability Allowance ☐ Higher Disability Allowance ☐ Old Age Allowance ☐ Normal/ Higher Old Age Living Allowance ☐ Community Care Fund: ☐ Subsidy for Eligible Patients to Purchase Ultra-expensive Drugs ☐ Others, please specify: .....
17. Do any of your **family member(s)** who are **living under the same roof** receive any social security support offered by the government?	☐ Yes ☐ No
If yes: a) Which scheme(s)/allowance(s) do the family members receive?	☐ Comprehensive Social Security Assistance (CSSA) ☐ Social Security Allowance: ☐ Normal Disability Allowance ☐ Higher Disability Allowance ☐ Old Age Allowance ☐ Normal/ Higher Old Age Living Allowance ☐ Community Care Fund: ☐ Pilot Scheme on Living Allowance for low-income carers of persons with Disabilities ☐ Others, please specify: .....
18. What type of transportation do you utilise to get to healthcare and community service/ resource providers? *(you can select more than one)*	☐ Taxi ☐ Bus ☐ Minibus ☐ MTR ☐ Private car ☐ Rehabus ☐ Accessible Hire Car Service ☐ Others, please specify: .....
19. In the past **6 months**, what is the **average cost spent per month** on **transportation** to get to healthcare and community service/ resources providers?	..... (HKD)
20. Do you utilise **centre service(s)** provided by non-governmental organisation (NGO) **due to your condition**?	☐ Yes ☐ No
If yes: a) What type of service(s) do you use? *(you can select more than one)*	☐ Homework guidance/ tutorial class ☐ Therapeutic training ☐ Counselling services ☐ Recreation services ☐ Others, please specify: .....
21. Are you a member of any patient support group(s)?	☐ Yes ☐ No
If yes: please specify:	.....

HEALTHCARE SERVICE & RESOURCE UTILISATION

22. Please list **all** the **public and/or private** healthcare services utilised in the past **6 months** **due to your condition**: *(Please try to fill in as detailed as possible. Add additional sheets if necessary)*

Services include: accident & emergency / inpatient / outpatient / day care / allied health / surgery / medical procedure / treatment / residential and community medical services

Service	Public / Private	Specialty	Frequency	Duration per visit/ admission
Accident & Emergency (A&E)				
e.g.	*Public*	*Neurology*	*2*	*20 minutes*
1.				
2.				
3.				
.				
.				
.				
Inpatient				
e.g.	*Public* *Public*	*Orthopaedics* *Orthopaedics*	*1* *1*	*20 days* *10 days*
1.				
2.				
3.				
.				
.				
.				
Outpatient				
e.g.	*Private*	*Psychiatry*	*3*	*15 minutes*
1.				
2.				
3.				
.				
.				
.				
Day care		*(please write down the specific procedure)*		
e.g.	*Public*	*Haematology: blood transfusion*	*2*	*4 hours*
1.				
2.				
3.				
.				
.				
.				

Allied health		*(please write down the specific allied health professional)*		
e.g.	*Public*	*Physiotherapist*	*5*	*45 minutes*
	Public	*Dietician*	*2*	*15 minutes*
	Private	*Occupational therapist (sensory integration training)*	*8*	*45 minutes*
	Public	*Optometrist*	*2*	*30 minutes*
1.				
2.				
3.				
.				
.				
.				
Surgery / medical procedure / treatment		*(please write down the specific procedure/treatment)*		
e.g.	*Public*	*Cardiology: Echocardiogram*	*2 times*	
	Private	*Cardiology: Heart valve surgery*	*1 time*	
1.				
2.				
3.				
.				
.				
.				
"Community Medical Service" program provided by the Hospital Authority				
e.g.		*Community Nursing Service*	*2*	*30 minutes*
1.				
2.				
3.				
.				
.				
.				

☐ I did not use any of the above services in the past 6 months.

If yes to any of the above: a) In the past **6 months**, how much **on average** did you spend out-of-pocket **per month** on the above services? ..... (HKD)

23. In the past **6 months**, have you used any alternative medicine **due to your condition**?

Method	Number of visits	Average duration per visit (minutes)
Chinese medicine		
Acupuncture		
Massage therapy		
Others, please specify:		

☐ I did not use any alternative medicine in the past 6 months.

If yes to any of the above: a) In the past **6 months**, how much **on average** did you spend out-of-pocket **per month** on the above methods? ..... (HKD)

24. In the past **6 months**, have you taken any medications **due to your condition**? *(please list all over-the-counter and prescription medications)*:

Medication name	Dosage (unit)	Frequency	Duration (days)	Prescribed by Hospital Authority?

☐ I did not take any medication in the past 6 months.

If you have taken any medication(s): a) How much **on average** did you spend out-of-pocket **per month** on the above medications? ..... (HKD)

25. In the past **6 months**, have you used any medical devices/consumables **due to your condition**?

(For each item, please write down the number used over the past 6 months; for consumables, please write down the quantity and/or frequency used over the past 6 months, if applicable)

Item / Consumable	Quantity / frequency	Item / Consumable	Quantity / frequency
Wheelchair		Special diet	
Walking stick		Specialised milk formula (e.g. 10g per day)	
Ventilator			
Aspirator		Others, please specify:	
Hearing aid			
Disinfectant/ wound dressings			
Diapers (e.g. 2 per day)			

☐ I did not use any medical devices/consumables in the past 6 months.

If yes to any of the above: a) In the past **6 months**, how much **on average** did you spend out-of-pocket **per month** on the above resources? ..... (HKD)

26. In this question, we are moving away from services utilised by yourself to services utilised by your **family members** who are living under the same roof.

In the past **6 months**, has any of your **family members** used any healthcare/ community services **as a result of your condition**? *(excluding services utilised by you)*

Service	Number of visits	Average duration per visit (minutes)
Family doctor		
Psychiatrist		
Psychologist		
Social worker		
Counsellor		
Family planning service		
Marriage guidance		
Advice line		
Self-help group		
Chinese medicine practitioner		
Others, please specify:		

☐ My family members did not use any services as a result of my condition in the past 6 months.

EDUCATION & EMPLOYMENT

27. Highest level of education

☐ Primary education or less
☐ Secondary education
☐ Post-secondary/associated degree or equivalent
☐ Bachelor's degree
☐ Master's/doctoral degree

28. What is your **current** education/employment status?

☐ Student
☐ Full time employment, position: .....
☐ Part time employment, position: .....
☐ Housewife/househusband
☐ Retired
☐ Unemployed, last paid employment *(mm/yy)*: .....
☐ Others, please specify: .....

29. What is the main source of your income?
(you can select more than one)

☐ Earned salary
☐ Comprehensive Social Security Assistance (CSSA)
☐ Social Security Allowance (SSA)
☐ Community Care Fund
☐ Others, please specify: .....

Continue to answer the following questions if you are currently studying;
Jump to answer from question 35 if you are currently employed;
Jump to answer from question 39 if you are currently unemployed.

30. What type of school/course do you attend?

- ☐ Mainstream school
- ☐ International school
- ☐ Support services in mainstream school
- ☐ Hospital school
- ☐ Special school:
  - ☐ Visual impairment ☐ Hearing impairment
  - ☐ Physical disability ☐ Intellectual disability
  - ☐ Social development
- ☐ Vocational Training Council (VTC)
- ☐ Higher education institutions
- ☐ University
- ☐ Home schooling
- ☐ Others, please specify: .....

31. Has your condition affected your learning? ☐ Yes ☐ No

If yes: a) please select all the related problems:

- ☐ Health condition ☐ Tired
- ☐ Worried/anxious ☐ Feeling down
- ☐ Inability to concentrate ☐ Left early/arrived late/ absent to attend medical appointment
- ☐ Others, please specify: .....

b) how often do these problems affect your school days?

- ☐ Less than once a month ☐ Once or twice a month
- ☐ Once or twice a week ☐ Once or twice a day
- ☐ More than twice a day

32. Have you been absent from school due to your condition? ☐ Yes ☐ No

If yes: a) how many days were you absent from school in the past **6 months**? ..... (days)

33. In the past **6 months**, how much **on average** did you spend **per month** on education? ..... (HKD)

34. In the past **6 months**, have you seen any of the following professional(s) in school **due to your condition**?

Professional	Number of visits	Average duration per visit (minutes)
School nurse		
Social worker		
Physiotherapist		
Speech and language therapist		
Occupational therapist		
Educational psychologist / clinical psychologist		
Special educational needs coordinator		
Others, please specify:		

☐ I did not see any professionals in school in the past 6 months.

Continue to answer the following questions if you are currently employed; *Jump to answer from question 39 if you are currently unemployed.*	
35. Average number of working days **per week** over the past **6 months**:	..... (days)
36. Average number of working hours **per week** over the past **6 months**:	..... (hours)
37. Is your work affected by your condition?	☐ Yes ☐ No
If yes: a) How many **hours less** have you worked **per week** than usual? *(e.g. late/early leave)*	..... (hours)
b) Please select all related problems at work:	☐ Health condition ☐ Tired ☐ Worried/anxious ☐ Feeling down ☐ Inability to concentrate ☐ Left early/arrived late/ absent to attend medical appointment ☐ Others, please specify: .....
c) How often do these problem(s) affect your work?	☐ Less than once a month ☐ Once or twice a month ☐ Once or twice a week ☐ Once or twice a day ☐ More than twice a day
38. Number of days you have been absent from work due to your condition in the past **6 months**:	..... (days)
39. Has your condition affected your employment opportunity?	☐ Yes ☐ No ☐ I am currently studying and not employed
If yes: a) major impact on employment: *(you can choose more than one)*	☐ Resignation/loss of job ☐ Early retirement ☐ Changed from full time to part time employment ☐ Employment options ☐ Absence from work ☐ Changes in working hours ☐ Others, please specify: .....
40. What was your employment status **prior to being diagnosed** with rare disease?	☐ Full time employment, position: ..... ☐ Part time employment, position: ..... ☐ Housewife/househusband ☐ Retired ☐ Student ☐ Previously not employed ☐ Others, please specify: .....

Thank you for completing the questionnaire!

Client Service Receipt Inventory Form (CSRI) (Chinese-Cantonese version)

香港罕見病患家庭服務使用紀錄 (CSRI-Ra)
[罕見病患者版本]

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是次問卷將由罕見病患者填寫。資料回顧期為填寫問卷前之 6 個月。
完成及歸還問卷將表示您同意參與是次研究。所有研究所收集的資料將不會被記名並嚴格保密。

背景資料	
1. 填寫問卷日期 (日日/月月/年年)	..../..../....
2. 性別	☐ 男 ☐ 女 ☐ 不想回答
3. 出生日期 (日日/月月/年年)	..../..../....
4. 種族	☐ 華人 ☐ 其他，請註明：....
5. 婚姻狀況	☐ 單身/未婚 ☐ 分開 ☐ 已婚 ☐ 同居 ☐ 離婚 ☐ 不知道 ☐ 再婚 ☐ 喪偶
6. 子女數目	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐其他，請註明：....
7. 所患的罕見病	....
如知道： a) 請填寫基因改變	....
b) 請填寫確診年份	....
8. 還有其他家庭成員患有罕見病嗎?	☐ 有 ☐ 沒有
如有： a) 其他患有罕見病的家庭成員數目	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐其他，請註明：....
b) 他(們)患有什麼罕見病?	....
家庭及照顧者支援	
9. 住屋類型	☐ 公共屋邨 ☐ 政府資助房屋： ☐ 購買 ☐ 租住 ☐ 私人樓宇 單位： ☐ 購買 ☐ 租住 分間樓宇單位/劏房：■ 購買 ☐ 租住
10. 您正與誰居住? *(可以選擇多於一個選項)*	☐ 自己居住 ☐ 父母 ☐ 單親父親/母親 ☐ 伴侶 ☐ 子女 ☐ 親戚/朋友 ☐ 住宿院舍/學校宿舍 ☐ 寄養家庭 ☐ 其他，請註明：....

1

11. 有否因應您的狀況而作出任何家居改裝? ☐ 有 ☐ 沒有

如有： a) 請選擇已有的家居改裝
(可以選擇多於一個選項)
☐ 扶手 ☐ 病患者移動吊架
☐ 淋浴椅 ☐ 緊急求助裝置
☐ 其他，請註明：.....

12. 在過去 **6 個月** 內，您有否因為自己的狀況而接受非受薪照顧者的家居照顧?

(可以選擇多於一個選項；請填寫每位照顧者每天照顧您的時數，例：☑伴侶，3 小時)

	每天時數(小時)
☐ 母親	.....
☐ 父親	.....
☐ 伴侶	.....
☐ 子女	.....
☐ 親戚/朋友	.....
☐ 其他，請註明：.....	.....
☐ 沒有接受任何非受薪照顧者的家居照顧	

13. 非受薪照顧者的工作/就業機會有否因為您的狀況而受到影響?
☐ 有 ☐ 沒有
☐ 他們沒有工作 ☐ 沒有接受任何非受薪照顧者的家居照顧

如有： a) 請選出對非受薪照顧者就業的影響：

(可以選擇多於一個選項；請列出就業受到影響的非受薪照顧者
例：☑ 提早退休：母親，伴侶)

☐ 辭職/失業：.....
☐ 提早退休：.....
☐ 從全職改為兼職：.....
☐ 就業選擇：.....
☐ 工作缺勤：.....
☐ 工作時數上的改變：.....
☐ 其他，請註明：.....

b) 非受薪照顧者需要減少工作時數/天數來提供照顧嗎?

(請填寫他(們)平均每星期因提供照顧而減少的工作時數(小時)，以及在過去 6 個月內所缺席的天數)

	每星期減少的工作時數(小時)	過去 6 個月缺席天數
☐ 母親	.....	.....
☐ 父親	.....	.....
☐ 伴侶	.....	.....
☐ 子女	.....	.....
☐ 親戚/朋友	.....	.....
☐ 其他，請註明：.....	.....	.....
☐ 沒有減少工作時數/天數來提供照顧		

14. 在過去 **6 個月** 內，您有否因為自己的狀況而接受受薪照顧者的家居照顧?

(可以選擇多於一個選項；請填寫照顧者的數量，以及每位照顧者每天照顧您的時數，例：☑ 家庭傭工，2 名，每位 10 小時)

	數量	每天時數(小時)
☐ 家庭傭工	.....	.....
☐ 時薪家務助理	.....	.....
☐ 陪診員	.....	.....
☐ 其他，請註明：.....	.....	.....
☐ 沒有聘請受薪照顧者		

15. 每月家庭總收入

(稅前每月家庭現金收入總額，包括所有工作和社會保障支援計劃/政府津貼) (港幣)

☐ 少於 $10,000 ☐ $10,001 至 $20,000
☐ $20,001 至 $30,000 ☐ $30,001 至 $40,000
☐ $40,001 至 $50,000 ☐ $50,001 至 $60,000
☐ $60,001 至 $70,000 ☐ $70,001 至 $80,000
☐ $80,001 至 $90,000 ☐ $90,001 至 $100,000
☐ 其他，請註明：.....

社區支援	
16. 您有否接受任何由政府提供的社會保障支援?	☐ 有 ☐ 沒有
如有： a) 您正參與哪項支援計劃? *(可以選擇多於一個選項)*	☐ 綜合社會保障援助計劃 (綜援 CSSA) ☐ 公共福利金計劃： ☐ 普通傷殘津貼 ☐ 高額傷殘津貼 ☐ 高齡津貼 ☐ 普通/高額長者生活津貼 ☐ 關愛基金援助項目： ☐「資助合資格病人購買價錢極度昂貴的藥物」 ☐ 其他，請註明：.....
17. 您的其他同住家庭成員有否接受任何由政府提供的社會保障支援?	☐ 有 ☐ 沒有
如有： a) 您的其他同住家庭成員正參與哪項支援計劃? *(可以選擇多於一個選項)*	☐ 綜合社會保障援助計劃 (綜援 CSSA) ☐ 公共福利金計劃： ☐ 普通傷殘津貼 ☐ 高額傷殘津貼 ☐ 高齡津貼 ☐ 普通/高額長者生活津貼 ☐ 關愛基金援助項目： ☐「為低收入的殘疾人士照顧者提供生活津貼試驗計劃」 ☐ 其他，請註明：.....
18. 您使用哪種交通工具前往醫療/社區服務及資源機構? *(可以選擇多於一個選項)*	☐ 的士 ☐ 巴士 ☐ 小巴 ☐ 港鐵 ☐ 私家車 ☐ 復康巴士 ☐ 易達轎車 ☐ 其他，請註明：.....
19. 在過去 6 個月內，您平均每月前往醫療/社區服務及資源機構的交通支出是多少?	..... (港幣)
20. 您有否因為您的狀況而使用由非政府機構 (NGO) 所提供的服務?	☐ 有 ☐ 沒有
如有： a) 您使用了哪項服務? *(可以選擇多於一個選項)*	☐ 功課/學習輔導班 ☐ 治療訓練 ☐ 心理輔導服務 ☐ 康樂服務 ☐ 其他，請註明：.....
21. 您有否參與任何病人組織?	☐ 有 ☐ 沒有
如有： 請註明：	.....

醫療服務及物資使用紀錄

22. 請列出在過去 **6 個月** 內因您的狀況而使用的公營及/或私家醫療服務：*(請儘量詳細填寫。如有需要，請添加額外紙張)*

服務包括：急症室/住院/門診/日間護理/專職醫療/手術/醫療程序/治療/家居或社區醫療服務

服務	公營/私家	專科部門	使用次數	每次使用時數/日數
急症室 (A&E)				
例	*公營*	*神經科*	*2*	*20 分鐘*
1.				
2.				
3.				
住院				
例	*公營* *公營*	*骨科* *骨科*	*1* *1*	*20 日* *10 日*
1.				
2.				
3.				
門診				
例	*私家*	*精神科*	*3*	*15 分鐘*
1.				
2.				
3.				
日間護理		*(請註明具體項目)*		
例	*公營*	*血液科：輸血*	*2*	*4 小時*
1.				
2.				
3.				

專職醫療		*(請註明具體專職醫療服務)*		
例	*公營*	*物理治療*	*5*	*45 分鐘*
	公營	*營養科*	*2*	*15 分鐘*
	私家	*職業治療 (包括感覺統合治療)*	*8*	*45 分鐘*
	公營	*視光師*	*2*	*30 分鐘*
1.				
2.				
3.				
.				
.				
.				
手術/醫療程序/治療		*(請註明具體程序/治療)*		
例	*公營*	*心臟科：心臟起搏波*	*2 次*	
	私家	*心臟科：心臟手術*	*1 次*	
1.				
2.				
3.				
.				
.				
.				
社區醫療服務				
例		*社康護理服務*	*2*	*30 分鐘*
1.				
2.				
3.				
.				
.				
.				

☐ 我沒有在過去 6 個月內使用上述之任何醫療服務。

如有使用上述任何服務： a) 在過去 **6 個月**內，您平均每月用於以上服務的自費支出是多少? ..... (港幣)

23. 在過 **6 個月**內，您有否**因您的狀況**而使用任何替代治療/方法?

治療	次數	每次平均時間 (分鐘)
中醫		
針灸		
按摩療法/推拿		
其他，請註明：		

☐ 我沒有在過去 6 個月內使用上述之任何替代治療/方法。

如有使用上述任何治療： a) 在過去 **6 個月**內，您**平均每月**用於以上治療/方法的**自費支出**是多少? ..... (港幣)

24. 在過 **6 個月**內，您有否**因您的狀況**而使用任何藥物? *(請列出非處方及處方藥物)*

藥物名稱	劑量 (單位)	用藥次數	為期 (日數)	是否醫管局方?

☐ 我沒有在過去 6 個月內使用任何藥物。

如有使用任何藥物： a) 在過去 **6 個月**內，您**平均每月**用於以上藥物的**自費支出**是多少? ..... (港幣)

25. 在過 **6 個月**內，您有否**因您的狀況**而使用任何醫療設備/物資?

(如適用，請於每項醫療設備寫下過去 6 個月的使用數量；請於每項消耗品寫下過去 6 個月的使用數量及/或次數)

醫療設備/物資	數量/次數	醫療設備/物資	數量/次數
輪椅		特別餐	
拐杖		特別配方奶粉 *(例：每日 10 克)*	
呼吸機			
抽痰機		其他，請註明：	
助聽器			
傷口清潔液/敷料			
尿片*(例：每日兩片)*			

☐我沒有在過去 6 個月內使用任何醫療設備/物資。

如有使用任何醫療設備/物資： a) 在過去 **6 個月**內，您**平均每月**用於以上醫療設備/物資的**自費支出**是多少? ..... (港幣)

26. 現在我們從您自己使用的服務，轉到您的同住家庭成員所使用的服務。

在過 6 個月內，您的同住家庭成員有否因您的狀況而使用以下任何服務? *(不包括您使用的服務)*

服務	會面次數	每次平均時間 (分鐘)
家庭醫生		
精神科醫生		
心理學家		
社工		
輔導員		
家庭計劃服務		
婚姻輔導		
諮詢熱線		
自助小組		
中醫		
其他，請註明：		

☐ 我的同住家庭成員沒有在過去 6 個月內使用上述之任何服務。

教育及就業

27. 教育程度

☐ 小學或以下
☐ 中學
☐ 大專以上/副學士或同等學歷
☐ 大學
☐ 碩士/博士

28. 您現在的教育/就業狀況為?

☐ 學生
☐ 全職，職位：.....
☐ 兼職，職位：.....
☐ 家庭主婦/主夫
☐ 退休
☐ 無業，最後有薪工作日子(月月/年年)：.....
☐ 其他，請註明：.....

29. 您的收入來源是什麼?
(可以選擇多於一個選項)

☐ 工資
☐ 綜合社會保障援助計劃 (綜援 CSSA)
☐ 公共福利金計劃
☐ 關愛基金援助項目
☐ 其他，請註明：.....

若您現在是學生，請繼續回答以下問題；
若您現正就業，請由第 35 題開始回答；
若您現在沒有就業，請由第 39 題開始回答。

30. 您就讀於甚麼類型的學校/課程?

- ☐ 主流學校
- ☐ 國際學校
- ☐ 主流學校的支援服務
- ☐ 醫院學校
- ☐ 特殊學校：
  - ☐ 視覺受損
  - ☐ 聽覺受損
  - ☐ 肢體傷殘
  - ☐ 智力障礙
  - ☐ 群育學校
- ☐ 職業訓練局(VTC)
- ☐ 高等教育院校
- ☐ 大學
- ☐ 家居教育
- ☐ 其他，請註明：.....

31. 您的狀況有否影響您上學?

☐ 有　☐ 沒有

*如有：*a) 請選出所有影響上學的問題：

- ☐ 健康狀況
- ☐ 疲勞
- ☐ 擔心/焦慮
- ☐ 情緒低落
- ☐ 無法集中精神
- ☐ 因要覆診而早退/遲到/缺席
- ☐ 其他，請註明：.....

b) 這些問題對您上學的影響有多頻密?

- ☐ 每月少於一次
- ☐ 每月一次或兩次
- ☐ 每星期一次或兩次
- ☐ 每天一次或兩次
- ☐ 每天多於兩次

32. 您有否<u>因您的狀況</u>而缺課?

☐ 有　☐ 沒有

*如有：*a) 在過去 **<u>6 個月</u>**內，缺課了多少天?

..... (天)

33. 在過去 **<u>6 個月</u>**內，您<u>平均每月</u>用於教育上的<u>費用支出</u>是多少?

..... (港幣)

34. 在過去 **<u>6 個月</u>**內，您有否<u>因您的狀況</u>而在學校與下列的專業人員會面?

專業人員	會面次數	每次平均時間 (分鐘)
學校護士		
社工		
物理治療師		
言語治療師		
職業治療師		
教育心理學家/臨床心理學家		
特殊教育需要統籌主任		
其他，請註明：		

☐ 我沒有在過去 6 個月內在學校與上述任何專業人員會面。

*若您現在**就業**，請繼續回答以下問題；* *若您現在**沒有就業**，請由第 39 題開始回答。*	
35. 平均**每星期**的工作日數：	..... (日)
36. 平均**每星期**的工作時數：	..... (小時)
37. 您的狀況有否影響您的工作?	☐ 有 ☐ 沒有
如有： a) 您**每星期**因而**減少**了多少工作時數? *(例：遲到/早退)*	..... (小時)
b) 請選出所有影響工作的問題：	☐ 健康狀況 ☐ 疲勞 ☐ 擔心/焦慮 ☐ 情緒低落 ☐ 無法集中精神 ☐ 因要覆診而早退/遲到/缺席 ☐ 其他，請註明：.....
c) 這些問題對您的影響有多頻密?	☐ 每月少於一次 ☐ 每月一次或兩次 ☐ 每星期一次或兩次 ☐ 每天一次或兩次 ☐ 每天多於兩次
38. 在過去 **6 個月**內，**因您的狀況**而缺席上班的日數：	..... (日)
39. 您的狀況有否影響了您的就業機會?	☐ 有 ☐ 沒有 ☐ 我目前正在讀書，沒有工作
如有： a) 請選出對就業上的的影響： *(可以選擇多於一個選項)*	☐ 離職/失業 ☐ 提早退休 ☐ 從全職改為兼職 ☐ 就業選擇 ☐ 工作缺勤 ☐ 工作時數上的改變 ☐ 其他，請註明：.....
40. 在得知自己的狀況**前**，您的教育/狀況是?	☐ 全職，職位：..... ☐ 兼職，職位：..... ☐ 家庭主婦/主夫 ☐ 退休 ☐ 學生 ☐ 沒有工作 ☐ 其他，請註明：.....

感謝您的參與！

Appendix 5.11: EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

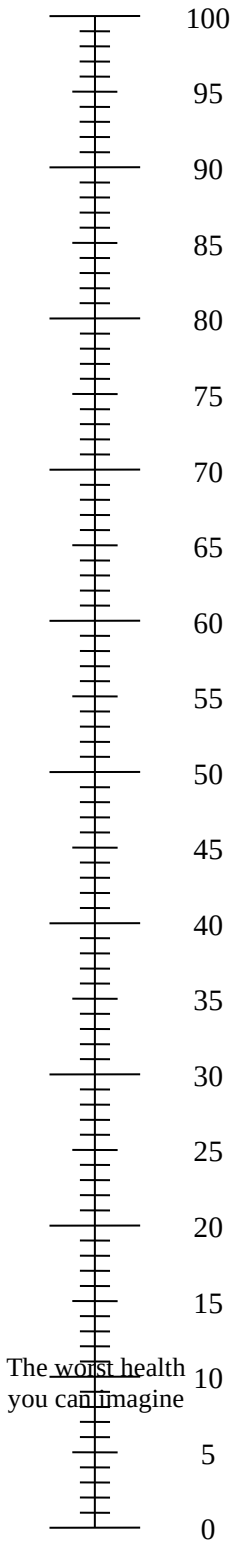
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

YOUR HEALTH TODAY = ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.



EQ-5D-5L (Chinese-Cantonese Version)

供香港地區使用之版本

請在每個標題下剔選最能形容您今天的健康狀況的一個方格。

行動能力

我可以四處走動，沒有任何問題 ❑

我的行動有輕微問題 ❑

我的行動有中度問題 ❑

我的行動有嚴重問題 ❑

我無法行動 ❑

自我照顧

我在洗澡或穿衣方面沒有任何問題 ❑

我在洗澡或穿衣方面有輕微問題 ❑

我在洗澡或穿衣方面有中度問題 ❑

我在洗澡或穿衣方面有嚴重問題 ❑

我無法自己洗澡或穿衣 ❑

平常活動 (*如工作、讀書、家務、家庭或休閒活動*)

我能進行平常活動，沒有任何問題 ❑

我在進行平常活動方面有輕微問題 ❑

我在進行平常活動方面有中度問題 ❑

我在進行平常活動方面有嚴重問題 ❑

我無法進行平常活動 ❑

疼痛 / 不舒服

我沒有任何疼痛或不舒服 ❑

我覺得輕微疼痛或不舒服 ❑

我覺得中度疼痛或不舒服 ❑

我覺得嚴重疼痛或不舒服 ❑

我覺得極度疼痛或不舒服 ❑

焦慮 / 沮喪

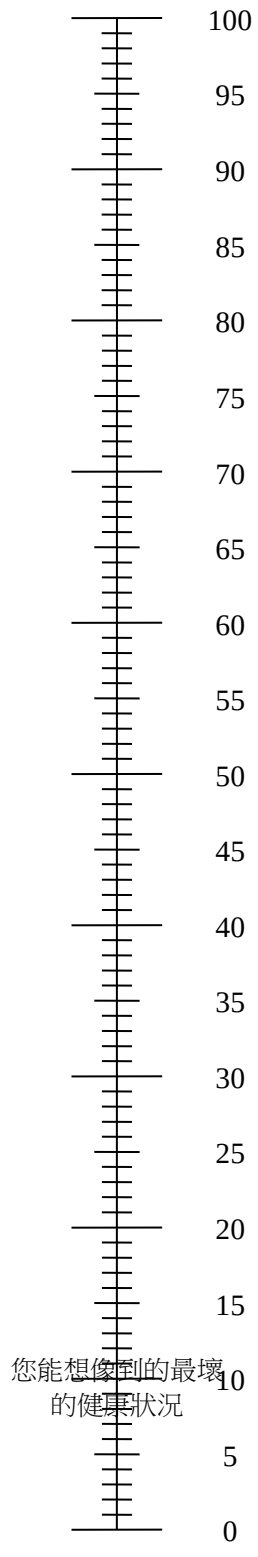
我不覺得焦慮或沮喪 ❑

我覺得輕微焦慮或沮喪 ❑

我覺得中度焦慮或沮喪 ❑

我覺得嚴重焦慮或沮喪 ❑

我覺得極度焦慮或沮喪 ❑



您今天的健康狀況=

- 我們想知道您<u>今天</u>的健康狀況有多好或多壞。
- 這個量度尺的**刻度**由 0 數到 100。
- 100 表示您能想像到的<u>最好</u>的健康狀況。

  0 表示您能想像到的<u>最壞</u>的健康狀況。
- 請在量度尺中打交叉，以顯示您<u>今天</u>的健康狀況如何。
- 現在，請在下面的方格中填寫您在量度尺上打叉的刻度。

Appendix 5. 12: Transcranial magnetic stimulation monitoring questionnaire

As part of our research programme, we routinely monitor the health of participants following TMS. We would be grateful if you could answer the questions listed below. Completing this form is entirely voluntary. The information you provide will be treated as confidential and will be held in secure conditions. Group results of this survey may be published, but no information will be disclosed that can identify any individual person.

If you are unsure how to answer any of the questions, please ask the researcher who gave you this form.

Name:
Current Date:
Date of Birth:
Handedness:

Please tell us if you experienced any of the following symptoms in the 24 hours following your most recent TMS session. If the answer is YES to any of these questions, we would be grateful for additional details

Seizure

☐Yes ☐No **Details:**

Fainting or Collapse

☐Yes ☐No **Details:**

Dizziness

☐Yes ☐No **Details:**

Nausea or vomiting

☐Yes ☐No **Details:**

Headache

☐Yes ☐No **Details:**

Muscular aches

☐Yes ☐No **Details:**

Muscle spasm or twitch

☐ Yes ☐ No **Details:**

Insomnia

☐ Yes ☐ No **Details:**

Sensory Problems

☐ Yes ☐ No **Details:**

Difficulties speaking or understanding speech

☐ Yes ☐ No **Details:**

Lack of coordination

☐ Yes ☐ No **Details:**

Slowness or impairment of thought

☐ Yes ☐ No **Details:**

Other (please specify)

☐ Yes ☐ No **Details:**

Any other comments

Appendix A 1: Paper 1

Therapeutic Advances in Chronic Disease *Meta-Analysis*

Effects of nonsurgical, minimally or noninvasive therapies for urinary incontinence due to neurogenic bladder: a systematic review and meta-analysis

Ther Adv Chronic Dis
2022, Vol. 13: 1–17
DOI: 10.1177/20406223211063059

Mohammed Usman Ali, Kenneth Nai-Kuen Fong, Priya Kannan, Umar Muhammad Bello and Georg S. Kranz

Abstract

Objective: To determine the effects of nonsurgical, minimally or noninvasive therapies on urge urinary incontinence (UUI) symptoms and quality of life (QoL) in individuals with neurogenic bladder (NGB).

Data Sources: Cochrane library, EMBASE, MEDLINE, PEDro, Scopus, and Web of Science databases were searched from inception to September 2021.

Review Methods: Randomized controlled trials that compared therapies such as intravaginal electrical stimulation (IVES), transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES), transcutaneous tibial nerve stimulation (TTNS), pelvic floor muscle training (PFMT), and behavioural therapy (BT) to control were included. Study screening, data extraction, and study quality assessments were performed by two independent authors.

Results: Fourteen trials with 804 participants were included in the study after screening of 4281 potentially relevant articles. Meta-analyses revealed a significant effect of electrical stimulation on UUI due to multiple sclerosis (standardized mean difference (SMD): −0.614; 95% confidence interval (CI): −1.023, −0.206; $p = 0.003$) and stroke (SMD: −2.639; 95% CI: −3.804, −1.474; $p = 0.000$). The pooled analyses of TTNS (weighted mean difference (WMD): −12.406; 95% CI: −16.015, −8.797; $p = 0.000$) and BT (WMD: −9.117; 95% CI: −14.746, −3.487; $p = 0.002$) revealed significant effects of these interventions on QoL in people with Parkinson's disease. However, meta-analyses revealed nonsignificant effects for PFMT (WMD: −0.751; 95% CI: −2.426, 0.924; $p = 0.380$) and BT (WMD: −0.597; 95% CI: −1.278, 0.083; $p = 0.085$) on UUI due to Parkinson's disease.

Conclusions: Our meta-analyses found electrical stimulation to be beneficial for improving the symptoms of UUI among people with multiple sclerosis and those with stroke. Our review also revealed that TTNS and BT might improve QoL for people with NGB due to Parkinson's disease, although the effects of PFMT and BT on UUI warrant further investigation.

Keywords: neurogenic bladder, systematic review and meta-analysis, therapies, urinary incontinence

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Introduction

Lower urinary tract dysfunction caused by nervous system lesions or trauma is termed neurogenic bladder (NGB)[1] and can be life-threatening if not managed adequately.[2] The epidemiology of NGB varies, including multiple sclerosis (40–90%), Parkinson's disease (37–72%), spinal cord injury (70–84%), stroke (57–83%) and spina

bifida (40–60.9%).[3,4] NGB represents a substantial issue in clinical practice in the United States, with a prevalence that increased from 26.1% in 2016 to 31.1% in 2018.[5] Neurogenic lower urinary tract dysfunction distorts detrusor pressure and bladder emptying regulation, leading to urge urinary incontinence (UUI).[1,6] UUI symptoms in people with NGB include increased urinary frequency, urgency and leakage, which is immediately preceded by a sudden urge to void.[7] The stress and discomfort associated with UUI due to NGB can have major negative impacts on quality of life (QoL), resulting in social isolation, depression and embarrassment.[8] Patients with UUI tend to experience low self-esteem, report effects on their social, sexual and work activities.[9] In addition, UUI causes psychological stress and can restrict participation in social activities.[10]

Pharmacological management options for NGB include oral agents such as anticholinergic drugs (antimuscarinics), beta-adrenergic and selective serotonin re-uptake inhibitor; intravesicular injection; transdermal agents.[11] However, the persistence rate for response to medication after 1 year is only 12–39%,[12] and people with NGB often discontinue medications due to adverse effects or a lack of improvement in symptoms.[12,13] Surgical interventions for NGB can be performed in patients who are unresponsive to conservative or less invasive treatments; however, the surgical management of NGB is expensive and associated with post-operative complications[14] and some requiring tension-free vaginal tape and translabial ultrasound assessing technical errors after mid-urethral transobturator tape.[15]

Nonsurgical, minimally or noninvasive therapies for NGB include transcranial magnetic stimulation,[16] transcranial direct current stimulation,[17] transcutaneous electrical nerve stimulation (TENS),[17] neuromuscular electrical stimulation (NMES),[18] biofeedback,[19] transcutaneous tibial nerve stimulation (TTNS),[20] intravaginal electrical stimulation (IVES),[21] pelvic floor muscle training (PFMT),[19] cognitive behavioural training and vaginal cones.[22] The efficacies of some of these interventions have been evaluated in previous systematic reviews.[2,23–27] However, previous reviews did not include meta-analyses,[23–26] evaluate the efficacy of only a single intervention,[23,25,26] result in inconclusive outcomes due to the limited number of included studies[26] or were not conducted within the last 5 years.[23,25] The current review is the first to include all nonsurgical, minimally or noninvasive therapies for the management of UUI due to NGB,[2,23–27] with the aim of evaluating treatment effects for symptom management and QoL.

Methods

Search strategy and study screening

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were incorporated during the development and reporting of this review.[28] The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42021236522) prior to the commencement of database searches. Six electronic databases, including the Cochrane library, EMBASE, MEDLINE, Physiotherapy Evidence Database (PEDro), Scopus, and Web of Science, were searched from database inception to 30 September 2021. Search terms for the review were formulated into three themes, including NGB, treatments and study design. The defined search terms within each of the individual themes were combined using the Boolean operator 'OR', and the three themes were combined using the Boolean operator 'AND'. A detailed description of the search terms developed for databases is presented in the supplementary file. The selection of studies for this review was based on the PICOS (Patient problem, Intervention, Comparison, Outcome measure, and Study design) framework.[29] The articles identified through electronic database searches were exported to the EndNote X9 citation manager (Clarivate Analytics, Philadelphia, Pennsylvania, USA) for screening. Ethical approval is not required for this review because data from previously published studies in which informed consent was obtained were retrieved and analysed.[30]

Study selection

Studies were included in this systematic review if they (1) were randomized controlled trials (RCTs), pilot RCTs, randomized cluster trials, randomized crossover trials, or unpublished theses; (2) included adults (of both sexes) with UUI due to NGB, due to spinal cord injury, stroke, Parkinson's disease, or multiple sclerosis; (3) compared therapies, such as IVES, TENS, NMES, TTNS, PFMT, behavioural therapy

(BT), against controls consisting of no treatment, sham, or PFMT and (4) trials that utilized the Overactive Bladder Questionnaire-V8 (OAB-V8), the Overactive Bladder Symptom Score Questionnaire, or a voiding diary to evaluate the symptoms of UUI, or trials that utilized the Qualiveen questionnaire, Incontinence Impact Questionnaire-7 (IIQ-7), or International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) to measure QoL. Studies were excluded if they (1) were published as non-English studies, (2) were quasi-experimental trials/cross-over studies/wait-list studies, (3) involved medical or surgical interventions or (4) were conference proceedings.

Data extraction

Electronic searches, title, and abstract screening were performed by one review author (M.U.A.). The full-text screening was performed by two independent review authors (M.U.A. and U.M.B.). Discrepancies were resolved by discussion between the two review authors until consensus was reached. For unresolved discrepancies, a third review author (P.K.) was consulted. Manual searching of the reference lists for included studies and relevant systematic reviews were also conducted to identify any additional potentially relevant articles. Data extraction for each included study was performed by two independent review authors (M.U.A. and U.M.B.). The following data were extracted from each included study: first author, year of publication, country of study, participant characteristics (mean age and standard deviation (SD)), the sample size of each group, intervention, control, outcome measure(s), and pre- and post-treatment results.

Quality assessment

For each included study, the methodological quality and quality of evidence were evaluated using the PEDro scale[31,32] and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool,[33] respectively. The PEDro scale has been reported as a reliable and valid tool for evaluating methodological quality.[31] The PEDro scale is an 11-item checklist: item 1 assesses external validity, items 2–9 assess internal validity, and items 10 and 11 assess interpretability.[34] Each item on the PEDro scale is scored as 'yes' or 'no', resulting in a maximum score of 10, with higher scores indicating higher study quality. Studies scoring ⩾7 are considered high quality, scores of 5 and 6 are considered moderate quality, and scores of 0–4 are low-quality.[31] One review author (M.U.A.) evaluated the methodological quality of the included studies, and the scores were compared against existing scores reported on the PEDro website.[35] Disagreements in scores between the author and the PEDro website score were resolved by discussion with a second review author (U.M.B.).

The quality of evidence was evaluated using GRADEpro software.[36] According to the GRADE system, the quality of a body of evidence can be categorized as 'very low', 'low', 'moderate', or 'high'.[37] The overall quality of evidence for an outcome measure was based on the lowest quality score for the assessed outcome.[37] The following factors were considered when rating the quality of evidence:

Study limitations. Evidence was rated according to the presence of methodological flaws, such as the absence of concealed allocation, inadequate follow-ups, and the inadequate reporting of outcome measures.[38] Given the nature of the intervention, studies were not downgraded for the lack of participant blinding; however, studies were downgraded by one level for the lack of either therapist or assessor blinding and by two levels for the lack of both therapist and assessor blinding.[38]

Indirectness of evidence. Studies were rated down if a substantial difference was identified between the intervention and control populations across the studies and when surrogate outcome measures were used which may reduce the quality of evidence.[39]

Imprecision. Studies were downgraded in quality of evidence for imprecision if the confidence interval around the estimate of treatment effect is not sufficiently narrow in the presence of small total sample size.[40]

Inconsistency of results across studies. Studies were downgraded for minimal or no overlap or evidence of statistical heterogeneity, as indicated by a large Chi-square value.[41]

Publication bias. If studies were industry-sponsored, likely to be industry-sponsored, or conflict of interest was reported, the quality of evidence was

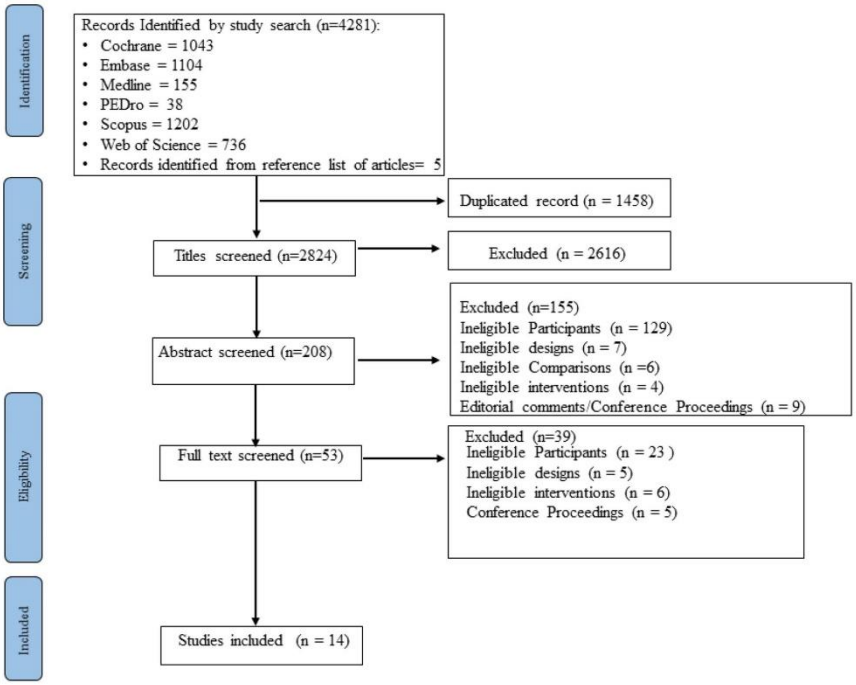

Figure 1. Flowchart of screened studies.

downgraded.[42] A funnel plot was planned if more than 10 studies were included in a meta-analysis.

Data analysis

The meta-analysis of the included studies was conducted using the Comprehensive Meta-Analysis software (version 3). Trials that used similar interventions and outcome measures were pooled together. Weighted mean differences (WMDs) and standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used to assess the intervention effects of continuous outcomes. Where studies used different outcome measures to assess the same outcome, SMD was computed using Hedges' *g*. Statistical heterogeneity was evaluated using the chi-square test ($I^2 > 50\%$ was considered substantial heterogeneity). When minimal heterogeneity was identified ($I^2 < 50\%$), a fixed-effects model was used, whereas a random-effects model was used when maximum heterogeneity was identified ($I^2 > 50\%$).[43,44] Asymmetry could not be evaluated by funnel plot analyses because fewer than 10 studies were included in the pooled meta-analyses.[29]

Results

Study selection

Figure 1 presents a flowchart of the screening process used to select studies, with the reasons for exclusion at each stage. The electronic database searches resulted in 4281 potentially relevant articles. Following import into the citation manager, 1458 duplicate records were identified and removed. The review of the study titles and abstracts resulted in the exclusion of 2616 and 155 articles, respectively. The full-text screening of the remaining 53 studies led to the exclusion of 39 articles, and 9 studies were determined to meet

the inclusion criteria of the study. A manual search of the reference lists for the included studies (forward search) and relevant systematic reviews revealed an additional 5 studies, resulting in 14 total studies included in the review. Interventions identified in the included studies include IVES,[45,46] TENS,[47,48] NMES,[18,49] TTNS,[20,50] PFMT,[51–53] and BT.[54,55] Studies evaluating the effects of other therapies, such as repetitive transcranial magnetic stimulation[16]and functional magnetic stimulation,[56–60] were also identified during the database searches; however, these interventions[16,56,61,62] could not be included in the review because they were evaluated in quasi-experimental trials lacking a control group.

Study characteristics

The characteristics of the included studies are presented in Table 1. The 14 included studies included a total of 804 participants. The sample sizes in the included studies ranged from 13 to 82. The ages of the participants ranged from 18 to 90 years. The included studies were published between 2004 and 2021, including 11 of 14 studies that were published within the last 7 years (2014–2021). Five studies were conducted in Brazil,[20,45,46,50,63] three in Denmark,[51–53] three in China,[18,47,48] two in the United Kingdom,[49,54] and one study from the United States.[55] Twelve studies evaluated UUI,[18,45–49,51–55,63] and four studies evaluated QoL.[20,50,54,55]

Methodological quality

The PEDro scores for the included studies are shown in Table 2. The mean PEDro score of the included studies was 6 out of 10, with a range of 4–9. Of the 14 included studies, 8 studies were of high methodological quality, 5 were of moderate methodological quality, and one study was of low methodological quality. Among the 14 included studies, 7 studies did not report allocation concealment, 10 lacked intention-to-treat analysis, 10 lacked assessor blinding, and 3 studies lost >15% of participants to follow-up. All 14 studies lacked therapist blinding.

Quality of evidence

Table 3 presents a summary of the findings generated by the GRADE profiler software. The GRADE quality of evidence for the 14 trials included in the five meta-analyses ranged from 'low' to 'moderate'. The overall GRADE quality of evidence for the included trials ranged from low to moderate for UUI and moderate for QoL.

Effects of interventions on UUI

Electrical stimulation versus *PFMT on UUI due to multiple sclerosis.* Four studies[45,46,49,63] compared the effects of electrical stimulation (IVES and NMES) with those of PFMT on UUI among people with multiple sclerosis. The number of treatment sessions in the four included trials ranged from 18 to 52.The stimulation parameters used in the four trials included a frequency from 2 to 40 Hz, an intensity from 450 μs to 1 ms, and a treatment duration of up 20 to 30 min. Among the four trials, three trials[45,46,49] measured UUI using OAB-V8, and one trial[63] measured UUI using a voiding diary.

The methodological quality of the four trials[45,46,49,63] was moderate to high, and the quality of evidence quality was moderate. A pooled analysis of the four trials (n = 74) revealed a significant reduction in UUI symptoms (SMD: −0.614; 95% CI: −1.023 to −0.206; p = 0.003; Figure 2(a)) in the intervention group compared with the control group.

PFMT versus *no treatment on UUI due to stroke.* Three studies[51–53] examined the effects of PFMT on UUI symptoms compared with a no-treatment control among people with stroke. The PFMT in the three trials consisted of 6 s of maximum contractions, followed by 6 s of rest, for a total of 30 s of maximum contractions and 30 s of rest. All exercises were repeated gradually 6–10 times while lying, standing or seated, 1–2 times each day, 7 days a week. All three trials[51–53] measured UUI with a voiding diary.

The methodological quality of the three trials[51–53] was evaluated as moderate- to high-quality, and the quality of evidence was low. The pooled analysis of the three trials (n = 80) revealed an insignificant reduction in daytime voiding frequency (WMD: −0.751; 95% CI: −2.426 to 0.924; p = 0.380; Figure 2(b)) for the intervention group compared with the control group.

Electrical stimulation versus *no treatment on UUI due to stroke.* Three studies[18,47,48] examined the effects of electrical stimulation (NMES[18] and TENS)[47,48] on UUI compared with a no-treatment

Table 1. Characteristics of included studies ($n = 14$).

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure(s)	Pre-treatment results	Post-treatment results
Araujo *et al.*[20] Brazil **8/10**	**Exp**: 64.2 ± 2.5 **Con**: 68.2 ± 2.3 **Exp**: $n = 15$ **Con**: $n = 15$	**TTNS** **Frequency**: 10 Hz Pulse Duration: 200 μs **Intensity**: 1mA at 1KΩ **Duration**: 20 min for 12 weeks	**TTNS** **Frequency**: <0.5 Hz **Pulse Duration**: 200 μs **Intensity**: not sufficient to trigger rhythmic toe flexion **Duration**: 20 min for 12 weeks	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** Exp: 27.8 ± 8.9 Con: 29.4 ± 8.4	Exp: 15.0 ± 6.9 Con: 25.9 ± 8.1 $p = 0.008$
Ferreira *et al.*[63] Brazil **5/10**	**Exp**: 43.25 ± 10.68 **Con**: 49.8 ± 16.5 **Exp**: $n = 12$ **Con**: $n = 12$	**NMES** **Frequency**: 2 Hz **Pulse Duration**: 1 ms **Intensity**: tolerable for patient. **Duration**: 48 sessions twice weekly for 6 months **PFMT** 3 sets of 10 reps daily for 6 months	**PFMT** 3 sets of 10 reps per day for 6 months	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp**: 1.69 (0.59) **Con**: 1.58 (0.71)	**Exp:** 0.62 (0.62) **Con:** 0.88 (0.62)
Ferreira *et al.*[45] Brazil **5/10**	Exp: 38.6 ± 13.5 Con: 49.8 ± 16.5 Exp: $n = 15$ Con: $n = 15$	**PFMT** During stimulation, participants perform 20 fast and slow contractions twice weekly for 6 months **IVES** **Frequency**: 2 Hz **Pulse Duration**: 1 ms **Intensity**: tolerable for patient. **Duration**: 30 min 48 sessions twice weekly for 6 months	**PFMT** 3 sets of 8–10 close-to-maximal contractions and 10 s sustenance daily for 6 months	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** **Exp**: 1.1 ± 1.1 **Con**: 0.7 ± 0.7	**Exp:** 0.3 ± 0.3 **Con:** 0.4 ± 0.4 $p = 0.002$
Guo *et al.*[47] China **4/10**	**Exp**: 68.1 ± 7.1 **Con**: 65.1 ± 9.8 Exp: $n = 32$ Con: $n = 29$	**PFMT + TENS** 30 min daily/60 days Pulse duration: 70 μs Frequency: 75 Hz Current: 16 mA (1 kΩ)	**PFMT** Basic therapy	OABSS	***UUI symptoms*** **OABSS** Exp: 5 ± 0.94 Con: 5 ± 0.69	Exp: 2.64 ± 0.98 Con: 4.09 ± 0.71
Guo and Kang[18] China **9/10**	**Exp**: 64.3 (11.8) **Con**: 62.5 (12.2) Exp: $n = 41$ Con: $n = 41$	**NMES** **Frequency**: 50 Hz **Pulse Duration**: 250 μs **Treatment duration**: 30 min (10 second on and 30 second off) Graded intensity based on patient's tolerance. Once daily 5 sessions weekly for 10 weeks	**Sham** NMES without active probe	OABSS	***UUI symptoms*** **OABSS:** Exp: 4.02 ± 0.76 Con: 4.18 ± 0.65 $p > 0.05$	Exp: 1.61 ± 0.32 Con: 3.86 ± 0.74 $p < 0.05$
Liu *et al.*[48] China **7/10**	Exp I: 66.30 (10.84) Exp II: 63.75 (8.92) Con: 67.91 (7.39) Exp I: $n = 27$ Exp II: $n = 27$ Con: $n = 27$	**TENS** **Frequency**: 20 Hz **Pulse Duration**: 150 μs **Treatment duration**: 30 min once daily for 90 days **TENS** **Frequency**: 75 Hz **Pulse Duration**: 150 μs **Treatment duration**: 30 min once daily for 90 days	**No-treatment** Only assessment of OABSS, BI, Urodynamics and Voiding diary on the first day and the 90th day.	Voiding diary	***UUI symptoms*** **Voiding diary:** **incontinence episodes in 24 h** Exp I: 10.07 (3.98) Exp II: 11.84 (3.05) Con: 10.63 (1.82)	Exp I: 2.10 (0.78) Exp II: 4.69 (1.05) Con: 9.54 (3.51)

(Continued)

Table 1. (Continued)

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure(s)	Pre-treatment results	Post-treatment results
Lúcio *et al.*[46] Brazil **5/10**	Exp I: 42 [27–54] Exp II: 45 [22–52] Con: 43.5 [25–51] Exp I: $n = 10$ Exp II: $n = 10$ Con: $n = 10$	**NMS + EMG Biofeedback + PFMT** **Frequency**: 10 Hz **Pulse Duration**: 200 µs **Treatment duration**: 30 min **TTNS + EMG Biofeedback + PFMT** **Frequency**: 10 Hz **Pulse Duration**: 200 µs **Treatment duration**: 30 min	**Sham NMS + PFMT** **Frequency**: 2 Hz **Pulse Duration**: 50 ms **Treatment duration**: 2 s with 60 s rest 30 min once daily for 90 days 30 slow maximal effort followed by 3 min of fast maximal effort	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** Exp I: 5.0 [0–8.3] Exp II: 4.0 [1.7–5.7] Con: 3 [1.7–6.3]	Exp I: 0.2 [0–2.3] Exp II: 0.7 [0–4.3] Con: 0.5 [0–3]
McClurg *et al.*[49] UK **9/10**	Exp: 48.3 [11.5] Con: 52.0 [8.8] Exp: $n = 37$ Con: $n = 37$	**PFMT + Biofeedback + Active NMES** **First Parameter Frequency**: 40 Hz **Pulse Duration**: 250 µs **Treatment duration**: 5 s of stimulation and 10 s of no stimulation with a ramp of 1 s at clinic and home for 30 min **Second Parameter Frequency**: 10 Hz **Pulse Duration**: 450 µs **Treatment duration**: 10 s of stimulation and 3 s of no stimulation with a ramp of 3 s at clinic and home for 30 min	**PFMT + Biofeedback + Placebo NMES** **Frequency**: 2 Hz **Pulse Duration**: 50 µs **Treatment duration**: 2 s of stimulation and 60 s of no stimulation with a ramp of 8 s at clinic and clinic for 30 min	Voiding diary	***UUI symptoms*** **Voiding diary:** **Incontinence episodes per in 24 h.** Exp: 2.1 ± 4.1 Con: 2.1 ± 4.0	Exp: 0.3 ± 1 Con: 1.1 ± 2.8 $p < 0.001$
McDonald *et al.*[54] UK **8/10**	Exp: 63.6 [1.7] Con: 69.8 [1.8] Exp: $n = 20$ Con: $n = 18$	**Bladder training Programme** • Instructions on urge suppression and distraction techniques • Coaching in PFMT • A personalized voiding schedule • A DVD training • For 12 weeks	Conservative advice	Voiding diary ICIQ-OAB	***UUI symptoms*** **Voiding diary: 72 h.** **Episodes of urgency** Exp: 4.7 [1.1] Con: 6.7 [1.9] $p < 0.366$ ***QoL*** **ICIQ-OOL Score** Exp: 63 [4.7] Con: 60 [6.3] $p < 0.743$	Exp: 2.1 [1.0] Con: 4.7 [1.2] $p < 0.184$ Exp: 50 [7.0] Con: 59 [4.1] $p < 0.224$
Perissinotto *et al.*[50] Brazil **6/10**	Exp: 63.5 [51.0–80.0] Con: 57.0 [50.0–68.0] Exp: $n = 8$ Con: $n = 5$	**TTNS** Pulse Width: 200 µs Frequency: 10 Hz Duration: 30 min for 5 weeks	**Sham** No active electrical stimulation	OAB-V8	***UUI symptoms*** **Overactive bladder-V8** Exp: 18.0 [6.0–27.0] Con: 29 [11.0–33.0]	Exp: 16.0 [6.0–25.0] Con: 21.5 [6.0–21.5]

(Continued)

Table 1. (Continued)

First author, year, country of study, PEDro score	Participant characteristics (mean age of participants (SD); sample size of each group)	Intervention	Control	Outcome measure(s)	Pre-treatment results	Post-treatment results
Tibaek *et al.*[53] Denmark **6/10**	Exp: 59 [56–72] Con: 62 [52–75] Exp: *n* = 12 Con: *n* = 12	**Standardized PFMT** • Close to maximum contraction (6 s contraction/ 6 s rest). • ~30% of maximum contraction possible (max 30 s contraction/30 s rest). • All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. • Group treatment in this population	**Normal rehabilitation programme** No specific urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary: Voiding Frequency Totally/24 h** Exp: 11 (6–10) Con: 11 (8–12) p = 0.46	Exp: 7 (5–10) Con: 8 (7–12) *p* = 0.02
Tibaek *et al.*[52] Denmark **7/10**	Exp: 59 [56–72] Con: 62 [52–75] Exp: *n* = 14 Con: *n* = 12	**Standardized PFMT** • Close-to maximum contraction (6 s contraction/ 6 s rest). • 30% of maximum contraction possible (max 30 s contraction/30 s rest). • All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. • Group treatment in this population	**Normal rehabilitation programme** No specific urinary incontinence treatment	Voiding diary	***UUI symptoms*** **Voiding diary: Voiding Frequency Totally/24 h** Exp: 10 (8–12) Con: 9 (8–13)	Exp: 8 (7–9) Con: 8 (7–12) *p* = 0.028]
Tibaek *et al.*[51] Denmark **7/10**	Exp: 68 [57–73] Con: 70 [64–75] Exp: *n* = 15 Con: *n* = 15	**Standardized PFMT** • Close-to-maximum contraction (6 s contraction/ 6 s rest). • 30% of maximum contraction possible (max 30 s contraction/30 s rest). • All exercises repeated gradually 6–10 times in lying, standing and sitting positions, 1–2 times daily. • Group treatment in this population	**General Rehabilitation** No specific urinary incontinence treatment	Voiding Diary	***UUI symptoms*** **Voiding diary: Voiding frequency, total per 24 h** Exp: 11 (6–10) Con: 11 (8–12)	Exp: 7 (5–10) Con: 8 (7–12) ***p* = 0.25**
Vaughan *et al.*[55] US **8/10**	Exp: 71.0 ± 6.1 Con: 69.7 ± 8.2 Exp: *n* = 26 Con: *n* = 21	**Behavioural Therapy** • Isolated PFMT without abdominal muscle recruitment (45 contractions and relaxation divided into 3 sets of 15 with one in each of the three positions: lying, sitting, standing) • Fluid management education (Decrease caffeine, daily drinking 6–8 ounce glasses of fluid) • Constipation management education (increase physical activity, fibre, fruit, and fluid) • Urge suppression strategy	Maintain 7-day bladder diaries for 8 weeks Mirrored-shaped drawing exercises	Voiding diary ICIQ-OAB	***QoL*** **ICIQ-OAB QoL score** Exp: 69.7 ± 23.8 Con: 74.7 ± 23.8 UUI symptoms **Voiding diary: Weekly Frequency** **Exp**: 13.9 ± 9.6 **Con**: 15.1 ± 11.1	Exp: 58.4 ± 21.5 Con: 81.0 ± 24.2 *p* < 0.037 **Exp**: 7.7 ± 10.5 **Con**: 8.5 ± 10.0 *p* = 0.05

Con, control group; Exp, experimental group; ICIQ-OAB, International Consultation on Incontinence Questionnaire – Overactive Bladder; IIQ, Incontinence Impact Questionnaire; IVES, intravaginal electrical stimulation; NMES, neuromuscular electrical stimulation; OABSS, Overactive Bladder Symptom Score; OAB-V8, Overactive Bladder – V8 Questionnaire; PEDro, Physiotherapy Evidence Database; PFMT, pelvic floor muscle training; QoL, quality of life; TENS, transcutaneous electrical nerve stimulation; TTNS, Transcutaneous Tibial Nerve stimulation; UUI, Urge Urinary Incontinence.

Table 2. Summary of methodological quality of the included studies according to the PEDro scale ($n = 21$).

PEDro Scale	Random allocation	Concealed allocation	Baseline Similar	Subject blinding	Therapist blinding	Assessor blinding	Adequate follow-up	Intention-to-treat analysis	Between-group comparison	Points estimate	Total Score/10
Araujo *et al.*[20]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8
Ferreira *et al.*[63]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Ferreira *et al.*[45]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Guo *et al.*[47]	Y	N	Y	N	N	N	N	N	Y	Y	4
Guo and Kang[18]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Liu *et al.*[48]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Lúcio *et al.*[46]	Y	N	Y	N	N	Y	N	N	Y	Y	5
McClurg *et al.*[49]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
McDonald *et al.*[54]	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Perissinotto *et al.*[50]	Y	N	Y	Y	N	Y	N	N	Y	Y	6
Tibaek *et al.*[53]	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Tibaek *et al.*[52]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Tibaek *et al.*[51]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Vaughan *et al.*[55]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8

N, No; PEDro, Physiotherapy Evidence Database; Y, Yes.

Table 3. Summary of the findings (GRADE) for the effects of interventions compared to control.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention group	Control group	Relative (95% CI)	Absolute (95% CI)	
4 McClurg *et al.*[49] Ferreira *et al.*[63] Lúcio *et al.*[46] Ferreira *et al.*[45]	Randomized control trials	Very serious[a]	Not serious	Not serious	Not serious	None	74	74	–	[1.055 lower to 0.208 lower]	⊕⊕◯◯ LOW
3 Tibaek *et al.*[53] Tibaek *et al.*[52] Tibaek *et al.*[51]	Randomized control trials	Very serious[b]	Not serious	Not serious	Not serious	None	41	39	–	[0.628 lower to 0.225 higher]	⊕⊕◯◯ LOW
3 Guo *et al.*[47] Liu *et al.*[48] Guo and Kang[18]	Randomized control trials	Serious[c,d]	Not serious	Not serious	Not serious	None	100	97	–	[4.219 lower to 1.635 lower]	⊕⊕⊕◯ MODERATE
2 Vaughan *et al.*[55] McDonald *et al.*[54]	Randomized control trials	Serious[e]	Serious[f]	Not serious	Not serious	None	46	39	–	[16.015 lower to 8.797 lower]	⊕⊕◯◯ LOW
2 Perissinotto *et al.*[50] Araujo *et al.*[20]	Randomized control trials	Serious[g,h]	Not serious	Not serious	Not serious	None	23	20	–	[14.746 lower to 3.487 lower]	⊕⊕⊕◯ MODERATE
2 Vaughan *et al.*[55] McDonald *et al.*[54]	Randomized control trials	Serious[e]	Serious[f]	Not serious	Not serious	None	46	39	–	SMD 1.365 SD lower (2.598 lower to 0.131 lower)	⊕⊕◯◯ LOW

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; SMD, standardized mean difference.
Explanations:
[a]Lack of intention-to-treat analysis (Ferreira *et al.*,[63] Lúcio *et al.*,[46] and Ferreira *et al.*[45]).
[b]Lack of intention-to-treat analysis (Tibaek *et al.*,[53] Tibaek *et al.*,[52] and Tibaek *et al.*[51]).
[c]Lack of concealed allocation (Guo *et al.*[47]).
[d]Lack of intention-to-treat analysis (Guo *et al.*[47] and Liu *et al.*[48]).
[e]Lack of concealed allocation (McDonald *et al.*[54]).
[f]Evidence of Statistical/Methodology (I^2 value $>$ 50%).
[g]Lack of concealed allocation (Perissinotto *et al.*[50]).
[h]Lack of intention-to-treat analysis (Araujo *et al.*,[20] Perissinotto *et al.*[50]).

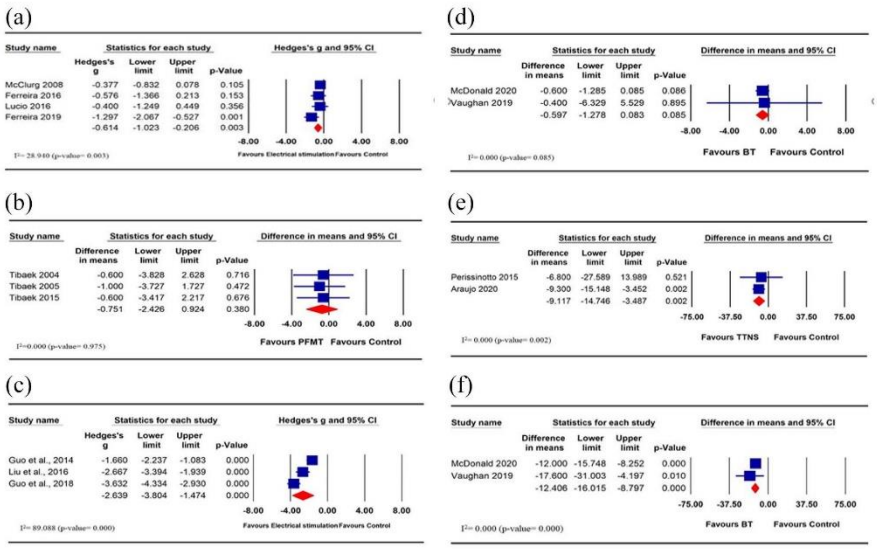

Figure 2. Forest plots. (a) Effect of electrical stimulation compared to PFMT on UUI in people with multiple sclerosis using voiding diary and OAB-V8. (b) Effect of PFMT compared to no treatment in stroke using voiding diary. (c) Effect of electrical stimulation compared to no treatment in stroke using voiding dairy and OABSS. (d) Effect of BT compared with usual treatment on UUI in Parkinson's disease using voiding dairy. (e) Effect of TTNS compared to no treatment in Parkinson's disease using OAB-V8. (f) Effect of BT compared to no treatment on QoL in Parkinson's disease using ICIQ-OAB.
BT, Behavioural Therapy; ICIQ-OAB, International Consultation on Incontinence Questionnaire-Overactive Bladder Module; OABSS, Overactive Bladder Symptom Score; OAB-V8, Overactive Bladder Questionnaire; PFMT, Pelvic Floor Muscle Training; QoL, Quality of Life; TTNS, Transcutaneous Tibial Nerve Stimulation; UUI, Urge Urinary Incontinence.

control group among people with stroke. The stimulation parameters across the three trials ranged from five to seven times each week, for a total of 40–90 treatment sessions, at frequencies ranging from 20 to 75 Hz, with intensities ranging from 70 to 250 μs, and lasting from 20 to 30 min. Of the three trials evaluated, two trials[18,47] measured UUI using the Overactive Bladder Symptom Score, and one trial[48] measured UUI using a voiding diary.

The methodological and evidence qualities of the three trials[18,47,48] were moderate. The pooled analysis of the three trials (n = 224) revealed a significant effect of the intervention on UUI symptoms (SMD: −2.637; 95% CI: −3.804 to −1.474; p = 0.000; Figure 2(c)) compared with the control condition.

BT versus *no treatment on UUI due to Parkinson's disease.* Two studies[54,55] compared the effects of BT against usual care (reduction of alcohol and caffeine intake and advice regarding the management of constipation and available containment products) on UUI symptoms in people with Parkinson's disease. The BT intervention delivered in the included trials include isolated PFMT, without abdominal muscle recruitment (45 contractions and relaxation, divided into 3 sets of 15, with each set performed in a different position: lying, sitting, and standing); fluid management education (decrease caffeine, daily intake of six 8-ounce glasses of fluid); constipation management education (increased physical activity, increased intake of fibre, fruits and fluids); and urge suppression strategies. The two trials[54,55] measured UUI with a voiding diary.

The methodological quality of both trials[54,55] was high, and the quality of evidence was low. The pooled analysis of the two trials (n = 85) revealed

to investigate the safety and acceptance of electrical stimulation (IVES and TENS) for the treatment of UUI due to NGB.

The pooled analyses of three studies[18,47,48] of moderate methodological quality with moderate quality of evidence revealed a significant effect for electrical stimulation (NMES or TENS) on UUI due to stroke. The mean estimate of the effect was large (SMD: −2.637, $p = 0.000$). A recent review found that NMES is generally safe for the treatment of post-stroke urinary incontinence in women.[73] Considering the safety of the intervention and the size of the effect obtained for this intervention in this review, electrical stimulation may be considered for clinical use.

The pooled analysis of data from three studies[51–53] of moderate to high methodological quality and low quality of evidence identified an insignificant effect of PFMT compared with no treatment on UUI symptoms due to stroke. According to the National Institute for Health and Care Excellence (NICE) guidelines, PFMT is recommended for NGB when voluntary pelvic floor muscle contraction is preserved.[74] PFMT for UUI involves performing a voluntary contraction of the pelvic floor muscles, avoiding a pelvic floor relaxation, until the urination urge is suppressed, an effect known as the 'guard reflex'.[74] According to the NICE guidelines, PFMT must be performed for a minimum of 3 months, consisting of at least eight contractions three times per day.[75] The participants of the three included trials[51–53] performed PFMT 6 to 10 times in lying, standing and sitting positions, one to two times daily, for 3 months. Based on the results of the current review, the efficacy of PFMT for UUI remains inconclusive. Future studies evaluating the effect of PFMT for UUI due to NGB must adhere to the NICE guideline.

The pooled analysis of two Parkinson's disease studies[54,55] of high methodological quality and low quality of evidence found a nonsignificant effect for BT compared with the no-treatment control on UUI symptoms. The rationale underlying BT is based on the premise that a potential precipitant of detrusor instability is the habit of frequent voiding and can be an indicator of uninhibited detrusor contraction and reduced bladder capacity.[76] BT aims to moderate the habit of frequent voiding through practising resisting the urge to void, postponing micturition and increasing the voiding interval, which improves bladder capacity and decreases detrusor instability.[77] BT alone, in the absence of other adjunctive treatments, might not lead to a positive result according to previous findings.[78] Based on the findings in this study, the effects of BT on UUI among individuals with Parkinson's disease remains inconclusive. We recommend future studies integrating BT with other interventions such as electrical stimulations for NGB in other to achieve better effects.

UUI has been reported to impair the QoL of people with Parkinson's disease,[79] and the degree of QoL impairment is associated with social predictors (e.g. age, sex, rural living, the number of household members, and financial problems) and clinical predictors (e.g. disease severity, disability, disease duration, motor impairment, depressive symptoms, complications of therapy, and gait impairment).[80] The pooled analyses of two studies[54,55] of high methodological quality and low quality of evidence revealed a significant effect of BT on QoL in people with Parkinson's disease compared with the no-treatment control. The size of the effect was large (0.9). Pooled analyses[20,50] also found that TTNS was beneficial for improving the QoL of people with Parkinson's disease compared with the no-treatment control. The size of the effect for TTNS was also large (12.4). Based on these results, TTNS and BT may be considered in clinical practice to improve QoL in people with UUI due to Parkinson's disease.

Study strengths and limitations

Our systematic review has several strengths. We adopted a comprehensive search strategy, using relevant search terms to identify RCTs evaluating the effects of nonsurgical, minimally or noninvasive therapies for the management of UUI. A sound, systematic methodology was employed for the identification and evaluation of the included studies. Only RCTs were included in the study to ensure the rigour of the pooled meta-analyses. Psychometrically sound quality assessment tools were employed to evaluate the quality of the methodology and evidence reported by the included studies. Limitations associated with this study include limited size of the pooled analyses and the inability to access some interventions due to lack of RCTs. Although the systematic review of RCTs can provide findings that are considered to represent the highest level of clinical evidence, excluding studies due to study

an insignificant effect of the intervention on UUI symptoms compared with the control condition (WMD: −0.597; 95% CI: −1.278 to 0.083; $p = 0.085$; Figure 2(d)).

Effects of interventions on QoL in people with Parkinson's disease

BT versus no treatment. Two studies[54,55] compared the effects of BT against usual care (reduction of alcohol and caffeine intake and advice regarding the management of constipation and available containment products) on QoL in people with Parkinson's disease. The two trials[54,55] measured QoL using the ICIQ-SF.

The methodological quality for both trials[54,55] was high, and the quality of evidence was low. The pooled analysis of the two trials ($n = 85$) revealed a significant effect of BT on QoL (WMD: −0.9117; 95% CI: −14.746 to −3487; $p = 0.002$; Figure 2(e)) in the intervention group compared with the control group.

TTNS versus no treatment. Two studies[20,50] examined the effects of TTNS on QoL compared with a no-treatment control group in people with Parkinson's disease. The stimulation parameters in the two trials included session lengths ranging from 5 to 12 weeks, a frequency of 10 Hz at an intensity of 200 μs, and a duration of 20–30 min. Both trials[20,50] measured QoL using the OAB-V8.

The methodological quality of the two trials[20,50] ranged from moderate to high, and the quality of evidence was moderate. The pooled analysis of the two trials ($n = 43$) revealed a significant improvement in QoL (WMD: −12.406; 95% CI: −16.015 to −8.797; $p = 0.000$; Figure 2(f)) in the intervention group compared with the control group.

Discussion

The effects of nonsurgical, minimally or noninvasive therapies on UUI symptoms and QoL in people with NGB was evaluated in this review. After review, 14 studies were identified with a total sample size of 804 participants. Our meta-analyses revealed a significant effect of electrical stimulation on UUI due to multiple sclerosis and stroke. The pooled analyses of TTNS revealed significant effects of these interventions on QoL in people with Parkinson's disease. However, meta-analyses revealed nonsignificant effects for PFMT on UUI due to Parkinson's disease.

The pooled analysis of four trials[45,46,49,63] of moderate to high methodological quality and moderate quality of evidence showed a significant effect of electrical stimulations (IVES, NMES, TENS) compared with PFMT on UUI symptoms in people with multiple sclerosis. IVES has been reported to cause a significant increase in pelvic floor muscle strength[64] in women with UUI. IVES depolarizes the somatic lumbar and sacral afferent fibres, thereby inhibiting bladder overactivity.[65] IVES has also been reported to cause profound bladder inhibition in animal models.[66] For the treatment of urge and mixed urinary incontinence, IVES at frequencies below 12 Hz is suggested for beneficial effects,[67] as frequencies below 12 Hz stimulate the pudendal nerve, reducing involuntary detrusor contractions.[68,69] Among the four trials providing evidence for the effects of electrical stimulation in the current review, three trials[45,46,49] utilized IVES at the recommended frequency for maximum benefits.

Considering the procedure of the IVES involving the participants being placed in supine position with 45° of hip and knee flexion, and the intravaginal electrode inserted in the vagina.[70] The acceptance and satisfaction with invasive IVES among women with UUI remain inconclusive, and previous studies[69,71] have reported mixed results. A previous study reported that women experienced pain and discomfort due to the vaginal probe used IVES.[68] However, another study examining women with mixed urinary incontinence reported that 80% of the study participants were satisfied with IVES.[69]

The mean estimated effect size for electrical stimulation when compared with PFMT on UUI symptoms obtained in this review was moderate (0.6).[69,72] However, the effect of electrical stimulation compared to no treatment control condition on UUI symptoms is much larger (2.6). This could be attributed to the effect of PFMT, although not significant in the current meta-analysis of only three pooled studies. The size of the effect, combined with the methodological quality of the included studies, indicated that electrical stimulation might be considered a viable treatment option of UUI due to multiple sclerosis. Future adequately powered studies are required

design could limit the scope of our study. The possibility of language bias could not be eliminated because we did not consider non-English and non-Chinese studies.

Conclusion

Our meta-analysis found that electrical stimulation (IVES and NMES) is beneficial for decreasing the symptoms of UUI among people with multiple sclerosis. Electrical stimulation (NMES and TENS) was also found to be beneficial for reducing the symptoms of UUI among people with stroke. These results were derived from trials of moderate to high methodological quality and moderate quality of evidence. This review also found that TTNS and BT were able to improve QoL in people with NGB due to Parkinson's disease. These results were derived from trials of moderate to high methodological quality and low to moderate quality of evidence. The specific effects of PFMT and BT on UUI remain uncertain. Future studies to evaluate the effects of PFMT and BT and other interventions that have received less attention, such as repetitive transcranial magnetic stimulation, transcranial magnetic stimulation and functional magnetic stimulation, on NGB outcomes are warranted.

Clinical message

- Electrical stimulation has strongest effects. However, might be unpreferable by all patients.
- Electrical stimulation is better than PFMT.

Author contributions

Mohammed Usman Ali: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft; Writing-review & editing.
Kenneth Nai-Kuen Fong: Conceptualization; Methodology; Supervision; Validation; Writing-review & editing.
Priya Kannan: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing-review & editing.
Umar Muhammad Bello: Data curation; Formal analysis; Investigation; Methodology; Writing-review & editing.
Georg S. Kranz: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing-review & editing.

Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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Appendix A 2: Paper 2

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Review article

Measures of quality of life of people with neurogenic overactive bladder: A systematic review of psychometric properties

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ABSTRACT

Objective: To identify psychometrically robust quality-of-life (QOL) outcome measures for evaluating QOL among people with neurogenic overactive bladder (OAB).
Study design: Electronic databases (CINAHL, EMBASE, MEDLINE, Scopus and Web of Science) were searched from inception to January 2023. Two independent reviewers participated in study screening, data extraction and quality appraisal. Studies were included if they validated at least one psychometric property of a QOL outcome measure among adults (age ≥ 18 years) with neurogenic OAB. The COnsensus-based Standards for selecting health status Measurement Instruments (COSMIN) checklist and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool were used to evaluate the methodological quality and quality of evidence, respectively for each included study.
Results: Database searches identified 47 studies that tested the psychometric properties of 15 QOL measures in a total of 19,994 participants with stroke, spinal cord injury, Parkinson's disease or multiple sclerosis. The Incontinence Quality of Life Questionnaire (I-QOL), King's Health Questionnaire, Overactive Bladder Questionnaire and Qualiveen were the best validated measures, with strong reliability, validity and responsiveness. I-QOL was the most robust, cross-culturally administered and psychometrically strong measure. The COSMIN checklist indicated sufficient methodological quality for 70% of measures, and the modified GRADE tool indicated quality of evidence ranging from moderate (67%) to high (33%).
Conclusions: This review identified the I-QOL as a culturally diverse measure with robust reliability, validity and responsiveness for assessing QOL among people with neurogenic OAB. These findings are supported by studies with good methodological quality (COSMIN) and high-quality evidence (GRADE).

Introduction

Overactive bladder (OAB) is a devastating and distressing condition associated with severe adverse consequences, such as participation restriction, social isolation and depression [1]. OAB is defined by the International Continence Society as 'urinary urgency, with or without urgency urinary incontinence, often associated with frequency and nocturia in the absence of infection or obvious pathology' [2]. Symptoms associated with neurogenic OAB have been implicated in impaired quality of life (QOL), with considerably negative impacts on physical and psychosocial functioning, depression and anxiety [3,4]. The level of QOL impairment varies with the level of awareness among individuals of symptom severity [5]. The number of voiding episodes reported during the day and night is considered a predictor of QOL among people with OAB [6].

Outcome measures for evaluating QOL are being applied increasingly during clinical assessments [7], leading to the development, application and validation of new QOL measures to provide evidence-based evaluations of clinical outcomes and monitor interventions [7]. In clinical settings, health status measures can be used to screen for

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functional problems, monitor disease progression and therapeutic response, and assess the quality of care [8]. Outcome measures must possess robust psychometric properties, such as validity, reliability and responsiveness, to be relevant in both clinical practice and research settings [9]. The International Consultation on Incontinence recommends the use of validated QOL measures when assessing therapeutic interventions for the management of urinary incontinence and clinical decision-making [10].

Previous systematic reviews have assessed the application of distinct measures of QOL for evaluating the impacts of interventions on QOL among people with stress urinary incontinence [11,12]. Multiple QOL measures exist for the assessment of people with urinary incontinence [12–14]; however, past reviews have not indicated which QOL measure is the most suitable for use among people with urgency urinary incontinence due to neurogenic OAB. Researchers and clinicians have been limited to generic QOL measures or measures developed for specific patient populations due to the lack of QOL measures designed explicitly for people with neurogenic OAB [15]. A previous systematic review of QOL measures by Wuytack et al. [16] largely focused on the application of disease-specific and generic QOL measures to women with stress urinary incontinence, with no consideration for neurogenic OAB. A focus on QOL measurement instruments applied to populations with neurogenic OAB is crucial for understanding the psychometric strengths of disease-specific QOL measures among people with OAB. Therefore, the present systematic review was conducted to identify psychometrically sound QOL measure(s) for evaluating people with neurogenic OAB, and make clinical practice and research recommendations for monitoring QOL.

Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [17]. This review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42021267409).

Search strategy and study screening

Database searches were conducted by two independent review authors (MUA and UMB). The following electronic databases were searched from database inception until 6 January 2023: CINAHL, EMBASE, MEDLINE, Scopus and Web of Science. Three themes were developed for the search terms: psychometric properties, outcome measures and OAB. A detailed description of the search strategy developed for EMBASE is presented in the online supplementary material. The reference lists of all included studies and relevant systematic reviews were searched manually to identify other potentially relevant studies. As data were retrieved and analysed from published studies that obtained informed consent, ethical approval was not required for this review [18].

Study selection

This systematic review utilized the Patient problem, Intervention, Comparison, Outcome measure, and Study design (PICOS) framework for study selection [19]. The studies included in this systematic review were selected based on the following criteria: (1) studies evaluating QOL among people with OAB of both sexes, aged ≥ 18 years; (2) studies testing the psychometric properties of OAB-specific QOL measures; and (3) studies assessing one or more of the following psychometric properties: internal consistency; intra-rater, inter-rater or test–retest reliability; measurement error; cross-cultural validity; content validity; face validity; structural validity; criterion validity; hypothesis testing; and responsiveness. The exclusion criteria included: (1) studies published in languages other than English; (2) systematic reviews or *meta*-analyses; (3) commentaries or editorials; (4) unpublished theses; (5) conference proceedings, abstracts or event annals; and (6) studies with inaccessible full-text.

Comprehensive study screening was conducted by exporting the search results from the searched databases to the citation manager EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). Duplicate studies were identified and removed. Titles and abstracts were screened for inclusion according to the predefined criteria by two reviewers (MUA and UMB). Two independent authors (MUA and DS) then screened the full texts of studies, with disagreements reconciled through discussion. Irreconcilable differences during the screening process were mediated by a third author (PK) until consensus was reached.

Data extraction

Data were extracted from the included studies by two independent authors (MUA and DS), and all discrepancies were addressed through discussion. A third author (PK) was consulted to address unresolved discrepancies during the data extraction process. The following data were extracted from each included study: first author; year; country of study; participant characteristics (mean age and standard deviation of participants; sample size for each group); population; outcome measure (s); psychometric property tested; and author's conclusion.

Risk of bias

The COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) risk of bias (ROB) checklist and the modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool [20,21] were used to evaluate the methodological quality and quality of evidence, respectively, for each included study. The COSMIN ROB checklist evaluates the ROB for each included study with respect to eight psychometric properties: reliability (relative measures including test–retest reliability, inter-rater reliability and intra-rater reliability); internal consistency; measurement error; content validity (including face validity); hypotheses testing; structural validity; criterion validity; cross-cultural validity; and responsiveness [20,21]. The methodological quality of an included study on each measurement property was graded using a four-point rating scale as 'very good', 'adequate', 'doubtful' or 'inadequate' [20,21]. To obtain an overall methodological quality score for each tested psychometric property, the lowest or worst score for any item on the checklist is considered [20,21]. After completing this step, the identified outcome measures were rated as sufficient (+), insufficient (−), inconsistent (±) or indeterminate (?), based on the pooled results for the individual included studies. An outcome measure was considered to be of sufficient overall quality (+) if the majority (>50 %) of the individual included studies were graded as sufficient [20,21]. Two independent authors (MUA and PK) evaluated the psychometric methodological quality of the included outcome measures. A third reviewer (SJW) assisted with addressing any unresolved discrepancies.

A COSMIN-modified GRADE assessment was performed to evaluate the quality of evidence cumulatively across each psychometric property for the identified outcome measures [20,21]. The outcomes of each included study were evaluated against the proposed revised criteria for good psychometric properties to determine a cumulative modified GRADE score [20,21]. The pooled psychometric properties included internal consistency, test–retest reliability (intra-class correlation/weighted kappa), validity and responsiveness. In this modified GRADE approach, the quality of evidence for each property was graded as high, moderate, low or very low [20,21]. The grading of the identified outcome measures starts with the assumption that the quality of the evidence is high, and the quality rating is then downgraded by up to three levels depending on the ROB, inconsistency, indirectness and imprecision of the evidence. Two independent authors (MUA and PK) were involved in evaluating the GRADE score for each included outcome

measure. A third reviewer (SJW) was consulted for unresolved disagreements.

Results

Study selection

This systematic review identified 6937 potentially relevant studies from electronic database searches and manual searches of the reference lists of relevant studies. After the search findings were exported into the citation manager, 1025 duplicate records were removed. Of the remaining studies, 47 [6,15,22–66] met the selection criteria for inclusion in the review. The reasons for study exclusion at the full-text screening stage are shown in the online supplementary material. A flowchart illustrating the screening process is presented in Fig. 1.

Characteristics of the included studies

This review included 47 studies with a total of 19,994 participants. The average sample size of the included studies was 425, with sample sizes ranging from 22 [63] to 1831 [58]. Participants were aged between 18 and 89 years. The included studies were published between 1997 [62] and 2021 [51], including 26 studies published within the last decade (2011–2021). Nine of the included studies recruited subjects with OAB secondary to specific health conditions, including multiple sclerosis alone ($n = 5$) [33,45,46,50,52]; spinal cord injury alone ($n = 1$) [51]; multiple sclerosis and spinal cord injury ($n = 2$) [48,49]; and multiple sclerosis, spinal cord injury and myelomeningocele ($n = 1$) [47]. The remaining 38 studies reported recruiting patients with neurological conditions without focusing on any specific health conditions [6,15,22–32,34–44,53–66]. Table 1 summarizes the characteristics of the included studies.

Descriptions of the outcome measures evaluated by the included studies

The 47 studies included in this review tested the psychometric properties of 15 outcome measures evaluating QOL among people with OAB due to multiple sclerosis (two outcome measures), spinal cord injury (one outcome measure), myelomeningocele (one outcome measure) and other OAB conditions with no specified cause (13 outcome measures). Table 2 summarizes the characteristics of the 15 evaluated outcome measures. All outcome measures are disease-specific measures that are available free of charge, although some are only free when used for clinical and research purposes. The Qualiveen [45–52] and King Health Questionnaire (KHQ) [59–65] were each tested in eight studies; the Overactive Bladder Questionnaire (OAB-q) was tested in seven studies [6,37–44]; the Incontinence Quality of Life Questionnaire (I-QOL) was tested in six studies [15,53–57]; the Incontinence Impact Questionnaire (IIQ) [29–33,66] and the UDI [29–33,66] were each tested in five studies; the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF) was evaluated in three studies [25–27]; and the Persian Female Lower Urinary Tract Symptoms (PFLUTS) [22], Bladder Control Self-Assessment Questionnaire (B-SAQ) [23], International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules (ICIQ-FLUTS) [24], International Consultation on Incontinence Questionnaire Overactive Bladder Quality of Life Module (ICIQ-OABqol) [28], Incontinence Symptom Severity (ISS) [34], Incontinence Utility

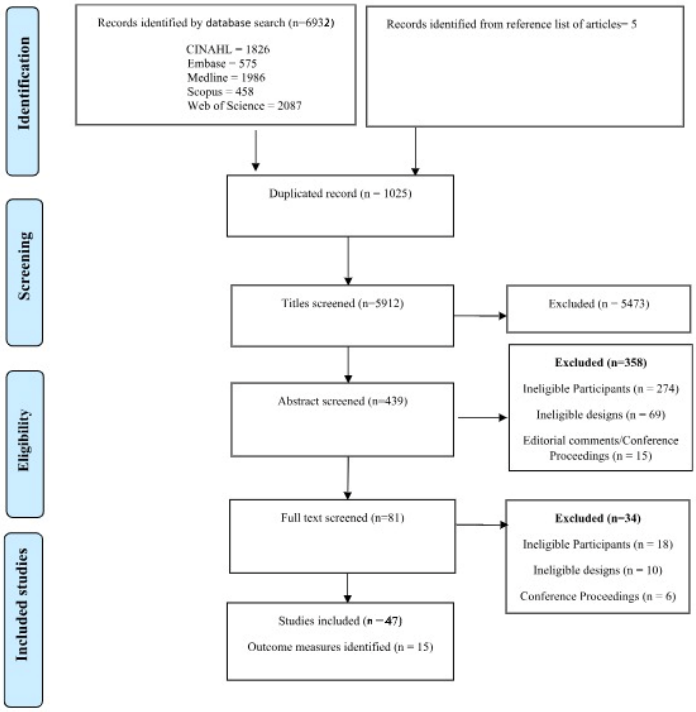

Fig. 1. Flowchart of screened studies.

Table 1
Characteristics of included studies ($n = 47$).

First author, year [reference], country of study	Participant characteristics (mean age of participants ± SD); sample size of each group	Population	Outcome measure(s)	Psychometric property tested	Author's conclusion
MS/spinal cord injuries/myelomeningocele					
Bonniaud et al., 2008 [46], Canada	Exp:58.45 ± 15.9 Con: 62.05 ± 19.9 $n = 121$	MS	Qualiveen	Test–retest reliability Criterion validity Construct validity Responsiveness	Qualiveen possesses excellent psychometric properties in clinical and research settings similar to the long version.
D'Ancona et al., 2008 [47], Brazil	36.33 ± 12.20 $n = 51$	Spinal cord injury MS Myelomeningocele	Brazilian Portuguese version Qualiveen	Internal consistency Test–retest reliability Construct validity	The Portuguese version of Qualiveen indicates good validation for investigating QOL among people with urinary symptoms due to neurological conditions.
Konstantinidis et al., 2020 [48], Greece	Paraplegia: 50.69 ± 13.78 Tetraplegia: 51.06 ± 10.47 MS: 51.15 ± 13.32 $n = 124$	Spinal cord injury MS	Greek version Qualiveen	Internal consistency Test–retest reliability Structural validity Criterion validity	The Greek version of Qualiveen indicates good reliability and validity following well-established psychometric assessment guidelines.
Milinis et al., 2017 [45], UK	50.8 ± 11.8 $n = 258$	MS	Qualiveen	Structural validity	Qualiveen demonstrates good validity in assessing the impact of urinary symptoms among people with MS.
Nikfallah et al., 2015 [49], Iran	35.3 ± 9.8 $n = 154$	Spinal cord injury MS	Persian version Qualiveen	Test–retest reliability Internal consistency Convergent validity Discriminant validity	The Persian version of Qualiveen is a reliable and valid measure in evaluating QOL among people with spinal cord injuries or MS.
Philippova et al., 2020 [50], Russia	37.9 ± 9.16 $n = 60$	MS	Russian version Qualiveen	Internal consistency Test–retest reliability Criterion validity	The Russian version of Qualiveen demonstrates good reliability and validity for evaluating the impact of urinary symptoms on incontinence-related QOL among people with MS.
Przydacz et al., 2020 [52], Poland	47.3 ± 15.6 $n = 189$	MS	Polish version Qualiveen	Test–retest reliability Internal consistency Content validity Criterion validity	The Polish version of Qualiveen demonstrates strong reliability and validity for evaluating the impact of urinary symptoms on incontinence-related QOL among Polish in clinical practice and research.
Przydacz et al., 2021 [51], Poland	46 (32–59) $n = 178$	Spinal cord injury	Polish version Qualiveen	Internal consistency Test–retest reliability Content validity Criterion validity	The Polish version of Qualiveen demonstrates acceptable validity and reliability for evaluating the impact of urinary symptoms on incontinence-related QOL among Polish.
Stievano et al., 2014 [33], Brazil	Con: 40.99 ± 14.85 MS: 41.26 ± 12.24 $n = 211$	MS	Brazilian version IIQ-7 and UDI-6	Internal consistency Test–retest reliability Criterion validity Responsiveness	The Brazilian versions of IIQ-7 and UDI-6 demonstrates good applicability, sensitivity, specificity and stability among people with MS.
Overactive bladder					
Brown et al., 1999 [30], USA	63.8 ± 11.6 $n = 63$	OAB	IIQ UDI	Test–retest reliability Internal consistency Face validity Construct validity Convergent validity Divergent validity	IIQ and UDI demonstrates good reliability and validity in a diverse population.
Cam et al., 2007 [31], Turkey	47.9 ± 11.0 $n = 302$	OAB	SF-IIQ-7. UDI 6	Internal consistency Test–retest reliability	The Turkish versions of IIQ-7 and UDI-6 could be reliable and valid measures for evaluating the impact and symptom severity on QOL among Turkish women with urinary incontinence.
Castejón et al., 2015 [35], Spain	60.4 (18–90) $n = 970$	OAB	IUI	Test–retest reliability Criterion validity Convergent validity Responsiveness	IUI possesses good measurement properties for valuing the impact and evaluating the urological symptoms of people with idiopathic OAB.
Chattrakulchai et al., 2020 [24], Thailand	Exp: 65.08 ± 11.68 Con: 55.25 ± 12.76 $n = 283$	OAB	Thai version ICIQ-FLUTS	Test–retest reliability Internal consistency Content validity Construct validity Known-group validity	The Thai version of ICIQ-FLUTS has excellent internal consistency, test–retest reliability, content and construct validity in evaluating lower urinary tract symptoms among Thai women.

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Table 1 (*continued*)

First author, year [reference], country of study	Participant characteristics (mean age of participants ± SD); sample size of each group	Population	Outcome measure(s)	Psychometric property tested	Author's conclusion
Chiu et al., 2013 [59], Taiwan	65.0 ± 11.8 65.0 ± 11.8 *n* = 346	OAB	Traditional Chinese version KHQ	Internal consistency Discriminant validity	The traditional Chinese version of KHQ indicates adequate validity and reliability in evaluating symptoms of OAB among Taiwanese.
Choi et al., 2015 [25], Hong Kong	64.4 ± 11.2 *n* = 133	OAB	ICIQ-UI SF	Test–retest reliability	The test–retest reliability of ICIQ-UI SF was better in females than males.
Coyne et al., 2002 [6], UK	58.5 ± 16.6 *n* = 990	OAB	OAB-q	Internal consistency Concurrent validity Discriminant validity	OAB-q is a valid and reliable measure that discriminates between health and clinically diagnosed incontinence and continent people with OAB.
Coyne et al., 2005 [42], USA	61.0 ± 14.7 *n* = 865	OAB	OAB-q	Responsiveness	The tool appears useful with high responsiveness in urinary urgency, frequency and urge incontinence symptoms.
Coyne et al. 2006 [41], USA	58.7 ± 13.2 58.8 ± 13.8 n1 = 548 n2 = 520	OAB	OAB-q	Minimally important difference	The tool may provide a sound minimally important difference and reasonable interpretation of OAB symptoms.
Coyne et al., 2007 [37], USA	Study 1: Continent: 58.8 ± 16.2 Incontinent: 62.5 ± 14.1 ITC: 60.9 ± 13.7 *n* = 865 Study 2: Continent: 53.8 ± 15.1 Incontinent: 61.0 ± 13.1 ITC: 58.0 ± 12.3 *n* = 520	OAB	OAB-q	Responsiveness	OAB-q is a valid and highly responsive measure of continent and incontinent people with OAB.
Coyne et al., 2011 [40], USA	59.6 ± 13.6 59.4 ± 13.5 59.9 ± 13.3 *n* = 516 *n* = 441 *n* = 882	OAB	OAB-q	Internal consistency Discriminant validity Responsiveness	The tool has good reliability, validity and responsiveness. It has psychometric equivalence to the 4-week recall version, and the validation offers an additional option for using OAB-q for researchers and clinicians.
Coyne et al., 2015 [58], USA	Study 1: 61.0 ± 14.7 *n* = 865 Study 2:C 52.1 ± 16.3 *n* = 523 C-OAB: 54.3 ± 16.7 *n* = 228 I-OAB: 60.0 ± 15.1 *n* = 168 Study 3: 66.0 ± 12.9 *n* = 47	OAB	OAB-q	Internal reliability Convergent validity Discriminant validity Responsiveness	OAB-q SF indicates good reliability, validity and responsiveness, is less time-consuming for completion, and evaluates the full spectrum of OAB Symptom Bother and QOL impact.
Coyne et al., 2015 [39], USA	Study 1: 48.9 ± 13.0 *n* = 974 Study 2: 58.0 ± 14.0 *n* = 163 Study 3: 66.0 ± 12.9 *n* = 47	OAB	UQ	Internal consistency Convergent validity Discriminant validity Responsiveness	The results provide quantitative evidence that urinary urgency, as assessed by UQ, is a pathological sensation distinctive from the usual urge to void, and suggest that UQ might be a reliable, valid and responsive instrument for evaluating the severity and health-related QOL impact of urinary urgency in OAB.
Gotoh et al., 2009 [26], Japan	Study 1: 62(53–70) *n* = 122 Study 2: 71(62–76) *n* = 58	OAB	Japanese version ICIQ-SF	Test–retest reliability Concurrent validity Discriminant validity Responsiveness	The Japanese version of ICIQ-SF indicates good reliability, validity and responsiveness in evaluating people with OAB urinary QOL symptoms.
Groenendijk et al., 2019 [38], Netherlands	Exp: 64.0 ± 13.0 Con: 41.0 ± 15.0 *n* = 103	OAB	OAB-q SF	Internal consistency Test–retest reliability Content validity Criterion validity Convergent validity	The Dutch version of OAB-q SF possesses good reliability and validity in evaluating symptom bother and incontinence-related QOL among people with OAB.
Hashim et al., 2016 [27], UK	Exp 1: 45.7(19–77) Exp 2: 37.8(18–73) Exp 3: 37.7(17–73) Exp 4: 37.2(16–73) *n* = 306	OAB	ICIQUI-SF	Test–retest reliability Internal consistency Content validity Discriminant validity Responsiveness	The Arabic version of ICIQ-SF demonstrates good reliability, validity and responsiveness, and the psychometric property remains uniform through the validation process and conforms to the UK-English ICIQ-SF.
Homma and Uemura, 2003 [60], Japan	Male: 65.6 ± 11.7 Female: 61.7 ± 11.2 *n* = 293	OAB	SF-KHQ	Internal consistency Structural validity Responsiveness	The psychometric properties and clinical value of SF-KHQ appear to be sound in the evaluation of the incontinence-related QOL instrument.

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Table 1 (*continued*)

First author, year [reference], country of study	Participant characteristics (mean age of participants ± SD); sample size of each group	Population	Outcome measure(s)	Psychometric property tested	Author's conclusion
Kang, 2015 [53], South Korea	51.1 ± 10.7 *n* = 176	OAB	Korean version I-QOL	Internal consistency Construct validity Convergent validity Discriminant validity	The Korean version of I-QOL is a valuable measure in assessing different domains of incontinence-related QOL among people with urinary incontinence.
Kelleher et al., 1997 [62], UK	51.4 (17–85) *n* = 285	OAB	KHQ	Internal consistency Test–retest reliability Face validity Content validity Criterion validity	KHQ is a valid and reliable measure for evaluating QOL and rapid appraisal among women with urinary incontinence across different clinical settings.
Lubeck et al., 1999 [66], USA	59.6 ± 13.9 *n* = 257	OAB	U-IIQ U-UDI	Internal consistency Test–retest reliability Discriminant validity	U-IIQ and U-UDI are valid, reliable and responsive measures that evaluate relevant and distinct domains of incontinence-related QOL.
Matza et al., 2005 [43], USA	66.0 66.8 63.8 *n* = 47 *n* = 35 *n* = 12	OAB	OAB-q	Test–retest reliability	OAB-q demonstrates reasonable test–retest reliability as outcome measures for OAB treatments.
Margolis et al., 2011 [63], USA	59.0 ± 11.1 *n* = 24	OAB	KHQ	Content validity	KHQ indicates excellent content validity with relevance and appropriateness in evaluating the impact of incontinence-related QOL among people with OAB.
Monteiro et al., 2020 [28], Brazil	42.46 ± 17.47 *n* = 118	OAB	Brazilian Portuguese version ICIQ-OABqol	Internal consistency Test–retest reliability Construct validity	The Brazilian Portuguese version of ICIQ-OABqol demonstrates satisfactory measurement properties in evaluating the QOL of people with OAB.
Nusee et al., 2016 [29], Malaysia	55.0 ± 13.5 *n* = 91	OAB	UDI-6 IIQ-7	Internal consistency Test–retest reliability Criterion validity	UDI-6 and IIQ-7 demonstrate appropriate test–retest reliability and internal consistency with good application in clinical settings.
Oh et al., 2012 [44], Korea	*n* = 58	OAB	Korean version OAB-q	Test–retest reliability Internal consistency Face and content validity Discriminant validity Convergent validity Responsiveness	The tool has excellent validity and is a reliable measure of outcomes in Korean individuals with OAB.
Okamura et al., 2009 [61], Japan	Men Sample A: 70.0 ± 9.0 Sample B: 67.0 ± 9.0 Women Sample A: 70.0 ± 8.0 Sample B: 68.0 ± 9.0 *n* = 1002	OAB	KHQ	Internal consistency Test–retest reliability Convergent validity Discriminant validity Construct validity	KHQ is a reliable and valid measure for evaluating incontinence-related QOL of people with lower urinary tract symptoms.
Otmani et al., 2020 [54], Morocco	57.6 ± 12.7 *n* = 100	OAB	Moroccan version I-QOL	Test–retest reliability Inter-rater reliability Discriminant validity Structural validity	The Moroccan version of I-QOL has acceptable validity and reliability in assessing the symptoms of urinary incontinence on incontinence-related QOL among Moroccans.
Patrick et al., 1999 [55], USA	Age range: (18–76) *n* = 259	OAB	French, Spanish, Swedish and German versions of I-QOL	Internal consistency Test–retest reliability Discriminant validity	I-QOL demonstrates good cross-sectional psychometric validity across the four European countries in evaluating the impact of urinary incontinence on incontinence-related QOL.
Patrick et al., 2013 [57], USA	Age range: (18–76) *n* = 313	OAB	I-QOL	Internal consistency Test–retest reliability Convergent validity Discriminant validity Responsiveness	I-QOL has good reliability and validity in evaluating symptoms of OAB on incontinence-related QOL.
Peterson et al., 2018 [36], Canada	59.0 ± 16.6 *n* = 1128	OAB	OAB-v8	Internal consistency Validity	OAB-v8 has strong validity and reliability, and could be appropriate across a wide range of OAB

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Table 1 (*continued*)

First author, year [reference], country of study	Participant characteristics (mean age of participants ± SD); sample size of each group	Population	Outcome measure(s)	Psychometric property tested	Author's conclusion
Possavino et al., 2013 [56], Italy	Continent: 62.2 (9.6) Incontinent: 60.2 (11.3) UI: 63.4 (9.2) Clinically incontinent: 55.9 (10.8) *n* = 298	OAB	Italian version I-QOL	Convergent validity Test–retest reliability Internal consistency	The Italian version of I-QOL demonstrates strong reliability and validity for evaluating symptoms of OAB on incontinence-related QOL among Italian women.
Pourmomeny et al., 2017 [22], Iran	48.8 ± 5.0 *n* = 114	OAB	Persian version BFLUTS	Internal consistency Test–retest reliability Content/ face validity Construct validity	The Persian version of BFLUTS indicates good internal consistency test–retest reliability and content validity.
Reese et al., 2003 [64], UK	60.9 ± 14.2 *n* = 1284	OAB	KHQ	Reliability Validity Responsiveness	KHQ demonstrates good reliability and validity in assessing symptoms of OAB on incontinence-related QOL.
Robinson and Shea, 2002 [32], USA	Phase I: 70 (50.1 + 18.3) Phase II: 65 (30–90) *n* = 139	OAB	UDI IIQ	Internal consistency Content validity Concurrent validity Construct validity	UDI and IIQ provided good validity and reliability for the evaluation of symptoms of urinary incontinence on incontinence-related QOL.
Sahai et al., 2014 [23], UK	62 (19–101) *n* = 50	OAB	Bladder Control Self-Assessment Questionnaire	Test–retest reliability Discriminant validity	The Bladder Control Self-Assessment Questionnaire is a valid measure in evaluating people with OAB.
Schurch et al., 2007 [15], Switzerland	41.2 (20–72) *n* = 59	OAB	I-QOL	Internal consistency Convergent validity Concurrent validity Responsiveness	I-QOL demonstrates strong validity, reliability and responsiveness of incontinence-related QOL among people with OAB.
Twiss et al., 2009 [34], USA	1st cohort: 59.1 ± 0.9 2nd cohort: 59.8 ± 0.7 3rd cohort: 63.3 ± 1.4 *n* = 345	OAB	ISS	Test–retest reliability Internal consistency Concurrent validity	ISS possesses strong reliability and validity for evaluating female urinary incontinence across clinical and research settings.
Uemura and Homma, 2004 [65], Japan	Male: 65.6 ± 11.70 Female: 61.7 ± 11.20 *n* = 293	OAB	Japanese version KHQ	Internal consistency Convergent validity Discriminant validity Construct validity	The Japanese version of KHQ indicates acceptable reliability and validity for evaluating symptoms of OAB on incontinence-related QOL.

B-SAQ, Bladder Control Self-Assessment Questionnaire; Con, control group; Exp, experimental group; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; ICIQ-OABqol, International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; ICIQ-UI-SF, International Consultation on Incontinence short-form questionnaire; IIQ-7, Incontinence Impact Questionnaire; I-QOL, Incontinence-quality of life; ISS, Incontinence Symptom Severity Index; IUI, Incontinence Utility Index; KHQ, Kings' Health Questionnaire; MUDI, Male Urinary Distress Inventory; MUSIQ, Male Urinary Symptom Impact Questionnaire; OAB, overactive bladder; OAB-q, Overactive Bladder Questionnaire; OAB-q SF, Overactive Bladder Quality of Life Short-form Questionnaire; OAB-v8, Overactive Bladder Questionnaire-v8; PFLUTS, Persian Female Lower Urinary Tract Symptoms instrument; QOL, quality of Life; SF-KHQ, Short Version of the King's Health Questionnaire; SF-Qualiveen, short form Qualiveen; UDI-6, Urogenital Distress Inventory; U-IIQ, Urge-Incontinence Impact Questionnaire; U-UDI, Urge-Urinary Distress Inventory; UQ, Urgency Questionnaire; PFDI, Pelvic Floor Distress Inventory; SD, standard deviation; MS, multiple sclerosis; UI, urinary incontinence.

Index (IUI) [35], Overactive Bladder-Validated 8-question Screener (OAB-V8) [36] and Urgency Questionnaire (UQ) [58] were each tested in one study.

Among the 47 included studies examining QOL among patients with neurogenic OAB, 22 studies [6,23,27,30,32,34,36,37,39,43,45,46,57,58,62,64,66–68] developed or tested the psychometric properties of the original outcome measures, whereas 25 studies [15,22,24–26,28,29,31,33,35,38,44,47–54,56,59–61,65,69] conducted cross-cultural validations of the original outcome measures. Among the studies performing cross-cultural validations, the outcome measures were assessed in versions adapted to the following languages: Japanese (*n* = 4 [26,60,61,65]), Brazilian Portuguese (*n* = 3 [28,33,47]), Polish (*n* = 2 [51,52]), Persian (*n* = 2 [22,49]), Arabic (*n* = 2 [27,54]), Spanish (*n* = 2 [35,55]), Turkish (*n* = 1 [31]), Thai (*n* = 1 [24]), Malay (*n* = 1 [29]), Korean (*n* = 1 [53]), Romansh (*n* = 1 [15]), Italian (*n* = 1 [56]), Belgian (*n* = 1 [15]), French (*n* = 1 [55]), German (*n* = 1 [55]), Chinese (*n* = 1 [59]), Chinese-Taiwanese (*n* = 1 [25]), Chinese-Cantonese (*n* = 1 [25]), Greek (*n* = 1 [48]) and Russian (*n* = 1 [50]).

Descriptions of the psychometric properties of the outcome measures assessed in the included studies

A complete list of the psychometric properties investigated for the identified outcome measures in the included studies is provided in Table 3. Reliability and validity were the most investigated psychometric properties, whereas responsiveness was the least frequently evaluated property. Most studies (70 %) reported acceptable internal consistency, with Cronbach's alpha scores > 0.70, and 64 % reported test reliability using intraclass correlation coefficients (ICC 0.50–0.75). Cronbach's alpha ranged from 0.79 to 0.99 (average 0.92 across six studies) for the I-QOL; from 0.63 to 0.95 (average 0.81 across seven studies) for the KHQ; from 0.70 to 0.96 (average 0.86 across three studies) for the OAB-q; and from 0.70 to 0.95 (average 0.84 across seven studies) for the Qualiveen. Cronbach's alpha scores < 0.5 represent unacceptable scores, scores from 0.5 to 0.6 indicate poor scores, scores from 0.6 to 0.7 indicate questionable scores, scores from 0.7 to 0.8 represent acceptable scores, scores from 0.8 to 0.9 indicate good scores, and scores > 0.9 represent excellent scores [70]. The ICC scores for test–retest reliability ranged from 0.81 to 0.99 (average 0.92 across four

Table 2
Descriptions of outcome measures.

Outcome measure, number of studies [reference]	Language of instruction Number of items Description of item Scoring scheme	Duration to complete Cost of outcome measure: free/licensed/ need to purchase	Strengths and limitations of outcome measure Population tested
PFLUTS ($n = 1$) [22]	Language of instruction: Persian Number of items: 12Description of item: A self-administered tool in clinical and research settings with two sections. The first section concerns symptoms and is evaluated using a five-point Likert scale (0 = never; 4 = always) with three domains: filling symptoms (four items, 0–15); voiding symptoms (three items, 0–12) and incontinence symptoms (five items, 0–20). The second section evaluates the extent of hurt and bother. Scoring scheme: Higher scores denote worse symptoms.	Duration to complete: Average 5.33 min Cost of outcome measure: Available free online	Strengths: Brief and helpful questionnaire, easy-to-use items, and facilitates communication between medical practitioners and people with urinary incontinence due to multiple sclerosis. Limitations: Educational level disparity could affect generalization to their counterparts. Population tested: Females with OAB.
B-SAQ ($n = 1$) [23]	Language of instruction: English Number of items: 8 Description of item: Four point-Likert scales developed by a European expert panel through a standardized multistep method such as expert panel discussion, questionnaire piloting, focused group interviews, and direct patient involvement. The questions are simple to understand, select and modify through piloting. If the symptom score is ≥ 4 and the bother score is > 1, the patient is recommended to seek medical attention.Scoring scheme: The severity of symptoms and bother are graded as none (zero), mild (1–3), moderate (4–6), severe (7–9) and very severe (10–12) . Higher scores denote worse symptoms.	Duration to complete: <5 min Cost of outcome measure: Available free online	Strengths: The closed format of the measure enabled subjective and qualitative evaluation of lower urinary tract symptoms. Limitations: Some of the items could be irrelevant and confusing. Population tested: Males and females with lower urinary tract symptoms.
ICIQ-FLUTS ($n = 1$) [24]	Language of instruction: Thai Number of items: 12Description of item: Five-point Likert scale (0–4) . ICIQ-FLUTS measures lower urinary tract symptoms and associated bother symptoms. Self-completed by people with OAB. Scoring scheme: 0–16 filling, 0–12 voiding, and 0–20 incontinence symptom subscales. The lower the score, the better the symptoms.	Duration to complete: 3–5 min Cost of outcome measure: Available free online	Strengths: Rigorous validation process (cultural and translation). Limitations: Questions were not designed to detect changes in OAB status. Population tested: Females with OAB.
ICIQ-UI-SF ($n = 3$) [25–27]	Language of instruction: Japanese, Arabic Number of items: 4 Description of item: A disease-specific measure that evaluates QOL and symptoms of urinary incontinence. It consists of four questions: frequency (0–5), amount of leakage (0–6), QOL (0–10) and perceived cause of leakage. Likert scale is used to grade the first three questions, with maximum scores possible of 5, 6 and 10, respectively. In the final question, people with urinary incontinence are evaluated on the circumstances under which urinary leakage occurs. Scoring scheme: The total score was derived from sum of the scores of the first three questions (range 0–21). Higher scores denote worse symptoms	Duration to complete: <5 min Cost of outcome measure: Available free online for clinical use. Permission is required for research purposes.	Strengths: Sound psychometric properties (reliability, validity and responsiveness) throughout the adaptation process. Limitations: Cultural diversity is not sufficient. Population tested: Men and women with urinary incontinence.
ICIQ-OABqol ($n = 1$) [28]	Language of instruction: Brazilian Number of items: 28 Description of item: The measure is a self-administered measure with grade A recommendation due to its psychometric robustness in investigating the QOL of people with OAB. It has four domains consisting of 28 questions: sleep, concern, social interaction, and symptom coping. Scoring scheme: Six alternative answers are available for the first 27 questions (1, none of the time; 2; a little of the time; 3, some of the time; 4, a good bit of the time; 5, most of the time; 6, all of the time), while question 28 evaluates the effect of urinary symptoms on the individual's daily activities, grading it on a scale of 0 (no effect) to 10 (severe effect) .	Duration to complete: 10–15 min Cost of outcome measure: Available free online for clinical use. Permission is required for research purposes.	Strengths: Brief and psychometrically robust self-administered measure for assessing incontinence-related QOL of people of both sexes with symptoms of OAB in clinical and research settings. Limitations: Lack of homogeneity of the studied population. Population tested: Males and females with OAB

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Table 2 (*continued*)

Outcome measure, number of studies [reference]	Language of instruction Number of items Description of item Scoring scheme	Duration to complete Cost of outcome measure: free/licensed/ need to purchase	Strengths and limitations of outcome measure Population tested
IIQ-7 ($n = 5$) [29–33,66]	Language of instruction: English, Brazilian, Turkish, Malay Number of items: 7 Description of item: Consists of seven items which are subdivided into four domains: relationships, emotional health, travel, and physical activity. The Likert scale for each measure item ranges from slight to moderate, moderate to great. Scoring scheme: Higher scores indicate reduced incontinence-related QOL and severity of symptoms.	Duration to complete: 5 min Cost of outcome measure: Administrative fees are required to use the measure.	Strengths: Predictive of urodynamic diagnosis Limitations: Low response rate. Population tested: Men and women with urinary incontinence.
ISS ($n = 1$) [34]	Language of instruction: Spanish Number of items: 8Description of item: A self-administered measure on a four-point Likert scale (0–3) for evaluating eight domains: incomplete emptying, sensation of urgency, nocturia, daytime urinary frequency, stress incontinence, urge incontinence, leakage with activity, and pad use. Scoring scheme: Each item score is evaluated as an independent domain without score summation.	Duration to complete: 5 min Cost of outcome measure: Available free online	Strengths: A useful measure for evaluating female voiding symptom severity and incontinence in clinical and research settings. Limitations: Lack of focus group discussion or consensus expert opinion in the tool development. Population tested: Females with urinary incontinence.
IUI ($n = 1$) [35]	Language of instruction: Spanish Number of items: 5 Description of item: Five items with three different levels from each of the items of the attribute. Scoring scheme: Higher scores indicate reduced incontinence-related QOL and severity of symptoms.	Duration to complete: <5 min Cost of outcome measure: Available free online	Strengths: Derived from I-QOL and neurogenic modules. Limitations: Anchoring of the measure was anticipated. Population tested: Men and women with OAB.
I-QOL ($n = 6$) [15,53–57]	Language of instruction: Korean, Moroccan, Romansh, English, Italian, Belgium, French, Spanish, Swedish, German Number of items: 22Description of item: The measure evaluates the QOL of people with urinary incontinence and consists of 22 items on a five-point Likert scale from 1 (extreme) to 5 (not at all) , divided into three domains: avoidance and limiting behaviour; psychosocial impact; and social embarrassment.Scoring scheme: The total score is obtained by summing the individual scores of all items (0–100) . Higher scores indicate better urinary incontinence-related QOL.	Duration to complete: 5 min Cost of outcome measure: Copyrighted, can be purchased at the cost of $500 for commercial purposes. Freely available for clinical and academic purposes.	Strengths: Evaluates the broader impact of urinary incontinence on incontinence-related QOL. Limitations: Content validity not well assessed. Population tested: Males and females with urinary incontinence.
KHQ ($n = 8$) [59–65]	Language of instruction: English, Chinese, Japanese Number of items: 21 Description of item: A disease-specific self-administered measure of the incontinence-related QOL of people with urinary incontinence. Twenty-one items are subdivided into eight domains: urinary symptom severity; role limitations; physical functioning; social functioning; emotional problems; personal relationships; sleep disturbance; and general health.Scoring scheme: Scored on a four-point Likert scale ranging from 0 (best) to 100 (worst) .	Duration to complete: 5 min Cost of outcome measure: Available free online	Strengths: Responsive to clinically meaningful changes. Limitations: Limited generalizability due to racial homogeneity. Population tested: Men and women with OAB.
OAB-v8 ($n = 1$) [36]	Language of instruction: English Number of items: 8Description of item: Six-point Likert scale (0–5) . The tool is a self-administered questionnaire that evaluates the degree of OAB burden, bother symptoms and severity.Scoring scheme: Ranges from 0 (absence of symptoms) to 40 (maximal symptoms) : 0–8, low; 8–16, medium; 16–24, high. Higher scores indicate worse symptoms.	Duration to complete: 4–5 min Cost of outcome measure: No charge for academic and clinical use	Strengths: Brief and useful tool to evaluate OAB burden and severity. Limitations: Test–retest reliability could not be investigated because the participants received intervention in the study. Population tested: Women with OAB.
OAB-q ($n = 9$) [6,37–44]	Language of instruction: English Number of items: 33Description of item: Six-point Likert scale (0–5) . The tool is composed of an eight-item symptom bother scale and 25 items of QOL that comprise coping, concern, sleep and social interaction scales. Scoring scheme: Total score ranges from 0 to 100, with higher scores signifying worst symptoms.	Duration to complete: 5–7 min Cost of outcome measure: No charge for academic and clinical use	Strengths: Simple application captures both continent and incontinent people with OAB. Limitations: Eight-item symptom bother scale and 25 items of QOL Population tested: Males and females with OAB

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Table 2 (*continued*)

Outcome measure, number of studies [reference]	Language of instruction Number of items Description of item Scoring scheme	Duration to complete Cost of outcome measure: free/licensed/ need to purchase	Strengths and limitations of outcome measure Population tested
Qualiveen ($n = 8$) [45–52]	Language of instruction: English, Brazilian Portuguese, Greek, Persian, Russian, Polish, Slavic Number of items: 30 Description of item: The original Qualiveen has 30 items focusing on four aspects of daily life: nine items, bother with limitations; eight items, frequency of limitations; eight items, fears; and five items, feelings. Scoring scheme: Scored on a five-point Likert-type scale with 0 indicating absence of urinary symptom impact on QOL, and 4 indicating high urinary symptom impact on QOL.	Duration to complete: 5 min Cost of outcome measure: No charge for academic and clinical use	Strengths: Patients evaluated in this measure represent a highly selected cohort. Limitations: Floor and ceiling effect not observed. Population tested: Men and women with OAB.
UDI-6 ($n = 5$) [29–33,66]	Language of instruction: Brazilian, Turkish, English Number of items: 6 Description of item: A six-item measure subdivided into three subscales: stress, discomfort, and obstructive and irritable symptoms. Scoring scheme: Scored from 0 to 4, with higher scores indicating worst symptoms.	Duration to complete: <5 min Cost of outcome measure: Available free online	Strengths: Responsive to clinically meaningful changes. Limitations: Low response rate. Population tested: Men and women with urinary incontinence.
UQ ($n = 1$) [58]	Language of instruction: English Number of items: 15-point Likert scale items Description of item: The measure consists of a 15-point Likert scale of items measured into five responses from 'never' to 'all the time', which is subdivided into four domains: impact on daily activities; nocturia; time to control urgency; and fear of incontinence. Scoring scheme: Higher scores indicate worst symptoms.	Duration to complete: 5 min Cost of outcome measure: Available free online	Strengths: Provides a quantitative clear perceptual discrepancy among urge and urgency. Limitations: Lacks cultural diversity. Population tested: Men and women with OAB.

B-SAQ, Bladder Control Self-Assessment Questionnaire; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; ICIQ-OABqol, International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; ICIQ-UI-SF, International Consultation on Incontinence short-form questionnaire; IIQ-7, Incontinence Impact Questionnaire; I-QOL, Incontinence-quality of life; ISS, Incontinence Symptom Severity Index; IUI, Incontinence Utility Index; KHQ, Kings' Health Questionnaire; MUDI, Male Urinary Distress Inventory; MUSIQ, Male Urinary Symptom Impact Questionnaire; OAB, overactive bladder; OAB-q, Overactive Bladder Questionnaire; OAB-q SF, Overactive Bladder Quality of Life Short-Form Questionnaire; OAB-v8, Overactive Bladder Questionnaire-V8; OM, outcome measure; PFLUTS, Persian Female Lower Urinary Tract Symptoms instrument; QOL, quality of life; SF-KHQ, Short Version of the King's Health Questionnaire; SF-Qualiveen, Short form Qualiveen; UDI-6, Urogenital Distress Inventory; U-IIQ, Urge-Incontinence Impact Questionnaire; U-UDI, Urge-Urinary Distress Inventory; UQ, Urgency Questionnaire; CI, confidence interval; AUC, area under the curve; VAS, visual analogue scale.

studies) for the I-QOL; from 0.80 to 0.96 (average 0.88 across one study) for the KHQ; from 0.55 to 92 (average 0.78 across four studies) for the OAB-q; and from 0.62 to 0.97 (average 0.85 across six studies) for the Qualiveen. ICC scores < 0.5 represent poor reliability, scores from 0.5 to 0.75 indicate moderate reliability, scores from 0.75 to 0.9 indicate good reliability, and scores > 0.9 represent excellent reliability [71].

COSMIN methodological quality of the included studies

Six studies [15,53–57] reported the psychometric properties of the I-QOL. Among people with OAB, the I-QOL has been evaluated for internal consistency [15,53–57], test–retest reliability [55–57], convergent validity [15,53,56,57], discriminant validity [53–55,57], structural validity [53,54] and responsiveness [15,57]. The I-QOL was reported to have very good internal consistency in six studies [15,53–57] and very good test–retest reliability in three studies [15,53–57]. The I-QOL was also reported to have very good convergent [15,53,56,57] and discriminant validity [55,57], with two studies [53,54] reporting only adequate discriminant validity. Seven studies [59–65] evaluated the psychometric properties of the KHQ, including internal consistency [59–62,64,65], test–retest reliability [62], convergent validity [61,64,65], discriminant validity [59,61,64,65], structural validity [60] and responsiveness [60,64]. The KHQ was reported to have very good internal consistency in five studies [59–62,64,65], with only one study [62] reporting adequate test–retest reliability. The psychometric properties of the OAB-q were evaluated in nine studies [6,37–44], including internal consistency [6,38–40,44], test–retest reliability [37–44], content validity [38,44], convergent validity [38,39,44], discriminant validity [6,39,40,44], concurrent validity [6,40] and responsiveness [37,39–42,44]. The OAB-q was reported to have very good internal consistency in five studies [6,38–40,44] and adequate test–retest reliability in eight studies [37–44]. The psychometric properties of the Qualiveen questionnaire were evaluated in eight studies [45–52], including internal consistency [46–52], test–retest reliability [47–52], structural validity [45,48], content validity [51,52], criterion validity [46–48,50–52], convergent validity [46,49], discriminant validity [49] and responsiveness [46]. The Qualiveen was reported to have very good internal consistency in five studies [47,49–52] and very good test–retest reliability in two studies [47,52]. Table 4 details the COSMIN findings for each outcome measure assessed by the included studies.

GRADE findings for the psychometric properties of the assessed outcome measures in the included studies

The modified GRADE assessment was used to evaluate the quality of evidence for each of the 15 outcome measures based on pooled findings for the validated psychometric properties. According to the modified GRADE assessment, the quality of evidence for the pooled outcome measures of the included studies was high for 67 % of assessments and moderate for 33 %. The outcome measures with high-quality evidence

Table 3
Psychometric properties of the outcome measures.

Outcome measure, number of studies [reference]	Reliability	Validity	Responsiveness
PFLUTS ($n = 1$) [22]	Internal consistency: Cronbach's alpha scores for the first and second sections: good (0.83 and 0.89). Cronbach's scores for the incontinence, voiding and filling subscales: debatable, acceptable and good (0.87, 0.67 and 0.70, respectively) [22].Test–retest reliability: ICC: good (0.77) [22].	Face/content validity: All items were clear [22]. Criterion validity: Correlation coefficient for OAB and Persian FLUTS measure was 0.77 ($r = 0.77$, $p < 0.001$) [22].	None
B-SAQ ($n = 1$) [23]	None	Criterion validity: 0.86–0.89 for frequency, urgency, nocturia and urge incontinence [23] agreement between KHQ and B-SAQ. Discriminant validity: AUC 0.85 vs 0.68 for B-SAQ and OAB-v8 [23].	None
ICIQ-FLUTS ($n = 1$) [24]	Internal consistency: Cronbach's alpha coefficient: good (0.849) (95 % CI 0.819–0.864). Cronbach's alpha scores for the filling, voiding and incontinence subscales: debatable to acceptable (0.646, 0.709 and 0.792, respectively) [24].Test–retest reliability: >0.75. Test–retest correlation coefficients for the filling, voiding and incontinence subscales: good and excellent (0.925, 0.769 and 0.921, respectively) [24].	Face/content validity: All items were clear [24]. Known-group validity: A significant difference in the comparison scores was observed between clinical and community women in the filling, voiding and incontinence subscales ($p < 0.001$) [24].	None
ICIQ-UI-SF ($n = 3$) [25–27]	Test–retest reliability: moderate correlation using Kappa statistics (0.66 and 0.67 for items on coughing/sneezing and physically active/exercising, respectively) [25]. Kappa scores: high correlation (0.61 and 0.62, ICC values 0.90 and 0.91) [26] and Kappa values: 0.83–0.91 ($p < 0.0001$) [27].Internal consistency: Cronbach's alpha scores: acceptable (0.71 [27] and 0.78 [26]).	Content validity: Measure covers all important domains and is well interpreted [27].Concurrent validity: Moderate to high correlation with KHQ subscales (0.74, severity measures; 0.68, physical limitation; 0.59, social limitations; 0.55, emotions; $p < 0.05$) [26].Discriminant validity: A significant difference was observed between males and females among different types of incontinence ($\chi^2 = 35.4$; $p < 0.0001$) [27].	Responsiveness: ICIQ-UI-SF changes were significant (>0.5) with KHQ subscales [26]. Proportion of patient symptoms were reported to decrease correlation significantly on all three items ($p < 0.0001$ for all the items) [27].
ICIQ-OABqol ($n = 1$) [28]	Internal consistency: Cronbach's alpha coefficient: good (0.88 [28]).Test–retest reliability: ICC: excellent [0.906–0.933 ($p < 0.05$) [28]].	Construct validity: Confirmatory factor analysis and Kaiser–Mayer–Olkin test: adequate data adjustment of the domains [28]. Criterion validity: ICIQ-OABqol measure correlated with ICIQ-OAB with $r = 0.53$ and 0.59 [28].	None
IIQ-7 ($n = 5$) [29–33,66]	Internal consistency: Cronbach's alpha score: acceptable, good and excellent (0.90 [29], 0.95 [32], 0.87 [31] and 0.70 [33]).Test–retest reliability: ICC: excellent (0.95 [29], 0.85 [30]). Spearman's rho: 0.99 [31]. Pearson's correlation coefficient: 0.9431 [33].	Content validity: Percentage agreement scores of the three rounds of testing ranged from 67 % to 100 % for item fit and 100 % for item clarity [32]. Criterion validity: A positive correlation was observed between nocturia and emotional and physical activity subscales [29].Concurrent validity: The disattenuated correlation was 0.64 while the Pearson's correlation coefficient between MUDI and MUSIQ was 0.95 ($p < 0.001$) [32]. Construct validity: The mean measure scores varied for urine leakage, desire for socialization, and depression [32].Convergent validity: Moderate correlation (0.50–0.80) was observed within the domains: travel, feelings, physical activities and relationships [30].Divergent validity: Weak correlation (≤0.10) was seen in the sexual function domain [30]. No significant correlation with the sexual dysfunction domains of disability status expanded scale score [33].	Responsiveness: Significant changes were observed ($p < 0.0001$) for IIQ-7 for the control and multiple sclerosis groups with and without urinary incontinence [33].
ISS ($n = 1$) [34]	Test–retest reliability: Significant correlation was observed using Spearman's correlation coefficients for all eight items ($p < 0.0001$) [34].Internal consistency: Cronbach's alpha coefficient scores: debatable (0.69 [34]).	Concurrent validity: Significant correlations were observed between similar items of ISS, and both PFDI and UDI ($p < 0.0001$) [34].	None
IUI ($n = 1$) [35]	Test–retest reliability: ICC: excellent (0.900) (95 % CI 0.886–0.912) and excellent (0.944) (95 % CI 0.936–0.950) for baseline and week 12 of the abbreviated and original versions of I-QOL ($p < 0.001$) [35].	Convergent validity: Rasch analysis reveals significantly relevant differential items between the domains functioning of urinary symptom aetiology (neurogenic vs idiopathic) [35]. Criterion validity: After 12 weeks of interventions, a significant difference was	Responsiveness: Large differences were observed in the utility values between IUI, KHQ and SF-12 ($p < 0.001$) using the Bland–Altman methods [35].

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Table 3 (*continued*)

Outcome measure, number of studies [reference]	Reliability	Validity	Responsiveness
		observed for IUI scores across perceived levels, I-QOL scores and abbreviated health state descriptive system ($p < 0.001$) [35].	
I-QOL ($n = 6$) [15,53–57]	Internal consistency: Cronbach's alpha coefficient scores: acceptable, good and excellent (0.96 [53], 0.99 [54], 0.92–0.95 [55], 0.86 [57], 0.88–0.96 [56] and 0.79–0.93 [15]).Test–retest reliability: ICC: good and excellent (0.99 [54], 0.87–0.93 [55], 0.81 [57] and 0.99 [56]).	Convergent validity: The items were strongly correlated with the original subscale; avoidance and limiting behaviour (r = 0.71–0.80), social embarrassment (r = 0.76–0.86) and psychosocial impacts (r = 0.67–0.88) [53]. Strong correlation was observed between I-QOL total score and KHQ symptom score [57]. Moderate to strong correlations were observed between I-QOL subscale items and most SF-36 domains [15,56]. Discriminant validity: Low correlation of items to other subscales other than that own subscales was observed [53,57]. The measure differentiates between different self-reported severity levels with significant differences in I-QOL scores by number of incontinence-related medical visits ($p < 0.0001$) [54–56]. Construct validity: All items of the measure accounted for 54.85 % (total variance) loaded into 0.51–0.88 [53]. The comparative fit index and standardized root mean square residual were satisfying, while the Tucker–Lewis index and root mean square error of approximation were not [54].	Responsiveness: Cumulative distribution function indicates differentiation between intervention groups [57]. Responsiveness was observed to be strong for individual domains and total scores [15].
KHQ ($n = 8$) [59–65]	Internal consistency: Cronbach's alpha coefficient scores: acceptable, good and excellent (0.948 [59], 0.83–0.86 [60], 0.725–0.892 [62], 0.721–0.898 and 0.780–0.915 in men and women respectively [61], 0.70–091 [64] and 0.63 [65]).Test–retest reliability: ICC: good and excellent (0.80–0.96 [62]).	Content validity: Acceptable and understandable [63].Discriminant validity: Significantly higher scores were observed on all KHQ subscores in comparison with the control group ($p < 0.0001$) [59].Structural validity: Using exploratory factor analysis (promax rotation) , two factors limitation of daily activities social and travel, tired and depressed [60]. Criterion validity: Highly significant correlations were observed between the common domains of KHQ and SF-36 [62,64].Convergent validity: High correlation coefficients (0.762–0.784 and 0.722–0.752 in men and women, respectively) [61] (0.65–0.75 in males and 0.61–69 in females) [65] were observed in physical limitations, social limitations and role limitation. Divergent validity: Low correlation coefficients of 0.333 (LUTS impact), 0.476 (role limitations) and 0.464 (sleep/energy) in men, and 0.493 (LUTS impact) and 0.533 (emotions) in women [61], and 0.32 (coping severity), 0.29 (symptom severity scale) in men, and 0.27 (symptom severity scale), 0.28 (role limitation) and 0.29 (coping severity scale) in women [65] were observed in personal relationships with other domains.	Responsiveness: Significant change in clinical efficacy variables and self-perception of bladder condition across all domains [60].
OAB-v8 ($n = 1$) [36]	Internal consistency: Cronbach's alpha coefficient scores: good and excellent (0.891–0.910 [36]) Test–retest reliability: ICC: excellent (0.93 through local item dependence [36]).	Discriminant validity: Indicate good item-level characteristics and not sensitive to missing data estimates [36].	None
OAB-q ($n = 9$) [6,37–44]	Internal consistency: Cronbach's alpha scores: acceptable, good and excellent (0.70–0.95 [38]). The Cronbach's α test is quite good with scores > 0.85 across all items for all subscales [41]: good and excellent (0.89–0.96 [6]), while an excellent Cronbach's alpha coefficient: good (>0.82) was also reported [44].Test–retest reliability: ICC: moderate (>0.7 [38]) and good (0.81–0.92 [3]). Spearman's correlation coefficient: good (0.83–0.93; $p < 0.001$) [39]. Each item and the subscale scores have good test–retest reliability with reproducible results [44]. OAB-q subscales and SF ICC scores: poor and acceptable (0.55–0.77; $p < 0.001$) [44]. Item range: debatable, acceptable and good (0.69–0.89); total scale: good (0.88) [44].Strong correlation in OAB-q scores (visit 1 and 2). ICC scores: 0.83–0.95;	Content validity: Clear, understandable and easy to complete [38]. Criterion validity: Moderate to strong correlation was observed between the measure symptom bother and QOL with UDI-6 and ICIQ-Q [38]. Significant correlations were observed between OAB-q SF items and SF-36 domains [39]. Construct validity: Control group possess higher OAB-q SF QOL and lower OAB-q SF symptom bother scores than patient group [39].Concurrent validity: Moderate correlation was observed at baseline, while at week 12, it was moderate to strong. The strongest correlation was reported in symptom bother, coping, concern and QOL [41]. There was moderate correlation between OAB-q and SF-36 subscales (0.16–0.52) [6]. Discriminant validity: PPUS was used to evaluate	Responsiveness: Consistently greatest OAB-q change scores were observed for the incontinent at baseline and continent at week 12 [37]. Both QOL scales and symptom bother were differentiated between control, C-OAB and I-OAB patients ($p < 0.0001$) [39].Moderate to large effect sizes were observed in multiple assessments with responsive changes (Study 1, 0.73–1.53; Study 2, 0.44–1.17; Study 3, 0.55– 1.31) [41]. Another study also observed significant responsive change in OAB-q ($p < 0.001$) with the exception of social domain and OAB-q SF [44]. Significant differences were observed in all KHQ scores (except personal relationships scores) ($p < 0.05$) [44] and between OAB-q change scores and bladder diary (micturition frequency) changes from baseline to

(*continued on next page*)

Table 3 (*continued*)

Outcome measure, number of studies [reference]	Reliability	Validity	Responsiveness
	Spearman's correlation: good (0.80–0.94; $p < 0.001$) [43].	discriminant validity. Significant differences were observed in mean OAB-q scores and PPUS responses [41], with $p < 0.0001$ for OAB-q subscales among continent and incontinent patients [6]. Significant differences were observed in OAB-q and OAB-q SF subscales ($p < 0.001$) [44].Convergent validity: High correlation coefficients ($p < 0.05$) [44].	week 12 ($p < 0.001$) (0.13–0.35) with small to moderate change in magnitude [41,42].
Qualiveen ($n = 8$) [45–52]	Internal consistency: Cronbach's alpha scores: acceptable (0.75–0.90 [47]); acceptable (0.70 [48]); good (0.88 [45]); excellent (0.95 [49]); excellent (0.90 [50]); good (0.86 and 0.85) [51] and good (>0.80 [52]).Test–retest reliability: ICC: excellent (0.93 [46]); moderate and good (0.62–0.86 [47]); excellent (0.97 [49]); good (0.81–0.89 [50]); good (>0.80 [52]); good (>0.80 [51]).	Content validity: Clear, understandable and easy to complete [52].Criterion validity: High ICC was observed between Qualiveen original version and SF-Qualiveen ($r = 0.70–0.92$) [46]. Significant correlation was observed between the majority of Qualiveen scores and ICIQ-SF domains [47]. Correlation was observed with relevant domains of KHQ [48]. There was high correlation of SF-Qualiveen with NBSS [50]. Positive correlation was noted in Qualiveen/SF-Qualiveen and ICIQ-SF total scores (Qualiveen: $r = 0.693$ and $p < 0.001$; SF-Qualiveen: $r = 0.611$ and $p < 0.001$) [51]. Linear correlation was noted in Qualiveen/SF-Qualiveen and ICIQ-SF total scores (Qualiveen: $r = 0.565$ and $p < 0.001$; SF-Qualiveen: $r = 0.524$ and $p < 0.001$) [52]. Construct validity: There was less correlation with symptom type and incontinence severity of SF-Qualiveen and the original version [46]. Qualiveen fitted the Rasch analysis model and was unidimensional [45].Convergent validity: Positive correlations were observed between Qualiveen and ICIQ-UI SF (0.57) and SF-12 [49]. Discriminant validity: Significantly improved incontinent-related QOL was observed among patients with higher education and income [49].	Responsiveness: Similar standardized response means were observed consistently for the short and long versions of Qualiveen [46].
UDI ($n = 5$) [29–33,66]	Internal consistency: Cronbach's alpha scores: acceptable (0.73 [29]); good (0.89 [32]); acceptable (0.74 [31]); acceptable (0.70 [30]); acceptable (0.70 [33]).Test–retest reliability: ICC: good (0.85 [29]; 0.59 [30]). Spearman's rho: excellent (0.99 [31]). Pearson's correlation coefficient: excellent (0.933 [33]).	Content validity: Percentage agreement score of the three rounds ranged from 79 % to 100 % for item fit, and from 89 % to 100 % for item clarity [32]. Criterion validity: A good connection was observed between daytime voiding incidence and nocturia, and irritable and obstructive symptoms [29].Concurrent validity: The disattenuated correlation was 0.64, while Pearson's correlation coefficient between MUDI and MUSIQ was 0.95 ($p < 0.001$) [32]. Construct validity: Mean scores varied for mobility, urine leakage, desire for socialization, diabetes mellitus and prostate enlargement [32]. Divergent validity: Negative correlation in the urge symptoms of QOL [30]. No significant correlation with the sexual dysfunction domains of disability status expanded scale scores [33].	Responsiveness: Significant changes were observed ($p < 0.0001$) for the control and multiple sclerosis groups with and without urinary incontinence [33].
UQ ($n = 1$) [58]	Internal consistency: Cronbach's alpha score: acceptable, good and excellent (0.79–0.94 [58]). Test–retest reliability: ICC: good and excellent (0.80–0.94 [37]). Spearman's correlation: moderate, good and excellent (0.69–0.92; $p < 0.001$) [37].	Convergent validity: Significant correlation was observed between the micturition diary variables and VAS with UQ item scores [58]. Discriminant validity: Discrimination between symptom severity levels of subscale and VAS scores of UQ [58].	Responsiveness: All subscale and VAS scores of UQ were sensitive to change [58].

B-SAQ, Bladder Control Self-Assessment Questionnaire; CI, confidence interval; ICC, intraclass correlation coefficient; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; ICIQ-OABqol, International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; ICIQ-UI-SF, International Consultation on Incontinence short-form questionnaire; IIQ-7, Incontinence Impact Questionnaire; I-QOL, Incontinence-quality of life; ISS, Incontinence Symptom Severity Index; IUI, Incontinence Utility Index; KHQ, Kings' Health Questionnaire; MUDI, Male Urinary Distress Inventory; MUSIQ, Male Urinary Symptom Impact Questionnaire; OAB-q, Overactive Bladder Questionnaire; OAB-q SF, Overactive Bladder Quality of Life Short-form Questionnaire; OAB-v8, Overactive Bladder Questionnaire-v8; PFLUTS, Persian Female Lower Urinary Tract Symptoms instrument; QOL, quality of life; SF-KHQ, Short Version of the King's Health Questionnaire; SF-Qualiveen, Short form Qualiveen; UDI-6, Urogenital Distress Inventory; U-IIQ, Urge-Incontinence Impact Questionnaire; U-UDI, Urge-Urinary Distress Inventory; UQ, Urgency Questionnaire; PFDI, Pelvic Floor Distress Inventory; LUTS, lower urinary tract symptoms.

Table 4
COSMIN findings.

Outcome measure, number of studies [reference]	Reliability		Validity							Responsiveness
	Internal consistency	Test–retest reliability	Structural validity	Content validity	Criterion validity	Convergent validity	Concurrent validity	Discriminant validity	Known-group validity	
PFLUTS ($n = 1$) [22]	Very good [22]	Very good [22]	–	Adequate [22]	Very good [22]	–	–	–	–	–
B-SAQ ($n = 1$) [23]	–	–	–	Very good [23]	–	–	–	Adequate [23]	–	–
ICIQ-FLUTS ($n = 1$) [24]	Very good [24]	Adequate [24]	–	Doubtful [24]	–	–	–	–	Adequate24	–
ICIQ-UI-SF ($n = 3$) [25–27]	Very good [27]	Very good [25–27]	–	Very good [27]	–	–	Very good [26]	Very good [27]	–	Very good [26,27]
ICIQ-OABqol ($n = 1$) [28]	Very good [28]	Adequate [28]	–		Very good [28]	–		–	–	Very good [28]
IIQ-7 ($n = 5$) [29–33,66]	Very good [29–31] Doubtful [32,33]	Adequate [29–31,33]	–	Adequate [30,32]	Very good [29,32,33]	Very good [30]	–	Very good [30]	–	Very good [32,33]
ISS ($n = 1$) [34]	Very good [34]	Adequate [34]	–	–	–	–	Very good [34]	–	–	–
IUI ($n = 1$) [35]	–	Adequate [35]	–	–	Very good [35]	Adequate [35]	–	–	–	Very good [35]
I-QOL ($n = 6$) [15,53–57]	Very good [15,53–57]	Very good [55–57] Adequate [54]	Very good [54] Adequate [53]	–	Very good [15]	Very good [15,53,56,57]	–	Very good [55,57] Adequate [53,54]	–	Very good [15,57]
KHQ ($n = 7$) [59–65]	Very good [59,61,62,64,65] Doubtful [60]	Adequate [62]	Adequate [60]	Very good [63]	Very good [62]	Very good [61,64,65]	–	Very good [59,61,65] Doubtful [64]	–	Very good [60,64]
OAB-v8 ($n = 1$) [36]	Very good [36]	–	–	–	–	–	–	–	–	–
OAB-q ($n = 9$) [6,37–44]	Very good [6,38–40,44]	Adequate [37–44] Very good [44]	–	Very good [38] Adequate [44]	Very good [38]	Very good [38,39,44]	Very good [6,40]	Adequate [39]	–	Very good [37,39–42,44]
Qualiveen ($n = 8$) [45–52]	Very good [47,49–52] Adequate[46] Doubtful [48]	Very good [47,52] Adequate [49–51] Doubtful [48]	Very good [45,48]	Adequate [51,52]	Very good [46–48,50–52]	Very good [46,49]	–	Very good [49]	–	Very good [46]
UDI ($n = 5$) [29–33,66]	Very good [29–31] Doubtful [32,33]	Adequate [29–31,33]	–	Adequate [30,32]	Very good [29,32,33]	Very good 30	–	Very good [30]	–	Very good [32,33]
UQ ($n = 1$) [58]	Very good [58]	–	–	–	–	Very good 60	–	Very good [58]	–	–

B-SAQ, Bladder Control Self-Assessment Questionnaire; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; ICIQ-OABqol, International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; ICIQ-UI-SF, International Consultation on Incontinence short-form questionnaire; IIQ-7, Incontinence Impact Questionnaire; I-QOL, Incontinence-quality of life; ISS, Incontinence Symptom Severity Index; IUI, Incontinence Utility Index; KHQ, Kings' Health Questionnaire; OAB-q, Overactive Bladder Questionnaire; OAB-v8, Overactive Bladder Questionnaire-v8; PFLUTS, Persian Female Lower Urinary Tract Symptoms instrument; UDI-6, Urogenital Distress Inventory; U-IIQ, Urge-Incontinence Impact Questionnaire; U-UDI, Urge-Urinary Distress Inventory; UQ, Urgency Questionnaire.

Table 5
Summary of evidence, overall rating, and grading of the quality of evidence using GRADE Assessment.

Outcome measure, number of studies [reference]	Summary or pooled result	Overall rating	Quality of evidence
PFLUTS (*n* = 1) [22]	Internal consistency (summarized Cronbach's alpha coefficient): debatable, acceptable and good (0.67–0.89)Test–retest reliability (ICC score): good (0.77) Criterion validity: 0.77 Total sample size: 114	Sufficient	High
B-SAQ (*n* = 1) [23]	Criterion validity: 0.86–0.89 Total sample size: 50	Sufficient	Moderate (imprecision)
ICIQ-FLUTS (*n* = 1) [24]	Internal consistency (summarized Cronbach's alpha coefficient): debatable, acceptable and good (0.646–0.864)Test–retest reliability (ICC scores) : 0.769–0.925 Total sample size: 283	Sufficient	High
ICIQ-UI-SF (*n* = 3) [25–27]	Internal consistency (summarized Cronbach's alpha coefficient): acceptable (0.71–0.78)Test–retest reliability (ICC): moderate, good and excellent (0.61–0.91) Criterion validity: 0.55–0.74 Responsiveness: the result is in accordance with the hypothesis Total sample size: 619	Sufficient	High
ICIQ-OABqol (*n* = 1) [28]	Internal consistency (summarized Cronbach's alpha coefficient): good (0.88)Test–retest reliability (ICC scores): excellent (0.906–0.933) Total sample size: 118	Sufficient	High
IIQ-7 (*n* = 5) [29–33,66]	Internal consistency (summarized Cronbach's alpha coefficient): acceptable, good and excellent (0.70–0.95)Test–retest reliability (ICC scores): good and excellent (0.85–0.95)Test–retest reliability (Spearman's rho): excellent (0.99)Test–retest reliability (Pearson's correlation): excellent (0.9431) Total sample size: 826	Sufficient	Moderate (due to risk of indirectness)
ISS (*n* = 1) [34]	Internal consistency (summarized Cronbach's alpha coefficient): debatable (0.69)Test–retest reliability (ICC scores): moderate (0.69) Total sample size: 345	Sufficient	Moderate (due to risk of bias)
IUI (*n* = 1) [35]	Test–retest reliability (ICC scores): excellent (0.90) Responsiveness: the result is in accordance with the hypothesis Total sample size: 658	Sufficient	High
I-QOL (*n* = 6) [15,53–57]	Internal consistency (summarized Cronbach's alpha coefficient): acceptable, good and excellent (0.79–0.99).Test–retest reliability (ICC scores): good and excellent (0.81–0.99) Criterion validity: 0.76–0.86 Responsiveness: the result is in accordance with the hypothesis Total sample size: 1205	Sufficient	High
KHQ (*n* = 7) [59–65]	Internal consistency (summarized Cronbach's alpha coefficient): debatable, acceptable, good and excellent (0.63–0.948)Test–retest reliability (ICC scores): good and excellent (0.80–0.96) Criterion validity: 0.722–0.784 Responsiveness: the result is in accordance with the hypothesis Total sample size: 3527	Sufficient	High
OAB-v8 (*n* = 1) [36]	Internal consistency (summarized Cronbach's alpha coefficient): good and excellent (0.891–0.910) Test–retest reliability (ICC scores): excellent (0.93) Total sample size: 1128	Sufficient	Moderate (due to risk of bias)
OAB-q (*n* = 9) [6,37–44]	Internal consistency (summarized Cronbach's alpha coefficient): acceptable, good and excellent (0.70–0.95)Test–retest reliability (ICC scores): moderate, good and excellent (0.70–092) Responsiveness: the result is in accordance with the hypothesis Total sample size: 1807	Sufficient	High
Qualiveen (*n* = 8) [45–52]	Internal consistency (summarized Cronbach's alpha coefficient): acceptable, good and excellent (0.70–0.95)Test–retest reliability (ICC scores): moderate, good and excellent (0.62–0.97) Criterion validity: 0.70–0.92 Responsiveness: the result is in accordance with the hypothesis Total sample size: 1135	Sufficient	High
UDI-6 (*n* = 5) [29–33,66]	Internal consistency (summarized Cronbach's alpha coefficient): 0.70–0.89Test–retest reliability (ICC scores): moderate (0.59); good (0.85)	Sufficient	Moderate (due to risk of indirectness)

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Table 5 (*continued*)

Outcome measure, number of studies [reference]	Summary or pooled result	Overall rating	Quality of evidence
UQ ($n = 1$) [58]	Pearson's correlation: 0.933Spearman's correlation coefficient: 0.99 Responsiveness: the result is in accordance with the hypothesis Total sample size: 826 Internal consistency (summarized Cronbach's alpha coefficient): acceptable, good and excellent (0.79–0.94)Test–retest reliability (ICC scores): good and excellent (0.80–0.94)Spearman's correlation coefficient: 0.69–0.92 Total sample size: 1388	Sufficient	High

B-SAQ, Bladder Control Self-Assessment Questionnaire; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICC, intraclass correlation coefficient; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms; ICIQ-OABqol, International Consultation on Incontinence Questionnaire Overactive Bladder Symptoms Quality of Life; ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; ICIQ-UI-SF, International Consultation on Incontinence short-form questionnaire; IIQ-7, Incontinence Impact Questionnaire; I-QOL, Incontinence-quality of life; ISS, Incontinence Symptom Severity Index; IUI, Incontinence Utility Index; KHQ, Kings' Health Questionnaire; OAB-q, Overactive Bladder Questionnaire; OAB-q SF, Overactive Bladder Quality of Life Short-form Questionnaire; OAB-v8, Overactive Bladder Questionnaire-v8; PFLUTS, Persian Female Lower Urinary Tract Symptoms instrument; QOL, quality of life; SF-Qualiveen, Short form Qualiveen; UDI-6, Urogenital Distress Inventory; U-IIQ, Urge-Incontinence Impact Questionnaire; U-UDI, Urge-Urinary Distress Inventory; UQ, Urgency Questionnaire.

included the PFLUTS, ICIQ-FLUTS, ICIQ-UI-SF, ICIQ-OABqol, IUI, I-QOL, KHQ, OAB-q, Qualiveen and UQ, whereas the B-SAQ, IIQ, ISS, OAB-V8 and UDI were supported by moderate-quality evidence. The GRADE summary findings for each outcome measure are summarized in Table 5.

Discussion

This systematic review investigated the psychometric properties of outcome measures used to evaluate QOL among people with neurogenic OAB in 47 studies that met the inclusion criteria. Among the included studies, neurogenic OAB was attributed to multiple sclerosis alone ($n = 5$); spinal cord injury alone ($n = 1$); multiple sclerosis and spinal cord injury ($n = 2$); multiple sclerosis, spinal cord injury and myelomeningocele ($n = 1$); or no specific underlying cause ($n = 38$). The 47 included studies reported 15 outcome measures used to evaluate QOL among people with neurogenic OAB. The GRADE tool indicated that the quality of evidence for the pooled outcome measures ranged from high (67 %) to moderate (33 %). The I-QOL, KHQ, OAB-q and Qualiveen were the most extensively validated outcome measures for validity, reliability and responsiveness.

This review found that the I-QOL was the most psychometrically robust and culturally diverse measure tested in several countries [72]. Based on the findings of this study, the I-QOL demonstrates excellent internal consistency (Cronbach's alpha = 0.92) and test–retest reliability (ICC = 0.92); very good criterion, convergent and discriminant validity; and very good responsiveness. The pooled psychometric findings were assessed using the COSMIN and GRADE scales, which indicated sound methodological quality and high-quality evidence in the studies using the I-QOL to evaluate QOL among people with neurogenic OAB. In the studies included in this review, the I-QOL was translated for use in more than 10 countries. Based on the findings of this review, the I-QOL represents a widely used, highly translated outcome measure [15,53–57] with highly rated psychometric properties, with applications in Africa, America, Asia and Europe. These findings corroborate the findings of previous systematic reviews by Wuytack et al. [16] and Ross et al. [14], in which the I-QOL was identified as the most widely translated measure with sound psychometric quality overall and available in a number of languages. Although the present study included people of both sexes with urgency urinary incontinence due to neurogenic OAB, the findings were consistent with the findings of previous reviews [14,16] conducted specifically in women with urgency urinary incontinence due to OAB. A 50 % reduction in incontinence episode frequency, as evaluated by the I-QOL, is recognized as the minimal clinically important difference among patients [73].

This review identified that the KHQ possesses acceptable internal consistency (Cronbach's alpha 0.721–0.948), test–retest reliability (ICC 0.80–0.96) and responsiveness. The COSMIN evaluation revealed very good methodological quality for most of the psychometric properties examined in the included studies, and the GRADE findings found sufficient overall evidence quality, with some studies identified as having high-quality evidence. The KHQ has been validated and translated into three languages [59–65], and has been applied to large cohorts of people with urgency urinary incontinence due to OAB, indicating that the KHQ is broadly applied for evaluating OAB in clinical practice, and demonstrating its acceptance and benefits. The methodological quality of the included studies evaluating the OAB-q ranged from very good to adequate, with an overall COSMIN rating of sufficient. The GRADE evaluation identified high-quality evidence supporting the OAB-q. A previous review by Avery et al. [74] reported a high level of psychometric strength (sound, adequate and very good levels of evidence for internal consistency, test–retest reliability, validity and responsiveness) and scientific rigor for the OAB-q. The Qualiveen was found to have a sufficient overall COSMIN rating and high-quality evidence according to the GRADE tool. The Qualiveen is reported to be a useful outcome measure for clinical trials directed at improving urinary-specific QOL [75].

The cost, feasibility and clinical relevance of outcome measures are barriers to their recommendation and routine utilization by clinicians and researchers [8]. In addition to criteria such as validity, appropriateness, reliability, responsiveness and interpretability [76], clinically useful outcome measures must also be easy to use, easily understood, quick to complete, easy to score, and provide useful clinical data [76]. Based on the findings of the present review, the I-QOL is recommended as the first choice of outcome measure when evaluating QOL among people with neurogenic OAB. The I-QOL evaluates the broad impacts of urinary incontinence on incontinence-related QOL in both men and women with urgency urinary incontinence due to neurogenic OAB. The I-QOL can be completed within 5 min, has been applied in both community studies and clinical trials regardless of the OAB classifications or severity, and demonstrates suitable generalizability across different international settings and conditions [77–80].

Strengths and limitations

This review has several strengths. First, the COSMIN and GRADE guidelines were adopted to assess, summarize and compare methodological quality and the quality of evidence of studies using the identified outcome measures. Second, a robust, transparent, comprehensive search strategy was employed, using relevant search themes and terms to identify studies validating the outcome measures used to assess OAB QOL measures. This review also has some limitations. First, some of the requirements of the COSMIN checklist involve subjective judgements, which might influence the overall scores for these instruments [81].

Second, as most included studies did not report content validity, the findings need to be interpreted with caution. Third, the exclusion of non-English language studies introduces the potential for language bias, which may impair the external validity of the study. Fourth, the exclusion of conference abstracts, grey literature and unpublished reports may result in overlooking potentially vital information, leading to publication bias.

Conclusion and recommendations

This review identified the I-QOL as the most psychometrically robust, cross-culturally diverse and easily administered outcome measure based on studies with good methodological quality and high-quality evidence. Clinicians and researchers may use the I-QOL for the evaluation of QOL among people with neurogenic OAB. Content validity was not tested in the included studies among people with neurogenic OAB. Therefore, future studies need to evaluate the content validity to broaden these recommendations, and support the routine utilization of the I-QOL among people with neurogenic OAB in clinical practice.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2023.11.010.

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Appendix A 3: Paper 3

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Research Article

Does repetitive transcranial magnetic stimulation induce long-lasting neuroplastic changes to improve detrusor muscle function in stroke survivors with neurogenic overactive bladder?

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ABSTRACT

Neurogenic overactive bladder (OAB) is purported to result from damage to the central inhibitory pathways in the brain and spinal cord or peripheral afferent terminal sensitization in the bladder, which unmasks the primitive voiding reflex. Excitation of the pontine micturition center activates descending neural pathways to the spinal cord, resulting in sequential detrusor contraction and urethral relaxation. Damage to the central nervous system mechanism may disrupt normal micturition control, leading to involuntary micturition with concomitant detrusor overactivity.

Low-frequency repetitive transcranial magnetic stimulation (rTMS), causing long-term depression of neuronal synaptic transmission, results in presynaptic neuron stimulation within several milliseconds after postsynaptic neuron stimulation. Low-frequency rTMS of the primary motor cortex may induce cortical inhibition via suppression of neural overactivity in descending projections, thereby reversing lower urinary tract symptoms by increasing pelvic floor tonicity and enhancing bladder capacity and bladder filling. Given the role of low-frequency rTMS in improving detrusor overactivity, we hypothesized that low-frequency active rTMS would inhibit cortical excitability and induce long-lasting neuroplastic changes to improve detrusor muscle function in stroke survivors with neurogenic OAB.

Introduction

The International Continence Society (ICS) defines overactive bladder (OAB) as urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia [1]. Urgency is defined as a sudden compelling desire to void that is difficult to defer, while urgency urinary incontinence refers to the involuntary leakage of urine accompanied by or immediately preceded by urgency [2,3]. These OAB symptoms are commonly reported by stroke survivors [4,5]. The efficacy of repetitive transcranial magnetic stimulation (rTMS) in managing neurogenic OAB symptoms among stroke survivors is lacking evidence and is not well elucidated. Therefore, this study focuses on explaining the effect of low-frequency rTMS in overactivity bladder symptoms. The novelty of the hypothesis lies in the potential use of rTMS to modulate neural activity and its impact on lower urinary tract symptoms [6]. This approach represents an innovative and non-invasive method for addressing OAB symptoms, potentially offering a new avenue for treatment. The use of rTMS to induce cortical inhibition and its effects on pelvic floor tonicity and detrusor overactivity presents a novel and promising concept in the field of neuro-urology.

The coordination of multiple central nervous system pathways is crucial for the proper functioning of the lower urinary tract [4,7]. These pathways facilitate the transmission of signals between the brain and the spinal cord, allowing for the modulation of bladder function [4,7]. During urine storage, the periaqueductal gray (PAG) plays a role in transmitting signals indicating that the bladder is filling [7]. These signals are sent to supraspinal centers, such as the prefrontal cortex and hypothalamus, which then suppress the voiding process [8]. This suppression prevents the initiation of the voiding reflex, allowing for the storage of urine. However, during voiding, the suppression of the pontine micturition center (PMC) is disrupted by the activity of the primary motor cortex (M1), prefrontal cortex, and hypothalamus [9]. This disruption leads to the excitation of the PMC, which activates descending neural pathways to the spinal cord [10]. Noradrenaline is

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released and acts on β3-adrenoceptors in the bladder wall [11]. This activation leads to contraction of the detrusor muscle and relaxation of the urethral smooth muscle resulting in increased bladder compliance and sustained low-pressure filling of the bladder, allowing for the passage of urine [11]. The parasympathetic nervous system, mediated by the pelvic nerves, is responsible for the contraction of the detrusor muscle during voiding. In contrast, the sympathetic nervous system, mediated by the hypogastric nerves, is responsible for the relaxation of the bladder neck and urethral smooth muscle during urine storage [7,12].

Neurogenic OAB is reported to occur when there is damage to the central inhibitory pathways in the brain and spinal cord or sensitization of the peripheral afferent terminals in the bladder [13–15]. This damage can lead to the re-emergence of the primitive voiding reflex, causing detrusor overactivity, frequent urination, urinary urgency, elevated bladder storage, and voiding pressure [13]. While the exact cause of urinary incontinence before or after a stroke is not clear, it is believed to be related to the disruption of normal physiological functions of the detrusor [16]. Targeting specific pathways or receptors involved in these processes can help restore normal bladder function and improve the quality of life for individuals with urinary disorders [4].

Detrusor overactivity is an inappropriate excitation of the detrusor muscle

Detrusor overactivity is defined by the ICS as "a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked" [17]. The detrusor muscle is highly innervated, and bladder function is regulated by complex central and peripheral neurological mechanisms [7]. Any disruption to the neurological systems involved in bladder control can result in reduced bladder compliance, deterioration of the urinary tract, and increased bladder overactivity due to the loss of suprapontine inhibition [18,19]. Involuntary detrusor contraction may be attributable to the effects on the sensory mechanisms resulting in initiation of urgency bladder emptying in small quantities [20]. If left untreated, detrusor overactivity leads to urinary tract infections, bladder stones, fibrosis, trabeculation, and automatic dysreflexia in the presence of a neurological condition such as stroke [21].

Mechanism of TMS for neurogenic overactive bladder

TMS is a technique that stimulates the cortex using magnetic fields based on Faraday's principle of electromagnetic induction [22]. It is a safe and painless method that activates cortical neuron fibers by delivering intense and brief magnetic fields [23–25]. By directing alternating magnetic fields through a wire coil, TMS can modulate neurons and either excite or inhibit cortical activity depending on the frequency [26]. The magnetic field is reduced by extracerebral tissue, such as the scalp, bone, and meninges, while still maintaining sufficient potency to induce an electrical field that can depolarize superficial axons and activate cortical networks [27]. When applied correctly, TMS can depolarize neurons and generate action potentials [27]. Long-term changes in synaptic strength can be achieved through high-frequency repetitive TMS (rTMS) or low-frequency rTMS, resulting in long-term potentiation or depression, respectively [23,24]. By targeting cortical areas related to the pelvic region, rTMS can modulate cortical excitability and induce lasting neuroplastic changes [28]. The M1, which controls pelvic floor muscles and detrusor stability, is often targeted for rTMS interventions in neurological conditions including NOAB [29]. The latency of motor-evoked potentials from the striated urethral sphincter is a reliable response to TMS in investigations of micturition disorders [30]. Low-frequency rTMS has also shown temporary improvements in lower urinary tract dysfunction in individuals with advanced Parkinson's disease by enhancing bladder capacity and the first sensation of the filling phase [6]. By modulating pelvic floor tonicity and reducing detrusor overactivity, low-frequency rTMS of the M1 can reverse lower urinary tract symptoms and enhance bladder capacity and filling [6].

Low-frequency rTMS for cortical excitability inhibition and long-lasting neuroplastic changes

High-frequency rTMS at a frequency of 5 Hz or higher increases the excitability of the cortex even after the stimulation has ended, while low-frequency rTMS at 1 Hz decreases cortical excitability [31]. This modulation of the cortex has been associated with therapeutic effectiveness and clinical improvements [31]. When there are lesions in the corticospinal tract due to a brain injury, it leads to reduced excitability of cortical motor neurons and an imbalance in connectivity [32,33]. This activates inhibitory circuits within the M1 [32,33]. By using low-frequency rTMS to suppress the contralesional M1 and achieve increase excitability of motor neurons, it is possible to improve cortical performance by modulating and balancing the altered connectivity in the motor network [34,35]. The suppression of contralesional M1 is achieved by establishing effective communication between the ipsilesional M1 and the ipsilesional supplementary motor area. Resting-state functional magnetic resonance imaging (fMRI) studies have shown that effective connectivity from the premotor cortex to the ipsilesional M1 improves three weeks after low-frequency rTMS in subacute stroke patients [36]. These changes lead to remodeling of the neural network architecture, resulting in improved motor performance after the intervention [37]. Low-frequency rTMS stimulation for 15–25 min suppresses motor evoked potentials and enhances the efficiency of excitatory synaptic transmission, without significantly increasing calcium levels. This neural suppression of motor evoked potential could inhibit the cortical excitability thereby ultimately inducing inhibition of the descending pathways of the corticospinal tracts projecting to the detrusor muscles [6]. Multiple sessions of low-frequency rTMS significantly reduced the resting and active motor threshold of the affected M1 and were sustained for three months post-intervention [38]. By inhibiting cortical excitability, low-frequency rTMS provides neuroprotection against cellular mechanisms such as excitotoxicity, energy depletion, and free radical formation [39]. At low intensities, low-frequency rTMS preferentially activates low-threshold inhibitory interneurons over higher threshold excitatory interneurons, while pyramidal tract neurons are indirectly activated through synaptic inputs without causing them to discharge [40]. The clinical effectiveness of low-frequency rTMS may be due to its effects on the pontine micturition center, which is responsible for descending excitatory projections to parasympathetic sacral centers, and/or the periaqueductal gray, where the afferent proprioceptive projection of the bladder terminates [41] (Fig. 1). Given the consistent evidence of the inhibitory effects of low-intensity low-frequency rTMS on the human M1, it can be safely considered as a treatment approach in various clinical settings [42–44]. Low-frequency rTMS is a safe and effective therapeutic technique that has been shown to yield positive clinical outcomes, including increased bladder capacity and improved lower urinary tract symptoms.

Hypothesis

Low-frequency active rTMS is more likely to inhibit cortical excitability and induce long-lasting neuroplastic changes among stroke survivors with neurogenic OAB symptoms compared to the sham rTMS.

The scientific premise for the proposed hypothesis

Transcranial magnetic stimulation is employed to modulate the neural activity of striated sphincter motor afferents [24]. rTMS induces neural changes in regional brain activity that can last beyond the stimulation period [31]. Low-frequency rTMS of the M1 may induce cortical inhibition via suppression of neural overactivity in the descending projections and reverse lower urinary tract symptoms by increasing pelvic floor tonicity [6]; consequently, bladder capacity and

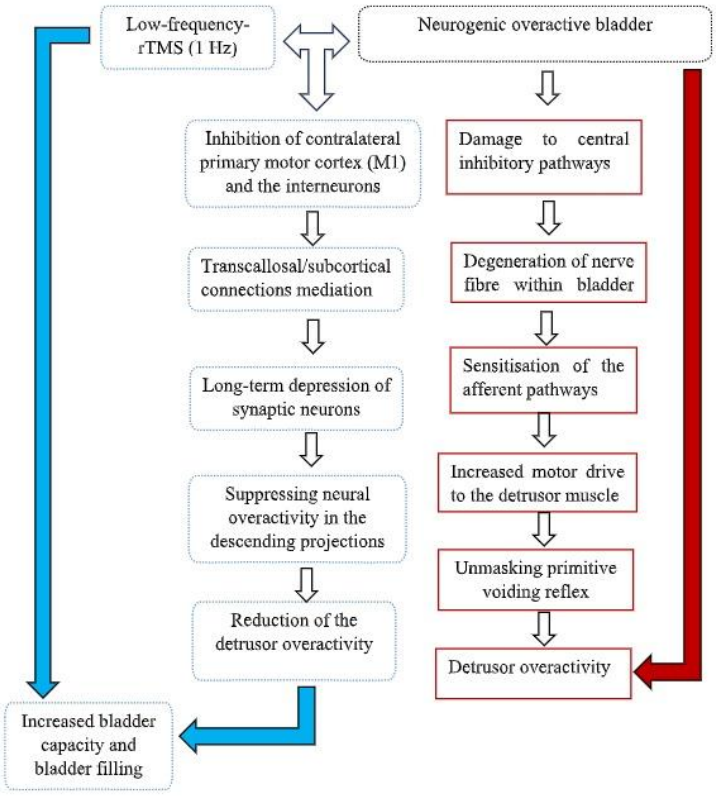

Fig. 1. Mechanisms of detrusor overactivity and proposed hypothesis. Red lines: development of detrusor overactivity among people with neurogenic overactive bladder. Blue dotted lines with shadow: proposed hypothesis- low-frequency active-rTMS results in an inhibition of cortical excitability and induced long-lasting neuroplastic changes to improve detrusor muscle function among stroke survivors with neurogenic overactive bladder.

bladder filling are enhanced through a reduction in detrusor overactivity [6]. Therefore, it is important to note that the potential benefits of using TMS to modulate neural activity could lead to a reduction in episodes of urinary incontinence, urgency incontinence, daytime frequency incontinence, and nocturia. This improvement in bladder control could have a positive impact on individuals' overall well-being and performance in the community, potentially enhancing their engagement and participation in community activities.

Evaluation of the hypothesis and empirical data

To test the proposed hypothesis, we conducted a sham-controlled, double-blinded, parallel group, randomized controlled trial (RCT; (ClinicalTrials.gov reference number: NCT05557175) using 60 stroke survivors with neurogenic OAB. The aim of the RCT was to investigate the clinical effectiveness of low-frequency active rTMS against sham rTMS for managing neurogenic OAB among stroke survivors. Participants were randomly assigned to two groups: active-rTMS group (experimental condition) and sham-rTMS group (control condition). Baseline (before the commencement of the study), post-intervention (after four weeks) and follow-up assessments (after eight weeks) were conducted among both active-rTMS and sham-rTMS groups. Participants randomized to the active-rTMS group received actual TMS intervention thrice weekly for a duration of 20 min (a total of 12 sessions). The sham-rTMS group received low-frequency stimulation at 20 % of the resting motor threshold using same coil as the active-rTMS but was configured to significantly reduce the TMS-induced electrical fields [45]. Preliminary results (n = 10) demonstrated a moderate effect size for perceived severity of OAB symptoms, as measured using the overactive bladder symptoms score (OABSS) at week 4 (effect size = 0.665; p = 0.031). The active-rTMS group reported an OABSS score of 6.5 ± 0.84 at baseline. Following the intervention, the OABSS decreased to 2.0 ± 1.95. At the follow-up assessment, the OABSS was reported to be 2.8 ± 0.98. This suggests a significant reduction in overactive bladder symptoms following the rTMS intervention, with some maintenance of improvement at the follow-up assessment. However, the sham-rTMS group reported an OABSS scores of 8.4 ± 2.51 at baseline. Following the intervention, the OABSS remained at 8.4 ± 1.95. At the follow-up assessment, the OABSS was reported to be 8.0 ± 2.00. This suggests that there was no significant change in overactive bladder symptoms in the sham rTMS group following the intervention or at the follow-up assessment (Fig. 2). In secondary outcome measures, the active-rTMS group reported an Incontinence Quality of Life (I-QOL) score of 47.55 ± 14.13 at baseline. Following the intervention, the I-QOL score increased to 83.65 ± 7.09, and at the follow-up assessment, it was 83.55 ± 8.39. This indicates a substantial improvement in the quality of life related to incontinence for the active-rTMS group. In comparison, the sham rTMS group reported an I-QOL score of 41.66 ± 3.19 at baseline.

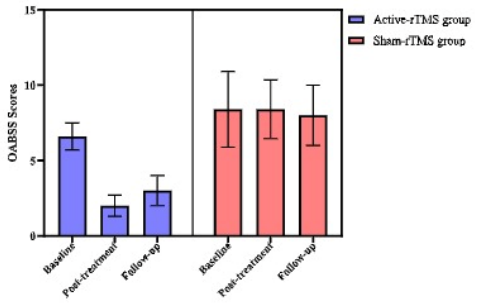

Fig. 2. Changes in OABSS scores from baseline, Post-treatment (visit 12) and follow-up (8 weeks).

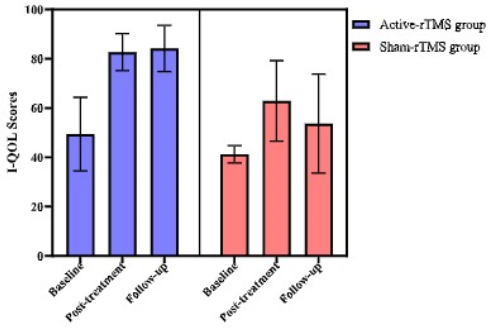

Fig. 3. Changes in I-QOL scores from baseline, Post-treatment (visit 12) and follow-up (8 weeks).

Following the intervention, the I-QOL score increased to 54.74 ± 9.19, and at the follow-up assessment, it was 45.84 ± 8.30. This suggests a minimal improvement in the quality of life related to incontinence for the sham rTMS group, with some decrease in the score at the follow-up assessment (Fig. 3). The participants receiving active-rTMS showed a large effect size for improvement in the quality of life as measured by the secondary outcome measure, I-QOL week 4 (effect size: = 0.846; p = 0.008).

The findings indicating a significant reduction in neurogenic OAB symptoms and potential improvement in the quality of life following the active-rTMS intervention are promising. The preliminary findings suggest that the observed changes may be linked to alterations in detrusor muscle function, potentially resulting in a decrease in urinary frequency and urgency. These results suggest that the rTMS intervention may be effective in addressing the clinical symptoms of OAB in this population, potentially offering a valuable treatment option for individuals with neurogenic OAB resulting from stroke. The preliminary findings of the RCT appear to support the initial hypothesis regarding the potential effectiveness of the active rTMS intervention in managing OAB symptoms in stroke survivors. However, it's important to note that findings from the ongoing full-scale RCT are necessary to confirm the proposed hypothesis and to establish the potential long-term efficacy and safety of rTMS as a treatment for neurogenic OAB in stroke survivors. If the ongoing RCT continue to support these preliminary findings, it could have significant implications for the management of OAB among stroke survivors.

Implications of the hypothesis and discussion

Neurogenic OAB occur as a result of damage to the central inhibitory pathways in the brain and spinal cord, or sensitization of the bladder's peripheral afferent terminals [46–48]. One potential treatment approach is low-frequency rTMS of the M1 [6]. Low-frequency rTMS applied to the M1 has been shown to induce cortical inhibition by suppressing neural overactivity in descending pathways [6]. This can lead to a reversal of lower urinary tract symptoms, particularly detrusor overactivity. By modulating cortical activity, low-frequency active rTMS can improve the function of the detrusor muscle, which is responsible for bladder contraction [49]. In the context of stroke survivors with neurogenic OAB symptoms, low-frequency active rTMS has the potential to be clinically useful [50]. It can inhibit cortical excitability, improving detrusor muscle function and alleviating OAB symptoms [6]. Furthermore, the neuroplastic changes induced by low-frequency rTMS can have long-lasting effects on bladder control. Overall, low-frequency active rTMS of the M1 is a promising treatment option for neurogenic OAB symptoms, particularly in stroke survivors. By modulating cortical activity and inducing neuroplastic changes, it can help improve detrusor muscle function and alleviate OAB symptoms. Nonetheless, these findings suggest that active-rTMS could be of potential clinical utility in improving neurogenic OAB symptoms in stroke survivors by inhibiting cortical excitability and inducing neuroplastic changes. Therefore, thereby improving detrusor muscle function in stroke survivors with neurogenic OAB.

Authors' contributions

All authors (MUA, GSK, KNKF, PK) contributed equally to the conceptualisation, development, drafting, editing and revision of the manuscript. All authors have read and approved the final version of the manuscript.

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Ethical approval

The ethical approval with registration number HSEARS20210913002 was obtained from Institutional Review Board of the Hong Kong Polytechnic University, Hong Kong.

CRediT authorship contribution statement

Mohammed Usman Ali: Conceptualization, Data curation, Writing-original draft, Writing-review and editing, Investigation, Formal analysis, Methodology, Software. **Georg S. Kranz:** Conceptualization, Data curation, Writing-review and editing, Investigation, Validation, Formal Analysis, Methodology, Supervision and Software. **Kenneth N.K. Fong:** Conceptualization, Data curation, Writing-review and editing, Investigation, Validation, Formal Analysis, Methodology, Supervision and Software. **Priya Kannan:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Hong Kong Polytechnic University (Dean's Reserve, Faculty of Health and Social Sciences (Department of Rehabilitation Sciences)). Ref No. ZVSV.

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Appendix A 4: Paper 4

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Full length article

Evaluating repetitive transcranial magnetic stimulation for neurogenic overactive bladder management in stroke survivors: A randomized sham-controlled trial protocol

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ABSTRACT

Background: Neurogenic overactive bladder (OAB) is a distressing condition in stroke. Existing neurogenic OAB management is expensive, unstandardized regimens, or invasive. Evaluating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) remains crucial. We aimed to (1) compare the effectiveness of active-rTMS with sham-rTMS on neurogenic OAB symptoms, (2) analyze whether rTMS is cost-effective, and (3) explore the rTMS's experiences on participants' symptoms.

Methods: This is a randomized, sham-controlled, double-blinded trial with embedded qualitative and cost-effectiveness studies. A total of 110 stroke survivors with neurogenic OAB symptoms were screened for eligibility; 60 participants were eligible for inclusion and were randomly assigned to either the active (n = 30) or sham-rTMS (n = 30) groups using a computer-generated randomization schedule. The active-rTMS group received low-frequency rTMS of 1200 pulses per session lasting 20 min thrice weekly to pelvic floor muscle representation at the contralesional primary motor cortex. The sham-rTMS group received low-frequency stimulation at a 20 % resting motor threshold using the same coil as the active-rTMS but was configured to reduce the TMS-induced electrical fields significantly. The primary and secondary outcome measures were assessed at baseline, post-intervention (week 4) and follow-up (week 8). The analysis of covariance (ANCOVA) analysis compared changes in the study groups. Quality-adjusted life-years (QALY) were measured to evaluate the cost-effectiveness while EQ-5D-5L estimated QALY changes. Additionally, the focus group discussion data were thematically analyzed.

Conclusions: The findings from this rTMS intervention study will be useful in alleviating neurogenic OAB symptoms and enhancing patient satisfaction in a cost-effective way.

Background

Overactive bladder (OAB) is defined by the International Continence Society (ICS) as "urinary urgency with or without urgency incontinence, usually accompanied by frequency and nocturia, in the absence of urinary tract infection or other obvious pathology" [1]. Wein and Abrams [2] proposed the term "overactive bladder" from a symptomatic perspective, describing it as a clinical syndrome characterized by urgency and urgency urinary incontinence (UUI). Urgency, a primary symptom of OAB, is defined as a sudden, compelling desire to void that is difficult to defer [3]. UUI is characterized by involuntary urine leakage either during or immediately before the urgency [1]. According to the World Stroke Organization (WSO), there were more than 100 million reported cases of stroke worldwide in 2022 [4]. Among these stroke survivors, the prevalence of neurogenic OAB, which refers to overactive bladder symptoms experienced by neurogenic patients [5], is estimated to range between 32% and 79% [6–8].

Individuals having neurogenic OAB and their families face distressing psychological, social, and financial burdens [9]. Neurogenic OAB is often managed sub-optimally, leading to a high incidence of

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complications such as urinary tract disorders, isolation, anxiety, depression, hospitalization, increased disability, and increased risk of mortality [10]. Under-treatment of neurogenic OAB may be linked to embarrassment about seeking health care, social stigma, low patient adherence to treatment regimen, poor communication regarding continence needs, and insufficient information sharing among clinicians [11]. Neurogenic OAB demands significant attention from stroke survivors and their caregivers due to its negative correlation with functional outcomes and strong association with increased rates of institutionalization [12]. Kolominsky-Rabas et al. [12] found that 45 % of stroke survivors with neurogenic OAB were institutionalized, with 5 % living in custodial settings 12 months post-stroke. This situation highlighted significant personal economic burdens and reduced self-dependency. In the United States, the annual national cost for neurogenic OAB care was estimated at $65.9 billion in 2007, with projections reaching $82.6 billion by 2020 [13]. The yearly costs for community-dwelling adults and institutionalized elderly are reported to be $4.2 billion and $5.3 billion, respectively [14]. In 2015, the adult incontinence market in the United States amassed $7.3 billion, triggering the production and sales of incontinence products [15].

The pharmacological management of neurogenic OAB is associated with various adverse effects which may impact patients' medication compliance and long-term management persistence [16]. Behavioral therapies, intermittent urethral catheterization, indwelling, suprapubic catheters, open retropubic colposuspension, laparoscopic colposuspension, periurethral injections, and bladder neck needle suspension have shown some effectiveness [17]. However, these interventions pose risks such as being bothersome, semi-invasive, or invasive, can be expensive, and may lead to long-term complications [17].

Currently, physiotherapy treatments for neurogenic OAB include pelvic floor muscle training (PFMT) [18] either alone or in combination with electromyography (EMG) biofeedback [19] or electrical stimulation [20,21]. However, according to a recent review of existing literature [22], there is currently no standardized regimen for PFMT. EMG biofeedback and transvaginal or anal electrical stimulation are often not preferred by individuals with detrusor overactivity due to their invasiveness and the pain or discomfort associated with inserting vaginal or anal probes [23]. Additionally, individuals with functional limitations due to stroke may have difficulty inserting the vaginal or anal probes of biofeedback devices or electrical stimulators [24].

Given the limitations of existing interventions, exploring a safe, non-invasive, and effective intervention such as repetitive transcranial magnetic stimulation (rTMS) for neurogenic OAB is crucial. rTMS is a non-invasive device that painlessly delivers an intense, brief magnetic field to the brain [25]. It can depolarize neurons by generating electric currents of appropriate amplitude, duration, and direction, thereby inducing action potentials [25]. rTMS induces neural activity in the pelvic floor muscles representation and the striated sphincter motor afferents [26] that can last beyond the stimulation period [27]. Furthermore, it has the potential to modulate cortical excitability and induce long-lasting neuroplastic changes [26].

The primary motor cortex (M1) is implicated in neuro-urologic dysfunctions such as urinary incontinence [28,29] and is a target for rTMS interventions [30]. rTMS aims to induce detrusor stability by modulating suprapontine inhibition through corticospinal projections [31]. The application of low-frequency rTMS to the M1 may induce cortical inhibition, suppressing neural overactivity in descending projections and alleviating lower urinary tract symptoms [32,33]. This mechanism could improve bladder capacity and filling by reducing detrusor overactivity [32,33]. The present study aims to evaluate the efficacy of rTMS, in comparison to sham-rTMS, in alleviating neurogenic OAB symptoms among stroke survivors. Real-life experiences and the meanings people attribute to them were explored to reveal important insights about patients' perceptions of the therapeutic interventions [34]. The qualitative study was aimed at exploring the experiences and opinions of stroke survivors with neurogenic OAB toward the rTMS intervention and views regarding its impact on their neurogenic OAB symptoms and well-being. To achieve better health benefits and outcomes with a lower intervention cost, we aimed to analyze whether rTMS is cost-effective.

Methods

Research design, participant recruitment, and study setting

A prospective, randomized, sham-controlled, double-blind design embedded with semi-structured focus groups and an economic evaluation was conducted in Hong Kong. This mixed-method (RCT combined with qualitative and cost-effectiveness components) approach was adopted to enhance the comprehensiveness of the research evidence [35]. All study procedures involving stroke survivors with neurogenic OAB were conducted in accordance with the principles of the 1964 Helsinki Declaration, as revised by the 18th World Medical Association General Assembly, and relevant ethical guidelines. Ethical approval was obtained from the Institutional Review Board of the Hong Kong Polytechnic University (Ref No.: **HSEARS20210913002**) before enrolling the first participant. The study protocol was prospectively registered on ClinicalTrials.gov (**NCT05557175**). Written informed consent was obtained from all participants before their enrolment in the study. Participants were also given copies of the signed information sheets and consent forms for their records. The information sheet provides a detailed explanation of the treatments (active-rTMS and sham-rTMS interventions) including, commencement and completion of the trial, roles in the trial participation, the procedure, duration of treatment sessions, number of sessions required, risks and benefits of participating, rights as participants, follow-up assessments, contact of primary investigator, co-investigators and Institutional Review Board committee secretary. and potential adverse effects. Before obtaining the participants' consent for participation, any questions or concerns they may have about the study were provided in the information sheet.

Anonymity was maintained to ensure confidentiality and protect participant information within a relationship of trust unless consistent with the original purpose of the disclosure. Participants' records were safeguarded against disclosure outside the research setting or to unauthorized persons.

This randomized controlled trial (RCT) followed these steps: (1) a two-step eligibility screening phase; (2) baseline assessment (pre-intervention); (3) four weeks of active- and sham-rTMS interventions; (4) post-intervention assessment at the end of the 8-week intervention period; (5) a focus group discussion (limited to the active-rTMS group) conducted at the end of the five weeks post-intervention.

Participants for the RCT were recruited through snowball-convenience sampling techniques. In this approach, existing participants recommend another potential participant, who then refers another, creating a 'snowball' effect [36]. Additionally, recruitment was carried out through self-help organizations such as the Hong Kong Stroke Society.

Sample size

The required sample size for the study was 60 (30 for each group). G-power program 3.1.0 (Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany) [37] was utilized to calculate the sample size (power = 80 %, alpha = 5 %). The calculation was informed by data from previous pilot studies and RCTs [38–42]. An effect size of 0.40 from a previous study [43] with the same primary outcome, Overactive Bladder Symptom Score (OABSS), and a similar population (stroke) were used for determining the effect size. An additional eight participants were recruited to account for an anticipated 15 % attrition rate [53]. To achieve data saturation, 15 participants (grouped into three focus group discussions) from the active-rTMS group were recruited using convenience sampling for the focus group discussion [44].

Participants

The following inclusion criteria determined eligibility for recruitment in the RCT: (1) stroke survivors aged 18–80 years [40] diagnosed with neurogenic OAB; (2) moderate (OABSS scores: 6–11 points) to severe neurogenic OAB (OABSS scores: 12 points and above) [45]; (3) a Mini-Mental State Examination (MMSE) score of ≥24 [46]; and (4) willingness to be randomized.

The exclusion criteria were: (1) contraindications to rTMS as per the 13-question safety questionnaire [47], (2) presence of metals in the cranium, intracardiac lines, increased intracranial pressure, heart diseases, cardiac pacemaker, or use of sacral neuromodulation [48]; (3) pregnancy or in the postpartum stage (less than six months); (4) a family history of epilepsy or seizures; (5) current use of tricyclic antidepressants or neuroleptics [48]; (6) participation in other urinary incontinence-related research projects [48]; and additional exclusions including contraindications to magnetic resonance imaging (MRI), urologic cancer, prostatic pathology, severe pelvic pain, being within six weeks post-surgery, and having a non-neurogenic bladder [49].

Randomisation and blinding

The study adopted a randomized procedure involving a minimization method of computer-generated randomization (www.randomisation.com) to ensure equitable distribution between study groups. Sixty sealed, opaque envelopes prepared by individuals not involved in the study were used for allocation concealment. Outcome assessments and statistical analyses were blinded, with the groups coded 'Group A' and 'Group B.' These group codes were revealed only after completing all analyses. Both therapists and participants were blinded to recruitment, randomization, and treatment allocation, with the blinding achieved by concealing the allocation and randomization of participants, ensuring they remained unaware of the intervention specifics [50].

Procedure

Volunteers who contacted the research personnel via phone or email were invited to The Hong Kong Polytechnic University for eligibility screening, obtaining written informed consent, and conducting baseline assessments. During their initial visit, those who provided written informed consent completed the OABSS questionnaire and MMSE to determine eligibility and baseline urinary symptoms. Subsequently, all eligible participants completed the study's outcome questionnaires.

Interventions

Upon completing baseline assessments, participants were randomly allocated into two groups (active- or sham-rTMS). They received their respective interventions three times a week for four weeks, totaling 12 sessions. A four-week follow-up period may be sufficient to assess the initial effects of rTMS on neurogenic OAB, as some studies have reported significant improvements in symptoms within this timeframe [51,52]. However, it is important to note that the duration of treatment effects can vary widely among individuals, and longer-term follow-up may be necessary to determine the overall efficacy and durability of rTMS as a treatment for neurogenic OAB [53].

Active-rTMS group

Participants in the active-rTMS group received rTMS stimulation using a standard 70 mm figure-of-eight air-cooled coil (MagPro), targeting the sensorimotor cortex anterior-medially on one side. They received 1 Hz inhibitory low-frequency rTMS, delivering a continuous pulse of one pulse per second, totaling 1,200 pulses at 80 % of the active motor threshold [42,48]. Each stimulation session lasted 20 min and was conducted three times a week over four weeks (12 sessions in total) [42,48]. The motor hotspot was identified as the site with the greatest motor-evoked potential [41]. The resting motor evoked potential was measured using electromyography, specifically from the first dorsal interosseous muscle, in accordance with the recommendations of the International Federation of Clinical Neurophysiology [54]. To locate the vertex of the skull, the midway between the nasion-inion and preauricular points of both tragus was identified [15,55]. The coil was placed with its centre approximately 5 cm lateral and 2 cm anterior in a parasagittal plane from the vertex [15,16,56]. The coil was positioned tangentially at approximately right angle from the midline on the scalp over the hand area of the M1 [10,56], to identify the hot spot, which was the location on the scalp where stimulation of slightly sub-threshold intensity elicited the largest MEP in the first dorsal interosseous muscle [11,12]. Beginning rTMS intervention with low intensity (30–35 %) of single pulse stimulation every 3–5 s. The rTMS intervention began with low intensity (30–35 %) of single pulse stimulation every 3–5 s, with the coil slowly moved around the estimated location of the M1, applying 1 or 2 pulses at each site [16]. Starting at a low intensity is important to relax the study participants and avoid discomfort during the procedure [15]. The absence of movement or twitch in the contralateral hand indicates that the RMT for the participant was higher than the current TMS output setting [17,55]. Consequently, the intensity was increased by 5 %, and the response was assessed at various sites of the M1. When the hand and/or twitch movement was observed, the applied intensity was close to the RMT [17]. Test responses in a number of areas were marked on the scalp site, which appears to produce the greatest motor response. The intensity was increased when movement or twitch was not produced on each pulse. The coil was moved at 0.5–1 cm increments laterally and medially of the marked point to determine the optimal site of stimulation in the lateral/medial plane [15]. Providing stimulation with pulses of approximately 0.2 Hz at the optimal location (no more frequent than one pulse every 5 s). At this hotspot, the motor threshold was determined as the lowest intensity of single-pulse TMS necessary to elicit a motor-evoked potential greater than 50 μV in more than five out of 10 consecutive trials [8,15]. Low-frequency rTMS protocols targeted the hotspot in the contra-lesional M1 [18–20]. For effective stimulation of M1, the coil was positioned at a right angle to the skull [57–59]. Participants in the active rTMS group received stimulation at a subthreshold intensity sufficient to induce muscle contraction without causing painful peripheral sensations [54,60,61].

Sham-rTMS group

Participants in the sham-rTMS group received low-frequency stimulation at 20 % of the resting motor threshold. This sham stimulation used the same coil as the active-rTMS but was configured to significantly reduce the TMS-induced electrical fields in the cortex [62,63].

Study setting

Study interventions were administered for four weeks in the neuroscience laboratory at the Department of Rehabilitation Sciences, Hong Kong Polytechnic University. Follow-up assessments were conducted at four and eight weeks.

Safety and adverse events associated with rTMS application

rTMS is generally a well-tolerated, safe, non-invasive modality with no significant side effects or safety concerns [64]. Participants were informed about the possibility of experiencing mild, transient headaches, neck pain, or local scalp pain at the stimulation site, which could be effectively managed with paracetamol analgesics [64–66]. To prevent any potential adverse effects from the intervention, strict adherence to rTMS contraindications was maintained, and participants underwent thorough screening [65]. Should any side effects occur, they typically subside after the first few days of starting the rTMS treatment [66]. Participants were observed for adverse effects during and after each treatment session. All reported adverse effects associated with rTMS intervention are well documented. All adverse effects associated with

rTMS intervention have been thoroughly documented and recorded.

Outcome measures

Primary measure

Incontinence severity was evaluated using the self-reported OABSS questionnaire [67]. The OABSS is considered a reliable and valid questionnaire for quantitatively assessing overactive bladder symptoms in the Hong Kong population (Intraclass Correlation Coefficient [ICC] = 0.82) [68]. This measure comprised four questions on OAB symptoms with maximum domain scores ranging from two to five: daytime frequency (two points), night-time frequency (three points), urgency (five points), and UUI (five points) [69]. The total OABSS ranges from 0 to 15, with higher scores indicating greater symptom severity [69]. Severity is classified as mild (three to five points), moderate (six to 11 points), or severe (12 points or more) [45].

Secondary measures

The Incontinence Quality-of-Life Questionnaire (I-QOL) was used to evaluate the neurogenic OAB-related quality of life [70]. The I-QOL is reported to be a psychometrically robust incontinence-specific outcome measure for assessing the quality of life in individuals with OAB. It has 22 items subdivided into three subscales. Scores range from 0 to 100, where 0 represents the worst quality of life, and 100 indicates the complete absence of incontinence-related issues (ICC=0.93) [71]. When tested in the Chinese population, the I-QOL was found to be psychometrically robust, demonstrating high internal consistency (Cronbach's α: 0.963), excellent test–retest reliability (ICC: 0.74–0.96, $P < 0.01$), and acceptable construct validity [72].

The Brief Resilience Scale (BRS) was employed to measure resilience, defined as "*resistance to illness, adaptation, and thriving, the ability to bounce back or recover from stress*." The BRS has been reported to provide unique and critical information regarding "*people coping with health-related stressors*" [73]. It comprises both positively worded (items 1, 3, and 5) and negatively worded (items 2, 4, and 6) statements. Resilience serves as a coping strategy for individuals facing stressful environments and adverse life events [74]. Notably, resilience is often found to be lower in people with urinary incontinence of all age groups [74].

Adherence to the active-rTMS intervention was measured by calculating the percentage of prescribed rTMS sessions each participant attended. The stated reasons for missing any sessions were recorded.

Qualitative study

Upon completion of post-intervention assessment at four and eight weeks, invitations were posted to all the participants in the active-rTMS group inviting them to participate in the focus group interviews. The qualitative study used a phenomenological approach to explore the experiences of rTMS intervention and the views of participants regarding its impact on their urinary symptoms and well-being [34] Interested participants were asked to express interest in participation via telephone, email, or by Focus groups were scheduled at the end of the intervention in a private room at The Hong Kong Polytechnic University. Focus groups lasted for 45–60 min for each group. Homogeneity within and between groups was established through all participants having a similar underlying neurological condition (stroke).

A semi-structured focus group approach was used to discuss and elicit information on some predetermined questions and open-ended where the participants could express them freely. The following questions were included for discussion during the focus groups. (1) Which incontinence symptom (urge frequency, nocturnal frequency, urge accidents) would you most like further relief? (2) How did you find your experience with rTMS? (3) What differences did you experience in incontinence during your study participation? (4) Would you recommend rTMS to your family and friends with neurogenic urinary incontinence? (5) How do you get yourself motivated to be social? (6) In your opinion, what can help you improve and strengthen your resilience? All focus group sessions were audio recorded and additional notes were taken.

Economic evaluation

The cost estimation analysis was conducted from a societal perspective in Hong Kong. The client service recipient inventory (CSRI) was employed to evaluate the health and social care resources and service utilization in the last 6 months [75]. The CSRI has demonstrated its validity and reliability in generating an accurate inventory of cost data through which costs can be calculated [75]. Quality-adjusted life-years (QALY) was used as an outcome for economic evaluation [76]. The 5-level EQ-5D (EQ-5D-5L) version developed by the EuroQol Research Foundation was used to estimate the QALY gain or loss [77]. The unadjusted mean costs and cost differences between active-rTMS against sham-rTMS groups for total and disaggregated costs (intervention costs, healthcare utilisation costs, including healthcare services and medications utilised) were calculated [76].

Data processing and analysis

Data analysis and anticipated results

Hypothesis 1: All the statistical analyses were conducted on an intention-to-treat basis. To compare changes in the primary outcome (OABSS) and secondary outcomes (I-QOL and BRS) over time between active-rTMS and sham-rTMS groups, repeated measure analysis of covariance (ANCOVA) was employed. The analysis model was built with group allocation as the independent variable, the primary outcomes (OABSS), and the secondary outcomes (I-QOL, Brief Resilience Scores, age and gender as covariates [78]. Statistical analyses were conducted using SPSS version 28.0 (IBM, Armonk, NY). Socio-demographic variables are reported using the mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. A p-value of less than 0.05 was considered statistically significant. Missing data, data preparation and monitoring. Missing data can affect a study's statistical power and efficiency, leading to biased impact estimates of findings [79]. To reduce the occurrence of missing data, motivation to comply with the rTMS and follow-up phone call reminders will be utilised. Missingness of less than 5 % is negligible and will be valid to ignore the missing data, while more than 40 % missingness will be considered substantial using Jacobsen's algorithm principles [80]. Missing data due to early dropouts will not be considered as missing data at random since they were not evenly distributed within the study groups. The normality of the data was evaluated using the Kolmogorov-Smirnov test and Shapiro-Wilk test. Bonferroni corrections were applied for multiple comparisons [81].

Hypothesis 2: The focus group discussion was transcribed verbatim by an independent transcription service. Participant names were replaced with personal identification numbers, and code numbers were assigned to each participant for data entry. The accuracy of the data will be ensured by comparing the transcripts with the recordings.

The Braun and Clarke (2006) guidelines will be adopted for analyzing the data transcripts according to the six phases of inductive thematic analysis [82]. Qualitative data analysis will begin with data familiarization via reading and re-reading the transcribed data (Phase 1) [82]. In Phase 2 of the analysis, the team will identify quotations that answered the research questions and assign appropriate codes to these quotations. This process involved discussions among team members, continuing until a consensus was reached [83]. In Phase 3, the identified codes will be independently collated based on data relevancy into potential themes [83]. The fourth phase involved a two-level review of these themes. Level 1 focused on establishing a coherent pattern within the collated themes by examining how well the themes aligned with the coded data extracts [83]. Level 2 extended this examination to ascertain the working pattern of these themes within the entire dataset and verify each theme's accuracy and significance [83]. The fifth phase entailed

Table 1
Study visits and assessments.

Type of visits	Time from randomization in weeks					
	Screening	Week 0	Week 1	Weeks 2–3	Week 4	Follow-up (Week 5–8)
Informed consent	X					
Demographics	X					
Enrolment	X					
Eligibility checklist	X					
Randomization and allocation	X					
Assessments						
OABSS		X			X	X
I-QOL		X			X	X
BRS		X			X	X
CSRI		X			X	X
EQ-5D-5L		X			X	X
Adherence dairy			X	X		
Attendance			X	X		
Adverse events			X	X		
Stimulation sessions						
Active-rTMS			X	X	X	
Sham-rTMS			X	X	X	
Statistical analyses						X

OABSS: overactive bladder symptoms score; I-QOL: incontinence quality of life score; BRS: brief resilience scale; CSRI: client service recipient inventory; rTMS: repetitive transcranial magnetic stimulation.

defining and naming these themes based on their content. In the final phase, Phase 6, a review will be conducted to confirm that the final set of themes is comprehensive and coherently represents the data.

Hypothesis 3: Seemingly unrelated regression (SUR) analyses were used to estimate total cost differences (ΔC) and effect differences (ΔE), adjusting for baseline demographic and health characteristics of the groups [76,84]. EQ-5D responses were converted into utility scores to estimate the gain or loss in quality-adjusted life-years (QALY). The incremental cost-effectiveness ratio (ICER) was calculated using the formula ICER=ΔC/ΔE. Uncertainty surrounding the ICERs and the 95 % confidence intervals around cost differences were estimated using bias-corrected and accelerated bootstrapping with 5,000 replications [76]. The cost-effectiveness of the intervention groups has been geographically represented using the cost-effectiveness plane (CE). The threshold (λ) for cost-effectiveness, or the amount a country is willing to pay to gain one unit of effect (QALY), was calculated. Details of the schedule of study visits and assessments at each time-point is presented in Table 1.

Preliminary results

Baseline characteristics

The study was conducted from January to December 2023. A total of 110 S survivors with OAB symptoms were screened for eligibility. 60 participants fulfilled the eligibility criteria and were enrolled in the study. Study participants were randomly assigned to two groups: active-rTMS group (n = 30) and sham-rTMS (n = 30) groups (Fig. 1). The mean age of participants in the active-rTMS group was 62.10 years (SD 9.54) and 61.67 years (SD 8.29) in the sham-rTMS group. The age of participants in both groups was 37–78 years. Of the participants in both active- and sham-rTMS groups, 32 (53.3 %) were male, and 28 (46.7 %) were female, all belonging to the same ethnic group. There was no statistically significant difference in mean age or gender between the eligible

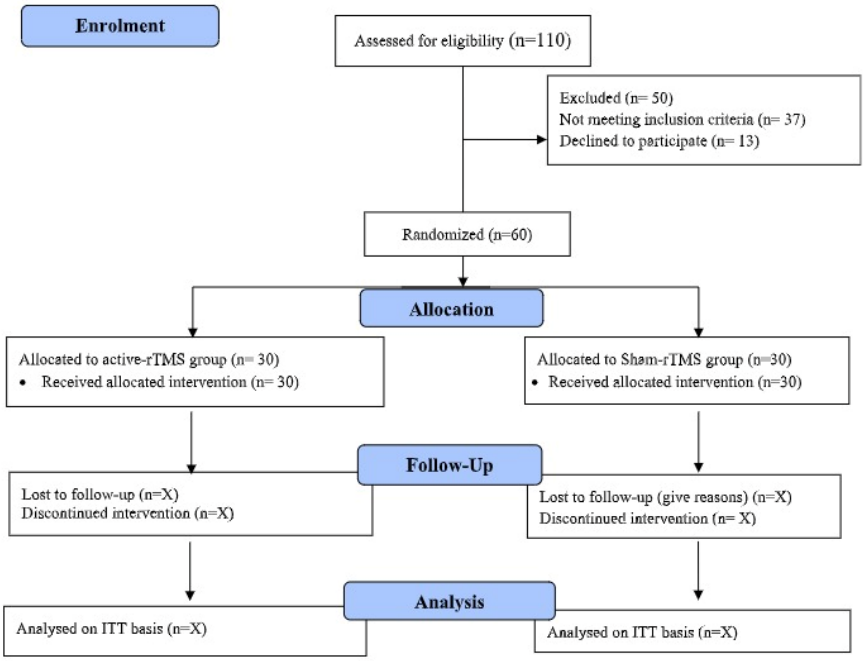

Fig. 1. CONSORT Flow Diagram of the trial. rTMS: repetitive Transcranial Magnetic Stimulation; ITT: Intention-to-Treat.

Table 2
Baseline characteristics of the study participants.

Characteristic	Active-rTMS group (n = 30)	Sham-rTMS group (n = 30)	*p*-value
Age, Mean ± SD	62.10 ± 9.54	61.67 ± 8.29	0.908*
Gender, *n* (%)			0.121†
Male	13 (43.3 %)	19 (63.3 %)	
Female	17 (56.7 %)	11 (36.7 %)	
Side of hemiplegia *n* (%)			0.071†
Right	18 (60 %)	11 (36.7 %)	
Left	12 (40 %)	19 (63.3 %)	
Marital status n (%)			0.634†
Married	19 (63.3 %)	22 (73.3 %)	
Divorced	8 (26.7 %)	5 (16.7 %)	
Single	3 (10 %)	3 (10 %)	
Level of education, *n* (%)			0.601†
Degree	3 (10 %)	2 (6.7 %)	
College Diploma	5 (16.7 %)	2 (6.7 %)	
High School	19 (63.3 %)	23 (76.7 %)	
Primary school	3 (10 %)	3 (10 %)	
Baseline assessments, Mean ± SD			
OABSS score	7.53 ± 1.72	8.13 ± 2.56	0.290*
I-QOL score	48.32 ± 8.92	46.52 ± 5.32	0.348*
BRS score,	3.13 ± 0.41	2.93 ± 0.42	0.076*
Time since stroke (months)	43.70 ± 28.92	48.18 ± 34.52	0.605*

rTMS: repetitive transcranial magnetic stimulation; OABSS: overactive bladder symptom score; I-QOL: incontinence quality of life questionnaire; BRS: brief resilience scale.
* Independent sample *t*-test.
† Fisher exact test.

participants who consented to enroll in the study at baseline. Additionally, no significant baseline differences in other demographic and clinical characteristics were observed between the two groups. The detailed baseline demographic and clinical characteristics of the participants are summarized in Table 2.

All participants in both the active- and sham-rTMS groups completed the entire four-week intervention protocol, except for three who were lost to follow-up. The rTMS treatment was generally well-tolerated. Few adverse effects were reported by newly recruited participants, with mild headaches being the most common, though these subsided before the next treatment visit. Specifically, two patients (3.3 %) in the active-rTMS group and one patient (1.6 %) in the sham-rTMS group reported mild headaches post-treatment. Notably, there were no instances of rTMS-induced seizures throughout the four-week low-frequency rTMS intervention.

Discussion and conclusion

This study is the first of its kind to evaluate the effectiveness of low-frequency rTMS in treating neurogenic OAB symptoms in stroke survivors. Our goal was to determine if active low-frequency rTMS is significantly more effective than sham-rTMS in reducing neurogenic OAB symptoms, improving quality of life, and enhancing patient satisfaction over a four-week period. Additionally, we aimed to evaluate whether any improvements observed could be sustained beyond the immediate post-intervention at four weeks and eight-week follow-up.

The findings from this study are anticipated to be valuable in reducing healthcare-related costs. By providing an effective treatment approach for neurogenic OAB in stroke survivors, we could potentially alleviate the socioeconomic burdens associated with neurological bladder issues. The findings are expected to offer novel insights for researchers and clinicians into the efficacy of rTMS in managing neurogenic OAB.

Similarly, the findings of this study will also contribute to exploring the experiences and opinions of stroke survivors with neurogenic OAB on the rTMS intervention. In this study, the participants could be able to express the therapeutic benefits and concerns derived from the rTMS intervention. These findings could help in evaluating their acceptance of the intervention and also identifying the key factors responsible for their adherence to the treatment regimen.

Moreover, the outcomes of this study would have significant implications for the stroke survivor community suffering from neurogenic OAB. It is hoped that the results will contribute to reducing discomfort associated with traditional interventions, such as the insertion of vaginal or anal probes. For physiotherapists specializing in stroke rehabilitation, the study's findings could offer new perspectives on neurogenic OAB management in patients.

The findings from exploring the experience of the study participants might yield information about the degree of acceptance of the treatment options to facilitate the utility of the rTMS intervention among stroke survivors with neurogenic OAB symptoms in clinical practice. This study might identify the patients' expectations and needs to achieve maximum therapeutic benefits and satisfaction regarding the rTMS intervention.

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Trial registration

This trial was registered at http://ClinicalTrials.gov (reference number: NCT05557175) before the recruitment of the first participant.

CRediT authorship contribution statement

Mohammed Usman Ali: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Crystal Kwan:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Kenneth Nai-Kuen Fong:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Georg S. Kranz:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Stanley John Winser:** Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Priya Kannan:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A 5: Paper 5

Original Research Article

CLINICAL REHABILITATION

Clinical Rehabilitation
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Clinical tools for evaluating the severity of overactive bladder: A systematic review of psychometric properties

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Abstract

Objectives: To systematically evaluate the evidence describing the psychometric properties of clinical measures for assessing overactive bladder symptoms (urinary urgency with or without urge urinary incontinence, urinary frequency and nocturia). To evaluate the quality of this evidence-base using the COnsensus-based Standards for selecting health status Measurement INstruments (COSMIN) checklist and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tools.

Data sources: Five electronic databases (CINAHL, EMBASE, MEDLINE, Scopus and Web of Science) were searched from dataset inception to August 2023.

Review methods: Study screening, data extraction and quality appraisal were performed by two independent authors. Inclusion criteria were studies testing one or more psychometric properties of clinical tools for the assessment of overactive bladder symptoms among adults aged 18 years and older for both sexes. The methodological quality and quality of the evidence were evaluated using the COSMIN checklist and GRADE tools, respectively.

Results: The search identified 40 studies totalling 10,634 participants evaluating the psychometric properties of 15 clinical tools. The COSMIN methodological quality was rated good for most measures, and the GRADE quality of evidence ranged from low (13%) to high (33%). The Overactive Bladder Symptom Score, Overactive Bladder Questionnaire and Neurogenic Bladder Symptom Score were of good methodological and high-GRADE evidence qualities.

Conclusion: Overactive Bladder Symptom Score, the Overactive Bladder Questionnaire and the Neurogenic Bladder Symptoms Score are promising psychometrically sound measures. The Overactive Bladder Symptom Score has been applied to the most culturally diverse populations supported by studies of good methodological and high-GRADE evidence quality.

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Clinical tools, overactive bladder, psychometric properties, reliability and validity

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Introduction

Overactive bladder is defined by the International Continence Society as 'urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology'.[1] The prevalence of overactive bladder is estimated to range from 16.5% to 23.3%, and the prevalence of urgency urinary incontinence has been reported as 31% for men and 25% for women, with prevalence increasing with age.[2,3] The annual economic burden associated with overactive bladder is estimated at US$26 billion, equating to US$267 annually per individual.[4,5] Reduced suprapontine inhibition of the micturition reflex, damaged spinal cord axonal paths, increased afferent nerve input, diminished peripheral inhibition and increased excitatory neurotransmission in the micturition reflex pathway could lead to overactive bladder.[6] Overactive bladder is a devastating condition that limits the ability of individuals to participate in activities of daily living and social engagements.[7] Overactive bladder has been associated with psychological stress, depression, participation restriction, impaired work-related productivity, sleep disturbance, sexual function deterioration and reduced quality of life.[8]

Given the significant negative impacts of overactive bladder, coupled with the high cost of management, there is a need to identify psychometrically sound clinical tools for the evaluation of symptom severity and monitoring of post-intervention recovery.[9] Previous psychometric systematic reviews of clinical tools for reporting overactive bladder symptoms focused on identifying and classifying clinical tools in screening overactive bladder symptoms,[10] evaluating the quality of life among individuals with spinal cord injury,[11] and generic and condition-specific clinical tools among women population.[12] None of the previous psychometric systematic reviews of clinical tools for reporting overactive bladder symptoms have evaluated psychometric properties, and few have objectively reported on the quality of the evidence.[10,12]

Researchers and clinicians are increasingly concerned with selecting psychometrically sound and condition-specific clinical tools to improve the evaluation of treatment effects and the monitoring of symptom improvements.[13,14] Individuals with neurological disorders may have difficulty responding to certain clinical tools, and the response rate and accuracy of these tools can be affected by subjective responses, a lack of motivation among patients to respond accurately, language or cultural barriers, cognitive decline or senility.[15,16] Currently, there is no consensus on recommended clinical tools for the evaluation of overactive bladder symptoms. Therefore, the need to identify psychometrically strong clinical tools for evaluating overactive bladder symptoms is paramount. Hence, the objectives of the present review are to systematically evaluate the evidence describing the psychometric properties of clinical measures for assessing overactive bladder symptoms (urinary urgency with or without urge urinary incontinence, urinary frequency and nocturia). To evaluate the quality of this evidence-base using the COnsensus-based Standards for selecting health status Measurement INstruments (COSMIN) checklist and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tools.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[17] guidelines were employed in conducting and reporting this systematic review. This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42022297811). Database searches were

performed by two review authors (MUA and SJW). The following electronic databases were searched from database inception until 30 August 2023: CINAHL, EMBASE, MEDLINE, Scopus, and Web of Science. Three themes were developed for the search terms, including psychometric properties, clinical tools, and overactive bladder. The themes for overactive bladder and lower urinary tract symptoms were developed according to the International Continence Society definitions of overactive bladder and adult neurogenic lower urinary tract dysfunction. A detailed description of the search terms developed for the MEDLINE database search can be found in the Supplemental Table 1. This systematic review utilized a PICOS (Patient problem, Intervention, Comparison, Outcome measure, and Study design) framework to select appropriate studies.[18]

Studies were included in this systematic review if they (1) tested the psychometric properties of clinical tools assessing the overactive bladder symptoms; (2) tested one or more of the following psychometric properties: internal consistency, test–retest reliability, inter-rater, and intra-rater reliability, content validity, structural validity, criterion validity, construct validity, convergent validity, divergent validity, or responsiveness; and (3) included adult patients aged 18 years and older of both sexes with overactive bladder. Studies were excluded if (1) the full text of the study could not be retrieved (even after contacting the authors); (2) they were systematic reviews, commentaries, or editorials; (3) they were conference proceedings, abstracts, or event annals; (4) they were published in languages other than English; or (5) they were unpublished theses/reports.

All studies identified through the electronic database searches were exported to the EndNote 21 citation manager (Clarivate Analytics, Philadelphia, Pennsylvania, USA). After duplicates removal, titles, abstracts and full-text screening were performed by two independent review authors (MUA and SJW). Any disagreements encountered during the screening process were discussed until a consensus was reached between the two reviewers. A third review author (PK) was consulted for unresolved discrepancies. Manual searching of the reference lists of included studies and relevant systematic reviews was also conducted to identify any additional potentially relevant studies.

Data extraction was performed by two independent review authors (MUA and SJW). A third review author (PK) was consulted for unresolved discrepancies during the data extraction process. The following data were extracted from each included study: first author, year, country of study, participant characteristics [mean age of participants (standard deviation); sample size for each group], population, clinical tool(s), psychometric properties tested and authors' conclusions.

For each included study and clinical tool, the methodological quality was evaluated using the COSMIN risk of bias checklist,[19] and the quality of evidence was evaluated using the modified GRADE tool.[20] COSMIN evaluates the methodological quality of studies designed to measure the psychometric properties of a given clinical tool and can be used to assess and select the most appropriate instrument for use in clinical practice and research.[21] COSMIN assesses nine psychometric domains, including reliability (relative measures, including test–retest reliability, inter-rater reliability and intra-rater reliability), internal consistency, measurement error, content validity (including face validity), hypotheses testing, structural validity, criterion validity and cross-cultural validity.[19] Based on the scores obtained for each domain, the methodological quality of the tested psychometric properties is rated using a 4-point rating scale as 'very good', 'adequate', 'doubtful' or 'inadequate'. An overall methodological quality score can be obtained for the psychometric properties of any clinical tool, which corresponds to the lowest score assigned to any item on the checklist for that tested property.[19] The methodological quality of each clinical tool assessed in the included studies was independently evaluated by two independent review authors (MUA and PK). For any unresolved discrepancies, a third reviewer was consulted (SJW).

The modified GRADE approach was employed to evaluate the cumulative quality of evidence supporting each psychometric property of the identified clinical tools.[22] The quality of the findings supporting the psychometric properties in each study was investigated and categorized as 'sufficient', 'insufficient' or 'indeterminate' in accordance with the updated

criteria for good psychometric properties proposed by Prinsen et al.[22] For each clinical tool examined in the included study, the quality of evidence supporting the psychometric properties was pooled and summarized using the modified GRADE approach, which categorizes quality of evidence as 'high', 'moderate', 'low' or 'very low'.[22] The modified GRADE approach begins by assuming high quality of evidence, and the quality of evidence is then downgraded for risk of bias, inconsistency, indirectness or imprecision.[23] The risk of bias was determined by evaluating reporting bias (selective outcome reporting), attrition bias (incomplete outcome data) and the availability of an a priori protocol. When applying the modified GRADE approach, we first consider the risk of bias, categorized as not serious, serious, very serious or extremely serious.[24] For a clinical tool to have no risk of bias, at least two studies with adequate quality of evidence or better or at least one study with very good quality of evidence must be identified.[24] Serious risk of bias was assigned when multiple studies of doubtful quality or at least one study with adequate quality were identified. Very serious risk of bias was assigned when multiple studies of inadequate quality were identified. Extremely serious risk of bias was assigned to clinical tools associated with only one study of inadequate quality.[24] The COSMIN evaluation of the psychometric performance of a given measure can be either quantitatively pooled or qualitatively summarized for comparison against the criteria for good psychometric properties, resulting in an assessment of whether the overall psychometric properties of the clinical tool in question are sufficient (+), insufficient (−), inconsistent (±) or indeterminate (?). The COSMIN approach was utilised for the evaluation of psychometric performance for the tools used in each included study while the evaluation of the quality of the evidence using GRADE presented for each tool to determine our confidence and trustworthiness in the pooled results or the overall rating.[22]

Results

The database searches identified 7112 potentially relevant studies for the screening process, among which 1328 duplicate records were detected and excluded. After all screening procedures were applied, 40 studies met our eligibility criteria and were included in the review. Supplemental Table 2 summarises the reasons for study exclusion during the full-text screening phase. A flow chart illustrating the study process is presented in Figure 1.

Characteristics of the included studies are summarised in Supplemental Table 3. This review included 10,634 participants from 40 studies, with sample sizes ranging from 20[25] to 1839.[26] The participants' ages ranged between 18 and 89 years. The included studies were published between 2002 and 2022, and 31 of the 40 included studies were published within the last decade (2011–2022). The included studies recruited patients with overactive bladder due to stroke ($n = 3$),[27–29] multiple sclerosis ($n = 1$),[25] multiple sclerosis and spinal cord injuries ($n = 3$)[30–32] and without specified underlying causes ($n = 31$).[26,33–60]

The included studies reported 15 clinical tools for evaluating urinary symptoms among people with overactive bladder due to stroke, multiple sclerosis, spinal cord injuries or other causes. The Overactive Bladder Symptom Score was evaluated by 10 studies,[36,37,42–44,46,57–60] and seven studies[26,38–41,48,52] evaluated the Overactive Bladder Questionnaire. Characteristics of the identified clinical tools, such as the languages of instruction, descriptions of the items and scoring schemes used, the duration necessary to complete the clinical tools, costs, strengths, limitations and populations tested are presented in Supplemental Table 4.

Reliability and validity were the most commonly tested psychometric properties, whereas responsiveness was the least commonly tested psychometric property. The Cronbach's alpha scores for assessing internal consistency reported by most of the included studies were of good to excellent correlation, only few studies were within the acceptable threshold ($\alpha = 0.70$).[36,42,45,46,49,53,61] The intra-class correlations for evaluating the test–retest reliability for most included studies were within the acceptable threshold ($\alpha = 0.70$).[28,32,33,42,49,55,56] Among the identified clinical tools, Overactive Bladder Symptom Score, Overactive Bladder Questionnaire and Neurogenic Bladder Symptom Score tend to have good to excellent internal consistency, test–retest reliability,

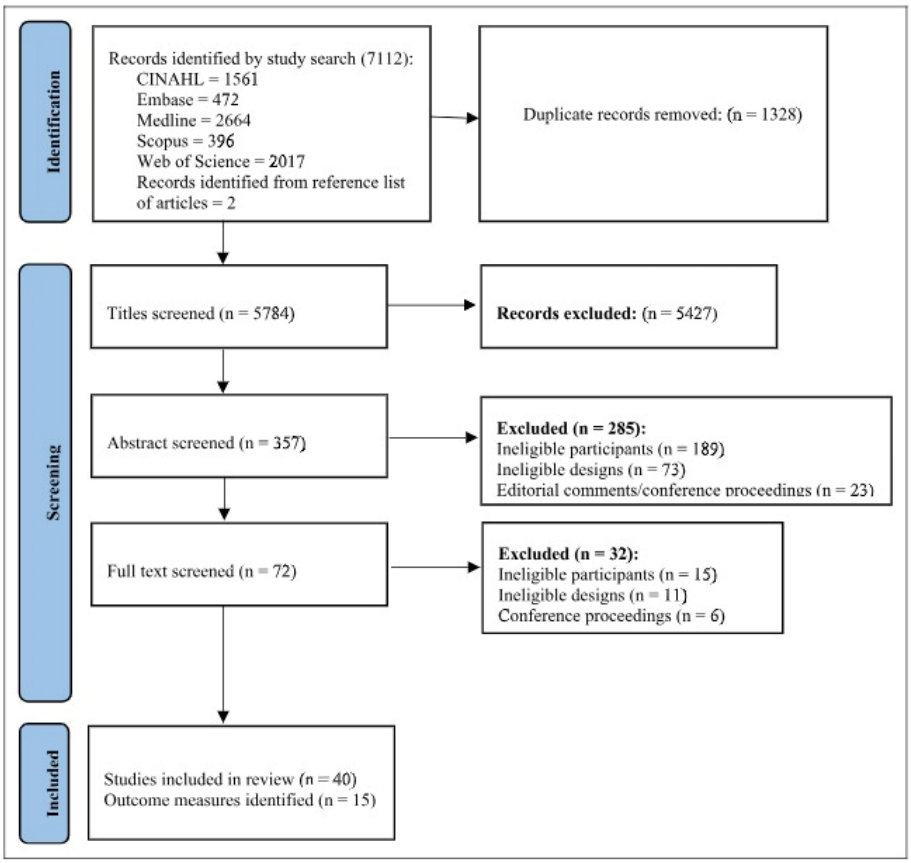

Figure 1. Flowchart of screened studies.

validity and responsiveness. Strong correlation of concurrent validity was observed in the Overactive Bladder Symptom Score to Overactive Bladder-V8 and International Consultation on Incontinence Questions Short form while Overactive Bladder Questionnaire has moderate correlation to the Short Form-36. Significant difference was observed in both Overactive Bladder Symptom Score and Overactive Bladder Questionnaire to discriminant validity in both International Prostate Symptom Score and Patient Perception of Bladder Condition Questionnaire, respectively.

Structural and criterion validities were not reported for the Overactive Bladder Symptom Score or Overactive Bladder Questionnaire, and only the Overactive Bladder-Bladder Assessment Tool was evaluated for structural validity. Among the psychometric properties examined for Overactive Bladder Symptom Score in the included studies, test–retest reliability was rated as very good in six of the eight studies in which it was examined (75%), internal consistency was rated as very good in five of seven studies (71%), validity was rated as very good in seven of eight studies (82%) and responsiveness

Table 1. COSMIN and GRADE findings.

	Reliability		Validity									
Clinical tools ($n = 15$)	Internal consistency	Test–retest reliability	Structural validity	Content validity	Criterion validity	Convergent validity	Concurrent validity	Discriminant validity	Known-group validity	Responsiveness	Overall rating (COSMIN)	Quality of evidence (GRADE)
Actionable Bladder Symptom Screening Tool ($n = 2$)[25,34]	Very good[25,34]	Doubtful[25]	-	-	Very good[25,34]	-	-	-	Very good[34]	-	Sufficient	Very low (due to risk of bias and imprecision)
Bristol Female Lower Urinary Tract Symptoms ($n = 1$)[55]	-	Adequate[55]	-	Very good[55]	Very good[55]	-	-	-	-	-	Sufficient	Moderate (due to risk of bias)
Danish Prostatic Symptom Score ($n = 3$)[27–29]	Very good[28]	Very good[28] Adequate[29]	-	Doubtful[27]	-	Very good[29]	-	-	-	-	Sufficient	Low (due to risk of bias)
International Consultation on Incontinence Questionnaire–Overactive Bladder ($n = 1$)[56]	Doubtful[56]	Adequate[56]	-	-	-	-	-	-	-	-	Insufficient	Low (due to risk of bias and imprecision)
International Consultation on Incontinence Questionnaire–Bladder Diary ($n = 1$)[62]	-	Adequate[62]	-	Very good[62]	Inadequate[62]	-	-	-	-	Very good[62]	Sufficient	Moderate (due to risk of bias)
International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms ($n = 2$)[43,63]	Very good[43,63]	Very good[43,63]	-	Very good[63] Doubtful[43]	Very good[63]	-	-	-	-	-	Sufficient	Moderate (due to risk of bias)
International Consultation on Incontinence Questionnaires–Male Lower Urinary Tract Symptoms ($n = 3$)[49,53,54]	Very good[49,53,54]	Adequate[49,53] Doubtful[54]	-	Doubtful[53,54]	Very good[53]	-	-	-	-	-	Sufficient	Moderate (due to imprecision)
Indevus Urgency Severity Scale ($n = 1$)[52]	-	Adequate[52]	-	Adequate[52]	-	-	-	-	-	Very good[52]	Insufficient	High
Neurogenic Bladder Symptom Score ($n = 3$)[30,32]	Very good[30–32]	Adequate[32] Very good[31]	-	Adequate[30] Adequate*[32] Doubtful[32]	Very good[32]	-	Very good[31]	-	-	-	Sufficient	High
Overactive Bladder–Bladder Assessment Tool ($n = 1$)[35]	Very good[35]	Very good[35]	Adequate[35]	-	-	Very good[35]	-	-	Very good[35]	-	Sufficient	Moderate (due to imprecision)
Overactive Bladder Questionnaire ($n = 7$)[24,38–41,45,52]	Very good[24,38,52]	Adequate[40] Very good[52]	-	Adequate[52]	-	Very good[52]	Very good[24,38]	Very good[24,38,52]	-	Very good[24,39–41,52]	Sufficient	Moderate (due to risk of bias)
Overactive Bladder Satisfaction with Treatment Questionnaire ($n = 1$)[47]	Very good[47]	-	-	-	-	-	Very good[47]	Very good[47]	-	-	Sufficient	Moderate (due to risk of bias)
Overactive bladder-V8 ($n = 1$)[33]	Very good[33]	Doubtful[33]	-	-	-	-	-	Adequate[33]	-	-	Sufficient	High
Overactive Bladder Symptom Score ($n = 10$)[24,37,42–44,46,59–62]	Very good[24,37,42,44,59–62]	Very good[37,42,44,59–62] Adequate[24,44] Doubtful[42,57]	-	Doubtful[46]	-	Very good[46,60]	Very good[42,44]	Very good[44,59] Adequate[57]	Adequate[44]	Very good[42,46] Adequate[57]	Sufficient	High
Patient Perception of Intensity of Urgency Scale ($n = 1$)[51]	-	Very good[51]	-	Very good[51]	-	-	-	-	-	-	Sufficient	Moderate (due to imprecision)

was rated as very good in two of three studies (67%). A summary of the psychometric properties assessed for the identified clinical tools used in the included studies is presented in Supplemental Table 5.

The details of the COSMIN and GRADE summary findings for the clinical tools evaluated by each of the included studies are presented in Table 1. The methodological quality of the studies evaluating the psychometric properties of the Overactive Bladder Symptom Score, Overactive Bladder Questionnaire and Neurogenic Bladder Symptom Score range from very good to doubtful. The psychometric scores were pooled to obtain GRADE findings for each clinical tool. The pooled properties include internal consistency, test–retest reliability (intra-class correlation/weighted kappa), validity and responsiveness. The GRADE evidence tests of quality of evidence for the evaluated clinical tools ranged from low to high, with 33%, 53% and 13% of the clinical tools assessed as having high, moderate and low quality, respectively. The COSMIN approach for psychometric performance of all clinical tools is graded as sufficient except for the Indevus Urgency Severity Scale which has insufficient rating. To avoid reporting bias, all included studies were assessed using the COSMIN risk of bias analysis and GRADE evidence reporting analysis, and the results reflect the findings of these analyses.

Discussion

The psychometric properties of clinical tools used to evaluate overactive bladder symptoms were investigated in this review. Our review included 40 studies reporting 15 clinical tools, including seven original scales and eight modified versions. The Overactive Bladder Symptom Score, Overactive Bladder Questionnaire and Neurogenic Bladder Symptom Score were the most extensively tested clinical tools among the original scales whereas the modified scales included the Overactive Bladder-Bladder Assessment Tool, International Consultation on Incontinence Questionnaires-Female Lower Urinary Tract Symptoms, International Consultation on Incontinence Questionnaires-Male Lower Urinary Tract Symptoms and International Consultation on Incontinence Questionnaires-Bladder Diary. Among the psychometric properties examined for Overactive Bladder Symptom Score in the included studies, test–retest reliability was rated as very good in six of the eight studies in which it was examined (75%), internal consistency was rated as very good in five of seven studies (71%), validity was rated as very good in seven of eight studies (82%), and responsiveness was rated as very good in two of three studies (67%). Overactive Bladder Symptom Score and Overactive Bladder Questionnaire were assessed as having similar GRADE evidence quality for a wide range of validation measures and similar COSMIN qualities. However, the Overactive Bladder Symptom Score appeared to be the most diverse and flexible clinical tools across different study settings.

Our study found that Overactive Bladder Symptoms Score and Overactive Bladder Questionnaire have the best rating in responsiveness across the identified clinical tools. This suggests that they can be highly sensitive clinical tools and detect treatment-related changes easily in patient's symptom scores. To achieve this clinical benefit of responsiveness, the International Consultation on Incontinence suggests the use of responsive condition-specific clinical measures in clinical practice and research to accurately detect and monitor patients' symptoms.[64] Our study found that both the Overactive Bladder Symptom Score and the Overactive Bladder Questionnaire are supported by high-GRADE evidence. However, the Overactive Bladder Symptom Score focuses only on overactive bladder symptoms whereas the Overactive Bladder Questionnaire evaluates quality of life and bother symptoms. The integration of quality of life and bother symptoms into a single clinical tool could affect the efficacy parameters of that tool.[65] By excluding bother symptoms, the Overactive Bladder Symptom Score may offer a more objective view of symptoms. For instance, patients who experience similar levels of incontinence have varied bother symptoms. Moreover, unlike the Overactive Bladder Symptom Score, the Overactive Bladder Questionnaire does not quantify overactive bladder symptoms.[65]

The applicability of clinical measures depends on the quality of the measure, which must be validated. A sound and validated measure offers an

appropriate, feasible, valid and reproducible evaluation of patients' concerns and can be used to monitor their recovery.[66] Clinical tools are recommended for use in clinical practice based on the clarity, simplicity, number, quality and strength of psychometric properties.[66] To receive a 'highly recommended' status from the International Consultation on Incontinence, the psychometric properties of an evaluated instrument, such as validity, reliability and responsiveness, must display established rigor and soundness.[64] The Overactive Bladder Symptom Score, which is widely used across culturally diverse populations,[36,37,42–44,46,57–60,65,67–70] demonstrated higher ratings for most of the tested psychometric properties than the other identified clinical tools. In addition, our study found that the Overactive Bladder Symptom Score provides a better assessment of overactive symptoms than both the Overactive Bladder Questionnaire and the Neurogenic Bladder Symptom Score, which are more focused on evaluating how an overactive bladder impacts and burdens daily life.[71] Blaivas and colleagues reported that the Overactive Bladder Symptom Score is a valid tool that evaluates all aspects of overactive bladder symptoms and may be used as a symptom score.[65]

Our systematic review employed a sound, systematic, comprehensive search strategy, using relevant search terms to identify studies validating clinical tools used to assess overactive bladder symptom severity. The COSMIN risk of bias and modified GRADE approaches were applied to assess the methodological and evidence quality of examined clinical tools in the included studies. Our review also has some limitations, including (1) the potential for language bias due to the exclusion of non-English studies; (2) the potential for publication bias due to the exclusion of conference abstracts, grey literature and unpublished reports, which may result in overlooking potentially vital information; (3) no study investigated the structural validity and only one study investigated the content validity of the Overactive Bladder Symptom Score and rated it doubtful.

Our review found that Overactive Bladder Symptom Score, Overactive Bladder Questionnaire and Neurogenic Bladder Symptoms Score as the most widely validated clinical measures across several countries with sound psychometric properties. Among the identified clinical measures, Overactive Bladder Symptom Score is the most culturally diverse and psychometrically sound clinical tool supported by studies of good methodological quality and high-GRADE evidence quality among people with urgency urinary incontinence due to overactive bladder. The Overactive Bladder Symptom Score might be adopted as a single clinical tool capable of assessing the symptoms of overactive bladder in clinical practice and research settings because it specifically evaluates all the overactive bladder symptoms. Although, no included study investigated the structural validity of the Overactive Bladder Symptom Score and only one study investigated the content validity of the Overactive Bladder Symptom Score and rated it doubtful. Further studies are required to investigate the content validity and structural validity of the Overactive Bladder Symptom Score.

Clinical messages

- The Overactive Bladder Symptom Score is characterized by sound, cross-cultural suitability with strong psychometric findings across diverse cultural backgrounds.
- The Overactive Bladder Symptom Score can be utilized to evaluate overactive bladder symptoms.

Author Contributions

Mohammed Usman Ali contributed to conceptualisation, data curation, formal analysis, investigation, methodology, writing original draft, review and editing. Stanley John Winser contributed to conceptualisation, methodology, supervision, validation, review and editing. Priya Kannan contributed to conceptualisation, formal analysis, methodology, investigation, supervision, validation, and review and editing. George S Kranz contributed to conceptualisation, methodology, investigation, supervision, validation, review and editing. Kenneth Nai-Kuen Fong contributed to conceptualisation, methodology, supervision, validation and review and editing.

Declaration of conflicting interests

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Supplemental Material

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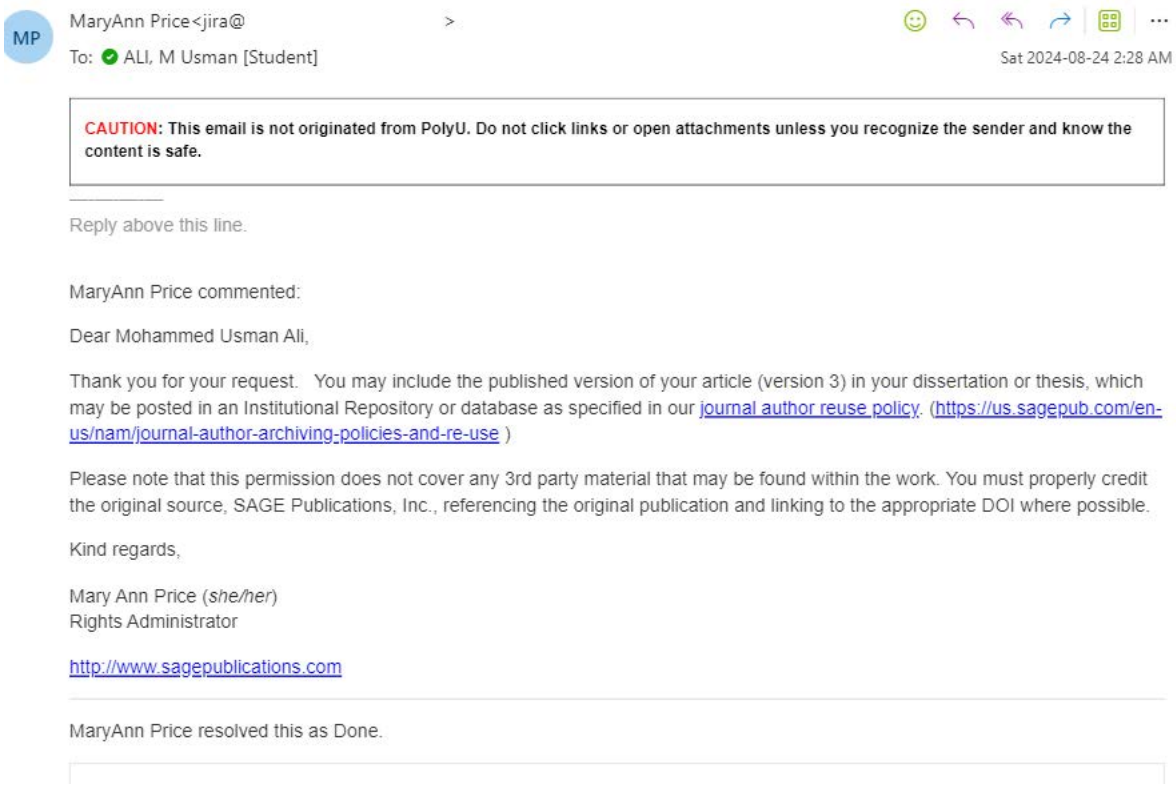

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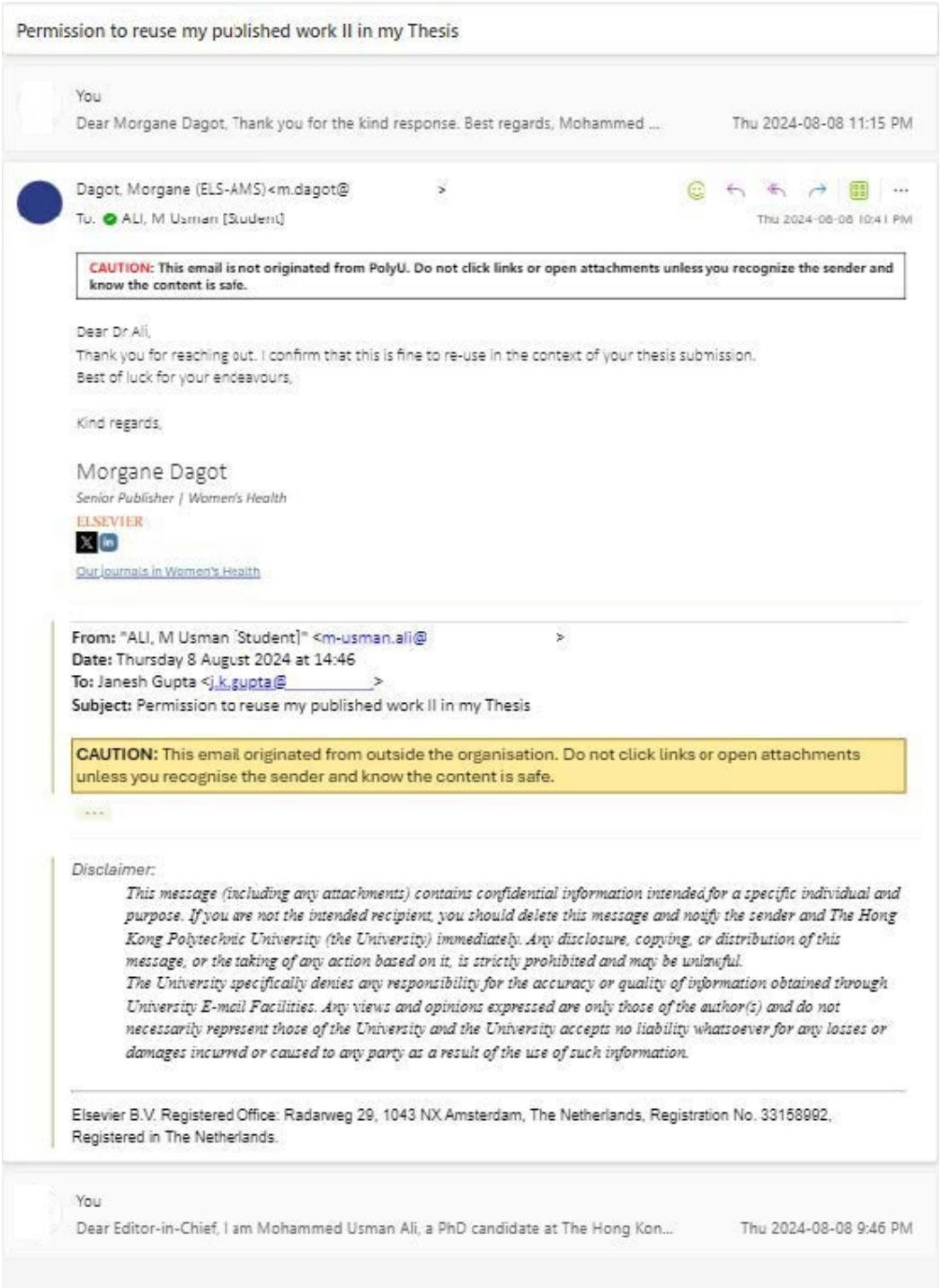

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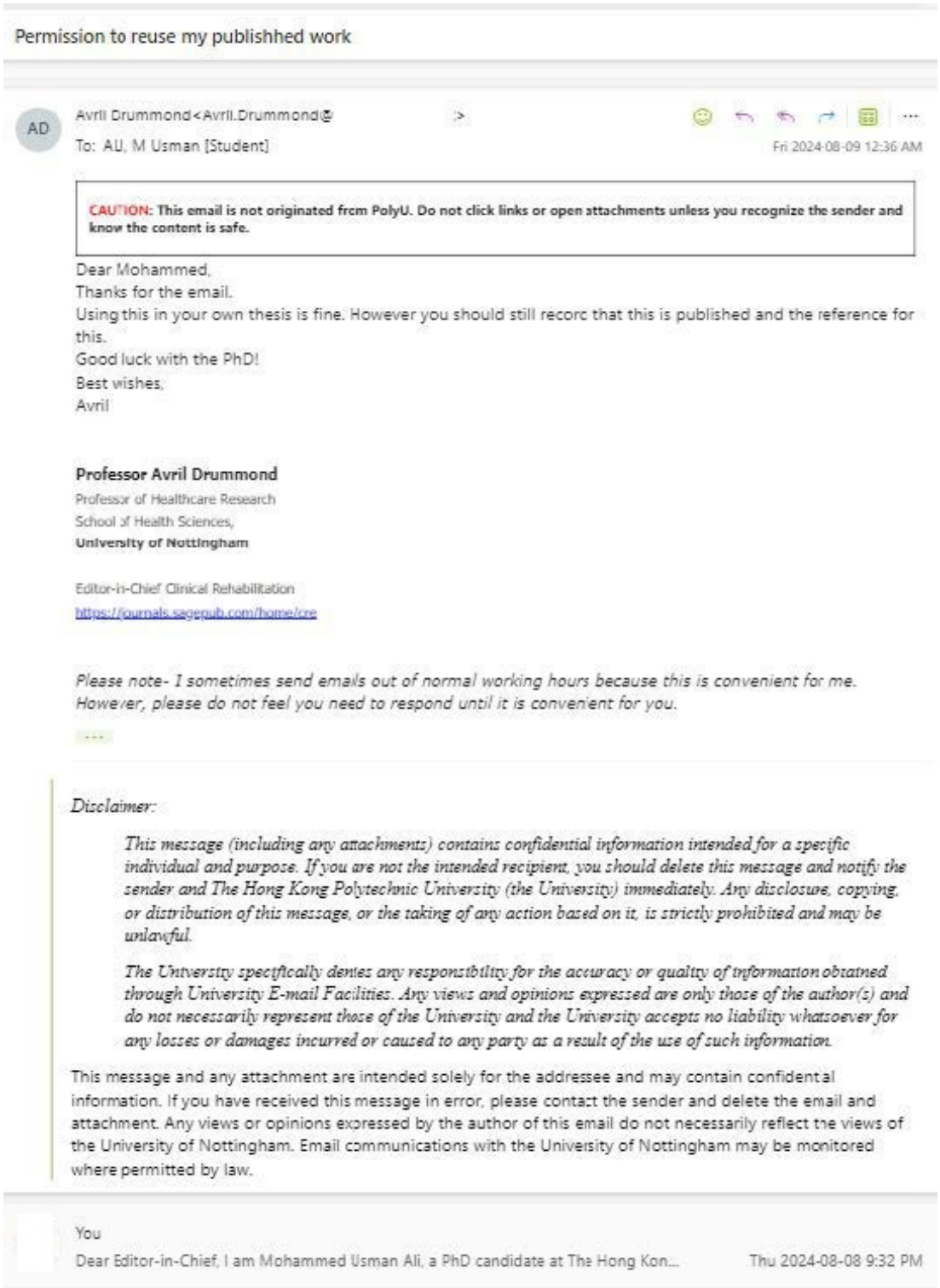

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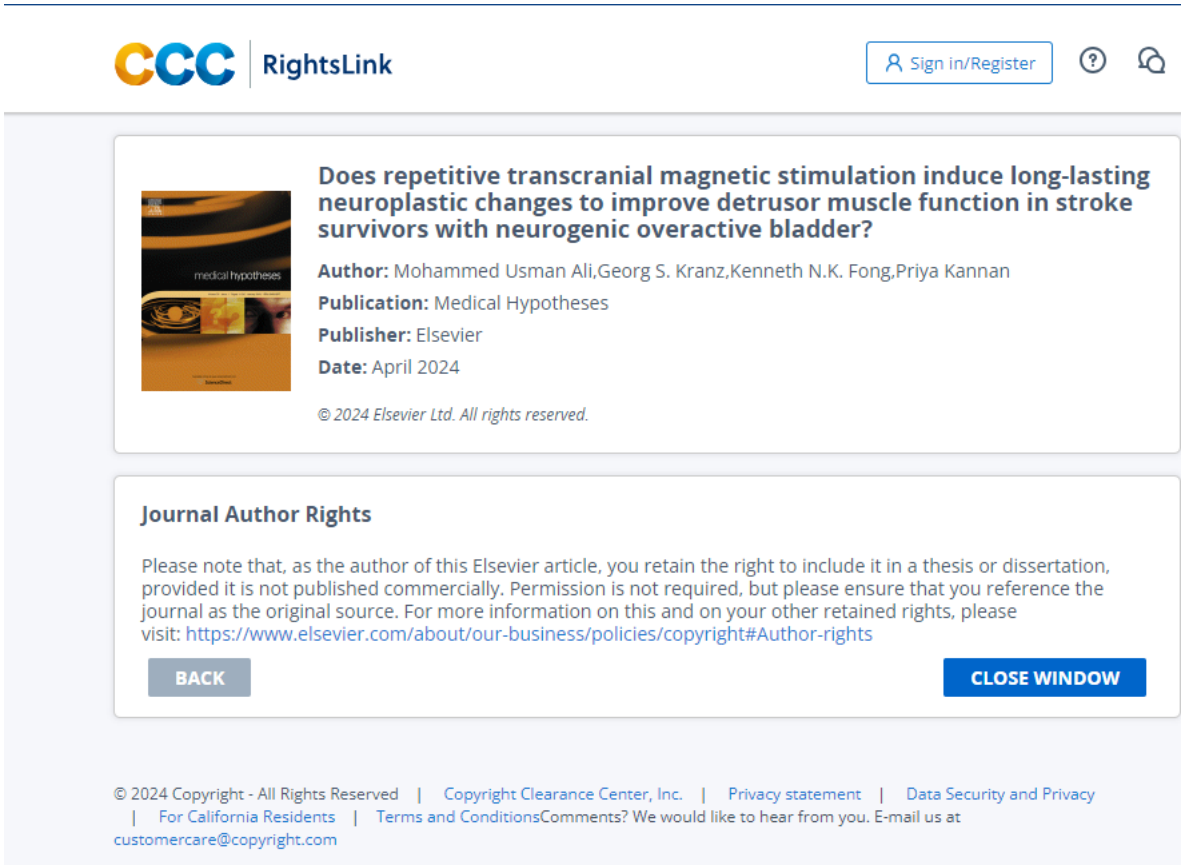

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Does repetitive transcranial magnetic stimulation induce long-lasting neuroplastic changes to improve detrusor muscle function in stroke survivors with neurogenic overactive bladder?

Author: Mohammed Usman Ali,Georg S. Kranz,Kenneth N.K. Fong,Priya Kannan

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