MONITORING OF SPINE CURVATURE PROGRESSION OF ADOLESCENT IDIOPATHIC SCOLIOSIS (AIS) PATIENTS USING THREE-DIMENSIONAL ULTRASOUND

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Monitoring of Spine Curvature Progression of Adolescent Idiopathic Scoliosis (AIS) Patients Using Three-dimensional Ultrasound

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Philosophy

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CERTIFICATE OF ORIGINALITY

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_ _ (Signed)

Lai Ka Lee (Name of Student)

ABSTRACT OF THE THESIS

To detect curve progression of adolescent idiopathic scoliosis (AIS), X-ray examination using the Cobb method is the gold standard in clinical practice with a 5-degree increment being the cut-off threshold. Three-dimensional ultrasound imaging, which is radiation-free, has been validated for the assessment of spinal deformity in AIS by locating specific bony landmarks. Although replacing X-ray examination by ultrasound can potentially lead to significant reduction of radiation for scoliosis patients, there is a paucity of study defining the role of three-dimensional ultrasound in monitoring scoliosis progression. The objective of this study was to investigate whether three-dimensional ultrasound can provide comparable results to radiographic Cobb angle in assessing curve progression in AIS patients.

In this study, the three-dimensional ultrasound system, Scolioscan, was first validated for its intra-rater and inter-rater reliability with 30 subjects respectively, and the results showed the measurement had excellent reliability. 200 subjects (62 male and 138 female subjects; 8-26 years of age, mean of 14.2 ± 2.8 years) with suspected AIS or diagnosed AIS of different severity (Cobb angle of 10 degrees to 85 degrees) were included for the evaluation of the feasibility of three-dimensional ultrasound in assessing scoliosis progression.

Each subject underwent bi-planar low-dose X-ray EOS and three-dimensional ultrasound Scolioscan scanning on the same date for each clinical visit. Subjects underwent second assessment with time intervals of 3-32 months. Manual measurement

of scoliotic curvature was conducted by drawing lines along the transverse processes and laminae on the coronal ultrasound images obtained by the volume projection imaging method, as ultrasound transverse processes angle. Traditional Cobb measurement was conducted on X-ray images. Cobb angle and ultrasound transverse processes angle increments of five degrees or more on the maximum curvature for each subject represented scoliosis progression detected by X-ray assessment and ultrasound assessment, respectively.

The correlation between the measurements from the three-dimensional ultrasound and X-ray was examined. A strong correlation in terms of R^2 value of 0.8679 was obtained between ultrasound transverse processes angle and radiographic Cobb angle for 432 curves. Using the radiographic Cobb angle as the gold standard, the sensitivity and specificity of the ultrasound transverse processes angle measurement for detecting scoliosis progression were presented. Among 200 subjects, 182 were found to possess scoliosis in the first visit or develop scoliosis in follow-up visits. Among 182 scoliosis subjects, 31 of them showed scoliosis progression in X-ray assessment while 27 of them showed scoliosis progression in both X-ray assessment and ultrasound assessment. The sensitivity and specificity of using three-dimensional ultrasound for detecting scoliosis progression were 0.87 and 0.93, respectively. The negative likelihood ratio of the diagnostic test for scoliosis progression by the three-dimensional ultrasound imaging system Scolioscan was 0.14. For the four false negative cases, the potential causes could be inconsistent postures between radiographs taken, the relatively poor ultrasound image quality on the transverse processes at the thoracic-lumbar region, and subject movement during ultrasound assessment.

This study indicated a strong correlation between the ultrasound transverse processes angle and radiographic Cobb angle with high sensitivity, specificity and low negative likelihood ratio of three-dimensional ultrasound imaging. Three-dimensional ultrasound imaging is sufficiently comparable to radiographs in monitoring scoliosis progression for the 200 subjects tested, indicating its potential for reducing AIS patient's exposure to radiation during follow-up examinations. Further studies with larger number of subjects for longer follow-up period are suggested.

PUBLICATIONS ARISING FROM THE THESIS

Journal Paper

1. Zheng YP, Lee TTY, Lai KK, Yip BH, Zhou GQ, Jiang WW, Cheung JC, Wong MS, Ng BK, Cheng JC, Lam TP. A reliability and validity study for Scolioscan: a radiation-free scoliosis assessment system using 3D ultrasound imaging. Scoliosis Spinal Disorders. *Scoliosis and Spinal Disorders.* 2016. 11:13.
2. Zhou GQ, Jiang WW, Lai KKL, Zheng YP. Automatic Measurement of Spine Curvature on 3-D Ultrasound Volume Projection Image With Phase Features. *IEEE Transactions on Medical Imaging.* 2017. 36(6):1250-1262.
3. He C, To MK, Cheung JP, Cheung KM, Chan CK, Jiang WW, Zhou GQ, Lai KK, Zheng YP, Wong MS. An effective assessment method of spinal flexibility to predict the initial in-orthosis correction on the patients with adolescent idiopathic scoliosis (AIS). *PLoS One.* 2017. 12(12):e0190141.
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5. Jiang WW, Zhou GQ, Lai KL, Hu SY, Gao QY, Wang XY, Zheng YP. A fast 3-D ultrasound projection imaging method for scoliosis assessment. *Mathematical Biosciences and Engineering.* 2019. 16(3):1067-1081.
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accurate for quantitative assessment of spinal deformity in Adolescent Idiopathic Scoliosis (AIS): a detailed analysis with EOS radiography on 952 patients. *Ultrasound in Medicine & Biology*. 2019. 45(11):2866-2877.

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9. Lai KKL, Lee TTY, Lee MKS, Hui JCH, Zheng YP. Scolioscan Air- Portable Radiation-free Three-dimensional Ultrasound Imaging Assessment System for Scoliosis: Development and Validation. *Sensor*. 2021. 21(8):2958.

Conference Proceeding

1. Lai KKL, Lee TTY, Cheng JJC, Castelen RM, Lam TP, Zheng YP. Monitoring of Spine Curvature Progression of Adolescent Idiopathic Scoliosis (AIS) Patients Using Three-dimensional Ultrasound. 2020 SOSORT World Meeting.

Journal Paper being Prepared for Submission

1. Lai KKL, Lee TTY, Cheng JJC, Castelen RM, Lam TP, Zheng YP. Monitoring of Spine Curvature Progression of Adolescent Idiopathic Scoliosis (AIS) Patients Using Three-dimensional Ultrasound. Being prepared for submission.

2. Lee TTY, Lai KKL, Cheng JCY, Castelein RM, Lam TP, Zheng YP. Investigation of the Phenomenon of Coronal-sagittal Curvature Coupling using 3D Ultrasound. Being prepared for submission.

3. Lee TTY, Lai KKL, Cheng JCY, Castelein RM, Lam TP, Zheng YP. 3D Ultrasound Imaging Provides Reliable Angle Measurement with Accuracy Comparable to X-ray on Patients with Idiopathic Scoliosis. Being prepared for submission.

4. Pang H, Wong YS, Yip BHK, Hung ALH, Chu WCW, Lai KKL, Zheng YP, Chung TWH, Sharma G, Cheng JCY, Lam TP. Using Ultrasound for Screening Scoliosis to Reduce Unnecessary Radiographic Radiation - A Prospective Diagnostic Accuracy Study on 442 Schoolchildren Corresponding. Being prepared for submission.

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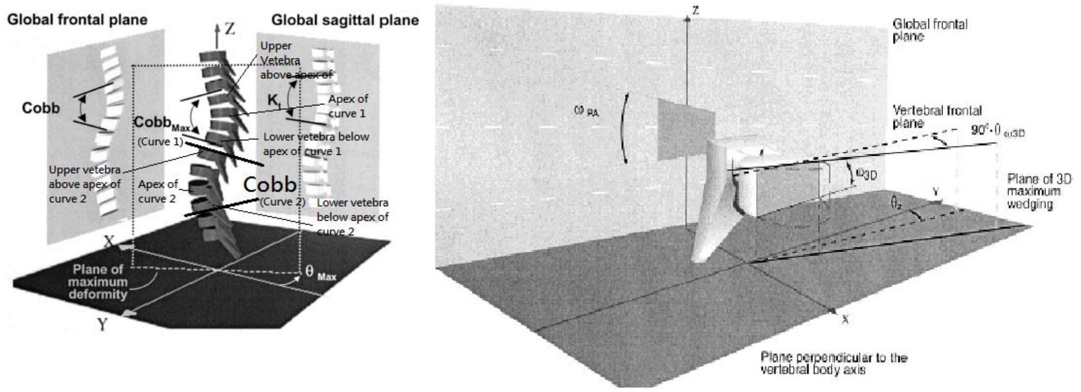

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LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
3DUS	Three-dimensional ultrasound
AIS	Adolescent idiopathic scoliosis
BMI	Body mass index
CT	Computed tomography
FN	False negative
FP	False positive
MRI	Magnetic resonance imaging
RCA	Radiographic Cobb angle
TN	True negative
TP	True positive
USTPA	Ultrasound transverse processes angle
USSPA	Ultrasound spinous processes angle
VPI	Volume projection imaging

CHAPTER 1 INTRODUCTION

1.1. Background

Scoliosis is a three-dimensional (3D) spine deformity including structural, lateral, rotated curvature, and it is associated with asymmetries of thoracic cage and extremities (Cheng et al. 2015, Brink et al. 2017). The spine curvature in the coronal plane is commonly measured by the Cobb method as Cobb angle. Scoliosis is diagnosed with the Cobb angle of 10 degrees or more (Cheng et al. 2015). Idiopathic scoliosis is the case with scoliosis that develops in childhood spontaneously, and the majority of idiopathic scoliosis occurs from ages 10 to 16 known as adolescent idiopathic scoliosis (AIS) (Cassella et al. 1991). The prevalence of AIS is 0.47-5.2% of the general population (Konieczny et al. 2013). In Hong Kong, the prevalence of AIS is 3-4% (Fong et al. 2015). Once the spine deformity is developed, there is a risk of progression and the progressive rate could reach up to ten degrees per year (Reamy and Slakey 2001). Risk factors include age, skeletal maturity and scoliosis apex location. Girls suffer from a higher risk of progression (Lonstein and Carlson 1984). Progressed scoliosis may cause compression onto nerves, hearts or lungs, leading to heart and lung problems (Reamy and Slakey 2001, Li et al. 2017).

Among a group of untreated AIS patients, only 29.1% showed curve progression while 17% of them had curve progression that required medical intervention (Lara et al. 2017). To find out those progressed cases for applying medical treatment, frequent monitoring of spine curvature progression is needed for AIS patients. Regular check-up for every 6 months is recommended for growing patients until skeletal maturity (Schulte et al.

2008). X-ray is the most commonly used technology in detecting scoliosis and curve progression (Greiner 2002). Cobb angle in coronal plane radiographs with 5-degree increment between visits indicates scoliosis progression (Cobb 1948, Soucacos et al. 1998). Cobb angle is defined by drawing a parallel line to the upper border of the most tilted vertebra above the curve's apex, and a second parallel line to the lower border of the most tilted vertebra below the apex. The angle between the two lines is the Cobb angle (Kim et al. 2010). The accumulation of radiation dose is reported with risk of cancers for AIS patients with regular follow-up of full spine radiography (Doody et al. 2000, Simony et al. 2016). Therefore, regular check-up interval of scoliosis is suggested to be at least 6 months apart, though the curve progression is fast (Levy et al. 1994).

There are several radiation-free technologies for detecting scoliosis progression but they are not commonly used clinically due to various limitations of the technologies. Surface and electromagnetic topography systems can only provide surface information but not internal anatomical information of spine (Komeili et al. 2015, Knott et al. 2016). Standing magnetic resonance imaging (MRI) requires specific and large installation space and extremely high operating cost and operating time (Ungi et al. 2014).

The feasibility of using freehand three-dimensional ultrasound (3DUS) imaging for evaluating 3D anatomic profiles of spines has been demonstrated (Huang et al. 2005a, Huang et al. 2005b, Chen et al. 2013, Li et al. 2015), as well as for single assessment of scoliosis (Chen et al. 2013, Cheung et al. 2015). There is a commercially available 3DUS assessment system, Scolioscan (Model SCN801, Telefield Medical Imaging Ltd, Hong Kong), for spine imaging and its feasibility for measuring coronal spine curvature has been reported in recent studies (Cheung et al. 2013, Cheung et al. 2015a, Cheung et al. 2015b, Zheng et al. 2016, Brink et al. 2018, Wong et al. 2019). The ultrasound transverse processes angle, through localizing transverse processes on spine phantom, had been demonstrated to correlate closely with radiographic Cobb angle (Lee at al. 2020). This technology can significantly reduce the unnecessary radiation exposure suffered by AIS patients, and its potential for monitoring spine curvature progression in regular follow-up visits is worth under further investigation.

Since spinal curves progress in 3D manner (Perdriolle et al. 1993, Villemure et al. 2001), 3D imaging assessments can provide a more comprehensive interpretation of spine deformities. The radiation-free 3DUS system is potentially useful to provide extra 3D information of spines for longitudinal follow-up.

1.2. Aim and Objectives

The overall aim of this study is to investigate the feasibility of using the 3DUS system – Scolioscan with ultrasound transverse processes angle measurement for monitoring spine curvature progression in AIS patients. The following specific objectives were aimed through this study:

A. To validate the intra-rater reliability and inter-rater reliability of Scolioscan

B. To evaluate the correlation between ultrasound transverse processes angles and radiographic Cobb angles

C. To evaluate the feasibility of using 3DUS for detecting the change of spinal deformities, using traditional radiographs as references

1.3. Thesis Outline

This dissertation is divided into the following chapters.

Chapter 1 introduces the background information and potential of the study, the overall aim and objectives of the study, and the dissertation outline.

Chapter 2 conducts comprehensive literature review on previous studies related to AIS, scoliosis progression, and scoliosis assessment.

Chapter 3 describes the details of the human subjects experiment including the experimental materials, protocols and evaluation methods.

Chapter 4 reports comprehensive results obtained from the human subject tests as well as various methods for data analysis.

Chapter 5 discusses the 3DUS performance in monitoring scoliosis curvature progression. Limitations of the methodology, potential applications and future research directions are also discussed.

Chapter 6 summarizes conclusions drawn from this study and some recommendations sprang up from this study.

CHAPTER 2 LITERATURE REVIEW

2.1. Adolescent Idiopathic Scoliosis (AIS)

2.1.1. Definition

Scoliosis is a three-dimensional (3D) spine deformity including structural, lateral, rotated curvature (Brink et al. 2017). It is associated with asymmetries of the thoracic cage and the extremities (Cheng et al. 2015). Lateral curvature of more than ten degrees in coronal plane is considered as clinically significant (Schwab et al. 2002). There are three common types of scoliosis classified by the Terminology Committee of the Scoliosis Research Society: idiopathic scoliosis, congenital scoliosis, neuromuscular scoliosis (Hebela et al. 2009). For idiopathic scoliosis, the spine is normal at birth but develops a deformity in childhood spontaneously, accounts for most cases of scoliosis. Majority of idiopathic scoliosis occurs from age 10 to 16, which is the period between the start of puberty and skeleton maturity, thus it is also known as adolescent idiopathic scoliosis (AIS) (Cassella et al. 1991).

2.1.2. Prevalence

A previous study reported the prevalence of AIS is 0.47-5.2% of the general population that varies by district and the study of the year (Konieczny et al. 2013). The prevalence of AIS is increasing in the recent years as high as 10% in the northern countries (Grivas et al. 2006a). The study also reported that the prevalence among girls is twice higher than that of boys. In Hong Kong, school screening for AIS consists of a voluntary 3-tier assessment provided by the Department of Health. The Government of the Hong Kong Special Administrative Region has been implementing the scheme since 1995

(Fok et al. 2020). With the public scoliosis screening scheme, two large population-based studies were carried out with 300,00 participants. It is reported that 3-4% of kids are affected by AIS (Luk et al. 2010, Fong et al. 2015). The prevalence is also found to be increased with the improved sensitivity of public screening technologies (Fong et al. 2015).

2.2. Detection of AIS

Scoliosis screening is a routine procedure for adolescents in certain countries for years. Scoliosis screening itself carries little cost and negligible risk to the patients (Horne et al. 2014). Physical examination with the scoliometer is commonly practiced clinically for screening, named forward bending test. The forward bending test was first described by William Adams for scoliosis detection in 1865 (Fairbank 2004). The subjects are first instructed to stand keeping the feet approximately 15 cm apart with knee braced back. Then, the subjects are instructed to bend forward at the waist with shoulder loose, elbow straight and palms opposed, while the observation and assessments of the symmetry of the back from behind are carried out by the clinicians (Figure 2-1) (Grivas et al. 2006b).

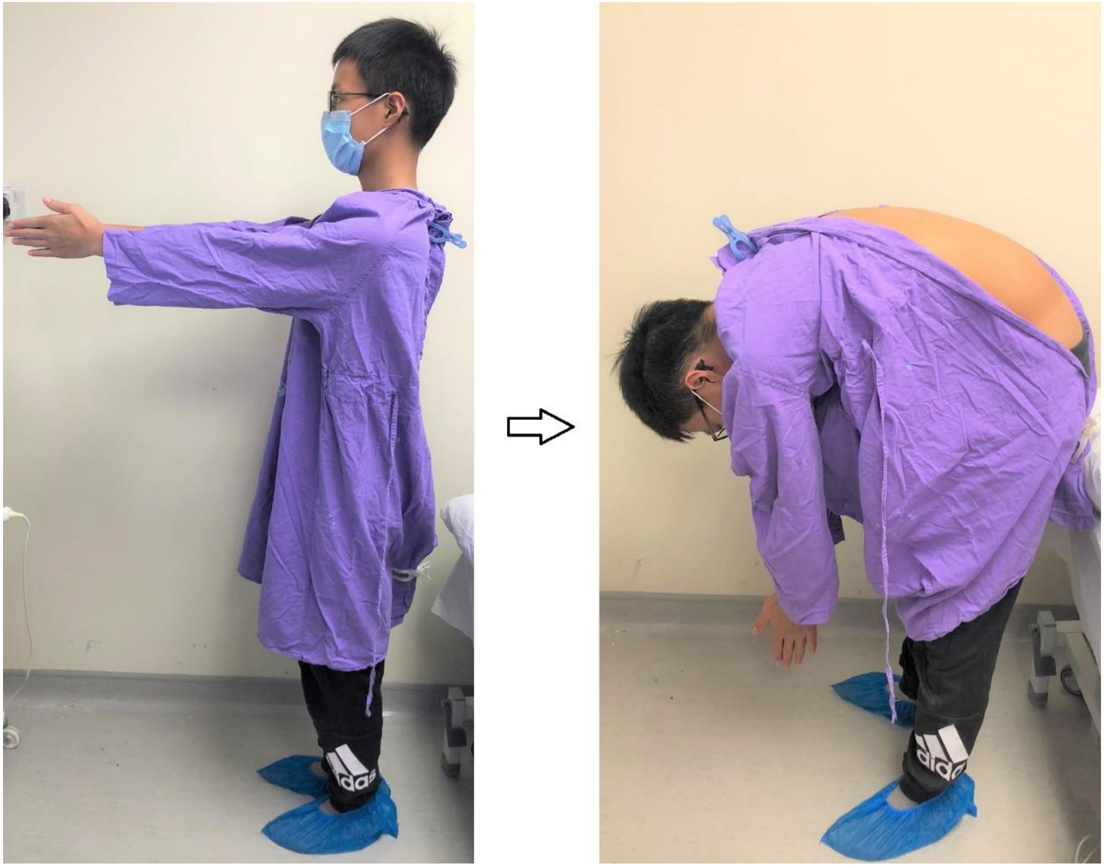


Figure 2-1. Diagram illustration of forward bending test

Scoliometer is commonly used for the assessment of back symmetry in forward bending test. A scoliometer is put flat on the patient's back with the greatest asymmetry in order to measure the angle of trunk rotation (Figure 2-2) (Roach 1999). For cases of more than five degrees in trunk rotation, radiographic imaging on spines is needed for diagnosis. For regular check-ups afterwards, radiographic imaging evaluation on spines are also recommended (Yawn et al. 1999).

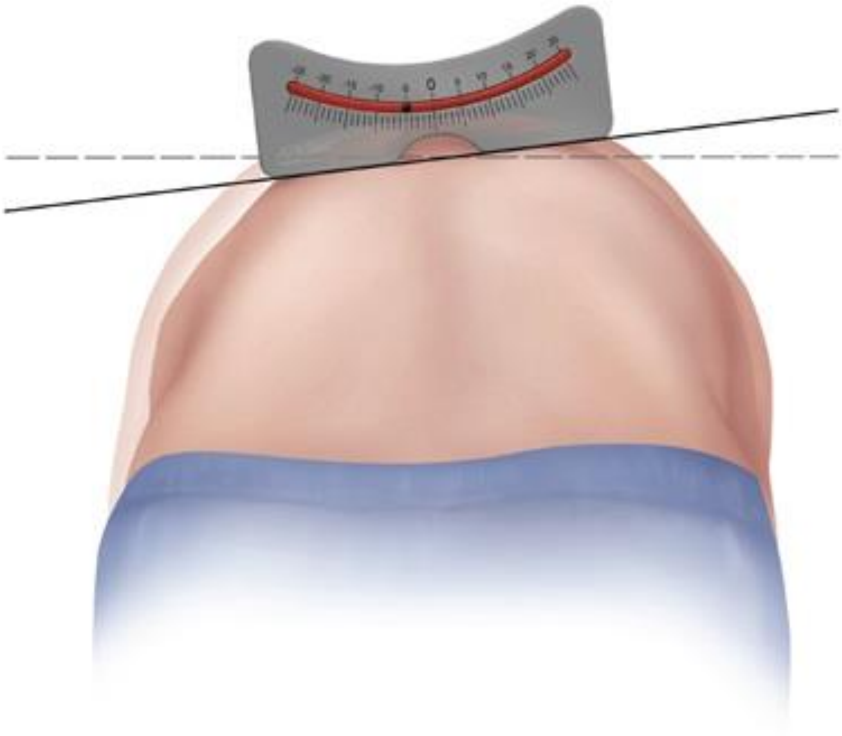


Figure 2-2. Diagram illustration of the usage of the scoliometer (Horne et al. 2014)

In Hong Kong public screening scheme, an adolescent with angle of trunk rotation exceeding five degrees in the forward bending test screening would be submitted to second-tier assessment by moiré topography (Fok et al. 2020). Moiré topography is an optical stereometric method of 3D perception of the formation of a surface (Takasaki 1970). Using the film with the standard raster, the subject is placed behind the moiré screen facing forwards with his back to the back of the raster. They are instructed to stand in the position with scapulae and buttocks touching the raster, and the arms hanging by the side of the body (Laulund 1982). The screen picture is taken with an ordinary camera and then evaluated for the asymmetry of the contour lines (Figure 2-3) (Willner 1979). The maximum asymmetry between the fringes of the convex and the concave half of the back is found above, below or lateral to the contact surface of the scapulae (Willner 1979). Cases of two or more moiré lines would be referred for further radiographic assessments (Fok et al. 2020).

Figure 2-3. Diagram illustration of moiré topography assessment (Laulund et al. 1982)

2.3. Progression of AIS

Once the spine deformity is developed, it may or may not progress. A recent study demonstrated a group of untreated patients with AIS longitudinally and only 29.1% of them showed curve progression, despite the gender not the curve type. No significant relationships were found between gender nor curve type and surgical intervention or curve progression. It also reported that only 17% of diagnosed patients with AIS have curve progression that requires medical intervention (Lara et al. 2017). Approximately 0.1-0.3% of diagnosed scoliosis patients with AIS requires operative treatment for deformity correction. Progression is more common in girls during the growth spurt at puberty (Negrini et al. 2018). Girls are eight times more likely to develop progressive curves and related severe diseases. Scoliosis affects the appearances in adolescents and the imbalance of spine muscles often causes back pain. In some cases, especially when it is untreated, it leads to visible deformity, emotional distress, and respiratory impairment from rib deformity (Horne et al. 2014). Severe scoliosis causes compression onto the nerves, heart or lungs, leading to heart and lung problems (Reamy and Slakey 2001, Li et al. 2017). All these related complications affect the ability to works and quality of life (Negrini et al. 2018).

To prevent developing severe scoliosis, frequent monitoring is needed for patients with AIS in order to detect the progressive curves. For growing children, a regular check-up from every six months is recommended until skeletal maturity (Schulte et al. 2008). Among those progressive curves, the progression rate varies with a few factors and could be more than ten degrees per year (Reamy and Slakey 2001). 5-degree increment in Cobb angle is an indicator of curve progression despite the inter- and intra-observer variability on curve measurements in radiographs of approximately 4° to 8° (Soucacos et al. 1998).

2.4. Three-dimensional (3D) Profile on Spine Curvature Progression

Spinal curves usually progress in 3D instead of only two-dimensional (2D) planes (Perdriolle et al. 1993, Villemure et al. 2001). Usually both disc wedging and vertebral body wedging occur with progressive scoliosis. The scoliotic curve progression begins at the intervertebral disc (Will et al. 2009). The deformation of the apical intervertebral disc initiates the progression of a scoliotic curve. The intervertebral discs wedging occurs followed by the scoliotic curve as to the apical vertebral wedging. When the spine deformity initiates, the intervertebral discs wedges and the spine deforms firstly at the level of the intervertebral discs. Due to the increased plasticity of the intervertebral disc, scoliotic curve then progresses through either torsion or apical vertebral wedging (Grivas et al. 2006c). And the vertebra rotation mainly follows the rib asymmetry which is the difference of ribs length between the convex and concave site. It is believed that autonomous nervous system asymmetrical action on the left and right site of the thoracic region triggers the blood drainage, nerve stimulation and muscle action imbalance between the two sites thus facilitates the asymmetric growth of ribs (Sevastik 2006, Castelein 2012, Brink et al. 2019). There are studies reported the progressive factors in idiopathic scoliosis, in 3D view. Those studies revealed that both asymmetric ribs, blood supply, and the intervertebral disc wedging leads to the deformation of vertebral body and posterior elements as transverse and spinous process as well as lamina. Then, develops the scoliotic curve progression (Korovessis et al. 2004, Grivas 2021).

A longitudinal study on a group of adolescents with progressive idiopathic scoliosis reported the vertebrae deformation in 3D during scoliosis progression. At the thoracic region, vertebral wedging increases with curve severity while axial rotation mainly increases towards curve convexity with scoliosis severity (Figure 2-4). In the Figure 2-4a, $Cobb_{max}$ for coronal curvature scoliosis and Kt for sagittal curvature thoracic kyphosis were labelled. In the Figure 2-4b, θz for axial rotation and $θω_{3D}$ for the vertebral wedging angle were labeled. There are also studies reporting the correlations of sagittal spinal shape and coronal scoliotic curvature (Hu et al. 2016, Hong et al. 2017). 3D imaging assessments can provide more complete interpretations of the spine deformities.

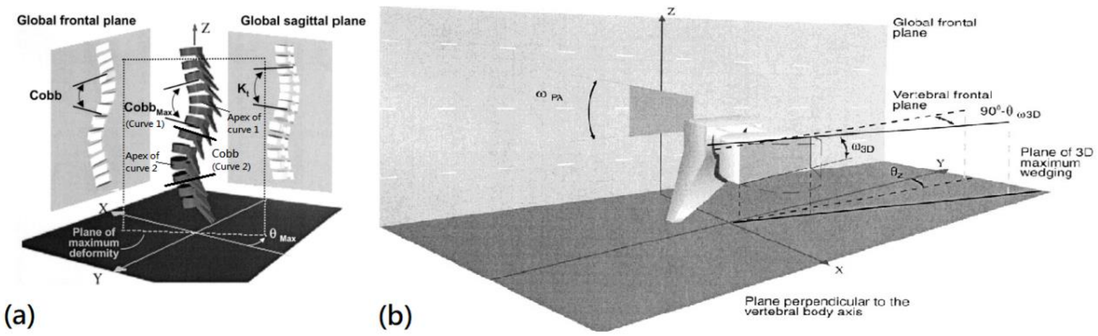


Figure 2-4. Deformed spine studied in various planes for (a) maximum curve angles ($Cobb_{max}$) in coronal profile and thoracic kyphosis (Kt) in sagittal profile; and (b) axial rotation (θ_z) and wedging angle ($\theta\omega_{3D}$) (Villemure et al. 2001)

Traditionally, computed tomography (CT) and magnetic resonance imaging (MRI) are used to reveal the 3D profile of spines (Birchall et al. 1997). However, they have several disadvantages like high radiation dose and long scanning time (Sett and Crockard 1991). There is a new EOS imaging unit which is a relatively low-dose X-ray system that allows 3D modelling of spines based on the biplanar X-rays (Newton et al. 2016, Rehm et al. 2017). Non-ionizing 3D ultrasound is also a potential assessment technology in studying the 3D profile of spines during curve progression.

2.5. Current Methods for Detection of AIS Progression

X-ray is the most commonly used technology in detecting scoliosis and curve progression (Greiner 2002). Using radiographs of full spine in coronal plane, the lateral curve of scoliosis can be presented by the Cobb angle (Figure 2-5).

2.5.1. Cobb Angle

Cobb angle is defined by drawing a parallel line to the upper border of the most tilted vertebra above the curve's apex and a second parallel line to the lower border of the most tilted vertebra below the apex. The angle formed from the two lines is the Cobb angle (Kim et al. 2010). X-ray does help in identifying scoliosis, as well as detecting curve progression. For traditional radiographs on spine, the case with a Cobb angle of ten degrees or more in the coronal plane is defined as scoliosis (Kim et al. 2010).

2.5.2. Progression Detected by X-ray

A change of five degrees or more in Cobb angle is an indicator of curve progression despite inter- and intra-observer variability on measuring the curves on radiographs (Soucacos et al. 1998). Radiograph-based Cobb's Method is regarded as the gold standard for assessing the progression of AIS thus AIS patients normally have to undergo regular x-ray assessment every four to six months until skeletal maturity is reached (Cobb 1960, Kim et al. 2010).

2.5.3. Limitation of X-ray

However, there is an accumulation of radiation dose, especially for AIS patients with regular follow-up for years. The repeated radiation exposure to X-ray is reported to be correlated with breast cancers (Doody et al. 2000, Simony et al. 2016). Therefore, regular check-up of scoliosis is suggested for at least six months intervals for growing children even though the curve progression is fast (Levy et al. 1994, Knott et al. 2014).

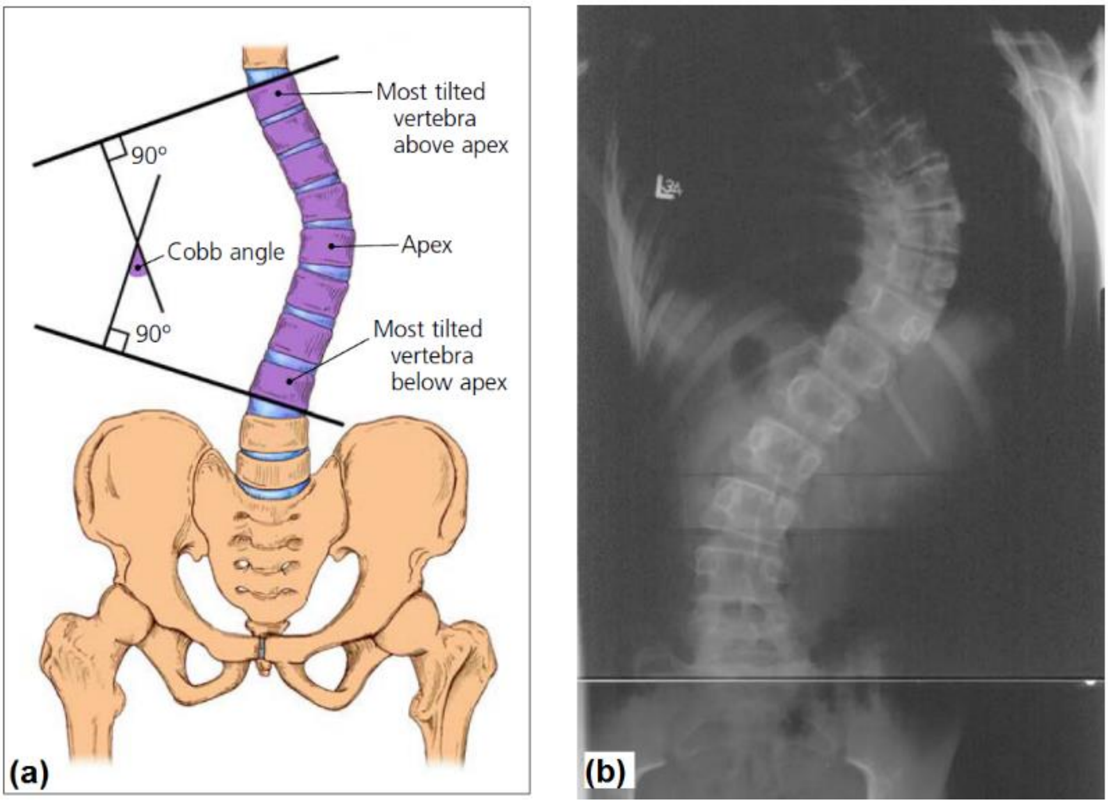


Figure 2-5. Cobb angle: (a) the most tilted vertebrae used in measuring the degree of scoliosis by Cobb method and (b) typical posteroanterior radiograph of spine in a scoliosis patient (Greiner 2002)

2.6. Alternatives for Detection of AIS Progression

To reduce the radiation exposure suffered by the patients with AIS, several alternatives have been developed like the surface topography system (Komeili et al. 2015, Knott et al. 2016) as well as the DIERS system (Girdler et al. 2020), low-dose bi-planar radiography EOS system, magnetic resonance imaging (MRI), and freehand three-dimensional ultrasound (3DUS) system (Ungi et al. 2014).

2.6.1. EOS Imaging

EOS is a biplanar X-ray imaging system manufactured by EOS imaging (formerly named Biospace Med, Paris, France) (Figure 2-6). It uses slot-scanning technology to produce high-quality images with less radiation than ordinary imaging techniques (Mckenna et al. 2012). This is a new radiography system with comparatively low dose of radiation, which contributed to the application of full body, simultaneous posteroanterior and lateral imaging procedures with radiation exposure concern (Figure 2-7) (Rehm et al. 2017). A previous study reported the effectiveness and efficiency of this technology. It reduces the radiation dose required to obtain a 2D image of the spine by 8 to 10 times with no significant difference in diagnostic information when comparing with traditional X-ray technology (Kalifa et al. 1998). The EOS imaging system has been used for the assessment of scoliosis progression in several studies with its low radiation dose and 3D features (Busscher et al. 2010, Wybier et al. 2013, Vergari et al. 2019). Despite, the radiation dosage of the EOS is considerably lower than traditional radiography but it is not negligible. It is also considered to be cost-ineffective due to its high equipment and installation cost (Mckenna et al. 2012). Using the EOS system for scoliosis longitudinal follow-up, there is still an accumulation of radiation dose that could lead to adverse effects related to diagnostic radiation.

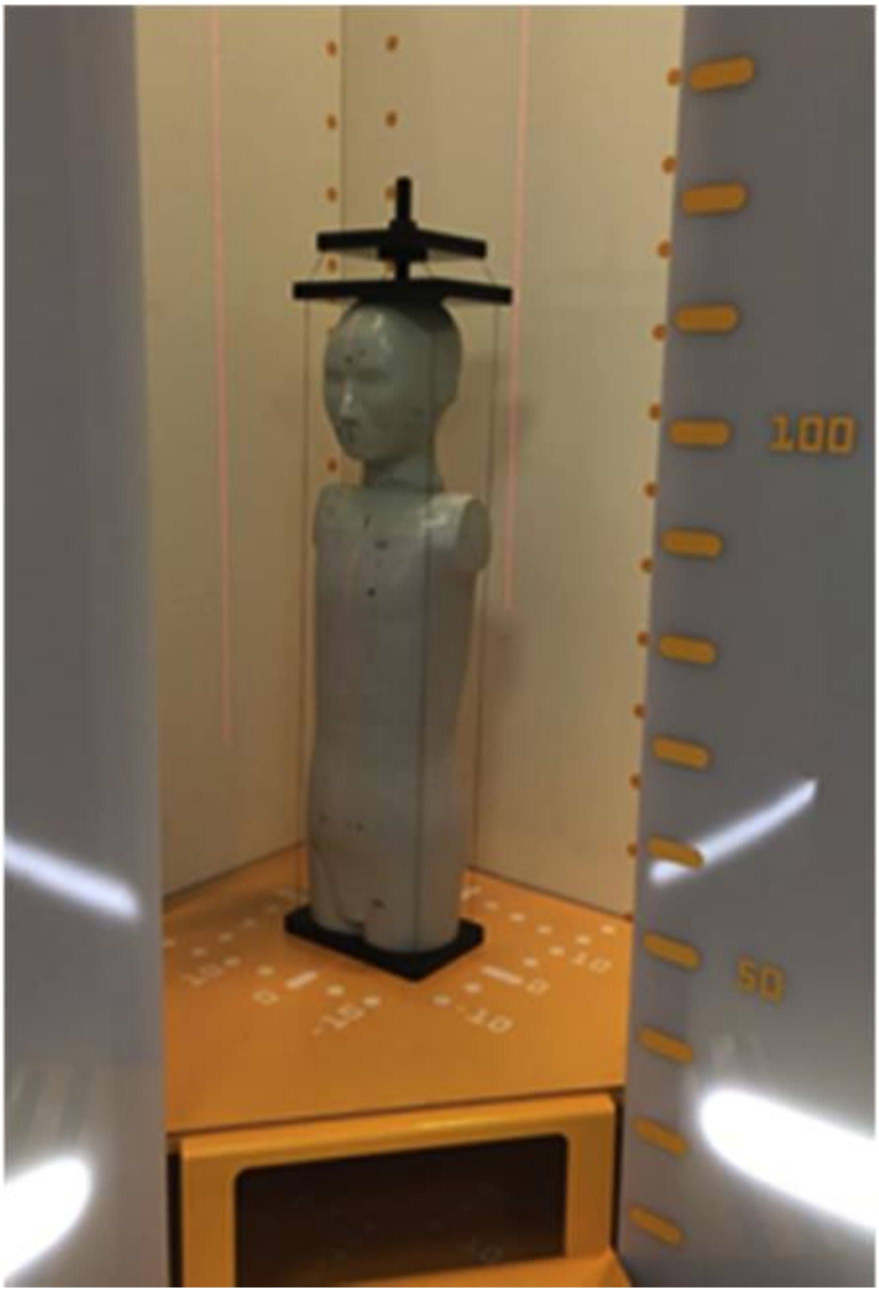


Figure 2-6. Diagram illustration of low dose X-ray EOS assessment on phantom (Alrehily et al. 2019)

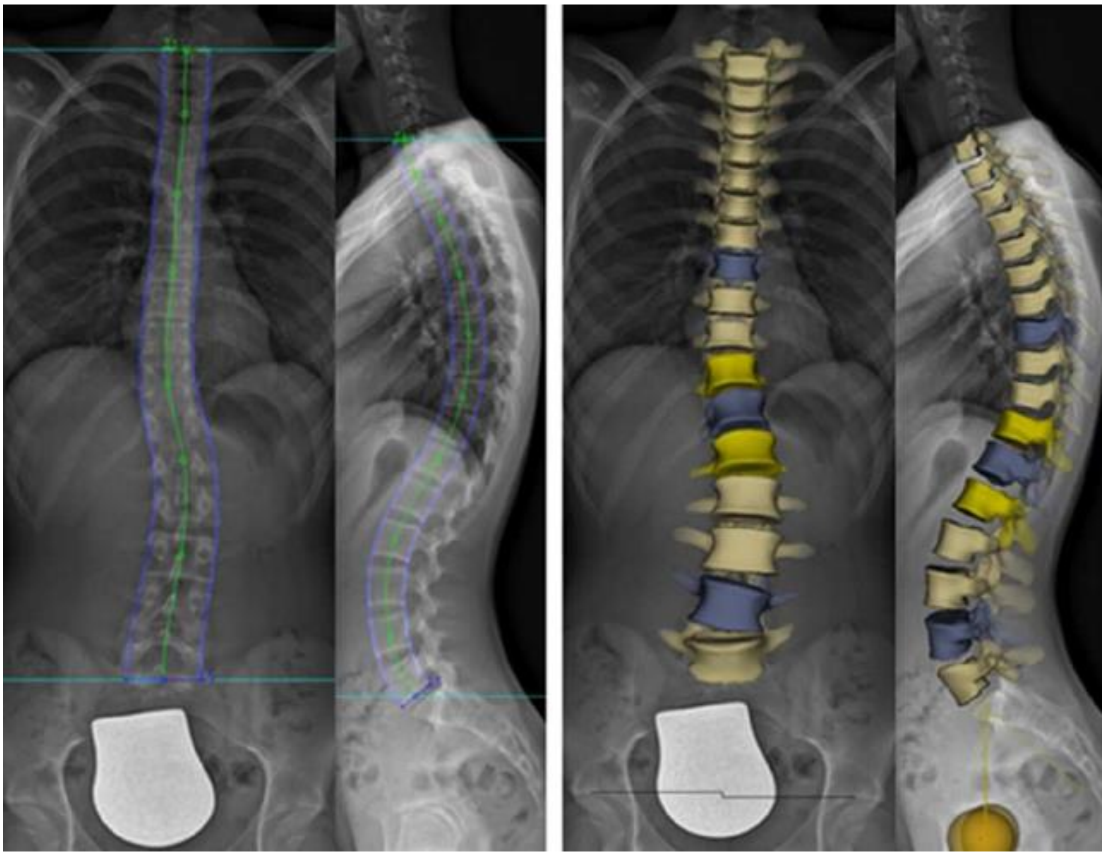
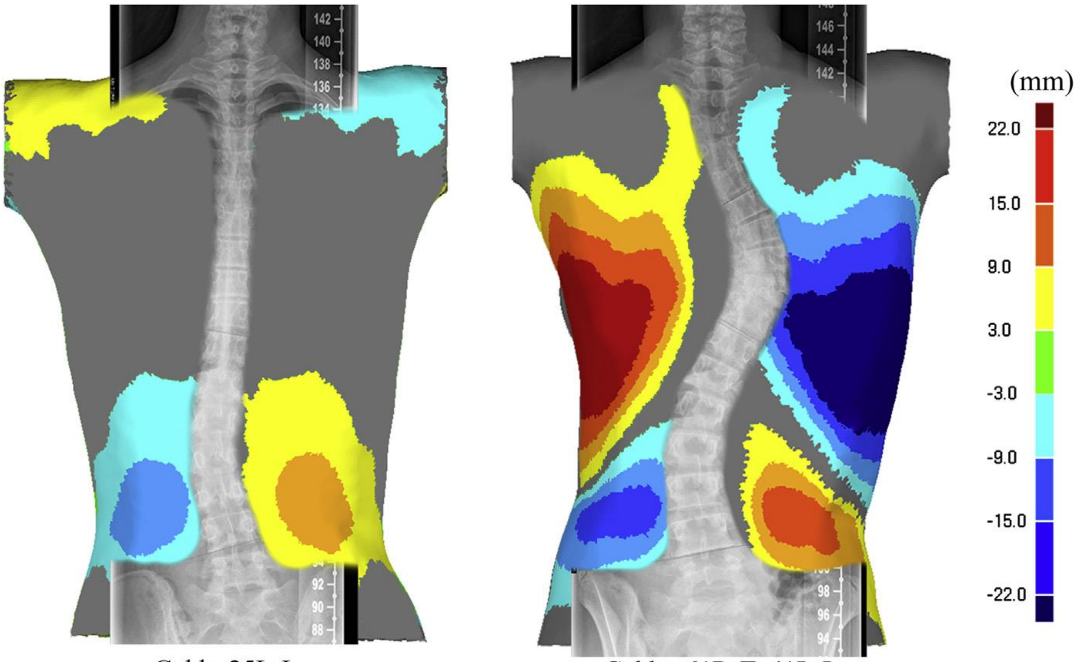


Figure 2-7. 3D reconstruction from biplanar X-rays using EOS (Rehm et al. 2017)

2.6.2. Surface Topography

Surface topography is a non-invasive method to investigate the 3D shape of the torso back surface (Figure 2-8). The abnormal torso shape usually correlates with scoliosis, and it is assumed when using this method for scoliosis diagnosis. Advanced to Moiré topography or other technique of measurement of back surface shape, there are several computed analysis methods for the back surface shape data collected by various surface topography scanners (Turner-Smith et al. 1988). Surface topography indices are usually calculated automatically by various surface topography scanners (Knott et al. 2016). Studies reported the attempt of using surface topography to project the Cobb angle and to monitor Cobb angle changes with various levels of success (Thometz et al. 2000, Goldbery et al. 2001, Adankon et al. 2013). A study demonstrated the potential of using surface topography asymmetry analysis for monitoring scoliosis progression. Using traditional radiography as a reference, the classification model of the surface topography system could detect 85.7% of the progression and 71.6% of the non-progression cases (Komeili et al. 2015). However, the actual internal anatomical information varies among individuals and the internal alignment of spine cannot be directly assessed, thus this kind of assessment of scoliosis is not accurate enough (Komeili et al. 2015, Knott et al. 2016).



Cobb=25L-L

Cobb= 61R-T; 41L-L

Figure 2-8. Diagram illustration of surface topography assessment results (Komeili et al. 2015)

2.6.3. DIERS

DIERS formetric 4-dimensional (4D; DIERS Medical Systems, Chicago, Illinois, USA) is one of the advanced surface topography systems developed in recent years and commonly applied in clinical procedures. Rasterstereography is a method of stereophotogrammetric surface measurement of the back, and the DIERS is a non-contact scanner to produce 3D reconstruction of the spine based on surface topography. A recent study reported the reliability of using DIERS for reconstruction of spinal deformities in patients with severe AIS (Girdler et al. 2020). Several studies reviewed its applications for 3D spinal measurements including coronal curvatures, sagittal curvatures and vertebral rotation (He et al. 2009, Betsch et al. 2015, Knott et al. 2016). However, the reconstruction technology is based on the assumption that the surface profile of spine reflecting the internal anatomical arrangement of the spine (Humphries et al. 2014). The rasterstereography (DIERS) demonstrated moderate accuracy in measuring the scoliosis degree and low accuracy in monitoring the curve progression in a recent study with 192 participants thus only early screening in large adolescent populations by DIERS is suggested (Bassani et al. 2019).

2.6.4. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) was first described as a mechanism to encode spatial information into nuclear magnetic resonance signal using magnetic field gradients (Lauterbur 1989). The technology was later developed for detecting severe spine curvature progression. It is a radiation-free technology that can provide detailed 3D information of spine. It can provide internal spine anatomical information together with muscular information and neurological information (Yeom et al. 2007). The MRI technology has been used for the evaluation of 3D spine deformities including vertebrae segmental deformity and neuraxial abnormalities (Faizah et al. 2016, Labrom et al. 2020). It has also been used to predict curve progression in AIS and manage AIS with nonsurgical treatment (Deng et al. 2015, Jada et al. 2017). However, traditional MRI scanning procedure requires patients to be assessed in supine postures for a relatively long duration. This method is used only for severe scoliosis treatment decision but not for longitudinal follow-up. Moreover, traditional MRI spine assessment scans patient in supine/prone position which the action of gravity on the spine may affect the natural shape of the scoliotic curve (which is commonly assessed in erect position). Lately, there is an innovative MRI device that can assess patient's spine in erect position but this is not commonly available in most clinic area. In addition, the installation and operation costs of MRI scanner (especially the erect MRI scanner) is high which hinders its common and wide use (Sett and Crockard 1991).

2.7. Previous Studies on Three-dimensional Ultrasound (3DUS) Assessment for Scoliosis

For the freehand 3DUS system, the feasibility of using specific landmarks in B-mode ultrasound images to evaluate the 3D anatomy profiles of spines has been reported (Huang et al. 2005a, Huang et al. 2005b, Chen et al. 2013, Li et al. 2015). Several studies have validated the application of 3DUS system for assessment and management of scoliosis (Chen et al. 2013, Ungi et al. 2014, Cheung et al. 2015a). Vo et al. (2015) and Wang et al. (2016) reported the validity of using 3DUS for measuring vertebral rotation. A study investigated the feasibility of using 3DUS to assess bone quality in AIS patients (Zheng et al. 2015). There are also studies evaluated the feasibility of using 3DUS for analysis of the sagittal profile and lateral curvatures of spine (Lee et al. 2019, Wu et al. 2020). 3DUS technology was also applied in the scoliosis treatment management including design and adjustment of corrective braces (He et al. 2017, Lou et al. 2017, He et al. 2019). Lately, the 3DUS technology was applied to the evaluation of physical exercise therapy outcomes on AIS patients (Liu et al. 2020).

A radiation-free 3DUS assessment system Scolioscan (Model SCN801, Telefield Medical Imaging Ltd, Hong Kong) for spine imaging has been commercially available, and its feasibility in measuring the spine curvature has been reported in recent studies (Cheung et al. 2013, Cheung et al. 2015a, Cheung et al. 2015b, Zheng et al. 2016, Brink et al. 2018, Wong et al. 2019, De Reuver et al. 2020). The ultrasound transverse processes angle, through localizing transverse processes on spine phantom, was demonstrated to correlate closely with Cobb angle (Lee at al. 2020). It can greatly reduce the unnecessary radiation exposure suffered by patients with AIS.

2.8. Significance of Using 3DUS for Detection of AIS Progression

With this innovative technology, repeated follow-up visits with high accuracy and low cost can be performed without inducing radiation accumulation risks. The feasibility of using freestanding ultrasound on detecting spine curvature progression was validated with an acceptable rate of undetected progressed cases (Zheng et al. 2018). The feasibility of using the coronal ultrasound image provided by the 3DUS system Scolioscan and specific software with ultrasound transverse processes angle measurement would be investigated for its potential in reducing traditional radiation in the follow-up visits.

CHAPTER 3 METHODS

The overall aim of this study is to evaluate the feasibility of using three-dimensional ultrasound (3DUS) for detecting spine curvature progression. The project involves two main tasks. The first task is to validate the 3DUS system. The second task is to detect spine curvature progression in subjects with adolescent idiopathic scoliosis (AIS) using 3DUS and X-ray.

3.1. 3DUS System – Scolioscan

3.1.1. Hardware

The Scolioscan® system (Scolioscan, Model SCN801, Telefield Medical Imaging Ltd, Hong Kong) (Figure 3-1) was used for ultrasound scanning. The Scolioscan system includes supporting boards with movable supporters to stabilize and record the scanning postures. The ultrasound modules with a linear ultrasound probe (central frequency of 7.5 MHz and 7.5 cm width) is responsible for acquiring cross-sectional B-mode images of spine, and the electromagnetic spatial sensor is used in getting the positional and orientational information of the cross-sectional images (Cheung et al. 2015a). The embedded software is responsible for subject data acquiring and retrieving, image collection, and data processing.

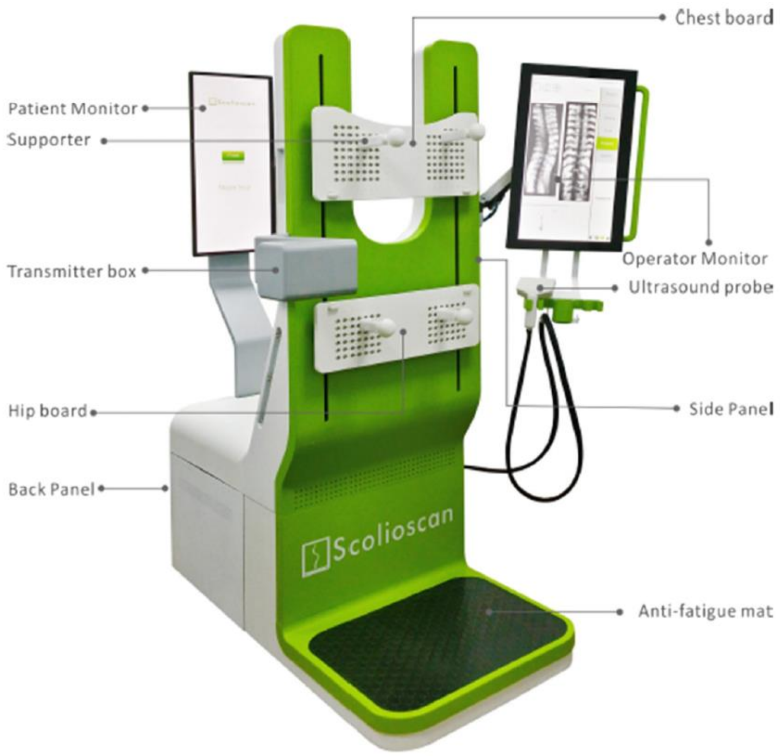


Figure 3-1. 3DUS assessment system Scolioscan with the components labelled

3.1.2. Assessment Protocol

The subject was instructed to undress, with ultrasound gel on the back. He/she was then instructed to step on the scanning platform with natural standing position, with the supporters (Figure 3-2). The scanning range was defined by vertebra level L5 to T1 with the aid of the real-time B-mode images.

Figure 3-2. Assessment by Scolioscan: (a) subject scanned by the US probe; (b) software interface shown during scanning and (c) a typical resulting image of a scoliosis subject

The ultrasound setting parameters are defaulted by machine's manufacturer for optimizing bone feature visualization which can be further customized to each subject by an experienced well-trained operator. Scanning was then performed by moving the ultrasound probe slowly along the back from the region below vertebra level L5 until over vertebra level T1 with the average scanning speed of one to two cm per second. During scanning, operator would keep observing the real-time window on the Scolioscan operation monitor to ensure optimal scanning speed that acceptable real-time preview image is shown (without black horizontal lines nor whiten horizontal lines) (Figure 3-3). On the same date of visit, the subjects were also arranged to undergo EOS scanning with a similar standing posture as the ultrasound scanning.

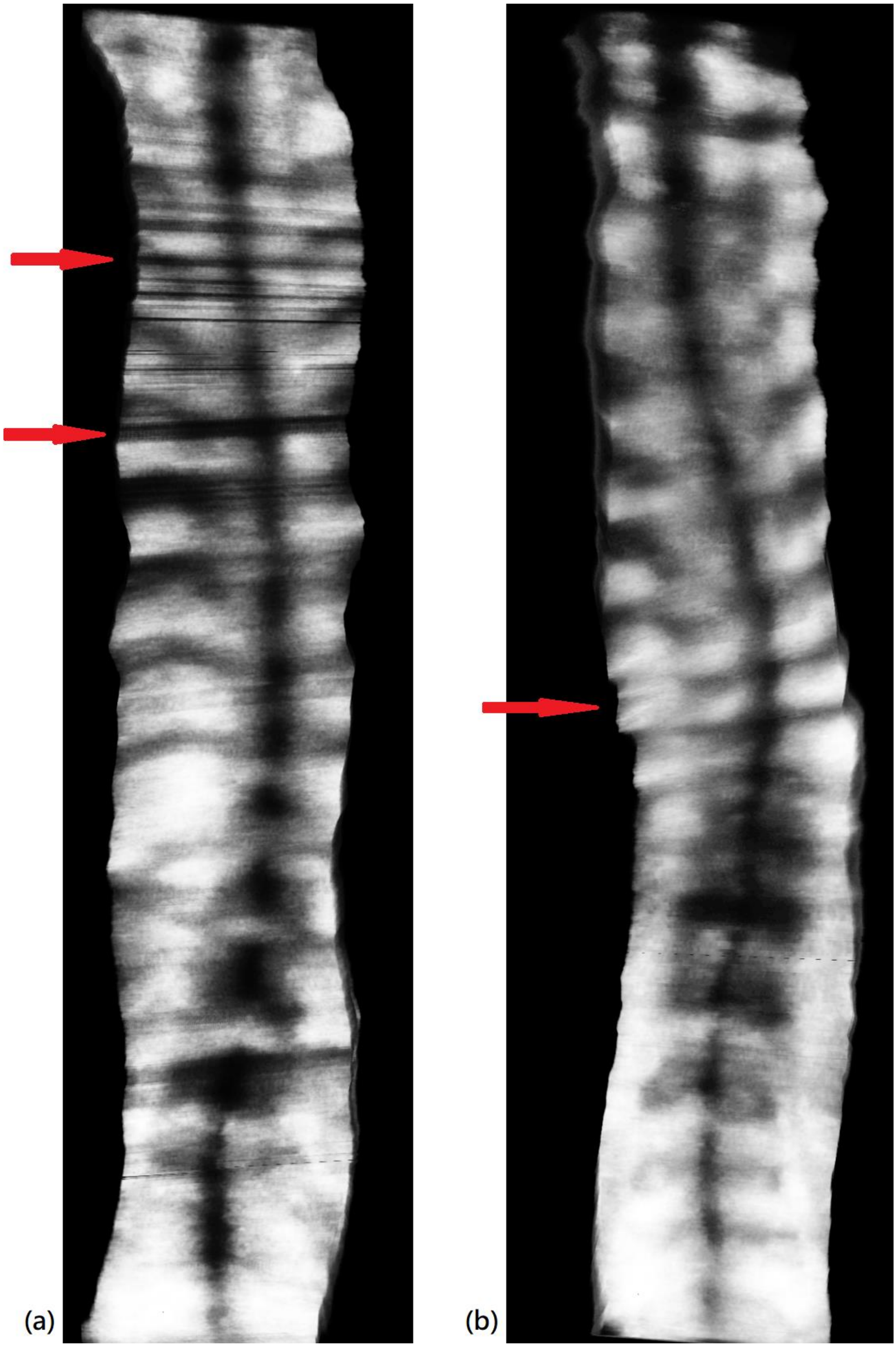


Figure 3-3. Typical ultrasound projection images when (a) scanning too fast (blacken horizontal strips); and (b) scanning too slow (whiten horizontal strips)

3.1.3. Data Processing

The acquired ultrasound B-mode images with three-dimensional (3D) spatial information were used to generate a 3D spine volume using a specific reconstruction method, volume projection imaging (VPI). With customized VPI projection by adopting a vertebrae-dependent distance, nine images of various depths following the skin surface curve profile were produced (Cheung et al. 2015b). Spine images in coronal plane were formed by the embedded software as assessment results. Among the nine spine images showing bony features in various depths, manual selection of the best layer showing most bony features and most clear transverse features by the operator was performed (Figure 3-4). A recent study reported automatic selection of the best layer with encouraging results (Lyu et al. 2021). The software is tested for over 1000 cases, and it gives very close selection results of the best layer when comparing with experienced operator for most cases. It may be used in future research and clinical applications.

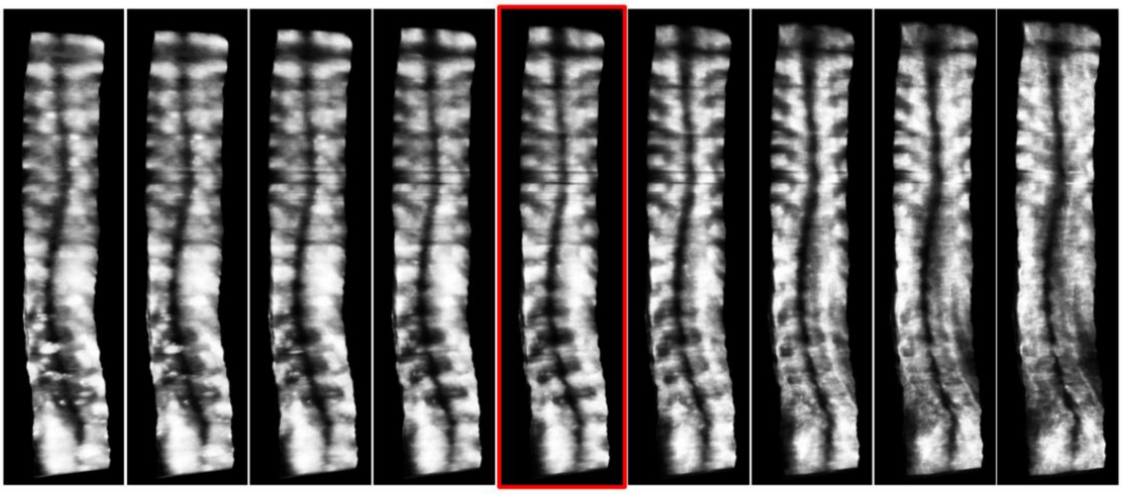


Figure 3-4. 3DUS VPI of various depths following the natural spinal curve, the best layer showing most bony features for the subsequent measurement

3.2. Validation of the 3DUS System Scolioscan

Before investigating the feasibility in detecting spine curvature progression using Scolioscan, the intra-rater and inter-rater reliability between two operators for acquiring images using Scolioscan were tested. The resulting projected ultrasound images were formed by the embedded software of Scolioscan. Ultrasound transverse processes angle (USTPA) representing the spinal curvatures was obtained by drawing lines above the upper most tilted vertebra and below the lower most tilted vertebra following the suggested protocol by a recent study, and its repeatability has been reported (Lee et al. 2020). The measurement software RadiAnt DICOM Viewer (Medixant, Poland) was used for viewing the ultrasound images and making angle measurements on them (Figure 3-5).

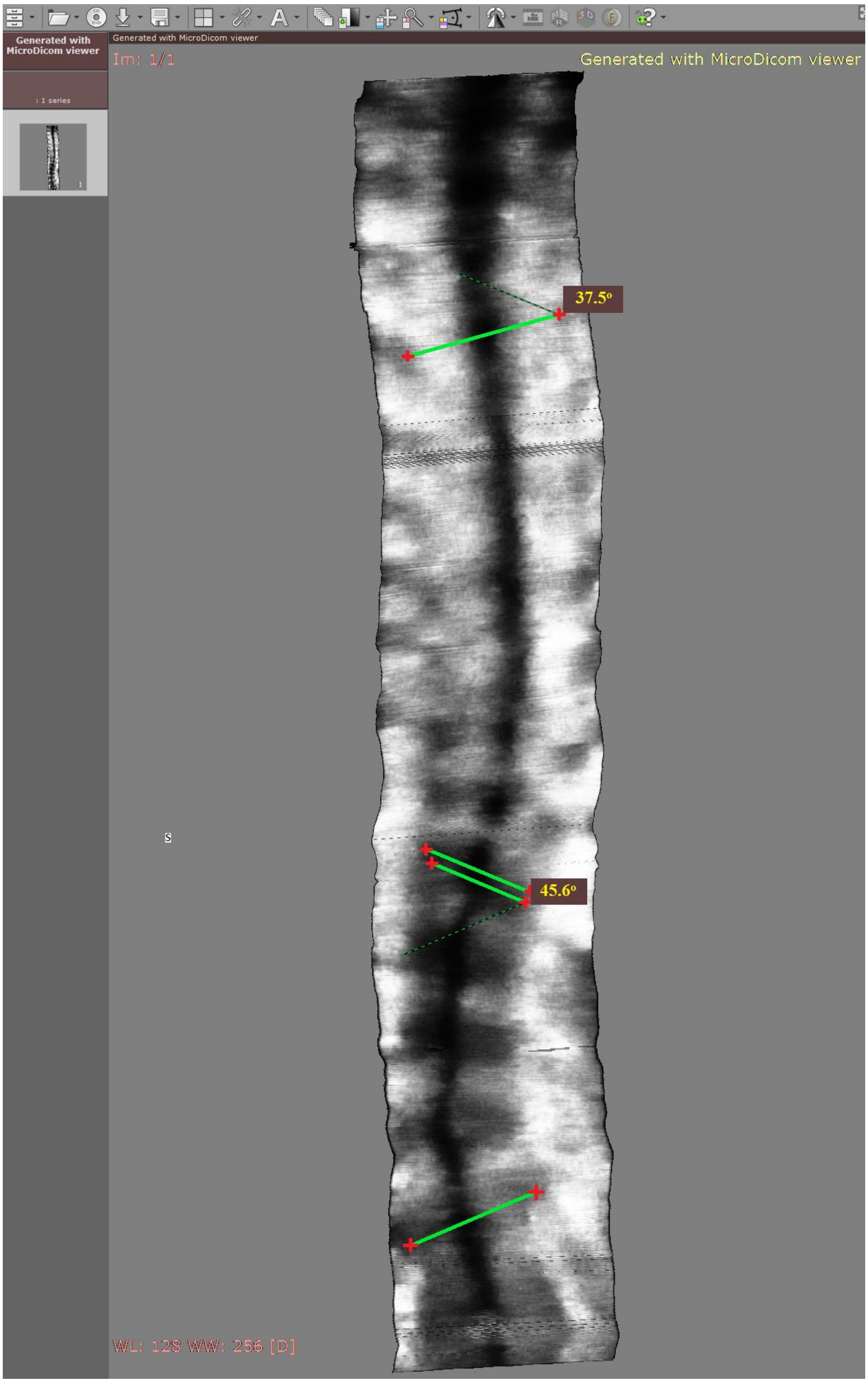


Figure 3-5. Measurement of USTPA representing spinal curvatures on scoliosis subject

3.2.1. Intra-operator Reliability Study

For the intra-operator reliability study, 30 subjects with AIS were recruited. The subjects were scanned twice by the Scolioscan using the protocol suggested by the manufacturer (Zheng et al. 2016) with five minutes of rest between two adjacent scans. The two sets of scans were carried out by the same operator. The subject was instructed to keep the same posture during scanning, and to leave the scanning platform after the first scan and repositioning with the supporters was performed to ensure the subject was located in the same position before the second scan. The resulting projected ultrasound images in coronal plane were selected by the operator and measured by the measurement software RadiAnt DICOM Viewer (Medixant, Poland). The spine curvatures represented by the USTPA of the two scans were compared and investigated.

3.2.2. Inter-operator Reliability Study

To reduce the total time required for each subject, the inter-operator reliability study was performed in another group of 30 subjects with AIS. They were scanned by two operators, using the same protocol as described in the intra-operator study. The only difference was that the second scan would be performed by the second operator, and the resulting projected ultrasound images would be selected by the second operator. The spine curvatures represented by the USTPA were also compared and investigated.

3.3. Detection of Spine Curvature Progression

3.3.1. Subjects

200 subjects with suspected or diagnosed AIS were recruited for this study, in the Prince of Wales Hospital. Human subject ethical approvals were obtained from the Chinese

University of Hong Kong. Subjects with metallic implants were excluded as it might affect the function of spatial sensing elements of the 3DUS system. Subjects with body mass index (BMI) higher than 30.0 kg/m^2 were also excluded as high BMI might lead to poor ultrasound image quality. In addition, subjects who had taken radiography with corrective braces were also excluded.

3.3.2. Imaging Technologies

The subjects were scanned by the 3DUS Scolioscan and X-ray EOS system on the same date during their first visit and sequential visits (within 6 to 30 months) (Figure 3-6). Patients with corrective braces were required to remove their braces 48 hours prior to the scanning session and clinical follow-up session as suggested by the orthopedic doctors so that the spine can settle back to its deformed position, and the curve can be accurately detected throughout longitudinal follow up.

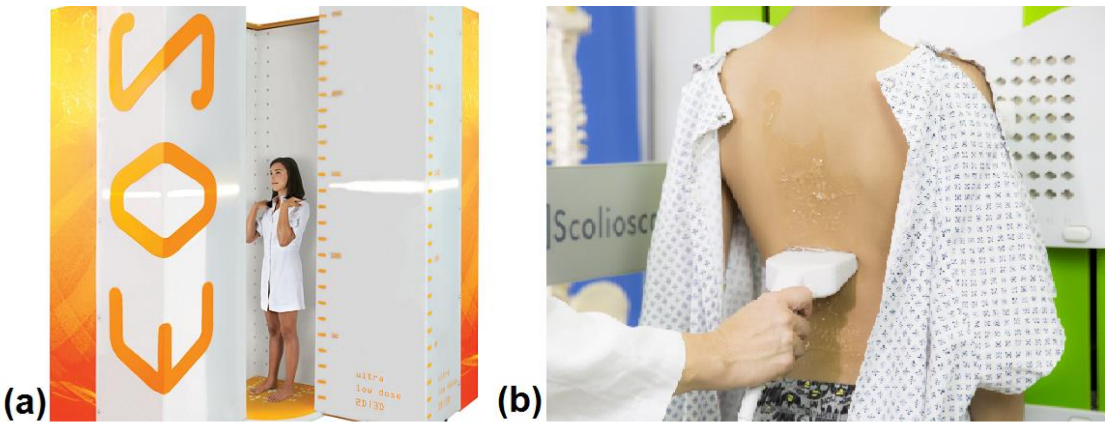


Figure 3-6. Imaging systems for the human experiment of scoliosis assessment: (a) X-ray EOS system (http://www.eos-imaging.com/professionals/eos/eos); (b) 3DUS Scolioscan system

3.3.3. Data Acquisition – Ultrasound Transverse Processes Angle (USTPA) and Radiographic Cobb Angle (RCA)

Using the images obtained by the Scolioscan, the spine curvatures were measured manually by firstly identifying the transverse processes and laminae-articular processes shadows on the coronal ultrasound images. Lines were drawn above the upper most tilted vertebra and below the lower most tilted vertebra, and the angle in between these two lines was defined to be the ultrasound transverse processes angle (USTPA) (Lee et al. 2020). The measurements were performed by RadiAnt DICOM Viewer (Medixant, Poland). Both the operators and the raters were blinded to the priori diagnostic results.

For the image obtained by the EOS system, the spine curvatures were measured by a trained rater using the traditional Cobb method as radiographic Cobb angle (RCA). The measurements were performed by RadiAnt DICOM Viewer (Medixant, Poland). Inter-rater repeatability tests were performed between two raters to ensure consistent Cobb angle results.

3.3.4. Study Design

The results (USTPA and RCA) obtained by the two assessment systems, during the two to three visits were compared and investigated following the study plan (Figure 3-7). Using the RCA as the reference in the subject's first visit, subjects with RCA of less than ten degrees would be regarded as non-scoliosis cases (Kim et al. 2010) and excluded from further study. For the scoliosis cases with RCA of at least ten degrees in their first visit, the main (maximum) curvature for the two kinds of assessments in each clinical visit would be extracted for further comparison.

A change of five degrees or more in RCA is an indicator of curve progression detected by X-ray (Soucacos et al. 1998) while a change of five degrees or more in USTPA is the indicator of curve progression detected by 3DUS. The changes of the main curvature detected by the two assessment method would further define the cases as progressive or non-progressive. When considering a subject as progressive or non-progressive scoliosis case, the main curvature (maximum RCA and maximum USTPA) was presented for each clinical visit (one angle representing one visit). All of the 200 subjects came for follow-up once or twice (168 subjects came back once and 32 subjects came back twice). For every visit, the subject underwent both X-ray assessment and ultrasound assessment. In another word, 200 of them had one follow-up scan, and 32 of them had two follow-up scans. For each visit, only the main curvature diagnosed by radiograph in the first visit was extracted for analysis, and only that angle was being monitored in the longitudinal follow up. With 432 single visits by 200 subjects, 432 curvatures were extracted and analysed. No curvature matching step was performed for the 432 visits of 200 cases as only the main curvature in each visit was presented.

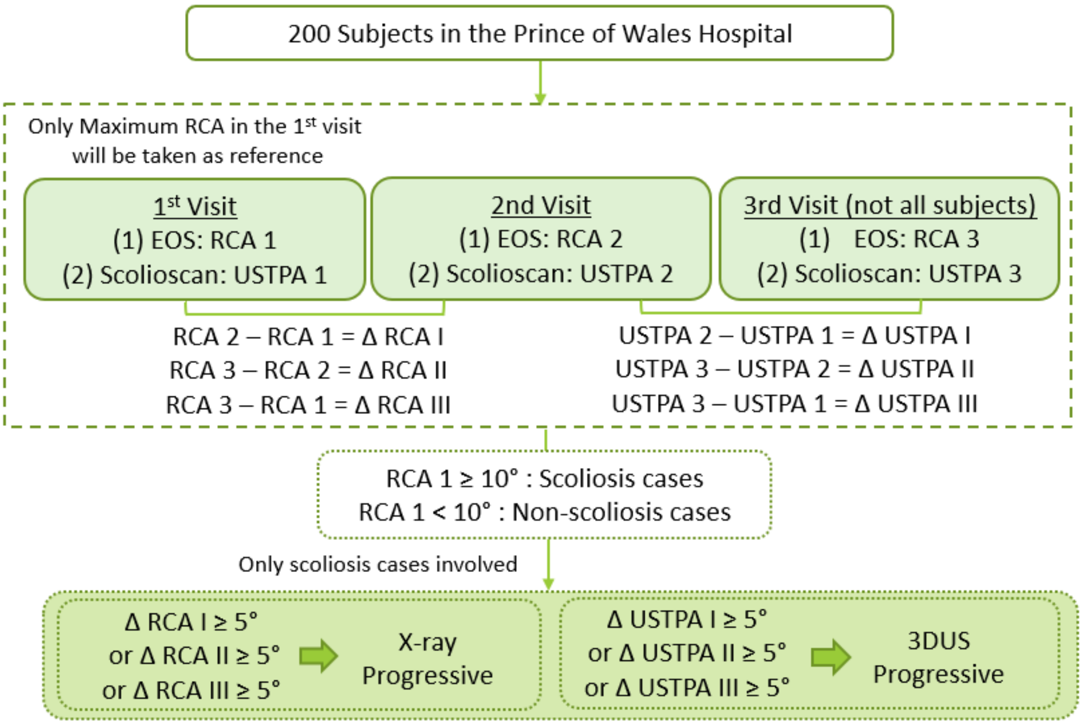


Figure 3-7. Schematic diagram showing the study design

3.3.5. Data Analysis

For the intra-operator study, the correlation between the USTPA obtained by the two assessments performed by the same operator was analyzed for statistical significance. The correlation of the two assessments was plotted as graphs, and the linear regression was presented.

For the inter-operator study, the correlation between the USTPA obtained by the two assessments carried out by two separate operators was analyzed for statistical significance. The correlation of the two assessments was also plotted as graphs, and the linear regression was presented.

For the scanning results by the 3DUS system Scolioscan, the spine curvatures detected by the trained rater manually following the ultrasound transverse processes method were presented as USTPA. For the scanning results by the EOS system, the spine curvatures measured by the trained rater were presented as RCA. Inter-rater study for RCA measurement was carried out for statistical significance. Linear correlation was then examined between the USTPA and RCA for 432 curves of 200 subjects. A correlation coefficient of 0.25 to 0.50 indicates poor correlation, 0.50 to 0.75 indicates moderate to good correlation, and 0.75 to 1.00 indicates very good to excellent correlation (Dawson and Trapp 2004).

For the scoliosis cases with RCA of at least ten degrees in their first visit, main (maximum) curvatures for the two kinds of assessments in each clinical visit were further investigated. For the spine curvature progression detection, the differences of USTPA obtained on the two or three separated visits for each subject were the progression detected by Scolioscan, while the differences of RCA obtained on the visits for each subject were the progression detected by X-ray.

For the spine curvature progression determination, for each subject, any RCA change of not less than 5-degree increment was regarded as progressive cases (X-ray positive results) by X-ray and any USTPA change of not less than 5-degree increment was regarded as progressive cases (3DUS positive results) by 3DUS. The cases with all RCA changes of less than 5-degree increment were regarded as non-progressive cases (X-ray negative results) by X-ray while the cases with all USTPA changes of less than 5-degree increment were regarded as non-progressive cases (3DUS negative results) by 3DUS.

For the subjects with positive results for both USTPA and RCA, it was regarded as true positive (TP). For the subjects with negative results for both USTPA and RCA, it was regarded as true negative (TN). For the subjects with positive results for RCA but negative results for USTPA, it was regarded as false negative (FN). For the subjects with negative results for RCA but positive results for USTPA, it was regarded as false positive (FP). The sensitivity of using 3DUS to detect scoliotic curve progression was determined by the factor of TP cases over radiographic positive cases (i.e. TP / (TP + FN)). The specificity of using 3DUS to detect scoliotic curve progression was determined by the factor of TN cases over radiographic negative cases (i.e. TN / (TN + FP)) (Figure 3-8).

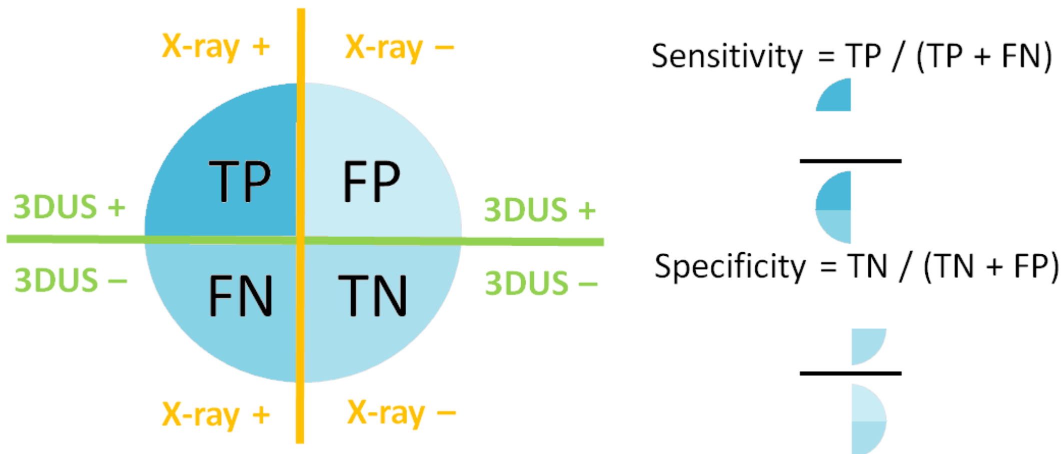


Figure 3-8. Illustration on the concept of sensitivity and specificity

The sensitivity and specificity can be further expressed as likelihood ratio which is more useful clinically. Likelihood ratio tells how many times more (or less) likely patients with a disease are to have a particular result than patients without the disease. By Bayes theorem, likelihood ratio can estimate an individual's post-test probability of disease conjunction with pre-test probability of disease, which is the individual's chance of having disease once the result of a test is known (Akobeng 2007). Likelihood ratio is a measure of the performance of a diagnostic test, and is calculated from the sensitivity and specificity of the test (Halkin et al. 1998). A negative likelihood ratio is “the probability of a patient testing negative who has a disease divided by the probability of a patient testing negative who does not have a disease” (Bolin and Lam 2013). Negative likelihood ratio of greater than 1 indicates a negative test results is more likely to occur in people with the disease than in people without the disease. Negative likelihood ratio of less than 1 indicates a negative test is less likely to occur in people with the disease compared to people without the disease. Large negative likelihood ratio increases the probability of disease (rule in disease) while a very low negative likelihood ratio (below 0.1) rules out the chance that a person has the disease (Jaescheke et al. 2002). In this study, the likelihood ratio for negative results detected by the 3DUS system Scolioscan with USTPA measurement was conducted by [(1-sensitivity)/(specificity)].

3.4. Three-dimensional (3D) Profile Change during Spine Curvature Progression

Each scanning by Scolioscan, volume data was collected by summing two-dimensional (2D) cross-sectional plane B-mode ultrasound images (Cheung et al. 2015b). Customized software ScolioStudio (Telefield Medical Imaging Ltd, Hong Kong) was used with the Scolioscan to identify specific bony landmarks on the images (Figure 3-9). The 3D structures on spines were imitated after manual identification of bone features. The 3D profile of spines was then investigated. Sagittal spine curvature would also be studied by viewing and re-slicing the spine volume in sagittal plane, and using the laminae as bony landmarks for evaluation (Figure 3-10). For the 3D profile changes during spine curvature progression, bony landmarks of spine in 3D were identified by corresponding software for observation.

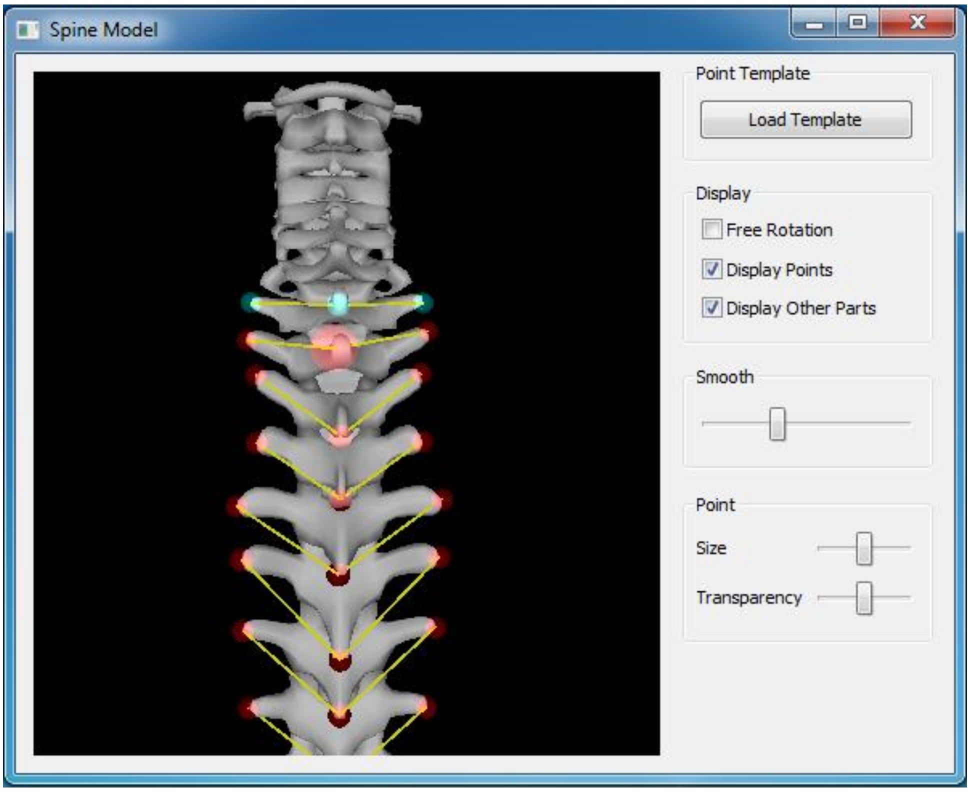


Figure 3-9. Software interface for studying the 3D profile on spines in the B-mode ultrasound image

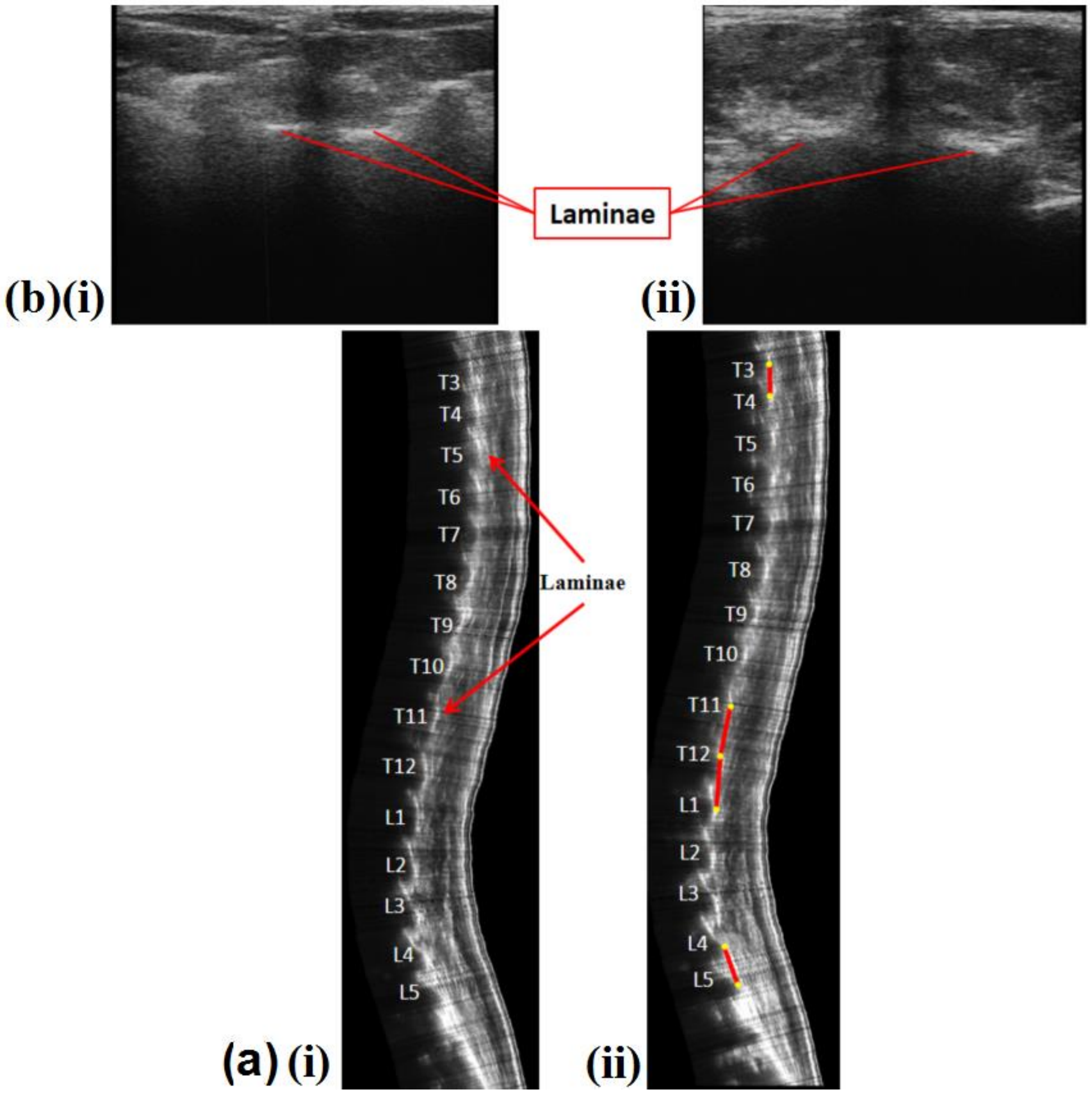


Figure 3-10. Software illustrating (a) (i) left and (ii) right ultrasound sagittal profile of the spine; and (b) B-mode ultrasound images in transverse plane with laminae features at (i) thoracic region and (ii) lumbar region of the spine

CHAPTER 4 RESULTS

4.1. Validation of the Three-dimensional Ultrasound (3DUS) System Scolioscan

4.1.1. Intra-operator Reliability Study

30 subjects with adolescent idiopathic scoliosis (AIS) were scanned twice in the same posture by the same operator using the Scolioscan with five minutes of rest between two adjacent scans (Figure 4-1). The spine curvatures represented by the ultrasound transverse processes angle (USTPA) of the two scans were compared and investigated (Figure 4-2 and Figure 4-3).

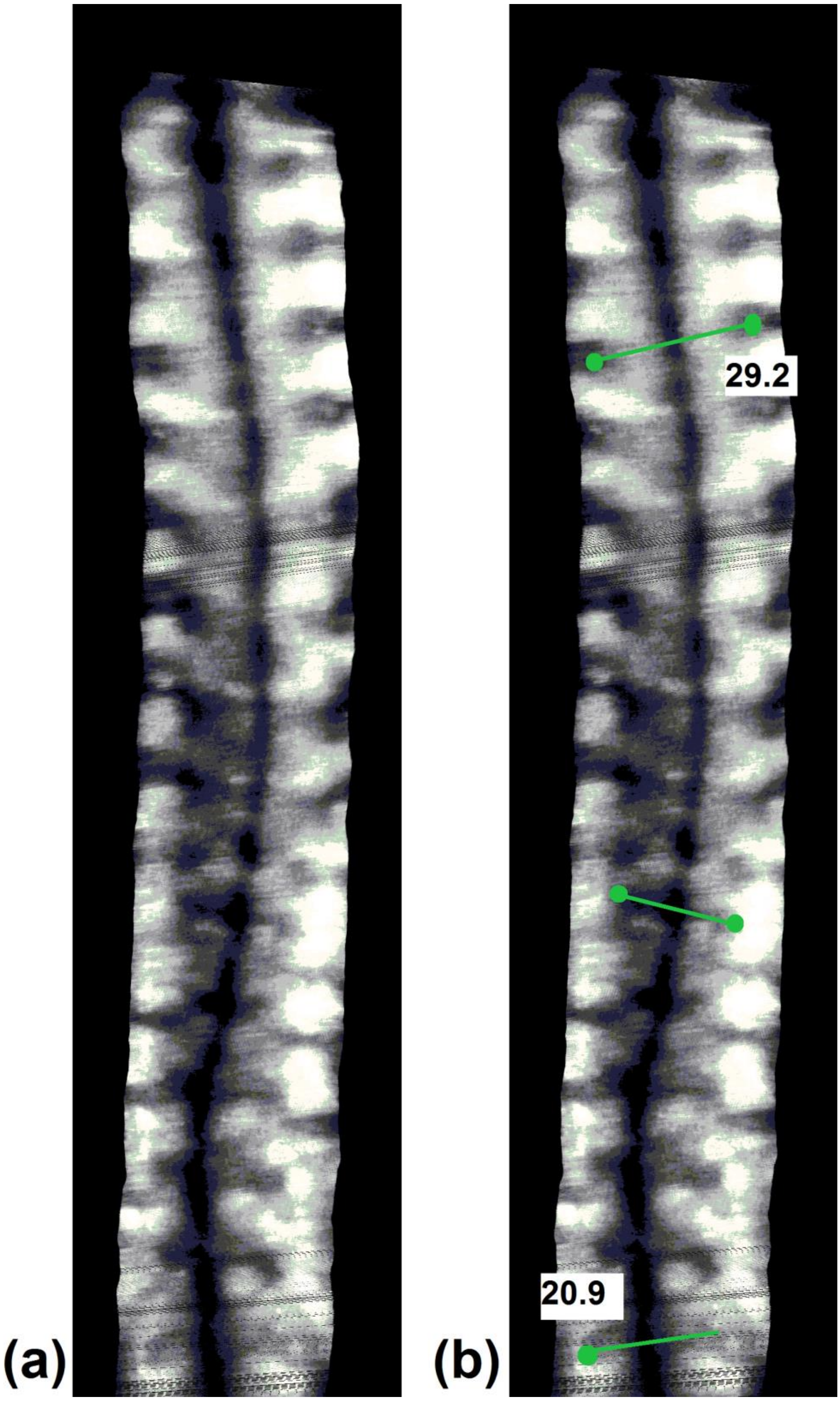


Figure 4-1. Typical coronal images obtained by the Scolioscan for an AIS subject (a) without measurement and (b) with USTPA measurement

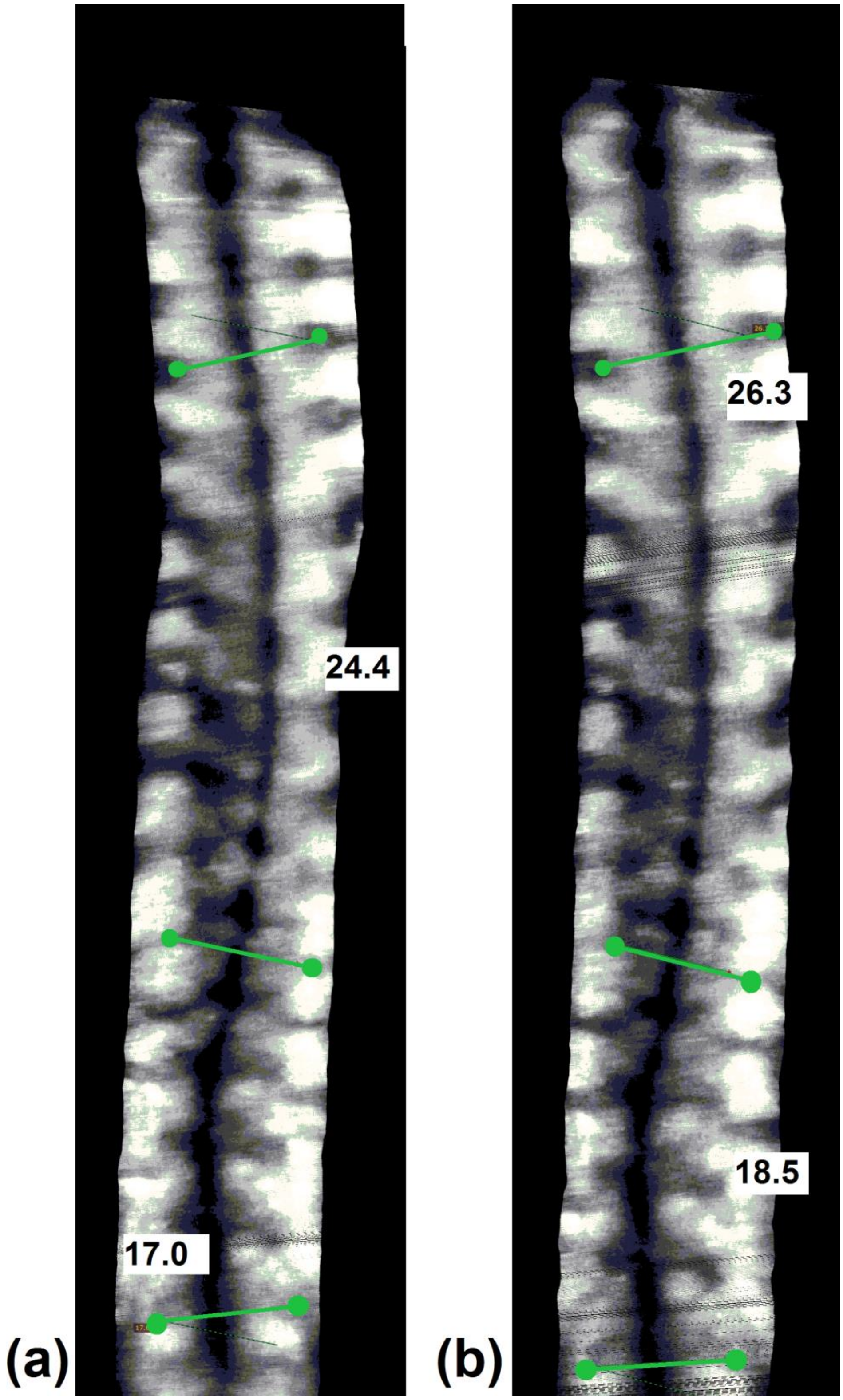


Figure 4-2. 3DUS results by Scolioscan with transverse processes angle measurement for the same subject and operator (a) scan 1 and (b) scan 2

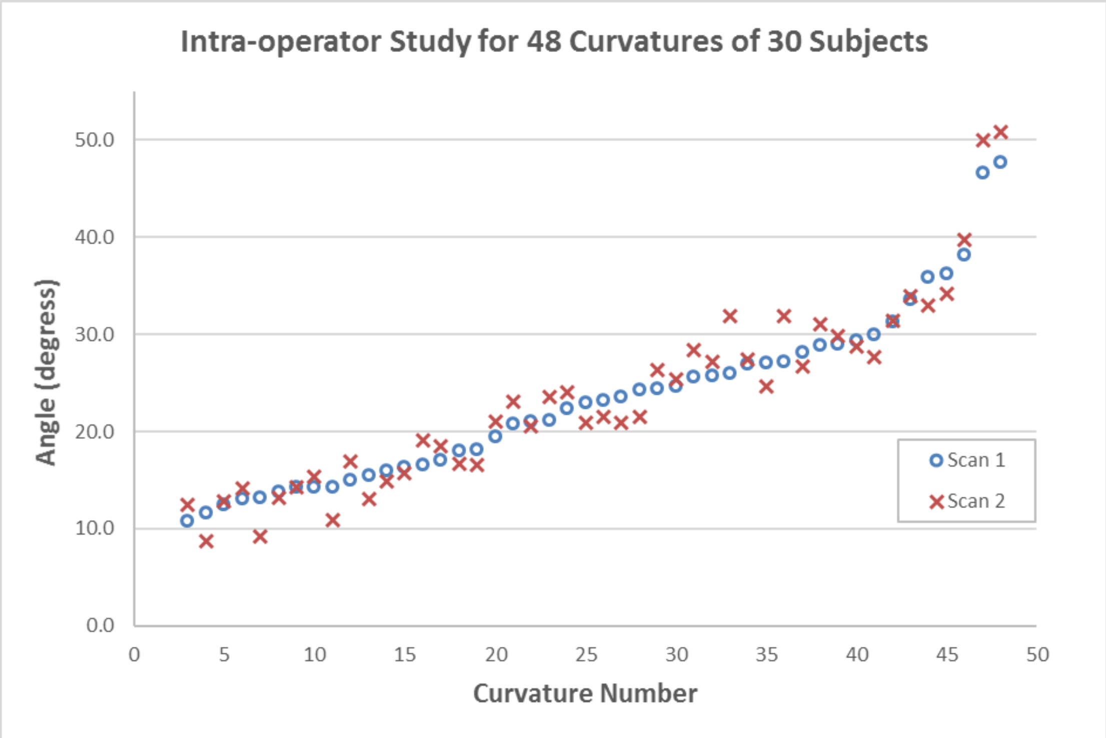


Figure 4-3. Distribution of the USTPA of the two scans of same subjects scanned by same operator

Among 30 subjects scanned by the same operator, the results obtained by the first scan ranged from 8 degrees to 48 degrees while those by the second scan ranged from 9 degrees to 51 degrees. The 48 pairs of curvatures for the two scans showed a significant correlation in terms of R^2 value of 0.9465 (Figure 4-4). The results demonstrated the high intra-observer repeatability for operating the Scolioscan system.

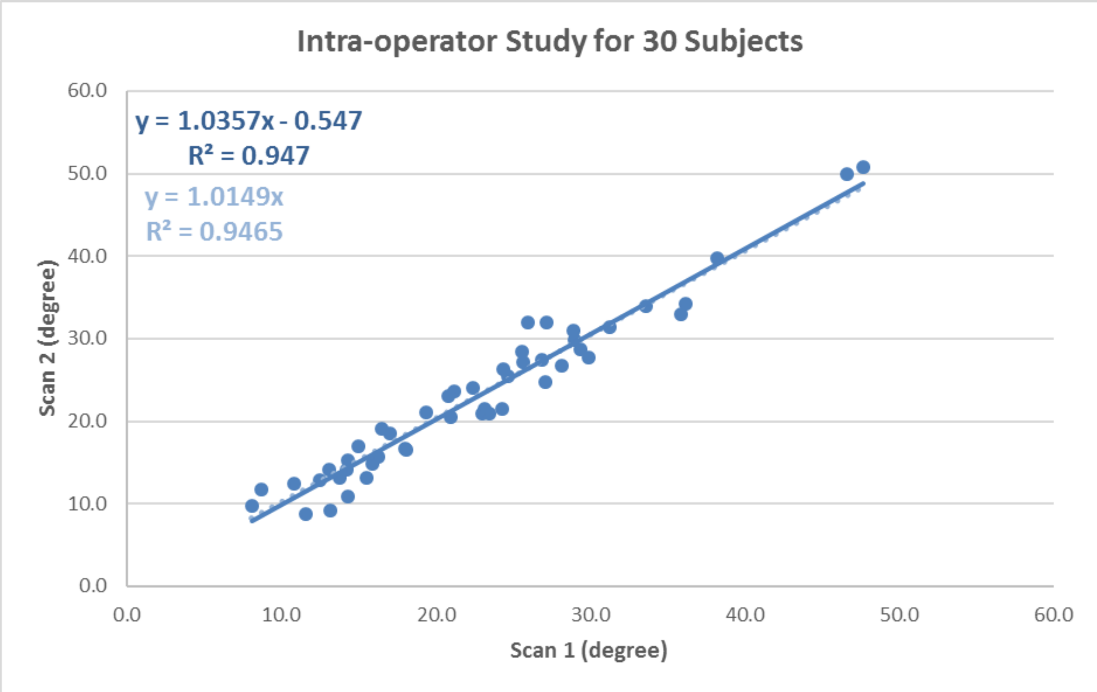


Figure 4-4. Comparison between the 3DUS results of two scans for the same subject and same operator

4.1.2. Inter-operator Reliability Study

30 AIS subjects were scanned by two operators, with the same protocol as the intra-operator study. The spine curvatures represented by USTPA of the two scans were compared and investigated (Figure 4-5 and Figure 4-6).

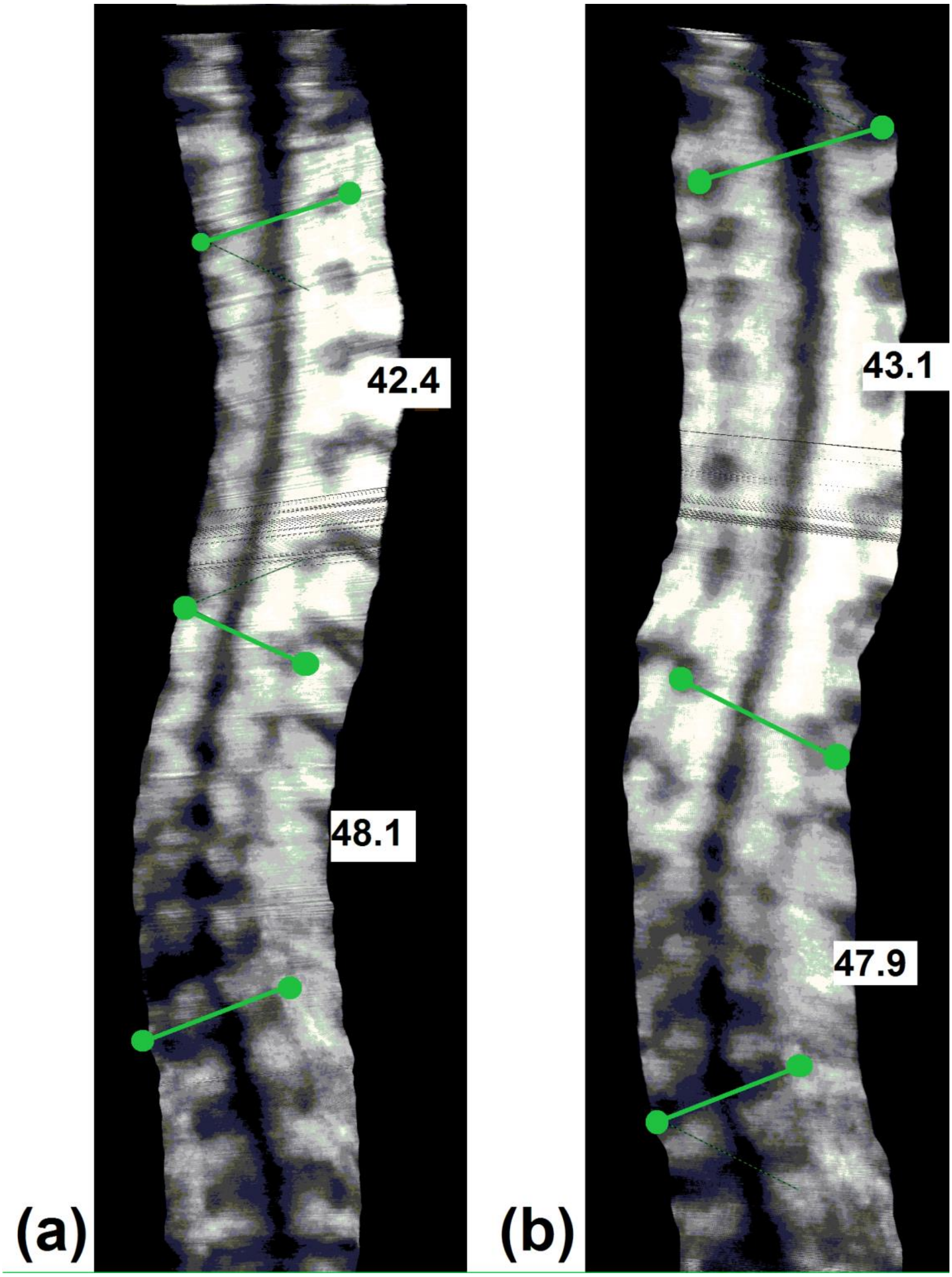


Figure 4-5. 3DUS results by Scolioscan with transverse processes angle measurement for the same subject scanned by (a) operator 1 and (b) operator 2

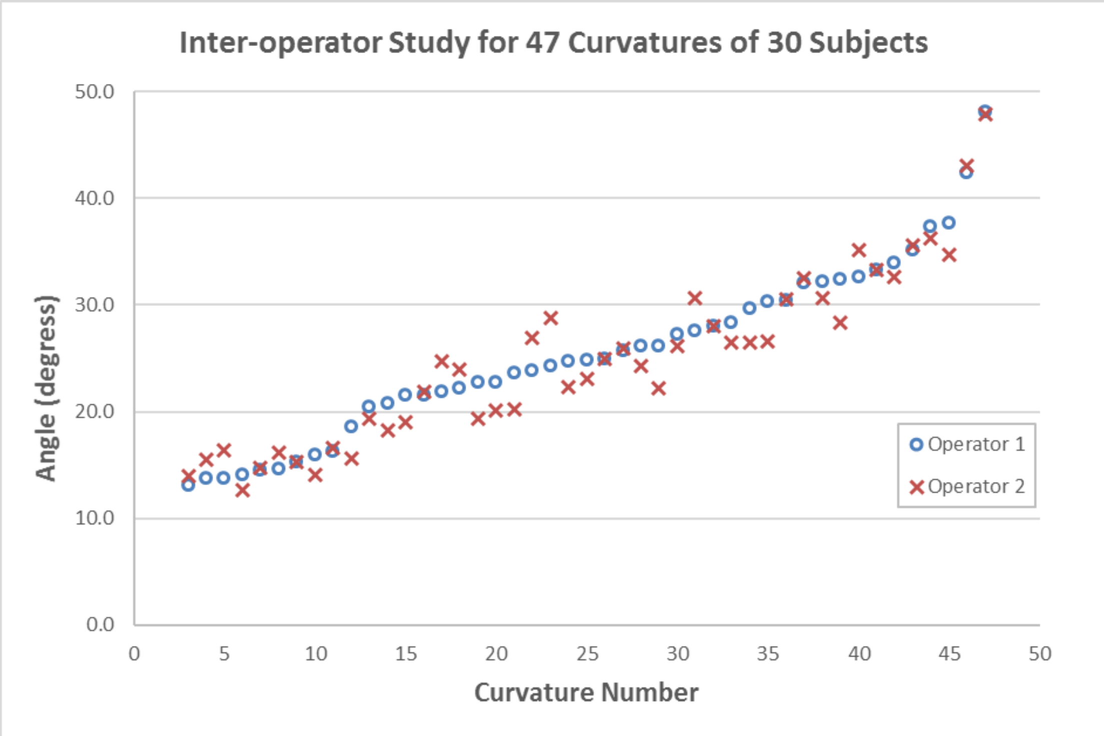


Figure 4-6. Distribution of the USTPA of the two scans of same subjects scanned by two operators

Among 30 subjects, the results obtained by the first operator ranged from 12 degrees to 48 degrees while those by the second operator ranged from 13 degrees to 48 degrees. The 47 pairs of curvatures measured by the two operators showed a significant correlation in terms of R^2 value of 0.9311 (Figure 4-7). The results demonstrated high inter-observer repeatability for operating the Scolioscan system.

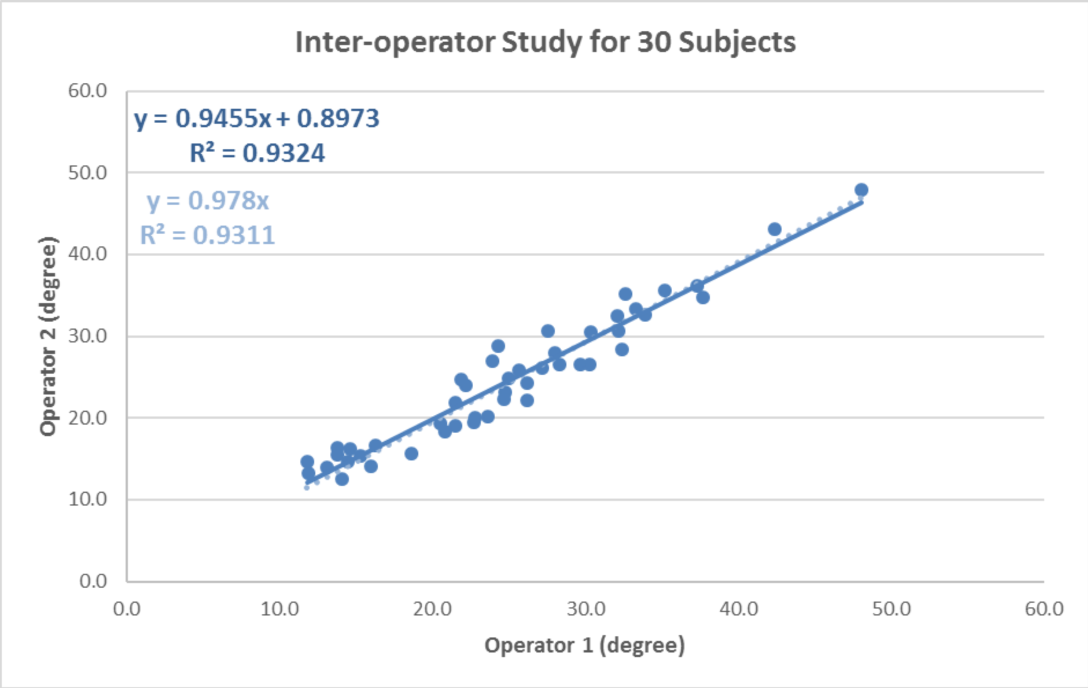


Figure 4-7. Comparison between the 3DUS results of the same subject by two operators

4.2. Detection of Spine Curvature Progression

4.2.1. Subjects

Total 200 subjects (62 male and 138 female subjects; 8-26 years of age, mean of 14.2 ± 2.8 years) with suspected AIS (batch A: 100 subjects) or diagnosed AIS (batch B: 100 subjects) were involved in this study (Table 4-1).

100 subjects with suspected AIS (47 male and 53 female subjects; 8-17 years of age, mean of 12.6 ± 1.7 years) were recruited as batch A, with the spine curvatures of 5.5 degrees to 27.9 degrees, mean of 14.0 ± 4.7 degrees. 83 of them came for two visits and 17 of them came for three visits. For each subject, the main (maximum) curvature for his/her first visit and the changes of such curvatures in the second and third visit were

studied. The duration between every two visits was 3-13 months, with a mean of 6.3 months.

100 subjects diagnosed with AIS (15 male and 85 female subjects; 9-26 years of age, mean of 15.7 ± 2.9 years) were recruited as batch B, with the spine curvatures of 6.4 degrees to 85.0 degrees, mean of 35.1 ± 15.4 degrees. 85 of them came for two visits and 15 of them came for three visits. For each subject, the main (maximum) curvature for his/her first visit and the changes of such curve in the second and third visit were studied. The duration between every two visits was 4-32 months, with a mean of 19.4 months.

For those diagnosed progressive cases, the mean inter-visit duration were 16.9 months (ranged from 4 to 31 months, ± 8.9 months) while the mean inter-visit duration of the non-progressive cases were 16.0 months (ranged from 4 to 32 months, ± 8.4 months). There was very slight difference that the progressive status was observed to be independent to the inter-visit duration. Indeed, subjects were arranged for regular clinical follow-up as suggested by orthopedic doctors but not participated for the follow-up visits due to various reasons, such as conflict of their schedule, etc.

Table 4- 1. Distribution of 200 recruited subjects

	Batch A (100 subjects with suspected AIS)	**Batch B (100 subjects diagnosed with AIS)**	**Combined Batch (200 subjects with suspected or diagnosed AIS)**

Gender	47 Male ; 53 Female	15 Male ; 85 Female	62 Male ; 138 Female
Age	12.6 ± 1.7 years (8 - 17 years old)	15.7 ± 2.9 years (9 - 26 years old)	14.2 ± 2.8 years (8 – 26 years old)
BMI	18.0 ± 2.4 kgm^{-2} (13.7 - 24.8 kgm^{-2})	18.6 ± 2.0 kgm^{-2} (14.9 - 23.0 kgm^{-2})	18.3 ± 2.2 kgm^{-2} (13.7 - 24.8 kgm^{-2})
Spine Curvatures	14.0 ± 4.7 degrees (5.5 - 27.9 degrees)	35.1 ± 15.4 degrees (6.4 - 85.0 degrees)	25.5 ± 15.8 degrees (5.5 - 85 degrees)

4.2.2. Spine Curvatures – Radiographic Cobb Angle (RCA)

The subjects were scanned by the Scolioscan and EOS system on the same date during their first visits, and they were scanned again by the same procedures at their second and third visits. For each visit, the subjects were instructed to keep the same postures during scanning. For the ultrasound projection image in coronal plane obtained by the Scolioscan, the spine curvatures were measured by a trained rater using the transverse processes angle method as ultrasound transverse processes angle (USTPA). For the images obtained by the EOS system, the spine curvatures were measured by the trained rater using traditional Cobb method as radiographic Cobb angle (RCA).

Cobb angles measured by orthopaedics doctors during clinical visits were not adopted in this study. The orthopaedics doctors follow certain clinical criteria when doing Cobb angle measurement during clinical visits that varies with individual clinical needs. Like, sometimes they measure only the maximum curve in some cases but both curves in some cases, or sometimes they measure the exact same level of vertebra for some case but not every case, or sometimes they measure the radiographs taken with brace in some cases but radiographs taken without brace in some other cases. The Cobb angle measurement information in the hospital database was incomplete. Therefore, Cobb angle measurement was carried out by individual trained rater (author) after full data collection. To ensure consistent Cobb angle measurement for all subjects, inter-operator repeatability tests were performed between two trained raters (Figure 4-8).

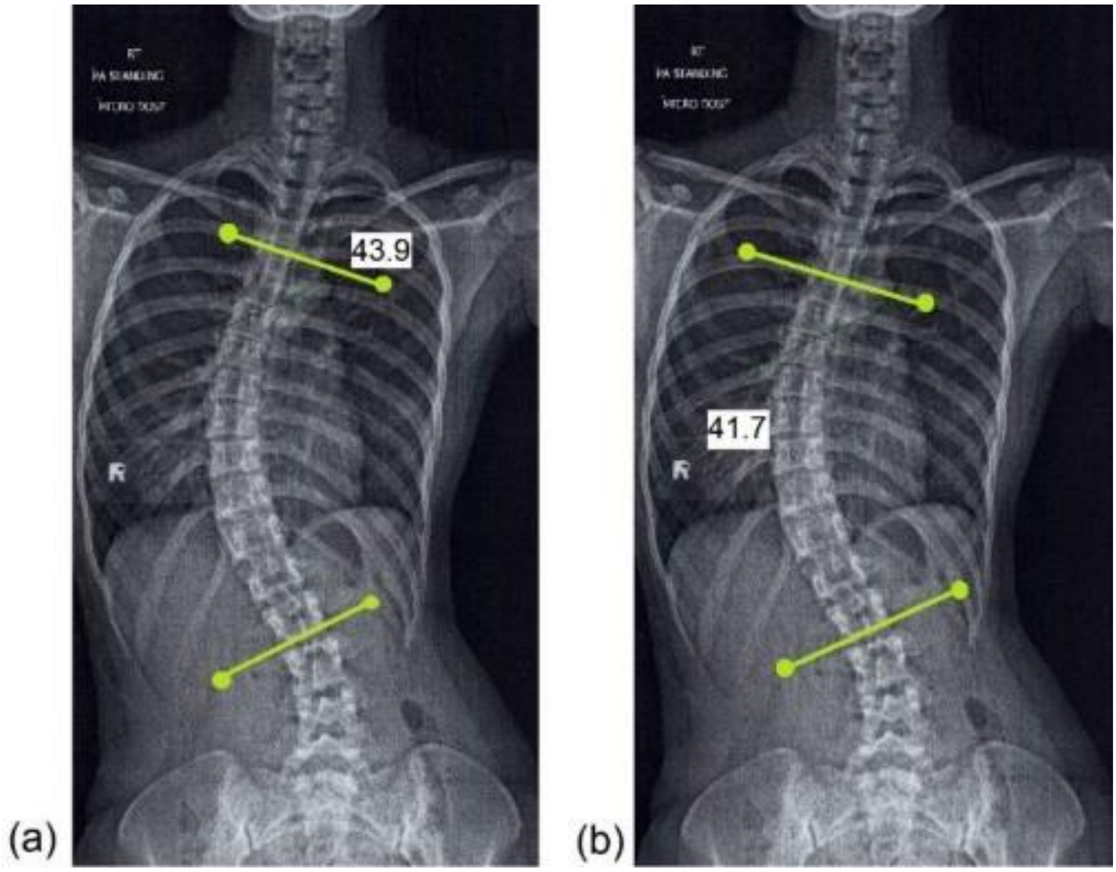


Figure 4-8. A typical set of radiographs with Cobb angle results from the same subject by (a) rater 1; and (b) rater 2

Combining the 200 subjects involved in both batch A and batch B, a total of 432 pairs of angles at different time points were included. The R^2 value between the RCA measured by the two raters for 432 pairs of angles is 0.964. (Figure 4-9). The results demonstrated high inter-rater repeatability for RCA measurement. Therefore, RCA measured by only one rater were used for further analysis between RCA and USTPA.

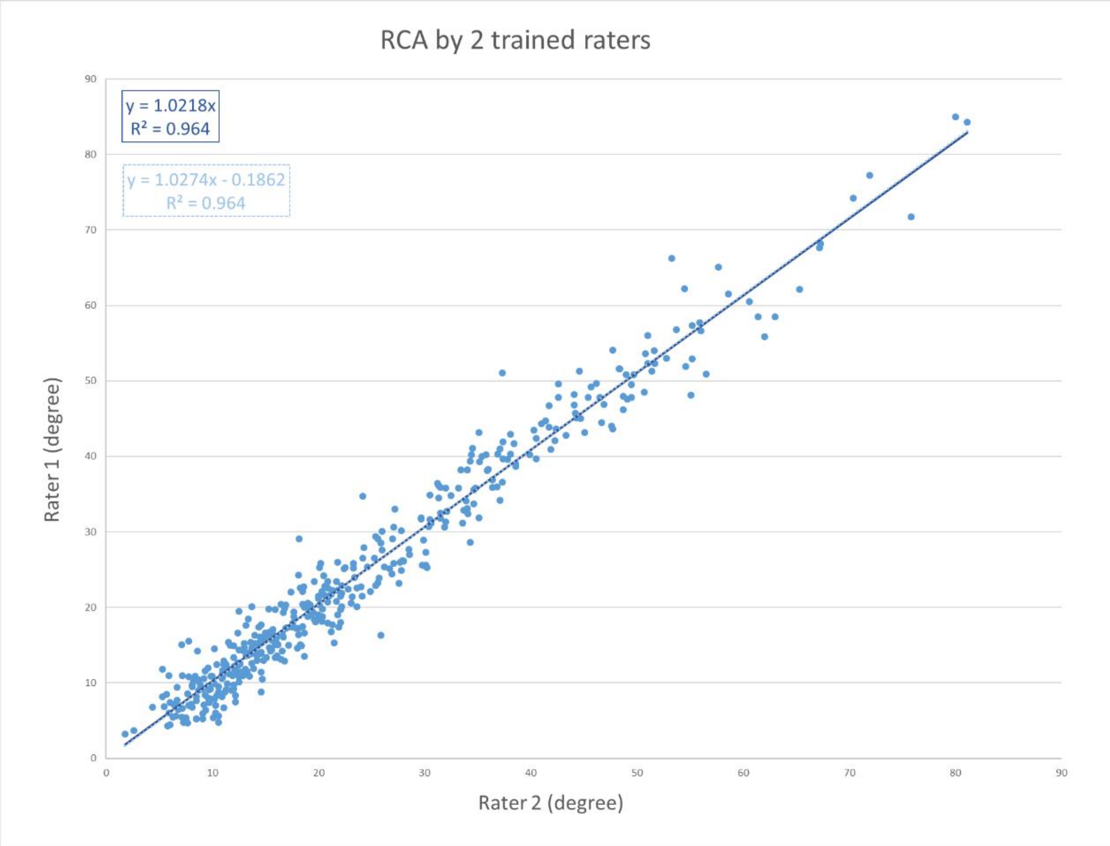


Figure 4-9. Correlation (R^2) and equations between the RCA results from the same radiograph by two raters

4.2.3. Spine Curvatures – Ultrasound Transverse Processes Angle (USTPA)

Coronal spine curvatures could be manually measured by drawing lines along spinous processes and transverse processes on the ultrasound projection images in coronal plane as ultrasound spinous processes angle (USSPA) and ultrasound transverse angle (USTPA) respectively. The USTPA was presented instead of USSPA for the ultrasound projection images in coronal plane, since the USTPA measurement method is closer to the Cobb method (drawing horizontal lines manually) (Figure 4-10). The correlation between USTPA and RCA was also reported higher than the correlation between USSPA and RCA (Lee et al. 2020).

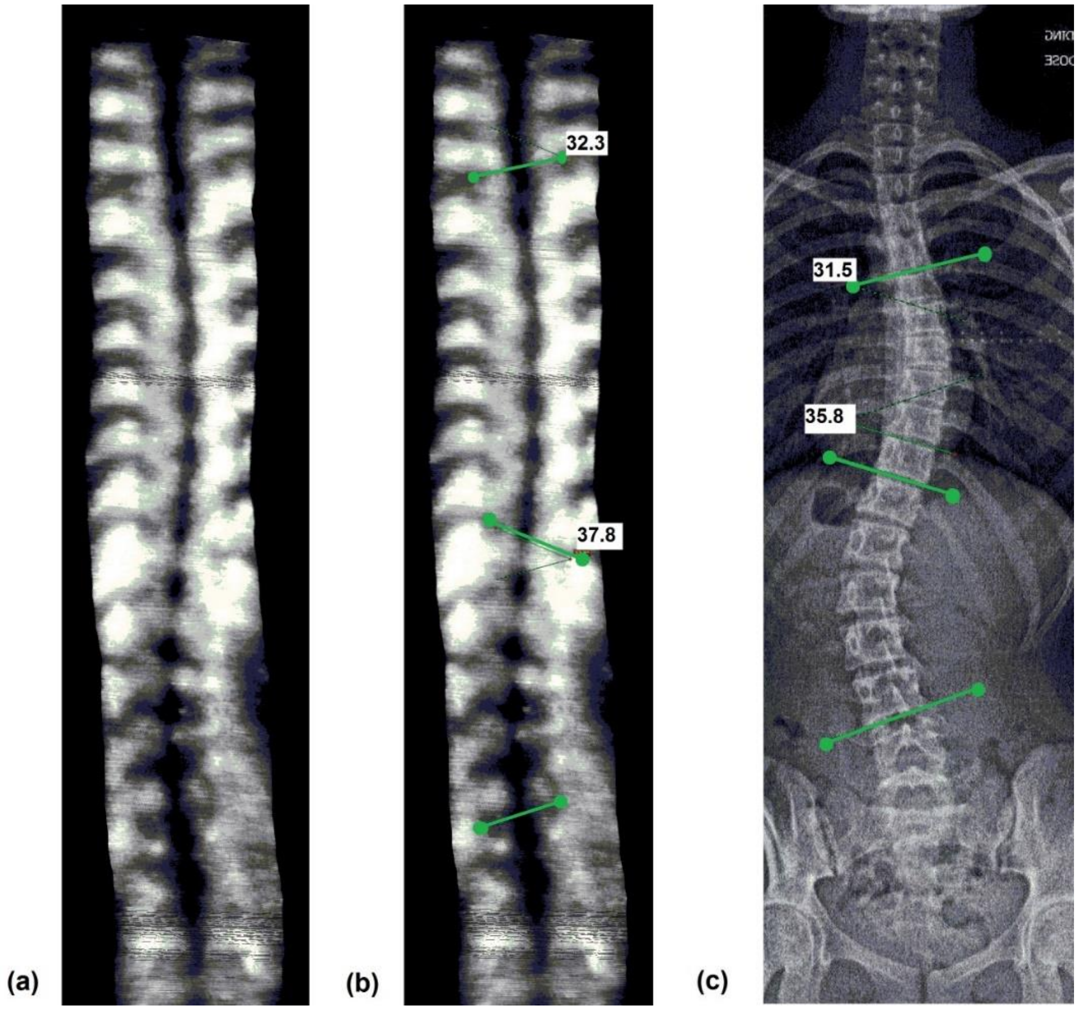


Figure 4-10. Diagram illustrating the (a) ultrasound projection image formed in coronal plane; (b) the USTPA measurement results on ultrasound image; and (c) the RCA measurement results on EOS image for the same subject

Combining the 200 subjects involved in both batch A and batch B, a total of 432 pairs of angles at different time points were included. The R^2 value between the USTPA and RCA for 432 pairs of angles is 0.8679. (Figure 4-11), indicating a high correlation between RCA results on radiographs and the USTPA results on the ultrasound projection images.

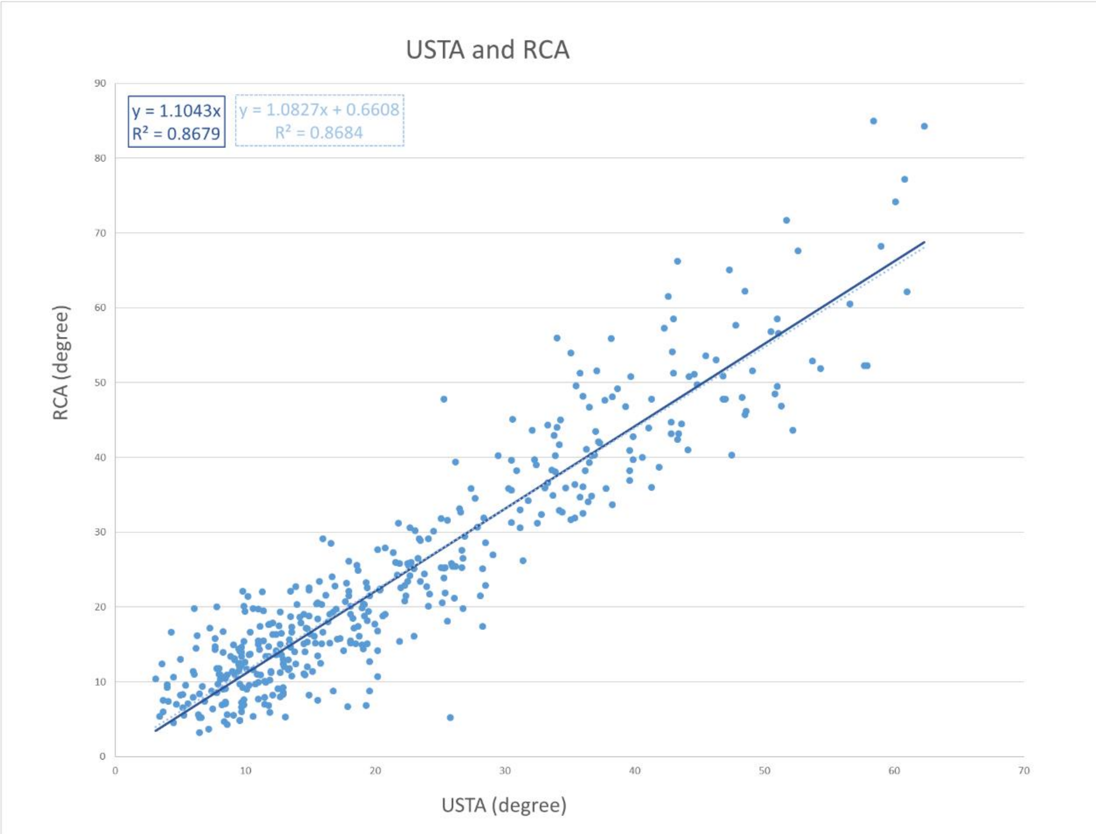


Figure 4-11. Correlation (R^2) and equations between the USTPA and the RCA

4.3. Sensitivity and Specificity of 3DUS in Monitoring Spine Curvature Progression

4.3.1. Scoliosis and Non-scoliosis

For traditional radiographs on spine, a Cobb angle of ten degrees or more in the coronal plane is defined as scoliosis (Kim et al. 2010). A change of five degrees or more in Cobb angle is an indicator of curve progression (Soucacos et al. 1998). For this study, any cases with RCA of ten degrees or more were considered as scoliosis, and a change of five degrees or more was considered as curve progression (Figure 4-12 and Figure 4-13).

Among the 200 subjects, 18 of them had no observed scoliosis (non-scoliosis group) and 182 of them had scoliosis (scoliosis group) for the whole observation period. Those 18 subjects were excluded from further results analysis.

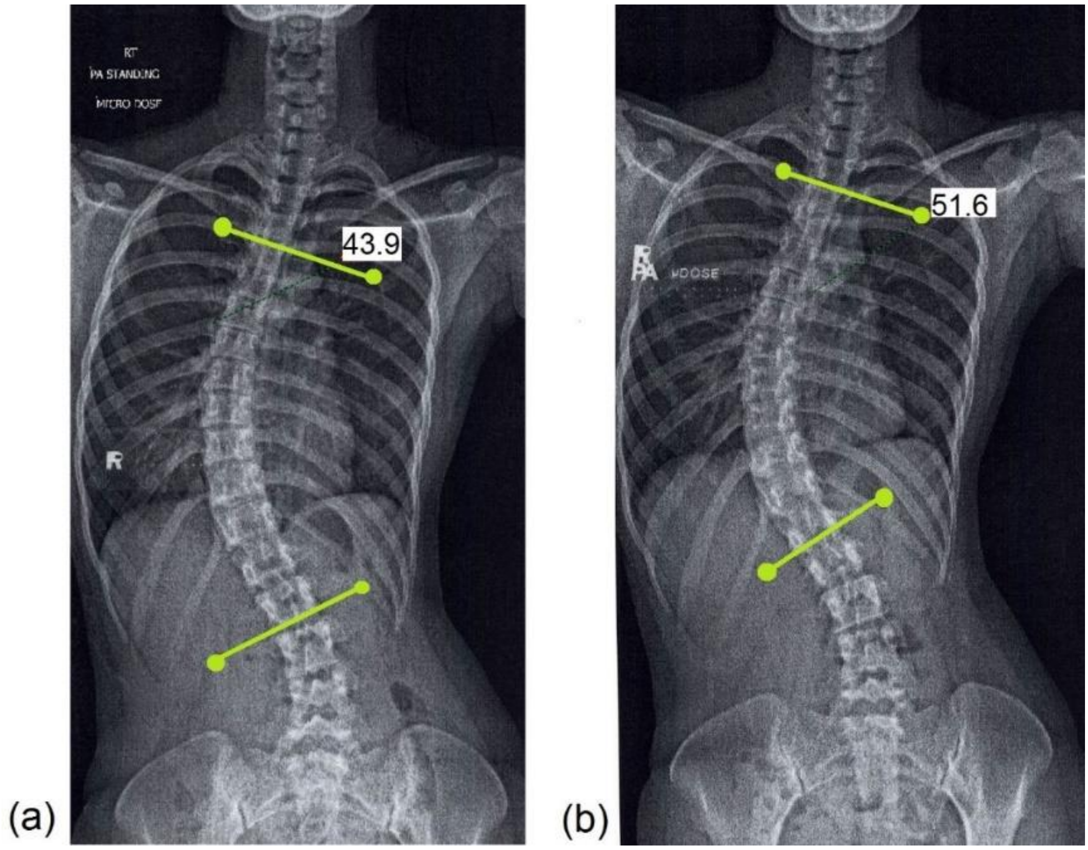


Figure 4-12. Typical progressive case with RCA measurements at (a) first visit; and (b) follow-up visit after 24 months

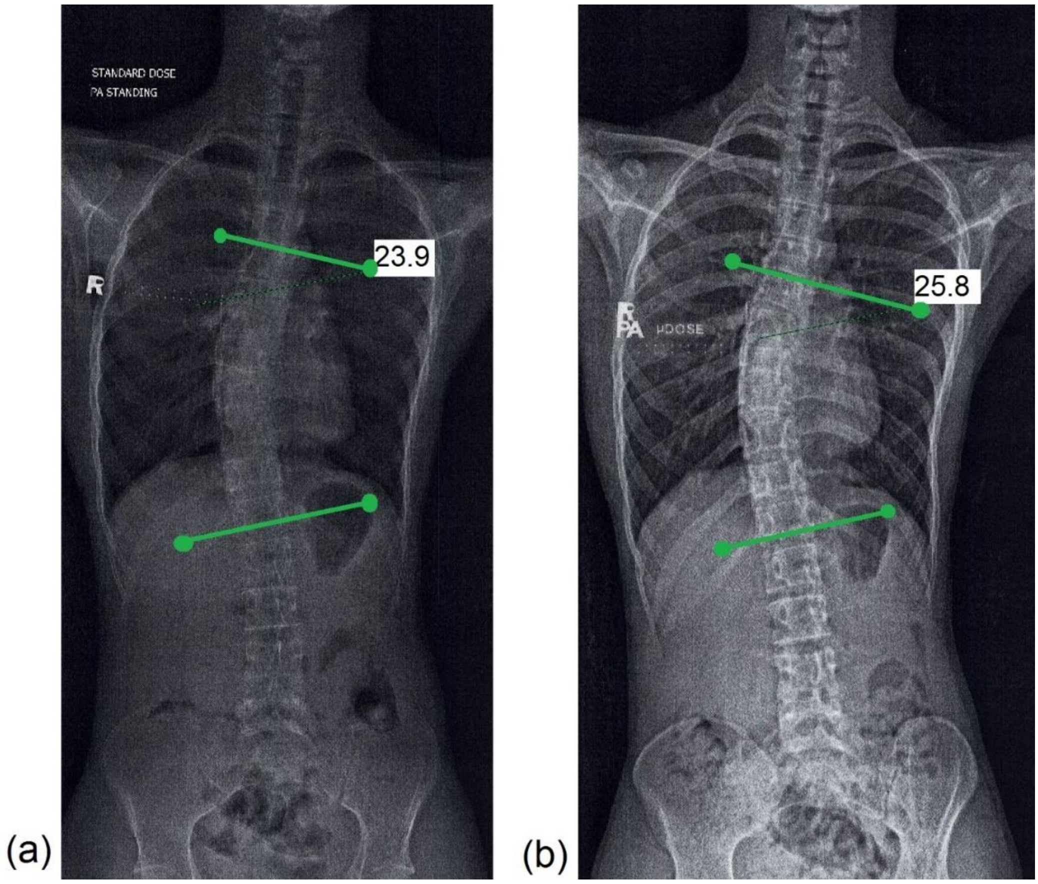


Figure 4-13. Typical non-progressive case with RCA measurements at (a) first visit; and (b) follow-up visit after 27 months

For ultrasound projection images, any USTPA change of five degrees or more was considered as curve progression (Figure 4-14 and Figure 4-15).

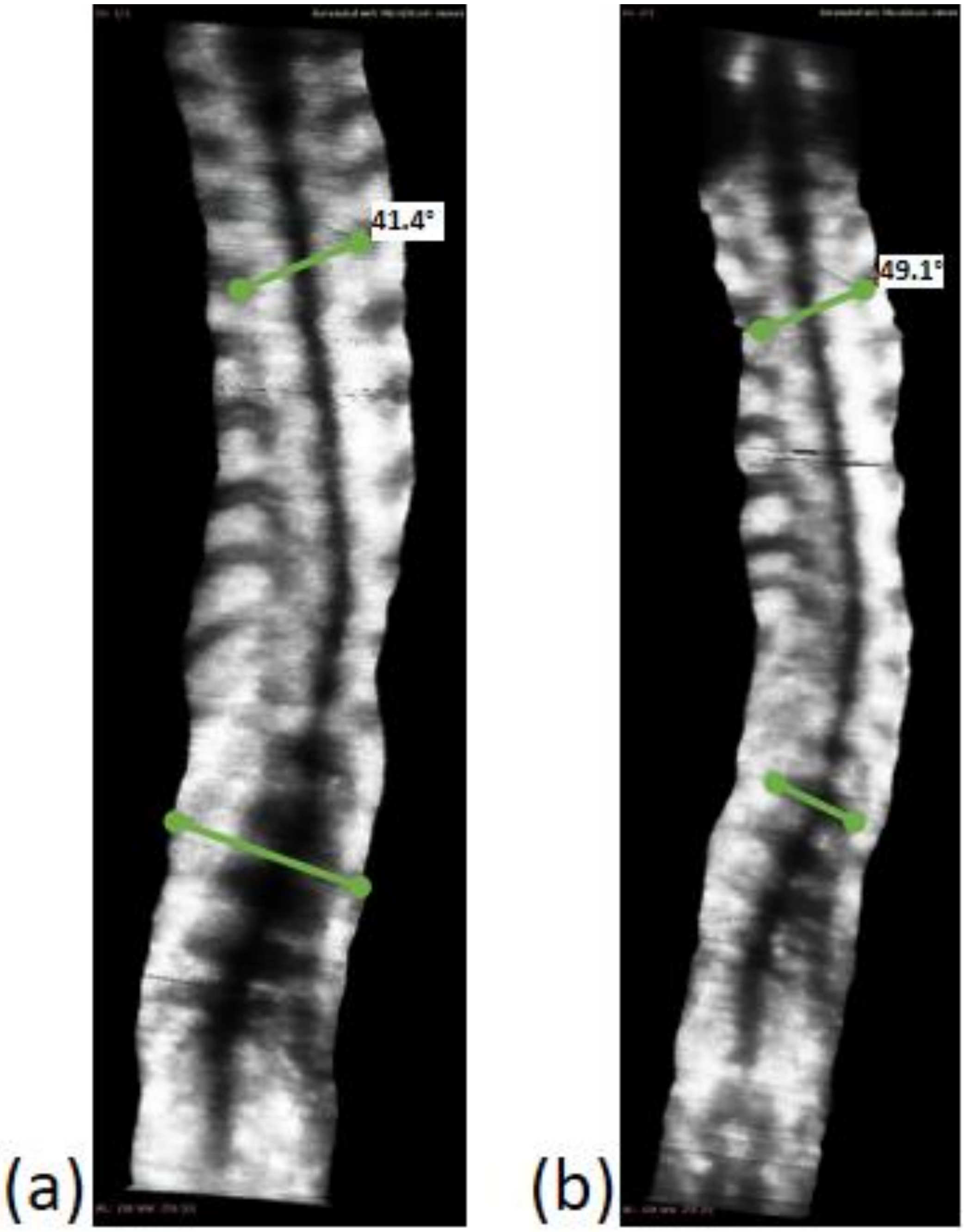


Figure 4-14. Typical progressive case with USTPA measurements at (a) first visit; and (b) follow-up visit after 24 months

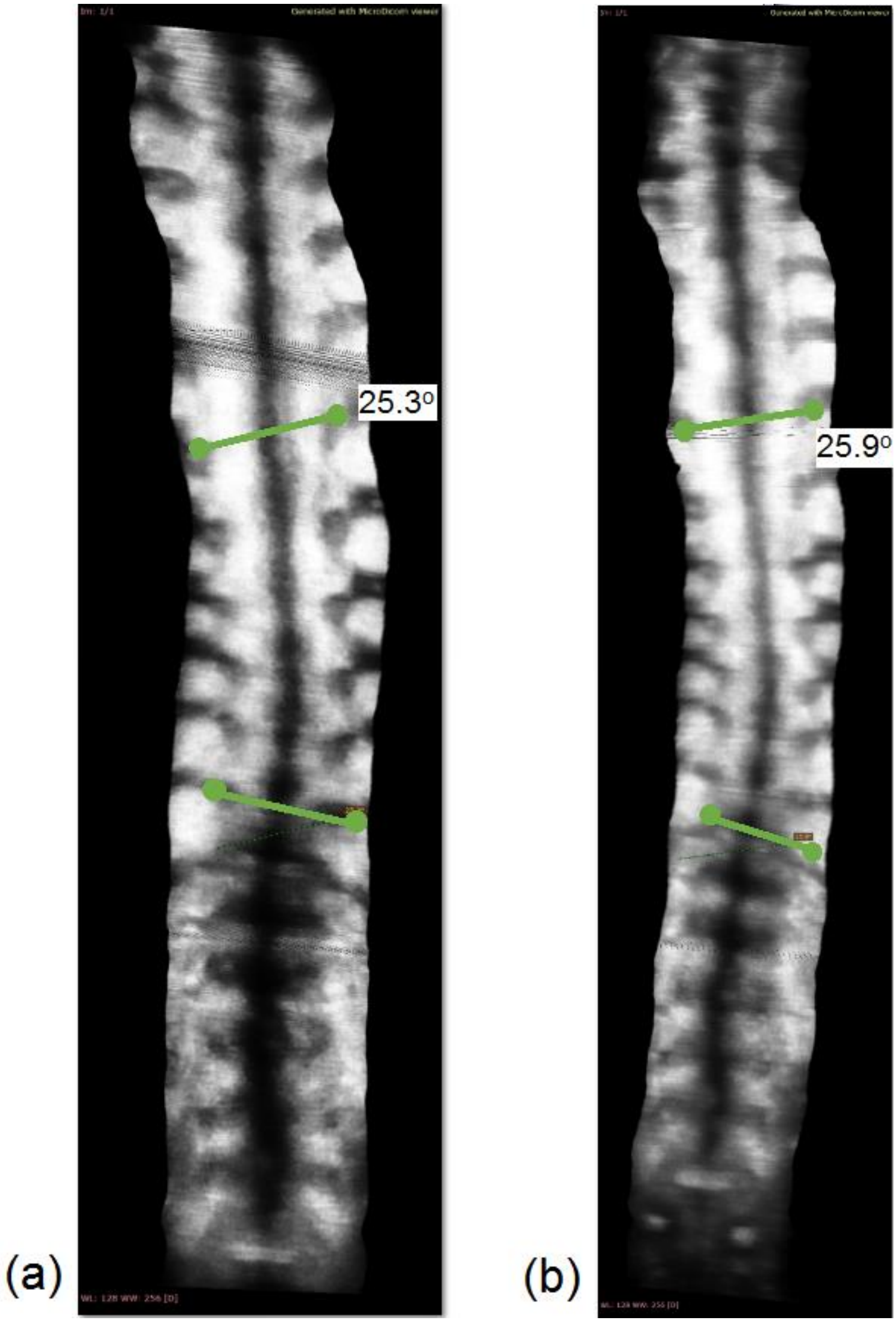


Figure 4-15. Typical non-progressive case with USTPA measurements at (a) first visit; and (b) follow-up visit after 27 months

4.3.2. Progressive and Non-progressive

For 32 subjects with three visits, those with any of the curvature changes between visits exceeding the threshold values were considered as progressive cases. Only the cases with all curvature changes within the threshold values among all visits (first visit and second visit, second visit and third visit, first visit and third visit) were considered as non-progressive.

For validating the feasibility of using 3DUS in monitoring spine curvature progression by setting the threshold of 5-degree increment in both USTPA and RCA, and using the main (maximum) curvature at the first visit for 182 subjects (exclusion of 18 non-scoliosis subjects), there were 31 and 38 progressive cases detected by RCA measurement and USTPA measurement respectively. And 151 and 144 non-progressive cases were detected by RCA measurement and USTPA measurement respectively.

4.3.3. Sensitivity and Specificity and Negative Likelihood Ratio

Among 31 progressive cases determined by RCA measurement, 27 showed positive results in USTPA and 4 showed negative results in USTPA. The true positive (TP) and false negative (FN) values were 27 and 4 respectively. Among 151 non-progressive cases determined by RCA measurement, 140 showed negative results in USTPA while 11 of them showed positive results in USTPA. The true negative (TN) and false positive (FP) values were 140 and 11 respectively. Using the RCA as references, the sensitivity and specificity of using 3DUS in monitoring the spine curvature progression were 0.87 and 0.93 respectively (Table 4-2). The negative likelihood ratio of the 3DUS test for scoliosis progression was 0.14 that only 14% probability of having progressive scoliosis if the 3DUS measurement detected as non-progressive.

Table 4- 2. Results for the curve progression detected by 3DUS and X-ray for combined batch

	3DUS – Yes	**3DUS – No**
X-ray – Yes	27 (True Positive)	4 (False Negative)
X-ray – No	11 (False Positive)	140 (True Negative)

By separating the results of batch A (suspected AIS cases) and batch B (diagnosed AIS cases), similar results were obtained (Table 4-3 and Table 4-4). For 100 subjects in batch A with suspected AIS, the sensitivity and specificity of using 3DUS in monitoring the spine curvature progression were 0.86 and 0.90 respectively. For 100 subjects in batch B diagnosed with scoliosis, the sensitivity and specificity of using 3DUS in monitoring the spine curvature progression were 0.88 and 0.95 respectively. The negative likelihood ratio for batch A and batch B were 0.16 and 0.13 respectively. The results demonstrated that it was feasible to use the 3DUS for monitoring spine curvature progression in scoliosis patients with various severities.

Table 4- 3. Results for the curve progression detected by 3DUS and X-ray in batch A

	3DUS – Yes	**3DUS – No**
X-ray – Yes	15 (True Positive)	2 (False Negative)
X-ray – No	4 (False Positive)	78 (True Negative)

Table 4- 4. Results for the curve progression detected by 3DUS and X-ray in batch B

	3DUS – Yes	**3DUS – No**
X-ray – Yes	12 (True Positive)	2 (False Negative)
X-ray – No	7 (False Positive)	62 (True Negative)

CHAPTER 5 DISCUSSION

5.1. Results in Comparison with Previous Studies

Overall, this study demonstrated the feasibility of using three-dimensional ultrasound (3DUS) for monitoring spine curvature progression with high system reliability, excellent correlation with traditional radiographs, high sensitivity and specificity in detecting spine curvature progression.

Several previous studies carried validation tests on various 3DUS systems for the assessment of scoliosis with high reliability (Chen et al. 2013, Cheung et al. 2013, Ungi et al. 2014, Cheung et al. 2015a, Vo et al. 2015 and Wang et al. 2016). There is a recent study validated that the 3DUS system Scolioscan used in this study with manual ultrasound spinous processes angle (USSPA) measurement, using traditional radiographic Cobb angle (RCA) as a reference. The correlation between USSPA and RCA was good in terms of R^2 value of 0.7593 for 49 subjects. The study also reported high intra-operator and inter-operator reliability of the 3DUS system Scolioscan on 20 subjects (Zheng et al. 2016). Another large-scale study also demonstrated the feasibility of using the Scolioscan for detecting spinal deformities with automatic USSPA measurement, using traditional RCA as references. There was a good correlation shown between the 3DUS automatic results and radiography results, but with suggested scaling factor for angle conversion (Wong et al. 2019).

In this study, more subjects were recruited in the intra-operator and inter-operator reliability tests and the validation test of the same 3DUS system Scolioscan. Ultrasound transverse processes angle (USTPA) manual measurement was applied instead of USSPA measurement. The obtained high intra-operator and inter-operator reliability on 30 subjects and strong correlation (R^2 value of 0.8679) between 3DUS and radiography results on 200 subjects demonstrated the feasibility of using 3DUS system Scolioscan with USTPA measurement on scoliosis patients. The strong correlation between USTPA and RCA without scaling factor showed the 3DUS system with USTPA measurement is potentially applicable for scoliosis patients with various severity, similar to previous related study outcomes (Lee et al. 2020).

Apart from detecting scoliosis in a single clinical visit, the 3DUS system is aimed at monitoring spine curvature progression longitudinally without radiation hazards. There are some studies reported the feasibility of using non-radiation imaging technologies for longitudinal follow-ups of scoliosis. A cross-sectional study reported the application of surface topography for monitoring scoliosis curve progression on 100 subjects. With some limitations, the reported sensitivity and specificity were 0.857 and 0.716 respectively (Komeili et al. 2015). Another study reported the sensitivity and specificity of using DIERS for detecting scoliosis curve progression were only 0.64 and 0.69 respectively (Bassani et al. 2019).

A study reported the application of an ultrasound system SonixTABLET (Analogic Ultrasound—BK Medical, Peabody, Massachusetts, US) equipped with a position and orientation tracking transducer, on 200 subjects. With promising 3DUS technology, the sensitivity and specificity for detecting scoliosis curve progression were 0.90 and 0.85 respectively, with the negative likelihood ratio of 0.08 (Zheng et al. 2018). Similar results were obtained in this study, using the 3DUS system Scolioscan for detecting scoliosis curve progression, with traditional radiography as a reference. High sensitivity of 0.87, high specificity of 0.93 and low negative likelihood ratio of 0.14 showed that using 3DUS for detecting scoliosis progression can reduce a large portion of radiation exposure on scoliosis patients.

5.2. False Negative (FN) Cases

Among the cases with false negative (FN) and false positive (FP) results, those cases with FN results are most concerned clinically as it may underestimate the curve severity of patients, causing the delay of treatment and related consequences. There were four FN cases, which showed curve progression in RCA but not USTPA. The unclear transverse processes in the thoracic-lumbar region and the postural difference between radiographs taken are the potential causes for the inconsistent results between 3DUS and traditional radiography. Unclear transverse processes may lead to manual drawing error of the horizontal lines for USTPA measurement while thick fat layer may cause the attenuation of the US wave as to limit the penetrating power to reach the bone surface. Figure 5-1 showed the difference between the B-mode images of spines obtained from subjects with low body mass index (BMI) and high BMI respectively. The subject with low BMI of 17 kg/m^2 has thin fat tissues layer of thickness 0.35 cm and 0.43 cm on T7 vertebra and L2 vertebra respectively. Subject with high BMI of 26 kg/m^2 has thick fat tissues layer thickness of 0.71 cm and 1.21 cm on T7 vertebra and L2 vertebra respectively.

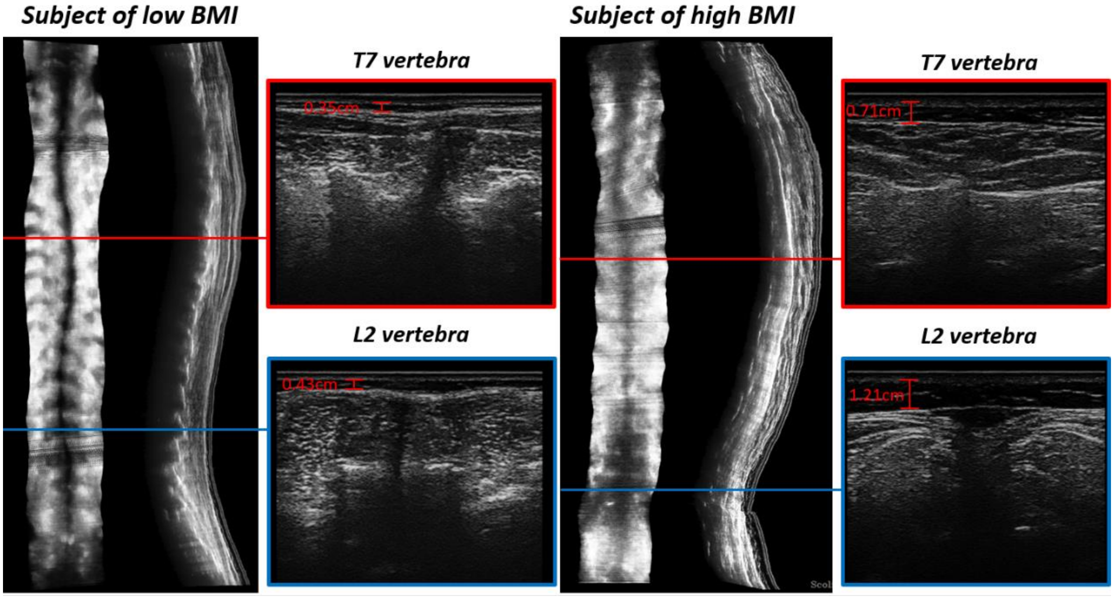


Figure 5-1. B-mode images of spines obtained from subjects with low BMI of 17 kg/m^2 and high BMI of 26 kg/m^2

For FN case 1, the RCA changed from 12.6 to 19.8 degrees while the USTPA changed from 10.0 to 6.1 degrees (Figure 5-2). In this case, there was observed postural deviation between radiographs taken. Lateral trunk shift between head and pelvis was observed in the follow-up visit but not the first visit (Figure 5-3). And, spine curvature was small that little manual deviation in horizontal line drawing may affect the positive/negative result. Moreover, the transverse processes were not clearly shown on the ultrasound projection images. Thick fat layer in the follow-up visit (high BMI > 23 kgm^{-2}) might contribute to the unclear transverse processes in the ultrasound image.

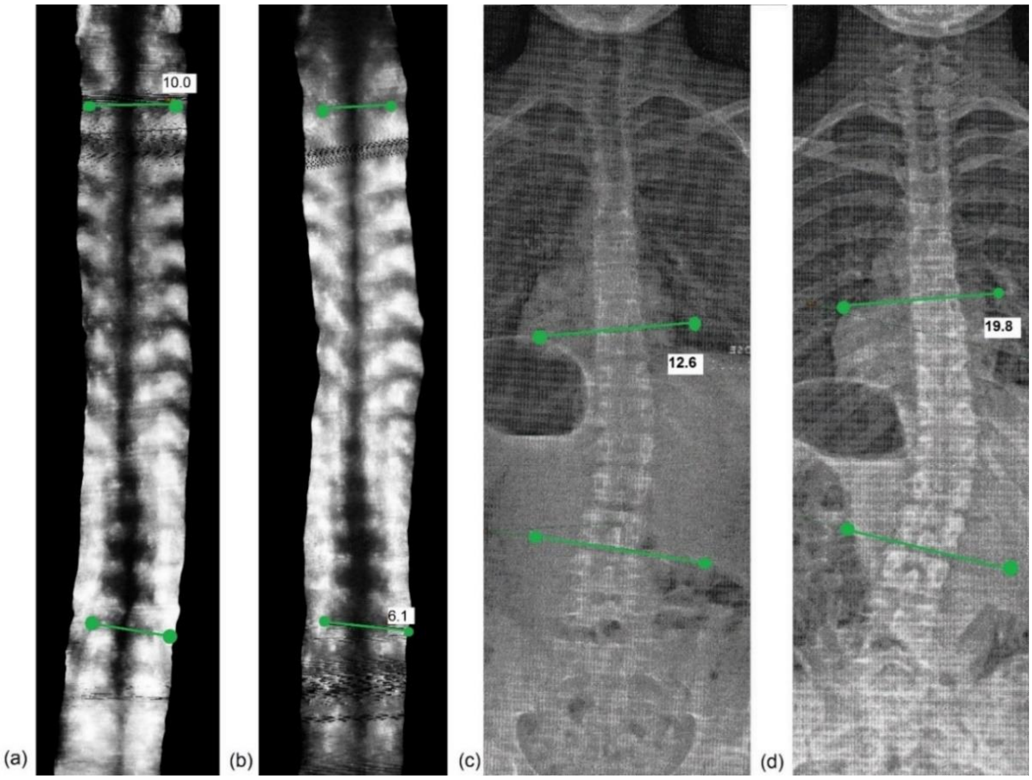


Figure 5-2. FN case 1 (ScoE-103) with USTPA at (a) first visit and (b) follow-up visit after 12 months; and RCA at (c) first visit and (d) follow-up visit after 12 months

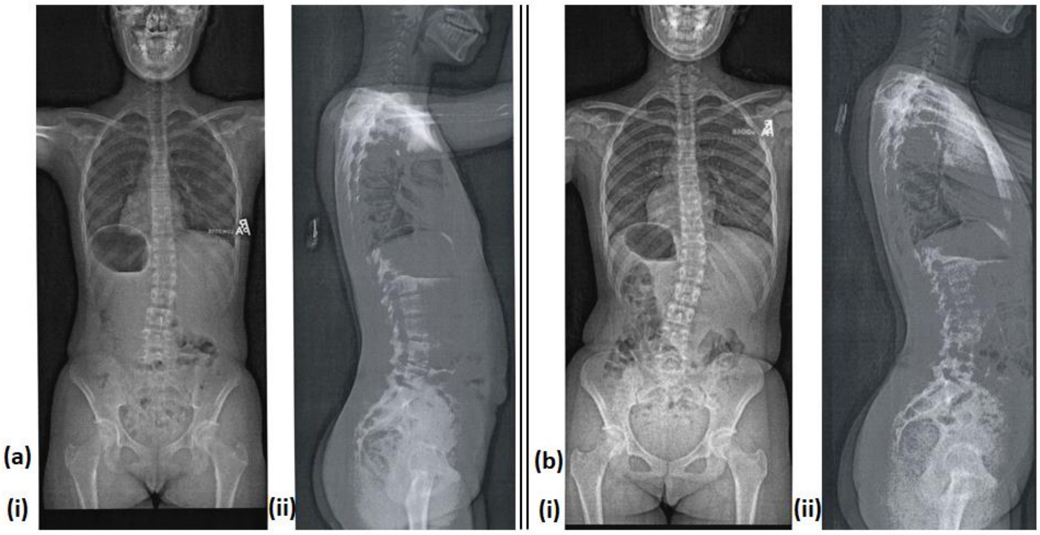


Figure 5-3. FN case 1 (ScoE-103) radiographs at (a) first visit of (i) coronal plane and (ii) sagittal plane; and (b) follow-up visit of (i) coronal plane and (ii) sagittal plane after 12 months

For FN case 2, the RCA changed from 6.8 to 14.2 degrees while the USTPA changed from 9.9 to 12.4 degrees (Figure 5-4). In this case, the spine curvature convexity was different in radiographs between visits. There was a comparatively larger curvature with the convexity on left at the follow-up visit. The potential cause for the inconsistency was the postural difference between visits during radiographs taken. As shown in the radiographs (Figure 5-5), the pelvis tilted much more during the follow-up visit compared with the first visit. The subject’s hands were put in front of her core touching her head in the follow-up visit but kept 90 degrees in the first visit.

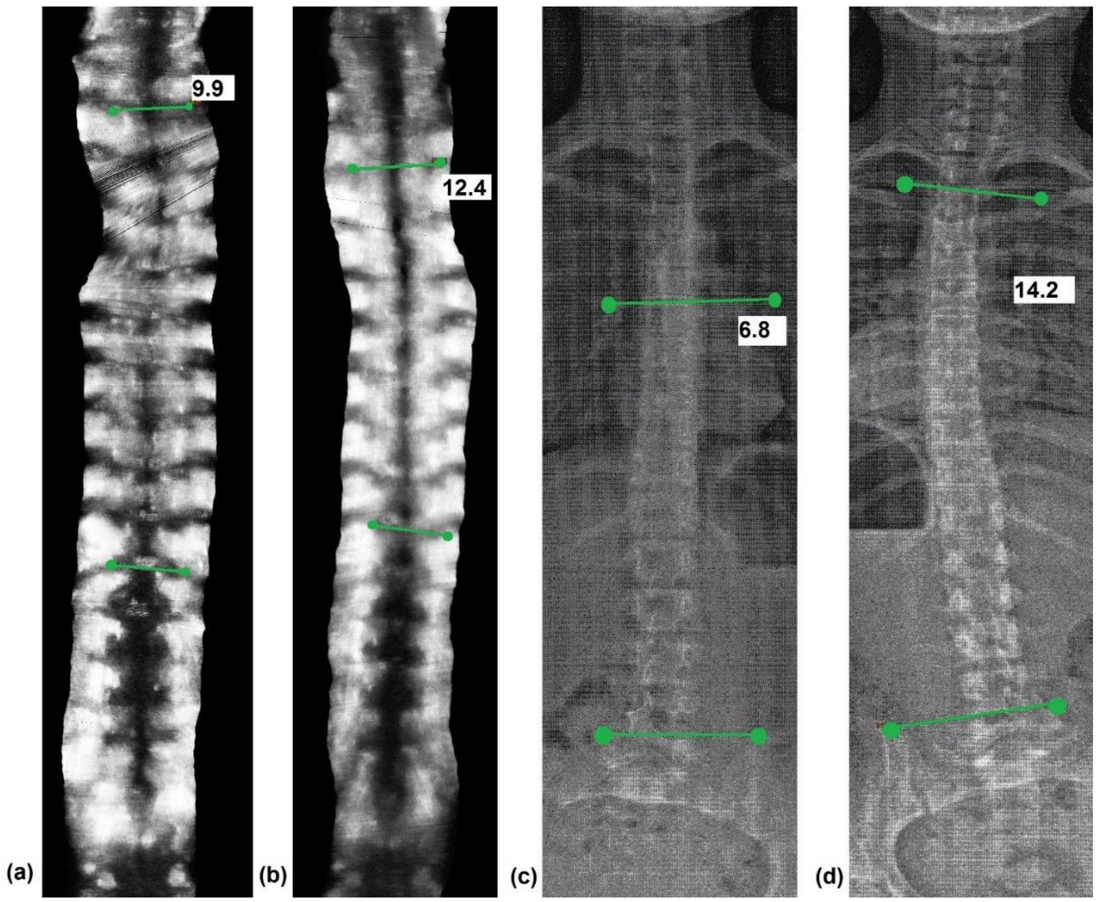


Figure 5-4. FN case 2 (ScoE-130) with USTPA at (a) first visit and (b) follow-up visit after 13 months; and RCA at (c) first visit and (d) follow-up visit after 13 months

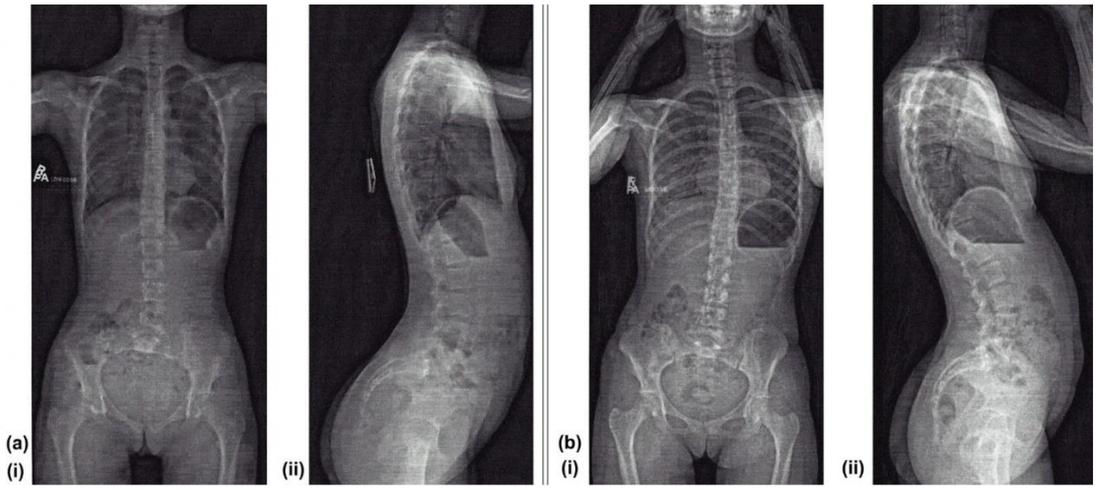


Figure 5-5. FN case 2 (ScoE-130) radiographs at (a) first visit of (i) coronal plane and (ii) sagittal plane; and (b) follow-up visit of (i) coronal plane and (ii) sagittal plane after 13 months

For FN case 3, the RCA changed from 14.9 to 27.7 degrees while the USTPA changed from 19.0 to 20.2 degrees (Figure 5-6). In this case, there was a comparatively larger curvature at the follow-up visit, and the potential cause for the inconsistency was the postural difference between visits during radiographs taken. As shown in the radiographs (Figure 5-7), the subject’s hands were lifted up and kept 90 degrees to her core body for the first visit, but freely put in front of her core body for the follow-up visit.

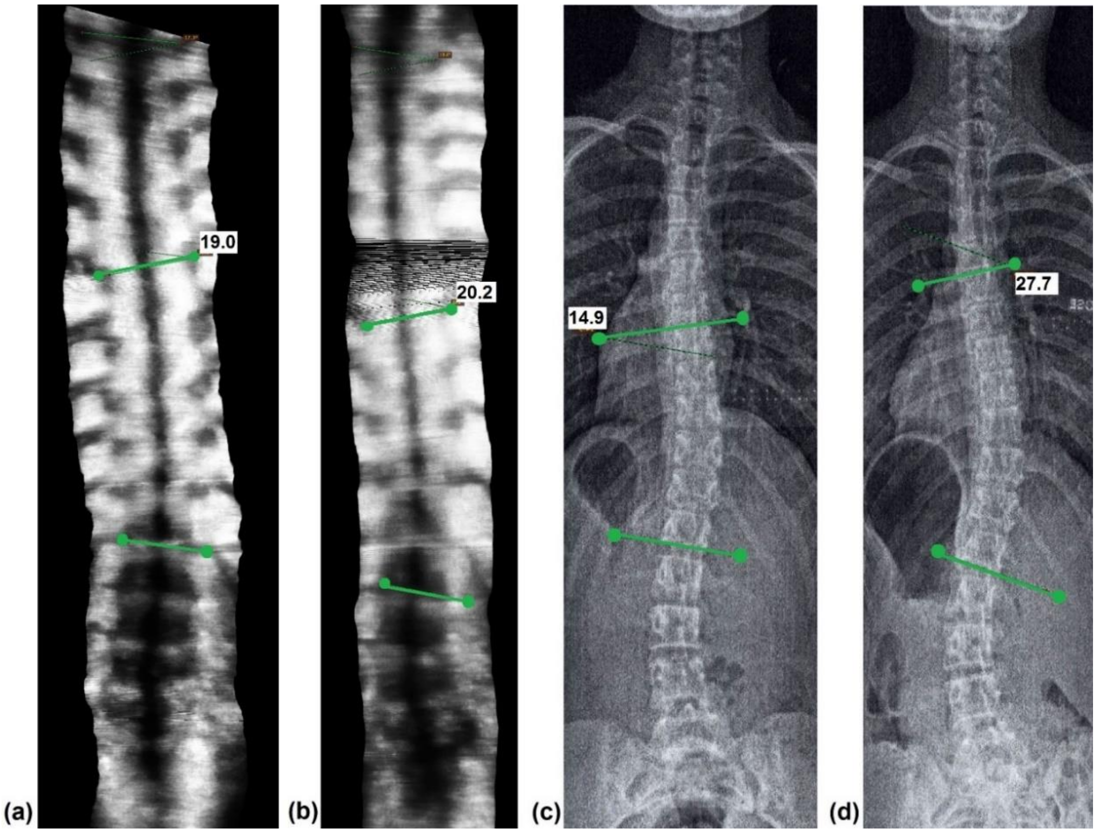


Figure 5-6. FN case 3 (PIII-0351) with USTPA at (a) first visit and (b) follow-up visit after 21 months; and RCA at (c) first visit and (d) follow-up visit after 21 months

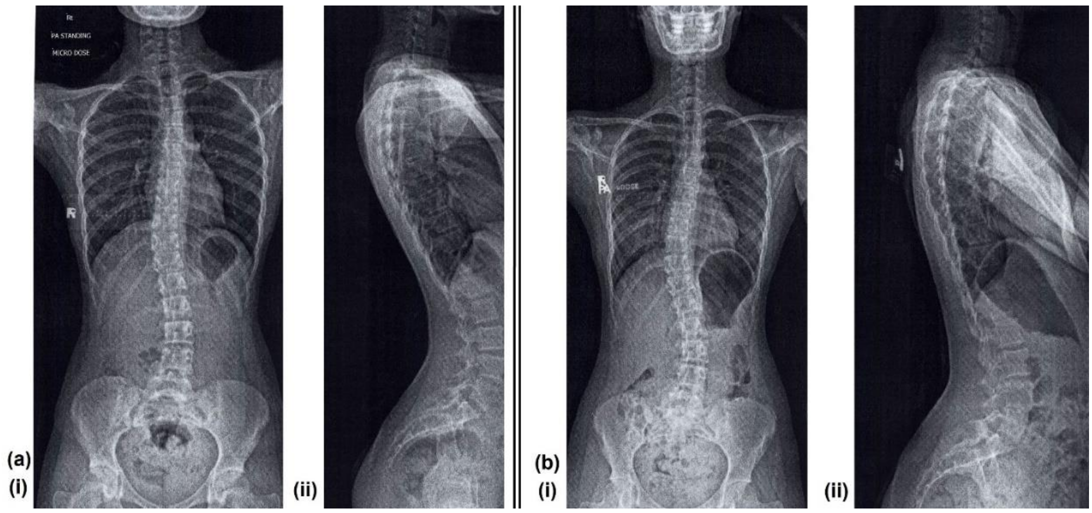


Figure 5-7. FN case 3 (PIII-0351) radiographs at (a) first visit of (i) coronal plane and (ii) sagittal plane; and (b) follow-up visit of (i) coronal plane and (ii) sagittal plane after 21 months

For FN case 4, the RCA changed from 46.7 to 56.0 degrees while the USTPA changed from 36.5 to 34.0 degrees (Figure 5-8). In this case, there was no observed postural deviation between radiographs taken (Figure 5-9), but the ultrasound image quality was not good enough due to the little subject movement during the ultrasound assessment. Moreover, the spine curvature of this subject was large with rotation. The transverse processes of spine could not be clearly recognized in the ultrasound images. In the ultrasound images, the upper most tilted vertebra was not clearly showed for USTPA measurement thus the nearest vertebra was used for manual measurement instead. This showed the importance of keeping the subject's posture stable and rigid during scanning, and the limitation of using ultrasound assessment for USTPA measurement on severe cases with obvious rotation.

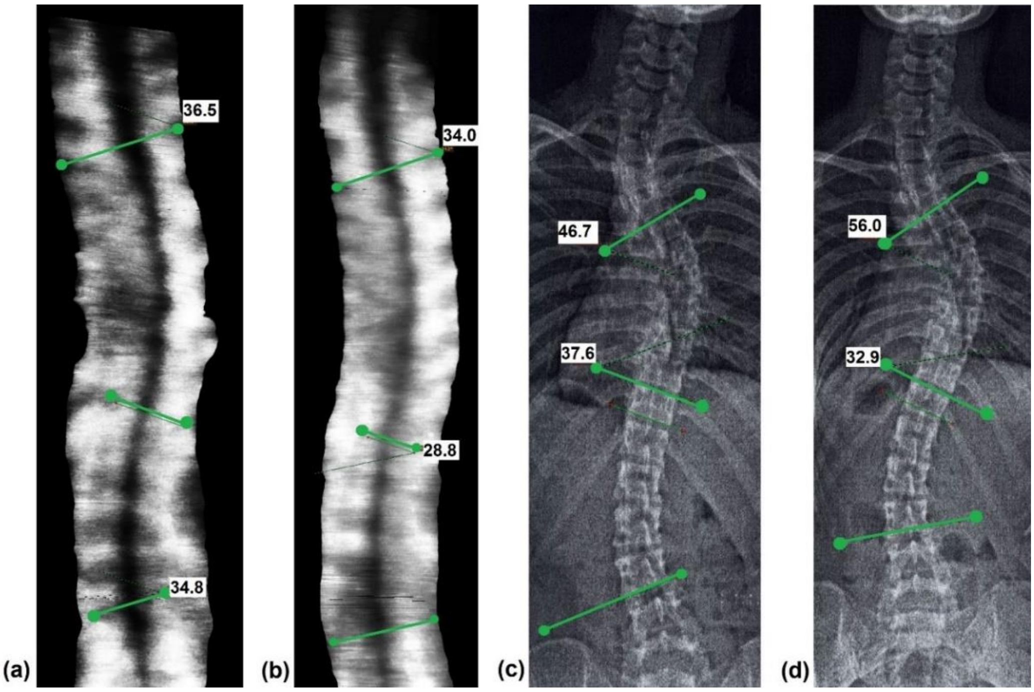


Figure 5-8. FN case 4 (PIII-0525) with USTPA at (a) first visit and (b) follow-up visit after 18 months; and RCA at (c) first visit and (d) follow-up visit after 18 months

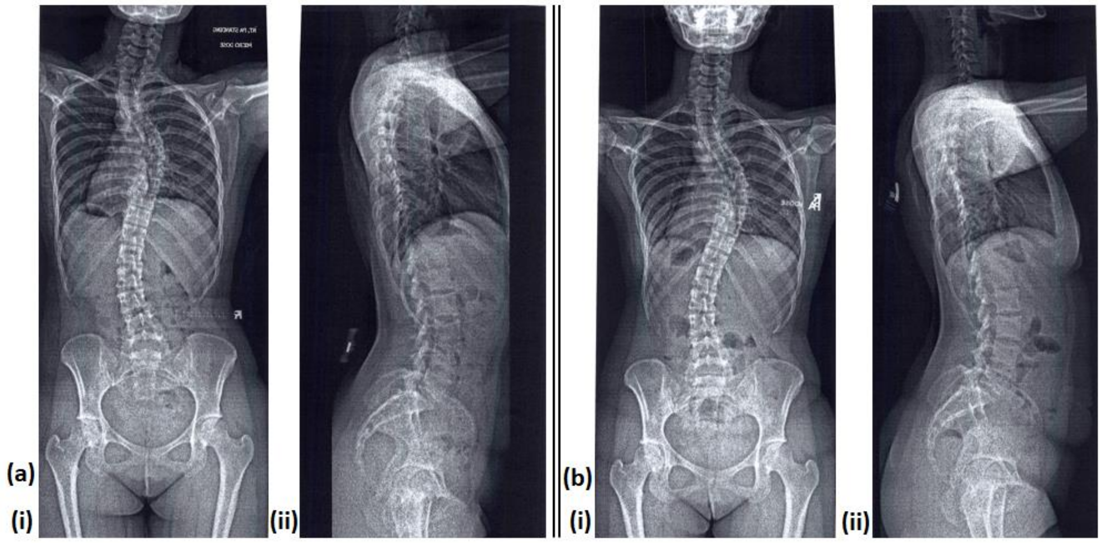


Figure 5-9. FN case 4 (PIII-0525) radiographs at (a) first visit of (i) coronal plane and (ii) sagittal plane; and (b) follow-up visit of (i) coronal plane and (ii) sagittal plane after 18 months

5.3. False Positive (FP) Cases

There was a relatively large number of FP cases with up to 11 cases among 182 subjects (Figure 5-10). Traditional Cobb method uses the vertebra body for measurement while the USTPA method uses the transverse processes for measurement, and the transverse processes are sometimes further apart from the center of the vertebra bodies especially on the lumbar region. Due to this feature, the rotation of the vertebra bodies may contribute to the over-estimated results, mainly in severe rotation cases.

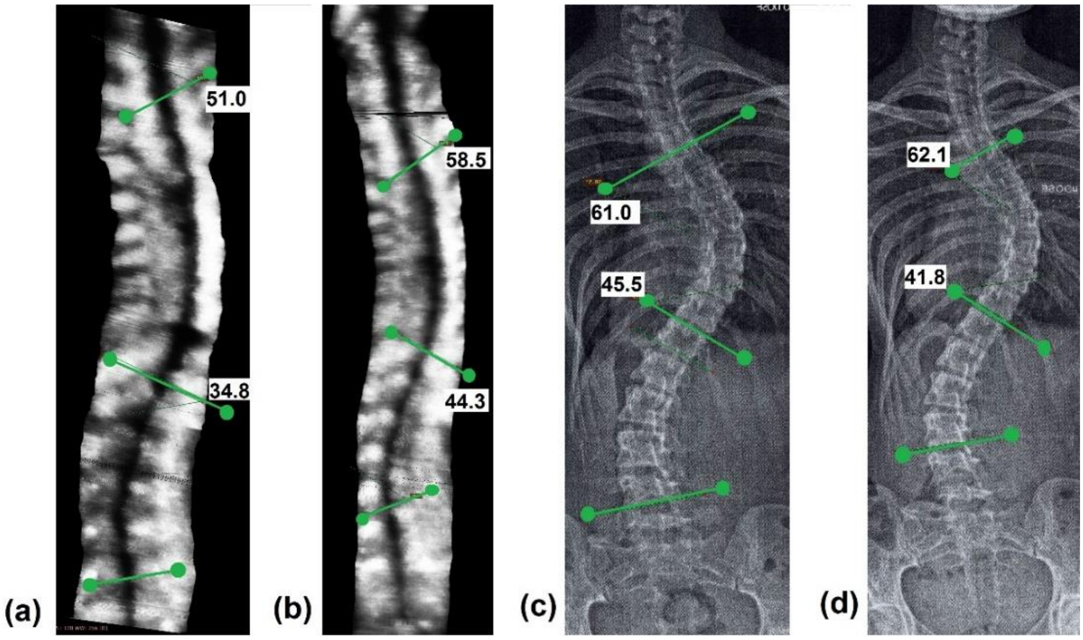


Figure 5-10. Typical FP case with USTPA at (a) first visit and (b) follow-up visit after 23 months; and RCA at (c) first visit and (d) follow-up visit after 23 months

Besides the obvious rotation in severe cases, there were some mild cases with FP results. The potential reason is the limitation of the existing ultrasound probe. As the transverse processes are comparatively further apart from the center of the vertebra bodies which may not be covered by the scanning width of the existing ultrasound probe. Moreover, for most cases, not all the transverse processes along the whole spine were clearly seen and identified in the ultrasound projected images as transverse processes are comparatively further away from the skin surface thus beyond the penetration power of the existing ultrasound probe. To facilitate the USTPA measurement as to reduce the number of FP cases, it is suggested the Scolioscan system may include an ultrasound probe with a wider width and higher penetration power.

5.4. Limitations of the Study

There were limitations due to the unfavorable ultrasound image quality which led to difficulties in transverse processes angle measurement. Some transverse processes of the vertebrae in lumbar region were not within the scanning width of the ultrasound transducer. Rotation on the vertebra body also resulted in comparatively poor ultrasound image after volume projection on single depth as bilateral vertebrae features could not be shown on the same plane (Lee et al. 2019). Varying muscle thickness and fat content on the patients' back would also affect the ultrasound image quality. Therefore, to improve the measurement, it is suggested that the system should adopt a curved surface probe or flexible surface probe, and changeable probes for fitting various subjects.

Moreover, there was an assumption for the transverse processes angle measurement in US image that vertebral body is typical symmetrical. But indeed, scoliotic curve usually appears with anatomical abnormalities like wedging that the above assumption maybe not be followed. In severe scoliosis with severe anatomical abnormalities of the transverse process, there may be discrepancy of the interpretation of the US image. In future application of the 3DUS system, may more bony features be included for angle measurement as to facilitate comprehensive understanding of the scoliotic curve for severe cases.

There was also a limitation for the application of the 3DUS system Scolioscan that manual procedures were included in scanning, best images selection among the 9 various depth projection layers, as well as angle measurement. Ultrasound image quality was also subjected to scanning activities and subjects' condition. Poor contact and undesired scanning movement might lead to blurry ultrasound images. More precise instructions to subjects and adequate training to operators was recommended. For inexperienced operator, ultrasound images with poor quality might resulted with inadequate scanning skills and experience, and non-optimal depth projection layer selected by inexperienced operator might contribute to scoliotic curve results discrepancy. Therefore, reliability on various depth projection layer selection study and reliability on ultrasound scanning study is suggested to be carried out between experienced operator and inexperienced operator. In addition, full training for operator with certain testing criteria is suggested to ensure proper use of the 3DUS system Scolioscan by professional operators.

In addition, there were limitations and areas for improvement in subject recruitment. The sample size involved (62 male and 138 female subjects; 8-26 years of age, mean of 14.2 ± 2.8 years) in this study was not big, and some of the subjects had already reached skeleton maturity that progression information is not very clinically concerned (Lam et al. 2013).

5.5. Future Studies

Among 182 subjects, only 31 cases showed progression that was lower than the general progressive rate. It is believed that there are some progressive cases among the remaining 151 subjects but our follow-up period did not cover the whole progression period (curve progressed and stabled before the first visit or after our last follow-up). For further study, it is suggested to involve more subjects in the period of higher change of curve progression (before skeletal mature), and extend the follow-up period to cover their curve development until the skeleton matures. More clinical information such as transverse rotation is also suggested to be recorded for further analysis. For a more complete understanding of the spine curvature progression mechanism, three-dimensional profile of spine can also be analyzed with the EOS biplanar X-ray system and 3DUS system.

CHAPTER 6 CONCLUSIONS

In this study, the feasibility of using three-dimensional ultrasound (3DUS) in monitoring spine curvature progression has been investigated. Firstly, the 3DUS system Scolioscan has been validated with high inter-rater and intra-rater reliability. Secondly, a strong correlation was demonstrated between the ultrasound transverse processes angle and radiographic Cobb angle in 200 subjects with 432 curves.

Using the radiographic Cobb angle as a reference, the sensitivity and specificity of using 3DUS for detecting scoliosis progression were 0.87 and 0.93, respectively. Judging from the high sensitivity and specificity, the 3DUS imaging system Scolioscan with ultrasound transverse processes angle measurement was sufficiently comparable to X-ray in monitoring scoliosis progression for the 200 subjects tested. With the low negative likelihood ratio of 0.14, it was demonstrated to be effective in reducing unnecessary diagnostic radiation for monitoring scoliosis progression. After separating the results of suspected or diagnosed scoliosis cases, similar sensitivity and specificity results were obtained. The feasibility of using the system in monitoring spine curvature progression was found to be the same for scoliosis patients with various severities.

This study demonstrated the potential of Scolioscan for reducing patient exposure to radiation during the assessment of curve progression. Further studies with larger number of subjects and longer follow-up period starting at earlier stage of skeleton maturity are suggested. Collection of more clinical information is also recommended for further validation of this innovative technology.

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