Development of a Detection Model for Curve Progression in Adolescents with Idiopathic Scoliosis

by

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Abstract

Adolescent idiopathic scoliosis (AIS) is a three-dimensional (3D) structural spinal disorder recognized by lateral curvatures. The routine for monitoring of AIS is taking an X-ray every six months to check the curve severity and curve progression. Taking repetitive radiographs is not desirable for children since it can increase the risk of cancer. Based on the literature, demographic and radiographic parameters may help predict curve progression. However, there is no accurate prediction model available yet. The objectives of this thesis were to develop and validate a detection model by combining curve characteristics, reflection coefficient (RC) from ultrasound (US) signals, and clinical information to accurately detect the progressive cases thus avoiding unnecessary radiographs.

The specific objectives were

a) To identify potential clinical predictors based on prediction models from the literature
b) To determine if the US reflection coefficient correlates with curve severity and curve progression
c) To determine whether other US parameters obtained from a single US scan associated with curve progression
d) To develop a predictive model to detect the progressive curves of AIS
e) To validate the model based on clinical data

To identify prognostic factors of curve progression, a systematic review was conducted. The results showed limited or conflicting evidence for most parameters, requiring further investigation. Among the most frequently found potential parameters, age, body mass index (BMI), menarche status, frontal X-ray Cobb, number of curve (NOC), and Risser sign were selected for model development. As new parameters, I suggested the US Cobb change, the US Cobb angle in plane of maximum curvature (PMC), the kyphotic angle (KA), and axial vertebral rotation (AVR) measured on US images. Also, the US RC, which can provide the bone quality information, was investigated.

Experimental and clinical studies were conducted to ensure the validity and reliability of this index. The results showed the larger the RC index value, the stiffer the bone. Also, a clinical study demonstrated that this index could be measured reliably and 68% of children with AIS without progression had a larger RC value than the progression group.

The kyphotic angle was also considered as a potential predictor in the literature. A new method was developed and a pilot study to investigate the reliability of the KA measurement on US images was conducted. The results showed KA could be reliably measured. The maximum difference of the KA measurements between the US images and radiographs was 4°. When a larger clinical study was conducted, it further confirmed the reliability of the KA measurements. The factor which might affect the accuracy of the KA measurements was the posture of the participants during data acquisitions.

Similarly, AVR was also reported as one of the potential predictors and was studied. Before using the AVR as a parameter in model development, the reliability of the AVR

measurements was studied. A clinical study was conducted, and the results showed a poor to moderate reliability, ICC≥0.49, with the maximum average difference between X-ray and US being 4.6°. The factors that showed a significant influence on the differences of the measurements were AVR measurements at the apical region and larger AVR severity. Prior to conduct a large clinical study, a pilot study on development of detection model was conducted. In this study age, menarche status, X-ray Cobb angle, RC index, and US Cobb change were used. Of these parameters, only RC and US Cobb change were retained as predictors of curve progression. To develop the final model, a large clinical study including 162 girls was conducted. Among those, 100 participants including 25 progression cases were used for model development. The selected parameters included demographic information: age, BMI, and menarche status; radiographic parameters: X-ray Cobb angle, NOC, and Risser sign; and the US parameters: US Cobb change, RC index, KA, maximum AVR, and PMC Cobb angle. The risk of progression equation was Log (p/1-p) =-1.40+0.28(US Cobb change)-39.45(RC)+1.36 (NOC). The model was then validated on 62 cases with 11 progressions. The sensitivity, specificity, and accuracy results were over 90%.

In conclusion, the developed model showed promising results and the accuracy was better than other studies in the literature. Further study on a larger sample size is needed to offer a stronger validation.

Preface

The research described in this thesis had received ethics approval from the Health Research Ethics Board from the University of Alberta. The project title is "Using Ultrasound to Assess Spinal Deformity for Adolescent Idiopathic Scoliosis", reference number: Pro00005707.

Some of the research in this thesis is formed from collaborative work with various co-authors.

Chapter 3 is based on a submitted paper:

- Khodaei M, Parent E, Hill D, Wong J, Chan A, Gergelé E, Ng K, Leung C, Le L, Lou E. Identifying Prognostic Factors of Curve Progression in Adolescents with Idiopathic Scoliosis: A Systematic Review. Submitted to *PLOS one*, 2021.

I conceived of the direction, performed screenings, extractions, quality appraisals, and compiled the data into the journal article. I collaborated with many reviewers to perform these tasks. Screening co-reviewers included: Dr. Eric Parent, Doug Hill, Dr. Andrew Chan, and Jason Wong. Extraction and quality appraisal co-reviewers were Eloi Gergelé, Jason Wong, Kenwick Ng, Carmen Leung, and Doug Hill. I also consulted with Liz Dennett, a medical librarian for constructing the search. Direction, guidance, and review were provided by Drs. Parent, Lou and Le.

Chapter 4 is based on one submitted and one published paper:

- Pham T, Le L, Khodaei M, Zheng R, Lou E. Investigation of Ultrasonic Soft Tissue-Bone Reflection Coefficients Correlating with Curve Severity in Children with Adolescent Idiopathic Scoliosis. Submitted to *Journal of Engineering in Medicine*, 2021.
- Khodaei M, Sayed T, Hill D, Parent E, Moreau M, Stampe K, Southon S, Le L, Lou E. Reliability of measurements of a reflection coefficient index to indicate spinal bone strength on adolescents with idiopathic scoliosis (AIS): a pilot study.

Eur Spine J. 2021 Jul;30(7):1888-1895. doi: 10.1007/s00586-021-06871-8. Epub 2021 May 25

For the first paper, I collected the clinical data, measured the data on US images, and helped for experimental set-up. Tu Pham was the first author and she performed experiments, collected the experimental data, analyzed the data, and prepared the manuscript. Dr. Zheng provided the fundamental theories for conducting the study. Advice, guidance, and review of the paper were provided by Drs. Le and Lou.

For the second paper, I collected the clinical data, measured the data on US images, analyzed the results and prepared the manuscript. Tehzeeb Sayed helped on data measurement and analysis. There was also consultation with the Edmonton scoliosis research group for clinical advice and guidance: Doug Hill, Dr. Moreau, Dr. Stampe, Sarah Southon. Direction, guidance, and review were provided by Drs. Lou, Parent, and Le.

Chapter 5 is based on two submitted papers:

- Sayed T, Khodaei M, Hill D, Lou E. Intra- and Inter-rater Reliabilities and Differences of Kyphotic Angle Measurements on Ultrasound Images versus Radiographs for Children with Adolescent Idiopathic Scoliosis – A Preliminary Study. Submitted to *Spine Deformity*, 2021.
- Khodaei M, Parent E, Le L, Lou E. Factors Influencing Kyphotic Angle Measurements on Ultrasound Spinal Images of Children with Adolescent Idiopathic Scoliosis (AIS). Submitted to *European Spine Journal*, 2021.

For the first paper, I collected clinical data, helped on development of the measurement method, measured the US images, and helped on the data analysis. Tehzeeb Sayed helped on data measurement, analyzed the data and prepared the manuscript for the publication. Dr. Lou also helped on data measurement. Direction, guidance, and review were provided by Dr. Lou and Doug Hill.

For the second paper, I collected clinical data measured the US images, performed data analysis, and prepared the manuscript. Dr. Lou also helped on data measurement. Direction, guidance, and review were provided by Drs. Lou, Parent, and Le.

Chapter 6 is based on one submitted paper:

- Khodaei M, Parent E, Le L, Lou E. Investigation of Factors Influencing the Reliability and Measurement Variation of Ultrasound Axial Vertebral Rotation on Adolescents with Idiopathic Scoliosis. Submitted to *The Spine Journal*, 2021.

I collected clinical data measured the US images, performed data analysis, and prepared the manuscript. Dr. Lou also helped on data measurement. Direction, guidance, and review were provided by Drs. Lou, Parent, and Le.

Chapter 7 is based on two submitted papers:

- Khodaei M, Parent E, Le L, Southon S, Hill D, Stampe K, Huang E, Lou E. Development and Validation of a Model to Predict X-ray Progression at a Follow-up Visit Based on Ultrasound and Clinical Parameters for Adolescent Idiopathic Scoliosis (AIS). Submitted to *Spine Deformity*, 2021.
- Khodaei M, Parent E, Le L, Southon S, Hill D, Stampe K, Huang E, Lou E. Identifying Prognostic Parameters to Develop a Detection Model of Curve Progression with Clinical Validation on Adolescents with Idiopathic Scoliosis (AIS). Submitted *European Spine Journal*, 2021.

For the first study, I collected clinical data measured the US images, performed data analysis, and prepared the manuscript. There was also consultation with the Edmonton scoliosis research group team for clinical advice and guidance: Doug Hill, Dr. Moreau, Dr. Stampe, Sarah Southon. Direction, guidance, and review were provided by Drs. Lou, Parent, and Le.

For the second study, I collected clinical data measured the US images, performed data analysis, and prepared a draft for the publication. Tehzeeb Sayed and Veena Logithasan also helped on data measurements. There was also consultation with the Edmonton

scoliosis research group team for clinical advice and guidance: Doug Hill, Dr. Moreau, Dr. Stampe, Sarah Southon. Direction, guidance, and review were provided by Drs. Lou, Parent, and Le.

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List of Abbreviations

2D: Two Dimensional

3D: Three Dimensional

AIS: Adolescent Idiopathic Scoliosis

ARC: Average Reflection Coefficient

AUC: Area Under the Curve

AVR: Axial Vertebral Rotation

BMD: Bone Mineral Density

BMI: Body Mass Index

BP: Blue Phantom

BUA: Broadband Ultrasound Attenuation

CA: Cobb Angle

CARC: Combined Average Reflection Coefficient

CI: Confidence Interval

COL: Center of Lamina

CT: Computed Tomography

CTLSO: Cervical-Thoracic-Lumbar-Sacral-Orthosis

DXA: Dual X-ray Absorptiometry

FAI: Frequency Amplitude Index

GPS: Global Positioning System

H: Soft Tissue Thickness

ICC: Intra-class Correlation Coefficient

IS: Idiopathic Scoliosis

KA: Kyphotic Angle

L: Lumbar

LAT: Lateral

MAD: Mean Absolute Difference

MIAS: Medical Image Analysis Software

MRC: Maximum Reflection Coefficient

MRI: Magnetic Resonance Imaging

MT: Main Thoracic

NOC: Number of Curves

NPV: Negative Predictive Value

PA: Posterior-Anterior

PMC: Plane of Maximum Curvature

PPV: Positive Predictive Value

PT: Proximal thoracic

QUIPS: Quality in Prognostic Studies

QUS: Quantitative Ultrasound

RC: Reflection Coefficient

RCS: Rough Curved Surface

ROB: Risk of Bias

ROC: Receiver Operating Curve

SCS: Smooth Curved Surface

SD: Standard Deviation

SEM: Standard Error of Measurements

SFS: Smooth Flat Surface

SI: Stiffness Index

SOS: Speed of Sound

SOSORT: Society on Scoliosis Orthopedic and Rehabilitation Treatment

SP: Spinous Process

SRS: Scoliosis Research Society

TGC: Time Gain Compensation

TL: Thoracolumbar

TLSO: Thoracic-Lumbar-Sacral-Orthosis

TP: Transverse Process

US: Ultrasound

UT: Upper Thoracic

VOS: Velocity of Sound

Chapter 1: Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional (3D) spine condition that has an unknown cause [1]. This condition is recognized by lateral curvature of the spine but can affect the axial and sagittal planes as well. To manage this condition, observation, non-surgical and surgical interventions are used. The major goal of the treatment is to improve the cosmetic appearance and preserve the curve progression.

1.1. Motivation

The current method to monitor the curve severity and check if the curve has progressed or not is taking consecutive radiographs every six months. These repetitive radiographs increase the level of radiation that children must be exposed to. This is an important issue because these adolescents are in the midst of their growth spurts. The ionizing radiation may not only have short-term negative effects such as increasing the cancer risk, but also have long-term effects for their future generations [2], [3]. Therefore, it is important to reduce the level of radiation for these children.

One way to lower the level of radiation is to reduce the number of radiographs. Based on the literature, only 15% of the children with AIS show curve progression [4]. This means that most of the radiographs acquired during follow-up visits are unnecessary and do not make any significant change in the management of their conditions. On the other hand, clinical parameters that have been associated with curve progression may help to predict the risk of curve progression [5]. Using these parameters, it is possible to develop prediction models for curve progression. However, there are still controversies on predictors to estimate curve progression among studies. Currently, there is no accurate prediction model available to use in everyday clinics [5]. Also, most of the reported models are lacking a comprehensive analysis and have not been validated.

Ultrasound (US) imaging has been proven to monitor scoliosis safely and effectively. A single ultrasound scan can provide images in coronal, axial, and sagittal planes. The spinal curvature information measured on US images is reliable and accurate [6], [7]. Since 38%

of children with AIS have been reported to have low bone mass [8], using US reflection signals from the spine to extract the properties of bone may have potential to help predict progression. Therefore, further investigation of the association of US parameters, as well as other clinical records with curve progression, to develop an accurate prediction model for children with AIS should be conducted.

The hypotheses of this research are:

a) a high accuracy curve progression detection model can be developed using ultrasound parameters and clinical information for AIS children at a follow-up visit.

b) using the developed model, children with AIS will not need to undergo unnecessary radiographs and this may save them from extra exposure.

1.2. Objectives

The specific objectives of this research are:

1. To identify potential prognostic predictors based on state-of-the-art prediction models from the literature
2. To extract a new US parameter called reflection coefficient (RC) index from US reflection signal, investigate the repeatability and reliability of this index in clinical practice, and correlate it with curve severity and progression
3. To investigate the reliability and accuracy of kyphotic angle (KA) measurements on ultrasound images and investigate their association with the progression of scoliosis
4. To investigate the factors influencing the reliability and variation of US axial vertebral rotation (AVR) measurements and investigate the association of AVR with curve progression
5. To develop and validate a detection model based on US parameters and clinical information to accurately detect cases with progression at a follow-up visit for children with AIS

6. To investigate if we can reduce the number of radiographs and save children from unnecessary radiation exposure

1.3. Scope of Work

The first scope of work included understanding the current literature on the predictors of curve progression. Therefore, a comprehensive systematic review was conducted to learn about the potential prognostic factors found in high-quality studies for different progression criteria and follow-up intervals.

A new US parameter called RC index—extracted from US reflection data—was analyzed based on the fundamental theory of physics and through experiments. Then, the repeatability and reliability of this index were investigated before applying it to the development of a detection model.

Following the RC extraction from the US images, US kyphotic angle and axial vertebral rotation parameters measured on the sagittal and axial planes, respectively, were studied. The goal of the KA studies was to determine a method that could be used to measure the KA reliably on US images. Then, the reliability and factors influencing variation in the measurements of the ultrasound KA and AVR needed to be investigated.

After all of the US parameters and potential clinical parameters associated with curve progression were identified. The developed model was validated with clinical data.

1.4. Thesis Organization

This thesis is organized into eight chapters.

Chapter 1 states the motivations, specific objectives, and scope of work of this thesis, along with an overview of the thesis chapters.

Chapter 2 provides background information on spine anatomy, scoliosis, X-ray-based imaging modalities and the scoliotic curve characteristics measured on these modalities, non-ionizing imaging modalities for scoliosis, bone property assessment methods, the

potential predictors of curve progression, and the method used to develop the prediction model.

Chapter 3 presents a comprehensive systematic review for identifying the predictors of curve progression for AIS.

Chapter 4 describes a new US index which is called the reflection coefficient (RC). The fundamental theory of this index as well as its correlation with curve severity is explained. Also, a clinical study describes the reflection coefficient as an indicator of bone strength and presents the repeatability and reliability of this index and its association with curve progression.

Chapter 5 describes how to measure the kyphotic angle (KA) on ultrasound images for children with AIS. A pilot study investigating the reliabilities and differences in KA measurements on US images compared with X-ray is described. Then, factors influencing KA measurements on US images are reported.

Chapter 6 presents a clinical study investigating the factors influencing the reliability and measurement variation of US axial vertebral rotation (AVR) versus X-ray.

Chapter 7 presents a pilot and a large clinical study on the development of a detection model for curve progression in AIS at the follow-up visit using US and clinical parameters.

Chapter 8 provides a summary of this PhD thesis work, the major contributions, the clinical significance, the limitations, and future recommendations for this research.

Chapter 2: Background Information

2.1. Overview

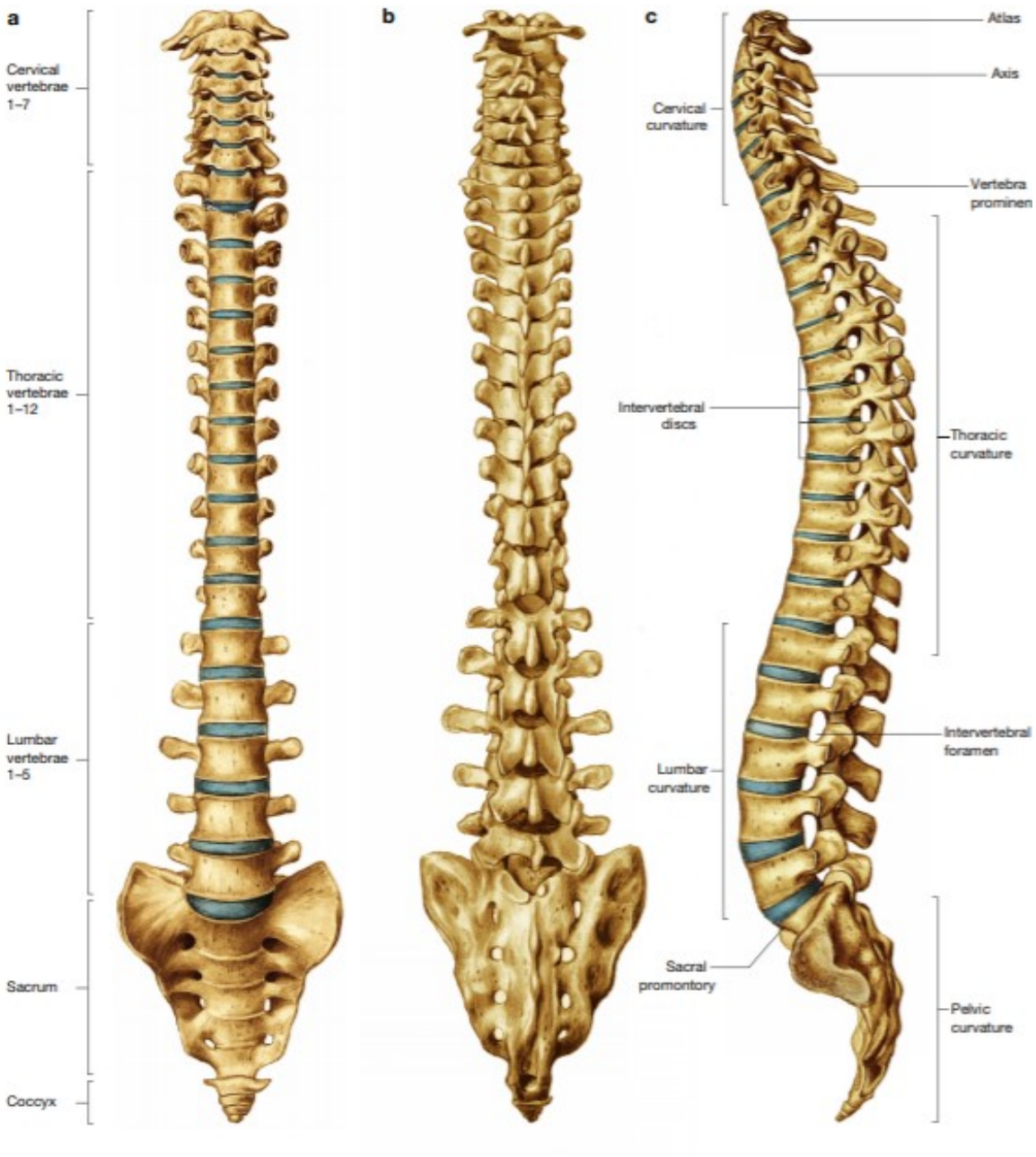
This chapter provides background information on spine anatomy, scoliosis, imaging of scoliosis, methods of bone properties assessment, and methods on prediction of progression. Section 2.2 provides the anatomy of the spine including structures and features of vertebrae. Section 2.3 presents an overview of scoliosis, curve progression, and available treatment options for scoliosis. Section 2.4 describes X-ray-based imaging modalities that are used for imaging scoliosis. In Section 2.5, the curve characteristics of scoliosis measured on X-ray based modalities are described. Section 2.6 describes the non-ionizing imaging modalities used for scoliosis. Section 2.7 presents the bone property assessment methods. In section 2.8, a summary of the predictors of curve progression (detailed description provided in Chapter 3) as well as the methods to predict curve progression are described.

2.2. Spine Anatomy

The human spine or vertebral column is a bony structure consisting of 33 individual vertebrae: 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, 5 fused sacral, and 4 fused coccygeal vertebrae from the superior to inferior direction as shown in Figure 2.1 [9]. When viewed from the front, the normal spine is vertically straight, but from the side, it has four curvatures including cervical, thoracic, lumbar, and sacral curves. The cervical and lumbar curvatures are concave posteriorly which is known as cervical and lumbar lordosis, while the thoracic and sacral curvatures are concave anteriorly called thoracic and sacral kyphosis (Figure 2.1) [10]. These curvatures help to maintain spine alignment and to distribute the mechanical loading incurred when the body is either at rest or in movement.

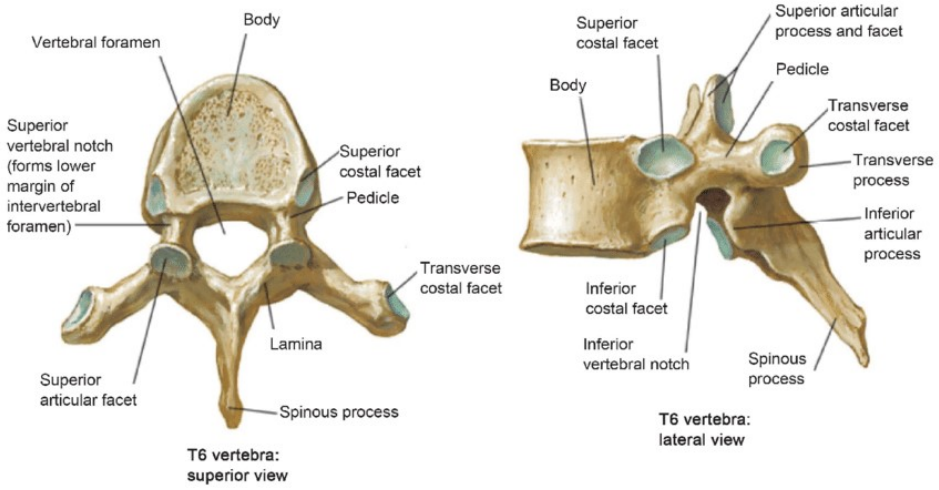
2.2.1. Vertebral Column Structure

Every vertebra is an irregular bone consisting of a vertebral body, a vertebral arch, and vertebral processes (Figure 2.2) [11]. The vertebral body is the largest part of the vertebra and is located anteriorly. The vertebral arch is located posteriorly and is formed by a pair of pedicles and a pair of laminae. The pedicles are short, thick processes that extend from the side of the vertebral body and join the body to the arch. The laminae are broad plates extended from the pedicle processes backward and medially forming a posteriorly protruding process known as the spinous process. The other processes include two transverse processes and four articular processes. The transverse processes are formed laterally at the junctional point of the laminae with the pedicles from either side of the vertebra. There are superior and inferior articular processes that are on each side of the vertebra having facet joints that connect each vertebra with the upper and lower vertebrae. The size and shape of vertebrae are different depending on their location. Normally, the size of the vertebrae increases from the top to the bottom of the vertebral column. As shown in Figure 2.2, distinctive features that only exist in thoracic vertebrae are the costal facets on each side of the thoracic vertebral body and on the transverse processes that articulate with the head and tubercles of the ribs, respectively.



(a) (b) (c)

Figure 2.1 The anatomy of the spine: (a) The front view, (b) the back view, and (c) the sagittal view [10]



(a) (b)

Figure 2.2 The landmarks of a thoracic vertebra (T6): (a) The superior view of a T6 vertebra, (b) the lateral view of a T6 vertebra [11]

2.3. Scoliosis

Scoliosis is a complicated structural spine condition that is generally characterized by lateral curvature of the spine which can also affect the axial and sagittal planes [12]. This leads to scoliosis being recognized as a three-dimensional (3D) spinal curvature condition. The causes of scoliosis are either non-idiopathic or idiopathic. Non-idiopathic scoliosis includes congenital, neuromuscular, and syndrome-related scoliosis. Congenital scoliosis is related to skeletal abnormalities including formation and segmentation failures appearing at the time of birth [13]. Neuromuscular and syndrome-related scolioses arise from a long list of neurological conditions, muscular abnormalities, and syndromes that are associated with scoliosis [14]. Some of these conditions include but are not limited to cerebral palsy, arthrogryposis, Marfan's syndrome, neurofibromatosis, Duchenne muscular dystrophy, and paralysis [15].

However, 80% of scoliosis has an unknown cause which is known as idiopathic [1].

2.3.1. Adolescent Idiopathic Scoliosis (AIS)

Adolescent idiopathic scoliosis (AIS) is the most common type of idiopathic scoliosis with a prevalence of 1-3% [16]. Patients with AIS normally present after 10 years of age corresponding with rapid adolescent growth [15].

Treatment choices for AIS are considered based on the severity of the curvature, the maturity status of the patients, the patients' self-image, risk of curve progression, and type of scoliosis [11, 12]. Under clinical circumstances, most treatment planning is based on the major curve progression (the largest curve of the spine). If the patients are left untreated, some future consequences may occur. These problems include worsening or progression of the curvature, back pain, increased risk of mortality, and negative psychological issues [18].

2.3.2. Progression of the Curvature

A scoliotic curve is comprised of three components: the apex (or the apical vertebra), and the superior and inferior end vertebrae along a curve. The apex is defined as the vertebra that has the largest lateral deviation from the axis passing through the center of the sacrum. The end vertebrae are those that define the end of the curve in a coronal or sagittal projection. The superior end vertebra is the first vertebra from the apex in the cephalad direction whose superior surface has the maximum tilt toward the concavity of the curve. The inferior endplate is the first vertebra in the caudal direction whose inferior surface has the maximum tilt toward the concavity of the curve. The severity or curve magnitude of AIS is measured using a standard clinical method known as the Cobb angle. As Figure 2.3 shows, the Cobb method measures the angle between the superior endplate of the proximal most-tilted vertebra and the inferior endplate of the distal most-tilted end vertebra [19]. A scoliotic curve is defined when the Cobb angle is greater than 10 degrees [20]. The Cobb angle is measured on a coronal x-ray. Curve progression is defined as an increase of curve magnitude >5° between two visits with a 6 to 12 month time interval [21]. The results of a study on untreated children with AIS showed that 68% of the untreated children showed

curve progression after skeletal maturity [18]. Overall, curvature less than 30° at skeletal maturity did not progress while the curvatures between 50 to 75°, particularly those located at thoracic regions, progressed at skeletal maturity [11, 16]. The reason why curve progression occurs has been explained by the Heuter-Volkmann Principle [23]. This principle is related to the function of growth plates which are at each end of vertebral bodies and are responsible for longitudinal spinal growth. When these plates are loaded, their growth rate is delayed. When the plates are unloaded, their growth is stimulated. Therefore, when there is a curvature in the spine, the uneven mechanical pressure on the vertebrae within the curve leads to uneven growth of the plates. The uneven growth of the plates exacerbates the curvature. This phenomenon is a vicious cycle and is the fundamental treatment theory of conservative treatment of AIS [24].

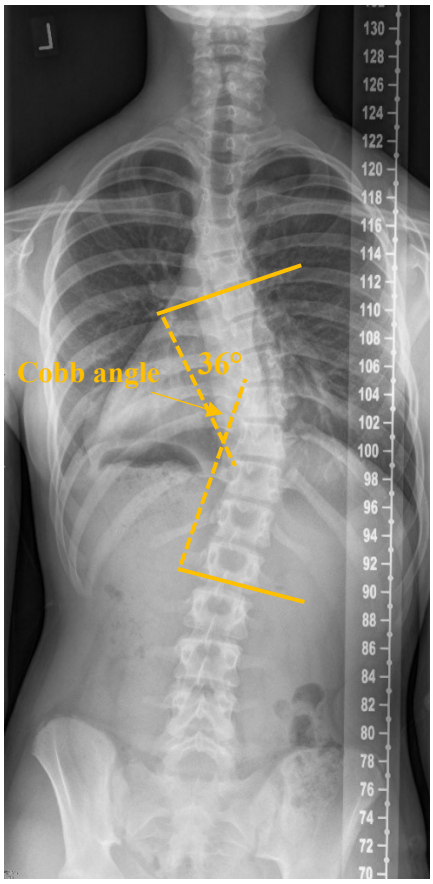


Figure 2.3 The Cobb angle method measuring the severity of the curve on a coronal X-ray

2.3.3. Treatment Options

The management of AIS includes three treatment options: observation, non-surgical, and surgical interventions. The non-surgical management of AIS includes both bracing and specific exercises [25], but bracing has been validated as effective [26]. The details of these methods are described in the following sections.

2.3.4. Observation

Observation means children with AIS are monitored by radiographs every 4 to 12 months to check if the curve has progressed or not. Observation is recommended for immature patients with mild curves of Cobb angle < 25° that show no sign of curve progression [16].

2.3.5. Orthotic Treatment

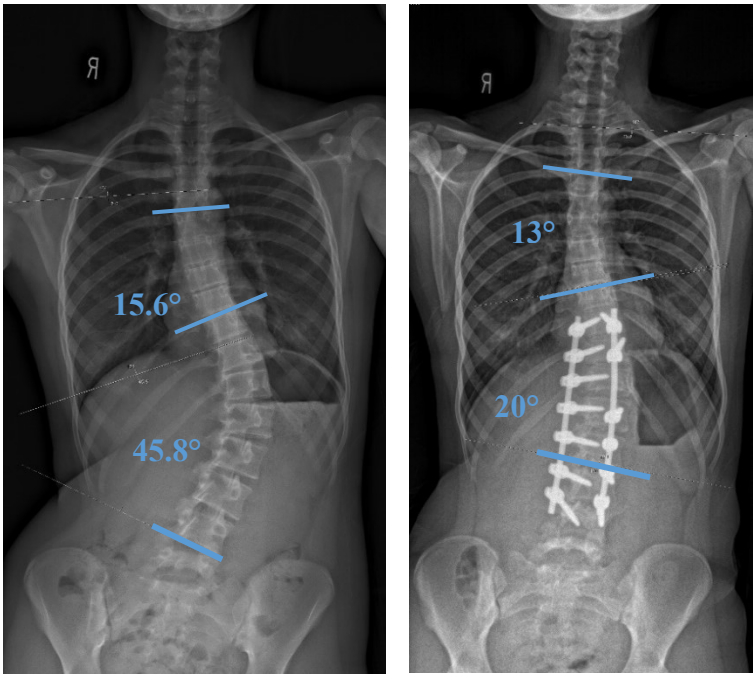
Orthotic treatment (bracing) management is recommended for immature children with moderate curves, Cobb angle between 25° and 45°[16]. A brace (orthosis) is a hard plastic shell that a scoliotic child wears to stop curve progression until maturity occurs. There are different types of braces mainly grouped as Thoraco-Lumbo-Sacral Orthosis (TLSO), Cervico-Thoraco-Lumbo-Sacral Orthosis (CTLSO), and night-time orthoses [27]. The TLSO covers the front and back from the pelvis to the armpits. Normally, these types of braces are used for curvatures with an apex at or below T8. The CTLSO is used for the curvatures with an apex at or above T8 [27]. The night-time braces are used during sleep with the most common one being the Charleston brace. Overall, bracing has been reported to decrease risk of curve progression and incidence of surgical intervention by 75% for skeletally immature children with AIS versus untreated ones [26]. A study reported that when a brace, prescribed for full time wear, has been worn for over 12 hours a day, the success rate can reach up to 93% [26]. However, long-time brace wear is not desirable for most children because most braces are bulky, uncomfortable to wear, and restrict children's activities.

2.3.6. Exercise Therapy

The general aim of exercise therapy is to reduce the progression of scoliotic curvature and postpone or avoid the need to wear a brace [28]. Exercise therapies for AIS, which include physical exercises to strengthen and mobilize the spine, machine-assisted exercises, breathing, and postural correction exercises, along with less important ones such as yoga and tai chi, help to improve trunk flexibility and strength. The Schroth method is a scoliosis-specific exercise that includes sensorimotor, postural, and breathing exercises, and is used to recalibrate normal postural alignment, static/dynamic postural control, and spinal stability [29]. Studies showed that physical exercises may help to improve back strength and breathing function significantly [30]. Also, they help to reduce the rate of curve progression and curve severity in AIS [31]. In addition to the improvement in scoliotic characteristics, function, and quality of life, exercises may also increase self-esteem and provide positive psychological outcomes [25], [30], [32]. The results of a systematic review showed that Schroth exercises significantly reduce the Cobb angle and improve quality of life in AIS with level II evidence of support [25].

2.3.7. Surgical Treatment

Surgical interventions are considered for severe curves greater than 45° to correct the curve, preserve sagittal alignment and balance, as well as improve the quality of life [27, 28]. The two main approaches for surgery are anterior and posterior fusions. In the posterior fusion, surgeons access the posterior surface of the spine for instrumentation (such as longitudinal rods, hooks, sublaminar wires, and pedicle screws) [35]. Figure 2.4 illustrates a pre- and post-operative radiograph using posterior spine fusion on a case with AIS. The anterior approach is usually used for thoracolumbar or lumbar curves [36]. For the anterior approach, less instrumentation is attached to the spine; however, some complications such as poorer pulmonary function as well as higher risks of injury to critical organs and vessels may occur [27, 30]. The most used approach is posterior fusion. Although surgery significantly corrects the curve, some complications such as hook dislodgment, infections, and neurologic deficits are still of concern [37].



(a) (b)

Figure 2.4 The posterior spinal fusion and instrumentation on a case with AIS: (a) Preoperative X-ray, (b) post-operative X-ray

2.4. X-ray Based Imaging Modalities Used for AIS

The X-ray based modalities used to image AIS include images acquired from:

- Conventional X-ray systems (screen-film and digital radiography)
- EOS imaging (2D/3D)
- Computed tomography (CT) scan

2.4.1. Basics of X-ray Based Imaging Modalities

Radiography is an imaging technique using X-rays to image the body. An X-ray system consists of an X-ray tube that generates X-ray photons which are exposed to the target of interest. The X-ray photons interact with the body and a portion of them are absorbed, some are scattered, and the rest is transmitted through the body and received by a detector. The higher density body tissues such as bone absorb more X-rays than soft tissue like muscle.

The detector is either a photographic film in analog radiography or a digital detector in digital radiography.

2.4.2. Conventional X-ray Systems

Generally, the most used method to image AIS is capturing an X-ray via conventional systems. Scoliosis radiography was generally performed by screen-film radiography. However, there are some drawbacks with screen-film radiography such as the image contrast cannot be changed after films are processed, the films are expensive, and the film processing procedures require the use of some hazardous chemicals and are labor-intensive [38]. In the last 2 decades, digital radiography has become more common. It includes two forms computed radiography (CR) and direct radiography (DR) [39]. The difference between CR and DR is related to the mechanism involved in the design of detectors to transfer X-ray energy to an electrical signal [39]. However, it is difficult to image the whole spine using digital radiography since the detector plates are not large enough to include the whole length [40]. One approach is to stitch together individual images acquired from different exposures into one image or image reconstruction which may cause image distortion and inferior image quality [41]. Nevertheless, changing from screen-film X-ray systems to digital radiography has reduced the X-ray retake from 5.5% to 1% which significantly prevents repeated exposure [42]. The absorbed dose for a imaging full spine significantly is reduced when DR is used versus CR and screen-film radiography [40]. A study reported that DR showed the lowest radiation to the whole body (effective dose), up to 43% lower than the other two methods (CR and screen-film radiography) [39].

2.4.3. EOS Imaging System (2D/3D)

The EOS X-ray machine is a Nobel prize-winning invention in physics capable of capturing biplanar (2D) X-ray images simultaneously by slot scanning the whole body in an upright and load-bearing position, while using low radiation doses [43]. The two source-detector pairs are positioned orthogonally so that two simultaneous coronal and sagittal images of

the spine are acquired. Figure 2.5 illustrates a coronal and sagittal view of a scoliotic spine on both 2D and 3D reconstructed EOS images.

The EOS imaging method is different from other X-ray based imaging in several ways including [44]:

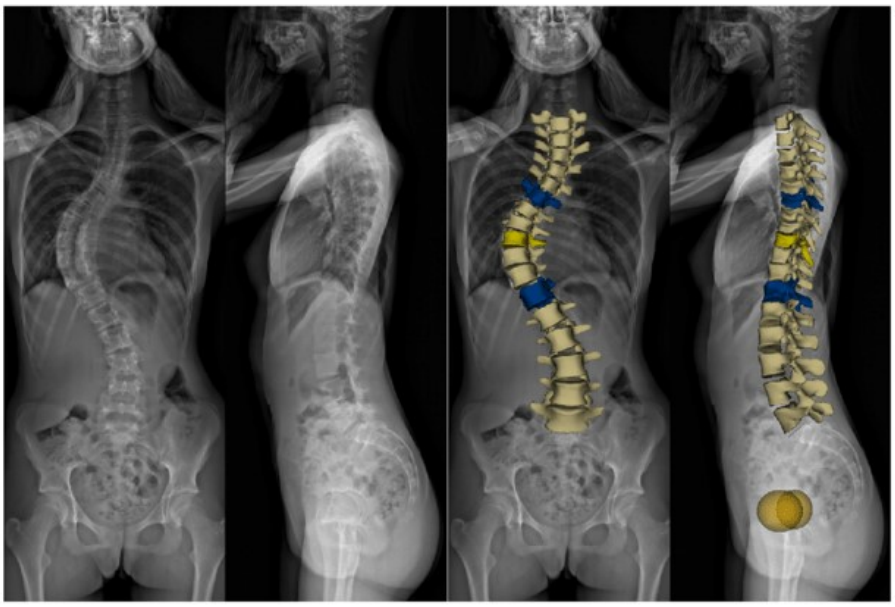
- It allows for scanning the whole body in a standing position
- It reduces the radiation
- It creates 3D model reconstruction of upright images of the skeletal structure

Whole-body scan in standing position: Since the ideal position to image AIS is in a standing position, EOS has been popular for imaging of AIS for orthopedics applications. This ability to perform a whole-body scan in standing position is very useful to evaluate the spinopelvic relationship and to investigate secondary reasons leading to scoliosis such as leg length discrepancy [45]. However, the lengthy data acquisition process may cause artifacts on the image due to movement that can degrade the image quality. Also, it cannot be used for children who cannot stand in the device or infants with scoliosis. In addition, the standing posture is important. The degree of shoulder flexion may affect the sagittal alignment. While studies suggest different positioning during scan capture, the most widely used position is putting hands on cheeks [46].

Radiation dose: The radiation dose is reduced by a factor of 2.5 to 10 using EOS versus conventional radiography [43], [47]. The dose reduction even reaches 800-1000 when compared with 3D CT scan [43], [48]. To compare the dose from EOS versus DR radiography, the average dose area product (DAP) is used. The DAP considers the absorbed dose for a specific area, in this context, the spine. The DAP was 23.6 $mGy \cdot cm^2$ /kg±4.32 for EOS versus 95.7 $mGy \cdot cm^2$ /kg±30.39 for digital radiography for both AP and lateral spine exposures in children with idiopathic scoliosis [44].

EOS 3D images: The simultaneous capture of AP and sagittal images by EOS enables us to generate a 3D reconstruction of the skeletal system using a special software as shown in Figure 2.5 c and d. This feature is suitable for imaging of AIS. When the 3D reconstruction process is complete, the software automatically generates measurement files which reports

the curve characteristics in coronal, axial, and sagittal planes, as well as pelvic parameters. However, a few situations may make the EOS 3D reconstruction difficult. The first scenario is when the scoliotic curve is severe; the operator may have difficulty identifying landmarks and performing adjustments to overlay a vertebra to the database model. Also, in abnormal anatomical situations such as sacralization of L5 (the fifth lumbar vertebra is fused to the sacrum bone) or lumbarization of S1 (the first sacral vertebra is not completely attached to its fused sacral components and instead the first sacral vertebra looks like a lumbar vertebra). The operator may have difficulty identifying the vertebrae correctly. The 3D reconstruction process is time-consuming. The mean reconstruction time is about 20–30 minutes for 3D reconstruction of the spine and 35–45 minutes for 3D spine and lower limb rendering [44]. For severe idiopathic scoliosis, it may take longer than an hour to reconstruct.



(a) (b) (c) (d)

Figure 2.5 The EOS image of a scoliotic spine: (a) The 2D coronal view of spine; (b) the 2D sagittal view; (c) the 3D reconstructed image of the spine projected in coronal view; (d) the 3D reconstructed image of the spine projected in sagittal view [49]

2.4.4. Computed Tomography (CT) Scan

Computed Tomography (CT) provides 3D images of the bony structures. The system includes an X-ray source and detectors that are located in opposite directions. During data acquisition, the source and detectors rotate around the patient and acquire a series of X-ray images from different angles. The X-rays are transmitted through the body and are recorded by the detectors. Then, a high-speed computer processes the data to provide cross--sectional images (slices). A CT scan can provide a more detailed image of the spine morphologies and structures [50] and is considered as a standard for the 3D reconstruction assessment method compared to the EOS imaging [51]. CT scans are recommended for complicated surgical cases, pre-operative imaging to evaluate the size of pedicles for surgical instrumentation, and post-operative imaging to check the correction [52].

2.5. Use of X-ray Systems to Image Curve Characteristics of AIS

Since AIS has a 3D nature it is important to evaluate this condition in the coronal, axial, and sagittal planes.

2.5.1. Cobb Angle

The methods that are used to measure the Cobb angle include manual methods such as using a protractor and pencil on the film radiography, and computer-aided methods on both CR and DR that identify the spine landmarks. All the methods have reproducibility within 5 degrees [53]. Good to excellent intra- and inter-rater reliabilities have been reported for both manual [54] and digital [55] Cobb angle measurements. However, an improvement on Cobb angle measurement was reported on digital measurement versus manual [53], [56]. This shows the importance of digital measurement since it is becoming the more prevalent method in scoliosis clinics [56]. A phantom study compared the Cobb angle measurement between the three X-ray methods EOS (2D), CR, and DR. The results showed that Cobb angle measurements using CR and DR methods had a high correlation with the EOS measurement with the R^2 value (coefficient of determination) close to 1 for both [57]. Also, the reliability results showed excellent intra-rater reliability, with an intraclass

correlation coefficient (ICC) > 0.9 and good inter-rater reliability (ICC≥0.74) for all three imaging methods [57]. In addition to the curve severity measurement, the Cobb angle information is also used to monitor the progression of the curve and to inform a decision on the treatment options.

2.5.2. Spinal Flexibility Assessment

Additional radiographs of children with AIS may be required for assessment of spinal flexibility. Spinal flexibility informs clinicians about the biomechanics of the curvature which is particularly helpful for surgical cases. This information advises surgeons about the structural extent of the curve, the surgical approach, and the level of fusion [58]. Yet, some studies suggest using flexibility information to estimate in-brace correction for bracing treatment, and as a predictor of curve progression [43, 44]. There are different radiographic techniques that are used to estimate spinal flexibility including:

(a) Supine side-bending: In this method, the patient voluntarily bends to the sides as far as she can. This method is the gold standard for spinal flexibility assessment [61]. The spinal flexibility is estimated by comparing the curvature in bending position versus the standing X-ray Cobb angle.

b) Push-prone: The push-prone method is performed by technicians applying forces at the apex or apices of curvature while counter forces are applied in the opposite direction around the pelvis and axilla [62]. However, it is difficult to determine what forces should be applied to obtain optimal correction with this method.

(c) Fulcrum-bending: In this method, a radiolucent fulcrum is placed under the curve apex while the patient is in a lateral position on the fulcrum. The results of a systematic review showed that the fulcrum bending method has the most accurate estimation of post-operative outcomes compared to other methods with the support of very low to low quality evidence [63]. The accuracy of the results for this method may vary based on size, rigidity, and placement of the fulcrum [64].

(d) Traction: The traction method has two options: with anesthesia or without. Greater curve correction is observed during traction under anesthesia versus without. Traction under general anesthesia is implemented by divergent forces applied on the ankles and axilla. Then translational pressure is applied at the apex of curvature [61], [62]. This method may provide better estimated outcomes for severe curves (Cobb angle >60°) compared with the side-bending method [61], [62]. However, since these images are acquired right before surgery, surgeons may not have sufficient time for thoughtful surgical planning.

In addition, Hirsch et al. used a new technique using EOS modality called the suspension test to investigate the spinal flexibility in 50 AIS surgical children [65]. In the Hirsch et al. study, EOS radiographs were captured while progressive traction forces were applied to patients through a rigid collar attached to cables. The EOS radiographs were taken when the patients were on tiptoes. This method was compared with the supine traction test. Higher forces were applied during this test and forces were more standardized than the traction method. Also, using the suspension method, it was possible to analyze the curvature changes in the three coronal, axial, and sagittal planes. The disadvantages were that the tolerance of the patient was lower in the suspension test and special equipment was required which prevented this method from being widely used [66].

Although the benefits of spinal flexibility assessments are undeniable, the extra radiographs and radiation children are exposed to is undesirable. This makes clinicians reluctant to request extra radiographs to obtain flexibility assessments for non-surgical cases.

2.5.3. Axial Vertebral Rotation (AVR)

The axial vertebral rotation (AVR) happens when the vertebra rotates around its longitudinal axis when projected in the axial plane [67]. The landmarks that are used to measure the AVR include the pedicles, spinous process, and vertebral body that are imaged on posteroanterior (PA) X-rays. The AVR measurement on plain radiographs was first introduced by Dr. John Robert Cobb [68]. In his method, the vertebral body and spinous

process are used to measure the AVR. Depending on the position of the spinous process, the degree of AVR is measured in five grades. However, the spinous process may be poorly visible on radiographs making the measurements difficult. Also, it is not possible to quantify the AVR using a grade system.

Another method was developed called the Nash-Moe method [69]. In this method, the half-width of the vertebral body reflected on the convex side of the curve is divided into three equal segments and the pedicle shadow on the convex side is considered the landmark. Therefore, depending on the location of the pedicles in these segments the AVR is graded from 0 to 4+. The visibility of the pedicle is an advantage in this method. However, the pedicle displacement percentage is used to estimate the AVR. Also, the size of the vertebral body is not accounted for.

In a different method, the pedicle at the convex side is used and a torsion meter is placed on an anteroposterior (AP) X-ray in an attempt to measure the AVR [70]. The AVR is quantified with ±5 degrees in this method [71]. Still, the differences of the vertebrae sizes particularly for irregular vertebral geometry based on different locations is not accounted for.

Stokes et al. developed a method that accounted for the pedicle offsets as well as vertebral asymmetry and the differences in vertebral body sizes from T4 to L4 [72]. As Figure 2.6 shows, the projected distances from the center of both pedicles to the center of the vertebra (a and b) are measured from the X-ray; w is the width of the lamina, and d is the maximum width of the vertebra from the center to the edge [73]. In this method, the errors in measurements were ± 1mm for identifying the landmarks and 2.7° for AVR measurement. However, outlining the vertebral edges still account for a large source of random errors in this method [73].

Another study also used the pedicle shadows along with the geometry of the vertebra and dimensional proportions to measure AVR [74]. A limitation of this method is when the AVR is over 30°, making it impossible to identify the pedicle.

Overall, the measurements of AVR on plain X-rays are not directly performed on an axial plane which limits the accuracy of the 2D AVR measurements on a coronal plane. Due to

the 3D ability of CT, AVR can be measured using this modality as well. The standard method with the most reliable results is the Ho method which measures the angle between a line going through the posterior surface of the vertebral body and the junction of the inner surface of the laminae, and the reference sagittal plane as demonstrated in Figure 2.7 [75]. Due to high levels of ionizing radiation, CT is normally not considered a routine image modality for children with AIS. Also, CT data acquisition is performed in the supine position which may affect the magnitude of the curvature in both the coronal and axial planes [76], [77]. Using the EOS 3D reconstruction, output parameters called vertebra vectors are found. This information helps to visualize the spine in 3D, providing a top view of the spine which allows for a better understanding of the vertebra size, position, and rotation [66]. The concept of the vertebra vectors was validated by comparison with the 2D radiograph measurements. The reliability was even higher than 2D measurements when the scoliosis was severe [78]. However, as mentioned earlier, 3D reconstruction by EOS is very time-consuming.

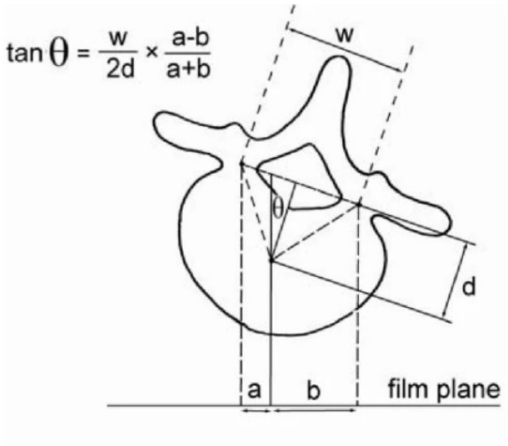


Figure 2.6 The axial vertebral rotation using Stokes' method. The projected distances of both pedicles from the center of vertebra (a and b) are measured. The "w" which is the width of the laminar and "d" is the maximum distance of the vertebra from the center to the edge. These measurements are implemented into Stokes' method equation and θ which is the vertebral rotation angle is calculated [73]

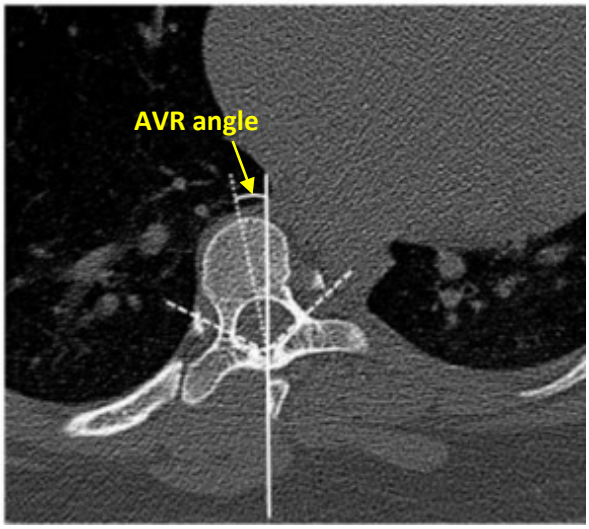


Figure 2.7 Ho's method of measuring AVR angle on a transverse view CT image of a vertebra [79]. The dashed lines are from a point at the laminar inner junction with the pedicle-lamina junction bilaterally, and the angle between these lines is bisected by a dotted line. The rotation angle (curved line) is measured between the bisector line and the vertical line.

2.5.4. Sagittal Plane Parameters

2.5.5. Kyphotic Angle (KA)

The most-reported sagittal parameters include kyphotic angle (KA) and lordotic angle (LA) which are important for AIS treatment management. Several radiographic techniques have been suggested to measure the KA such as the Cobb method, vertebral centroid method, the posterior tangent method, as well as various computer-aided methods [80]–[82]. Among all of these techniques, the Cobb method is the most popular and considered the gold standard to measure the KA [83]. As Figure 2.8 shows, the KA is measured on a standing lateral radiography by identifying the superior endplate of T1 and inferior endplate of T12. There are a few KA measurement approaches which use different end vertebral levels including T1-T12 [84], [85], T3-T12 [86], T5-T12 [87]. However, the reliability of the kyphotic measurement reported from most studies was not adequate for most tested levels. Of these levels, T1-T12 seems to be the most reported method. Carmen

et al reported partial reliability results of a kyphotic angle at T1 to T12 on 20 radiographs and the measurement error was 11 degrees with a 95% confidence interval [84]. Ohrt-Nissen et al. reported that the kyphotic angle measurements difference on intra- and inter-rater results from 8° to 13° [82]. They also reported that the best reproducibility in terms of agreement and reliability was achieved for KA measurements at the T4-T12 and T5-T12 levels.

According to the scoliosis research society (SRS), KA values ranging between 20 to 45 degrees are considered normal when using the Cobb method with the T1-T12 level approach. The limitation of the Cobb T1-T12 method relates to difficulties in identifying endplates, particularly at T1 due to overlap with the shoulder girdle on a conventional X-ray. Therefore, SRS recommends measurements of KA between the superior endplate of the highest measurable thoracic vertebra, usually T2 or T3, and the inferior endplate of T12.

2.5.6. Lordotic Angle (LA)

The techniques used to measure the lordotic angle are not universally agreed upon. The most used method is the Cobb method. The levels that are used to measure the LA are variable. Based on the Cobb method, the angle is measured between the perpendicular lines drawn from the superior endplate of L1 [88], or sometimes inferior endplate of T12 [89], and the inferior end plate of L5 [88], [90], with some studies using the superior end plate of S1 [85], [91] as an alternative. Most authors choose L1 as the superior end plate and S1 as the inferior level. These are the levels recommended by the SRS (Figure 2.8). For the cases where S1 is not visible, the inferior endplate of L5 is chosen. The normal range for the lordotic angle has been reported to be between 50 to 60° [92]. A study reported that the intra-rater and inter-rater reliabilities coefficients for LA measurements are within the range of 0.83 to 0.92 and 0.81 to 0.92, respectively, and 10 degrees of difference was considered an acceptable variation [93]. In that study, the best agreement of 92%, was obtained for measurements using the L1-L5 level. Sources of variation are the selection of vertebra as well as the vertebra end plate architecture.

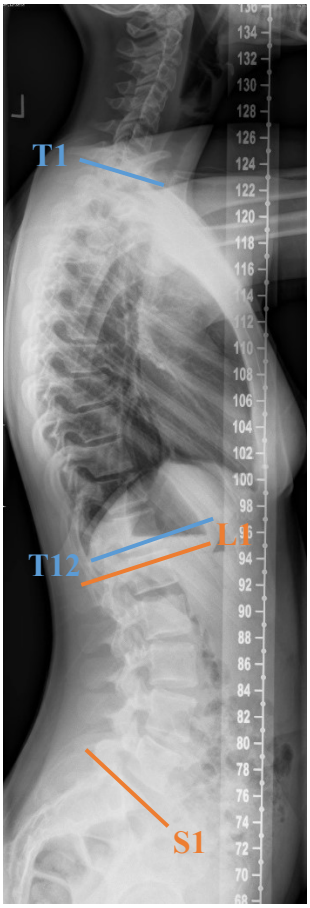


Figure 2.8 The measurement of kyphotic (blue lines) and lordotic angles (orange lines) using T1-T12 and L1-S1 endplates, respectively

2.5.7. The Negative Effects of Ionizing Radiation

On average, a 10 year old child who is diagnosed with scoliosis requires 10 to 22 radiographs over the course of the entire treatment period [94]. However, Soucacos et al. reported that only 14.7% of scoliotic cases would progress [4]. This means most patients receive unnecessary ionizing radiation because the purpose of radiographs is to determine if the curve progresses.

Ionizing radiation from X-rays has high enough energy to break molecular bonds in the body. When this bond damage is repaired incorrectly, it can affect chromosomes and may induce cancer [95], [96]. Additionally, the accumulated ionizing radiation increases the probability of adverse health issues including cancer and abnormal pregnancies [42].

Retrospective studies indicated children with AIS who received repetitive X-rays have approximately 2 and 3% increases in lifetime risk of breast cancer and heritable defects, respectively [2], [3]. Levy et al. estimated an increase in the risk of cancer to 0.01-0.07% per 100,000 men and 0.04-0.23% per 100,000 women for scoliotic patients from conventional spinal radiographs [97]. Ronckers et al. followed 5,513 females who were exposed to an average of 22.9 radiographs per person during treatment and follow-up for scoliosis [98]. Overall, the risk of mortality was 46% higher than the general population. Cancer was identified as the primary reason for 23% of these deaths. In terms of prevalence, breast cancer was the most common, followed by lung and then ovarian cancer. Enormous efforts have been made to reduce the radiation dose for X-ray imaging. Changing the exposure orientation from AP to PA exposures can reduce the dose to organs such as breasts and thyroid from 3 to 8 times [99], [100]. The latest technology implemented in detectors of EOS 2D/3D imaging lowers radiation significantly. A study showed that the detector structures used in EOS imaging enable the reduction of entrance skin dose up to 13 times for PA and 15 times for a lateral acquisition versus conventional film radiography without degrading the image quality [101]. A new feature of the EOS using micro-doses reduces the dose up to 5.5 and 45 times [42] when compared with standard low dose and conventional radiography, respectively.

As children have a longer lifetime to reflect the radiation damage than adults, the adverse effects of radiation can appear years after exposure. Nevertheless, the cumulative radiation matters even though the exposure dose is low. Therefore, it is important to consider radiation protection and minimize radiation for these children in order to meet the ALARA principle (as low as reasonably achievable) [42].

2.6. Non-ionizing Radiation Imaging Modalities for AIS

The non-ionizing radiation methods that are described in this thesis include:

- Magnetic resonance imaging (MRI)
- Ultrasound (US) imaging method

2.6.1. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is an ionizing radiation-free method that uses powerful magnets to force the nuclei (in particular, hydrogen nuclei which consist of a proton) of the body to align with that magnetic field. When a radiofrequency current is pulsed through the patient, the protons are stimulated, and spin out of equilibrium. By turning off the radiofrequency field, the protons realign with the magnetic field and energy is released as radio signals which are detected by MRI sensors. The time it takes protons to realign with the magnetic field, as well as the amount of energy released, helps clinicians distinguish between different types of body tissue. MRI is recognized as a suitable method to image soft tissues such as the brain, spinal nerve, and muscles, rather than bony structures, as they are seen much more clearly on the images. The MRI systems are either open or closed. The closed ones fully surround the body, while the open MRI is open on the sides. An open MRI has a lower image quality than a closed one because of a weaker magnetic field [102]. Both closed and open MRIs require patients to be in a supine position which can affect the application of this modality for AIS imaging. Since the effect of gravity is eliminated in supine position, the magnitude of the curvature is reduced. Recently, MRI machines that scan in standing or sitting positions have also been developed but their image quality is not as good as closed systems. MRI also provides images in three-dimensions including the coronal, axial and sagittal planes. The AVR and torsion of the vertebral body and discs may be measured using MRI [103], [104]. A study showed that the AVR could be measured accurately and reproducibly with a mean difference of 3 degrees between MRI and plain radiography [104]. However, MRI is more frequently used for scoliosis cases related to neurologic abnormalities such as tumors. It is uncommon for monitoring or diagnosis of AIS [105], [106]. Compared to CT scans, MRI scans typically take a longer time and are louder, and they need patients to enter a narrow tunnel. Therefore, subjects who are uncomfortable with confined spaces, called “claustrophobic”, do not feel comfortable using the closed MRI systems that fully surround the body [107]. In addition, people with medical implants or other metal inside the body may be unable to undergo an MRI examination safely.

2.6.2. Ultrasound (US) Imaging Method

Ultrasound (US) is a non-ionizing imaging modality that uses a sound wave with a frequency >20 KHz. The range of ultrasound frequencies for most medical applications is usually between 2 MHz to 10 MHz [108]. For ultrasonography, a pulse technique is used to transmit an US signal of mechanical waves to a region of interest. The ultrasound theory is that when the US signals travel through mediums, a fraction of energy reflects from the interface between two mediums to the transducer. The reflected energy can be processed to display images and used to indicate stiffness and elasticity of materials which are related to the acoustic impedance of the mediums [108]. The acoustic impedance of bone is significantly higher than the surrounding soft tissue, leading to a substantially stronger reflection at a tissue-bone interface when the ultrasound signal penetrates from soft tissue to bone. This implies that stiffer materials are expected to have stronger reflections.

2.6.3. Ultrasound for Imaging of AIS

Since the vertebral column, a region of interest throughout this thesis, has a bony structure covered by soft tissue, it is possible to image the posterior vertebra features using US imaging. Suzuki et al. was the first group to use ultrasound techniques for imaging patients with scoliosis [109]. They were able to identify the transverse processes and the laminae on US images. However, their approach only scanned patients in the prone position to measure the AVR. Dr. Lou's team is pioneering the proposal to measure the Cobb angle from US spinal images. A phantom feasibility study was first conducted to investigate the application of US for imaging of the spine [110]. That study showed that the posterior arch structures of the vertebra, which include the spinous process, transverse process, laminae, and superior articulate process of the vertebra, were detected on the image. The dimensions of these landmarks were within 4% error when compared with the phantom measurements. After the feasibility study, clinical trials were conducted to validate that US images could be used to assess and monitor AIS disorder [109]–[112]. The landmarks used in clinical practice to measure the curve severity on US images were the center of laminae (COL) [7], [111]–[113], spinous process (SP) [110], [114], transverse process (TP) [115], [116] and

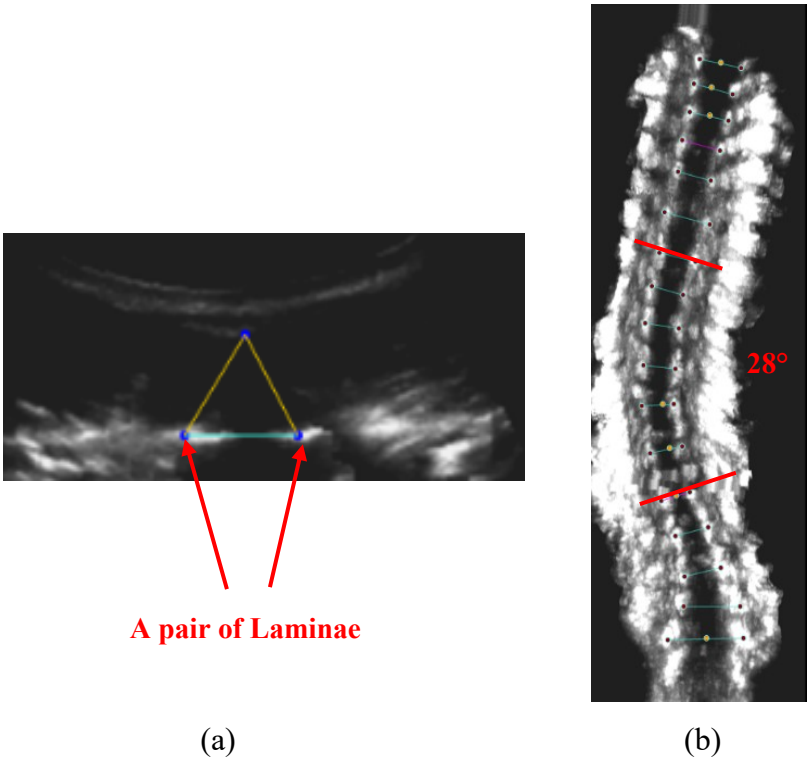
superior articulate process (SAP) of the vertebra [115]. In terms of the reliability of these landmarks, high intra-rater and inter-rater reliabilities were reported when SP was used to measure the severity; however, the curve magnitude was not measured directly by using this method [110]. Also, limited evidence was available on using TP and SAP to measure curve severity. Using the TP method, the variation of the reliability coefficient was relatively large, with the range for intra-rater and inter-rater reliability coefficients varying from 0.57–0.98 and 0.75–0.96, respectively [117]. A systematic review analysis on the reliability of all available ultrasound imaging methods for severity measurements on AIS revealed that among all of the proposed methods for measurement of Cobb angle, the COL was the most reliable [117]. Figure 2.9 illustrates the COL method on an AIS case on both the transverse and coronal views. In the COL method, the proxy Cobb angle is measured by the angle between the two most tilted lines, which connect the COL at each vertebral level, within a curve. The intra-rater and inter-rater reliabilities of US Cobb measurements using the COL showed high ICC [2, 1] >0.80 and the measurement difference between the radiography and the US method was between 3 to 5 degrees, which is within the clinically accepted error (<5°) [111], [113]. Moreover, a significant improvement in the Cobb angle measurement occurred with the aid of previous radiograph methods, and the intra-rater and inter-rater ICC [2, 1] were increased to >0.90 [7], [111].

The COL method was also used to measure the AVR in both *in-vitr*o and *in-vivo* studies. The results showed high intra-rater and inter-rater reliabilities for both (ICCs > 0.91, MAD < 1.4°) [112]. The US AVR measurements were compared with the Stokes' method on radiography and the results showed a good correlation for the *in-vitro* study (ICC = 0.84-0.85) with the mean absolute difference (MAD) within 4.5°-5.0°; while the agreement for the *in-vivo* study was poor to moderate (ICC = 0.49-0.54, MAD = 2.7°-3.5°). However, these studies were pilot studies with limited datasets, and this emphasizes the need for conducting a large clinical study to confirm the use of US for AVR measurement.

In addition, a study was conducted to investigate reliabilities of using US to measure the Cobb angle on the plane of maximum curvature (PMC). In this study, three raters were involved in measuring the PMC on US images. The US PMC Cobb values were compared

to the EOS PMC Cobb. The ICC values for intra-rater, inter-rater and inter-method reliabilities were all over 0.90. The MAD and the standard error of measurements (SEM) for both PMC Cobb were < 4° [118].

In this thesis, kyphotic angles on US images were investigated. Details of the studies are reported in Chapter 5.



(a) (b)

Figure 2.9 Ultrasound imaging of the spine for a case with AIS: (a) An US transverse plane of a vertebra showing the selection of the centers of laminae, and (b) measurement of the curve severity by using the center of laminae (COL) method

2.7. Bone Property Assessment

Approximately 27% to 38% of children with AIS have been identified as osteopenic or have low bone mass [8], [119]. Bone is composed of two main parts, cancellous (also called trabecular or spongy) and cortical (compact). The basic material comprising cancellous and compact bone appears identical, while the degree of porosity and the organization is different. The architecture of cancellous bone includes its porosity and connectivity, the extent to which structural elements are connected together [120]. Osteopenia is a condition

that affects bone and is characterized by low bone mass [121]. Bone mineral density (BMD) is the ratio of bone mineral content to bone size. The average BMD values of girls with AIS were 4.5% lower than that of the age- and sex-matched controls [122]. A study compared the BMD scores from the lumbar and the three regions of the femur of AIS children with the matched control group and the results showed that BMD was low in all these regions versus the control group [123].

Two methods of bone property assessments, dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS) imaging methods have been described in following sections.

2.7.1. Dual-energy X-ray absorptiometry (DXA)

Currently, the most common method to assess BMD is DXA which exposes patients to ionizing radiation. This method uses two beams of X-rays with different levels of energy. One beam with lower energy which, is absorbed by soft tissue and the other with a higher level of energy which is absorbed by bone. When the soft tissue X-ray absorption is subtracted, it is possible to estimate the absorption of each beam by bone; this is related to bone density. BMD is usually measured on the hip, spine, and forearm by using DXA. In this method, the BMD status of the patients is evaluated by Z scores. The Z scores compare children's BMD with age-matched norms and give clinicians a sense of the age-appropriateness of bone loss. When Z scores are less than or equal to –1 standard deviation, bone status is classified as osteopenia. When age-adjusted bone mineral density is above –1 standard deviation, it is counted as normal bone status. However, some drawbacks are prominent with DXA. It uses ionizing radiation which is harmful to children. The radiation dose from a DXA exam on the hip and spine is estimated to be between 10 to 15 micro-sieverts [Sv is a unit of dose equivalent (the biological effect of ionizing radiation)]. Although it is considered low radiation, for children with AIS who already must undergo many X-rays during the treatment, it is still worrisome. Also, DXA is a projectional technique, which means imaging a 3D object in 2D. For children with AIS who have large vertebral rotation, it may lead to an inaccurate analysis of BMD [124], [125]. Furthermore, DXA is only able to quantify the bone mass but not qualify it, and it is relatively costly and

may not be readily available in clinical settings [120]. Also, BMD may not truly represent bone strength. The strength of an object depends on the amount of material in that object, the internal structure, geometry, and the mechanical properties of the constituting material [126]. A term defined as bone quality might better explain bone strength than bone density [121]. Bone quality is described as a composite of properties including the internal structure, geometry, and the mechanical properties of the material that determine how well the bone can resist the fracture [126].

2.7.2. Quantitative Ultrasound (QUS)

Quantitative Ultrasound (QUS) has been introduced to assess bone quality. QUS systems are different in terms of the emitted frequency, pathways of US transmission inside the bone, and the skeletal site as the region of interest. The range of frequencies used in QUS devices is within 500 kHz and 1.25 MHz [127]. The majority of QUS devices can be used only for one skeletal site such as the proximal phalanges and calcaneus bone. QUS devices work based on the transmission of the US wave through the region of interest while the transmitter and receiver of the US are placed on the opposite side of the target.

The advantages of US over DXA are the lack of ionizing radiation, low cost, and portability. More importantly, the elastic nature of the ultrasound waves makes the US imaging method an ideal option to evaluate the bone quality [128]. The main QUS parameters associated with bone quality or bone strength are broadband ultrasound attenuation (BUA), the ultrasound velocity of sound (VOS), and stiffness index (SI) [129], [130]. BUA is a measure of frequency dependent ultrasound attenuation. It provides information about the cortical thickness, elasticity, and micro-architecture of bone. The VOS indicates the transmission velocity of ultrasound passing through bone. The VOS evaluates bone elasticity and density. The SI is a composite of BUA and VOS parameters, and it provides information about bone elasticity. Recently, researchers have investigated the use of QUS parameters for AIS. A study used QUS parameters to evaluate the bone quality of children with AIS and its correlation with BMD measured with DXA at the femoral neck. The QUS parameters BUA and SI measured in the calcaneus were lower

than the normal control group for mild curves (10 to 25 degrees). The results of QUS were then confirmed by the BMD measured at the femoral neck which was also significantly lower than normal controls [131]. Lam et al. investigated the correlation between QUS measurements at the heel area and curve progression in children with AIS [130]. They used the QUS parameters BUA, VOS, and SI and compared them with the BMD from the hip. They found low bone quality indicated by SI was a significant prognostic factor of curve progression with the odds ratio of 2 (1.0–3.7, 95% CI) while BUA and VOS were not [129].

Zheng et al. used a US pulse echo technique to measure the US reflection signals directly at the spine area [132]. In their study, the frequency amplitude index (FAI), a parameter dictated by the reflection coefficient of the soft tissue/bone interface for bone quality assessment, was captured. Only 18 subjects were recruited, and the results showed that the reflection index decreased as the curve severity increased. However, the correlation coefficient (R^2) was only 0.14. In that study, the effect of soft tissue was ignored which may have affected the results significantly.

Although studies have shown that US may provide information about bone quality, DXA is still the method of choice to estimate BMD for clinical practice. Further studies are required to evaluate the ability of US to estimate bone quality. In Chapter 4, a new US parameter that helps to estimate bone stiffness has been described.

2.8. Prediction of Curve Progression

Prognostic factors are the variables that are used to predict whether a health condition will get worse or not. A list of different prognostic factors including radiographic, demographic, physiologic, and genetic-related parameters have been reported and related with curve progression [5], [123], [130], [133]–[137]. A comprehensive systematic review on the prognostic factors of curve progression has been described in Chapter 3.

2.8.1. Methods for Prediction of Curve Progression

The methods for prediction of progression include linear regression analysis and classification analysis. Under classification methods, the logistic regression analysis was

selected to perform the prediction model development analysis for this PhD thesis. Logistic regression analysis is a popular method for developing prediction models in medical research because it is an easy, fast and simple classification method compared to other classification methods which require complicated programming [138]–[141]. The dependent variable is whether a patient show curve progression or not. This simply implies that the dependent variable is binary (assumes a value of either 0 or 1) or dichotomous [142]. The predicted dependent variable is a function of the probability that a particular patient will be in one of the categories (0, 1). Probability is the likelihood something will happen, and it takes a value between 0 to 1. The odds are the ratio determined by dividing the probability that an event will occur by the probability that an event will not occur. The key component of logistic regression analysis is logit which is simply the natural logarithm (ln) of the odds (Equation 2.1). Therefore, the logistic regression will be:

Equation 2.1 Shows the logistic regression equation.

$$\text{Log of odds: } \ln[\text{prob(an event occurs)/prob(event not occur)}] = B_0 + B_1(X_1) + B_2(X_2) + \ldots + B_n(X_n) \quad (2.1)$$

The B_0 is the intercept and B_1, B_2..., Bn indicate the effect of the predictor variable on the odds of the predicted variable.

2.9. Summary

This chapter describes spine anatomy, scoliosis, different imaging modalities to image scoliosis, bone property assessment methods, and the method of choice to develop the prediction model. A detailed analysis on predictive factors of curve progression as an essential part of this PhD thesis have been described in Chapter 3.

Chapter 3: A Systematic Review on Prognostic Factors of Curve Progression in AIS

3.1. Overview

This chapter reports a systematic review study on identifying prognostic factors of curve progression in AIS. Systematic review studies stand at the highest position compared to other study designs based on the hierarchy of evidence. The reason could be related to the design of systematic reviews that focus on answering a specific question and following a step-by-step comprehensive approach that assess the quality of studies to ensure a non-biased conclusive statement. To answer one of the main objectives of this PhD thesis as "identifying the prognostic factors of curve progression", it was necessary to conduct this systematic review to learn about current literature, deficits and strength and tailor this PhD research project accordingly. Section 3.2 to section 3.6 include the manuscript with the title "Identifying Prognostic Factors of Curve Progression in Adolescents with Idiopathic Scoliosis: A Systematic Review" which has been submitted to PLOS One journal. Section 3.7 summaries the key findings which lead to the final predictors of progression supported by different level of evidence and for different progression criteria and follow-up durations.

3.2. Introduction

Adolescent idiopathic scoliosis (AIS) defined as a lateral curvature of the spine is the most common type of scoliosis affecting 2-4% of children [1]. The standard measurement of the severity of AIS is the Cobb angle on a standing posteroanterior radiograph of the spine [2]. A curve change >5° between two consecutive radiographs (within 6 to 12 months) is considered curve progression [1]. However, only 14.7% of children show curve progression which implies that most radiographs do not detect any difference [2]. These unnecessary radiographs expose children to ionizing radiation and can increase risk of cancer [3].

Literature suggests that scoliosis progression may be predicted by clinical parameters [4-9]. Potential predictors include: large Cobb angle, osteopenia, age<13 years at diagnosis, skeletal immaturity, pre-menarche status, and multiple indices combining radiographic, demographic, and physiologic characteristics [4-9]. Lonstein et al. reported that the Risser sign, magnitude of the curve and patient's age at the initial examination are highly correlated with curve progression [6]. However, it was not clarified whether the prediction was for the next visit or during later follow-ups. In another study, a Risser sign of 0 or 1, an apical level cephalad to the T12, absence of coronal imbalance (≤10 millimetre), and lower chronological age predicted progression over a short-term interval (within one year follow-up) [10]. Tan et al. found that a larger initial Cobb angle was the most important predictor for prediction of long-term progression [9].

There is a wide variety of parameters which have been reported as predictors for curve progression. The quality of studies to identify predictors has been questioned. Also, studies used different definitions of curve progression measured at different follow-up intervals. Therefore, a comprehensive systematic review study to investigate what are the best predictors for different progression thresholds as well as for short- and long-term follow-up intervals is needed. A systematic review and meta-analysis on identifying predictors on curve progression for scoliosis was reported in 2015 [8]. The keywords and database used in this study did not include all the common clinical parameters and instead included only a few parameters acquired through complex medical, physiologic, biochemical, and genetic tests. Considering that physicians are interested to identify predictive factors of progression for different thresholds and follow-up intervals, in their review, studies were analyzed based on different categories of predictive factors rather than progression criteria or follow-up intervals. Moreover, their review was not registered which makes it unclear whether a standard systematic review protocol determined a priori was followed.

Thus, the goals of this study were to identify predictive factors for three curve progression categories including curve magnitude a) increases by ≥5°, b) reaching ≥ 30° or surgery threshold, and c) changes in Cobb angle as °/year on any two radiographs over both short-term (within ≤ 1-year) and long-term (>1-year) follow-up intervals.

3.3. Methods

3.3.1. Protocol and Registration

The systematic review protocol was registered in PROSPERO (CRD42019116211) and followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis-PRISMA checklist [11].

3.3.2. Inclusion Criteria

The eligibility criteria for each phase starting from abstracts to full-texts review and extraction phase contain: 1) human participants, 2) diagnosis of AIS, 3) Mean±SD age between 10 and 18 years, 4) includes a follow-up, 5) Mean±SD of Cobb ≥10°, 6) radiographic or ultrasonic imaging of the spine at follow-up. For the full-text screening, one more criterion was assessed: 7) reporting on the prediction of curve progression.

3.3.3. Exclusion Criteria

Exclusion criteria were: 1) congenital, neuromuscular, syndromic, and secondary diagnoses of scoliosis, 2) using only specialized parameters as predictors (such as laboratory test results including level of enzymes or hormones, brain-function, genetic, electromyography tests), 3) using only non-radiographic imaging to assess curve progression such as in vitro studies, engineering methods (simulations, finite element method, and machine learning), magnetic resonance imaging (MRI), computed tomography (CT), and questionnaires, 4) having scoliosis surgery at baseline, 5) samples with less than 10 participants, 6) case reports, conference proceedings, commentary and opinion letters, and reviews, and 7) non-English studies. These criteria were used for all phases.

3.3.4. Information Sources and Search Strategy

The search terms were determined after consultation with scoliosis experts (EP and EL) and a medical librarian. Five databases including MEDLINE (OVID), EMBASE (OVID),

Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (Web of knowledge), and CINAHL (EBSCO) were selected. The search was performed on the same day, from inception to October 18th, 2018, for all databases. The search strategy developed for Medline by the librarian was adjusted for each database (Appendix 3.1). Zotero was used to manage the references [12].

3.3.5. Study Selection

Five independent reviewers were involved in the abstract and full-text screening stages. The primary reviewer (MK) screened all the articles for the first round paired with one of the four other reviewers (AC, JW, DH, EP). For the second round of screening, again the main reviewer (MK) assessed all the articles, and each full-text article was screened by one of the four other reviewers (AC, JW, DH, EP). Three students and two experts contributed for the study selection part. All students were graduate trainees working on scoliosis field with more than 2 years of experience. The two experts (DH, EP) had more than 10 years of experience working on scoliosis. The reviewers were trained prior to screening. For the training, the criteria were explained clearly, and the reviewers were asked to screen the first 10 articles. Then, the votes were compared and ensured that all the reviewers were confident to continue the screening. The Covidence software (Veritas Health Innovation, Melbourne, Australia) which is specifically devised to conduct systematic reviews was used for the abstract screening. Three options were presented to reviewers for each decision about each article: yes, no, unsure. For the full-text screening, Microsoft Excel forms were designed to capture screening decisions. Reviewers decided which articles to include according to the selection criteria and chose included, excluded or unclear in separate forms for each reviewer. The articles that were excluded along with the reasons have been provided in the Appendix 3.2.

3.3.6. Data Collection Process and Data Items

The eligible articles were included for the full–text extraction phase. An extraction form devised based on the key characteristics including study origin, study design, baseline

description of the population, descriptions of the potential prognostics predictors, descriptions of the outcomes as curve progression, and the reports on the statistical analysis and results. Six reviewers contributed for the extraction. The primary reviewer (MK) extracted the information for all the articles and the rest of reviewers (DH, JW, EG, KN, CC) helped for the second round of extraction. The results were compared for reliability assessment. For the extraction phase, two more reviewers were added to the same group with two of them (EG, KN) as graduate (over two years of experience in scoliosis) and one undergraduate (CC, as a novice researcher) students. The same training procedure was followed for the extraction phase.

3.3.7. Risk of Bias of Studies

The Quality in Prognostic Studies (QUIPS) tool [13] was used for quality appraisal. As recommended, six different domains were appraised and tailored for risk of bias assessment (ROB) for this study (Appendix 3.3). The QUIPS domains include study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and results. For each domain a list of key characteristics determined by consensus of the authors were defined and the questions of each domain were scored according to the available information (Appendix 3.3). An overall score as high, moderate, and low risk of bias was assigned to each article. To determine the overall score for each article, the questions under each domain were prioritized based on their importance for our study and reviewers relied most on the information provided for those specific questions (the questions highlighted in Appendix 3.3, as red, yellow, and green illustrate on the importance, respectively) to assign the overall score for each article. Articles that were missing the information about those questions achieved lower scores.

3.3.8. Summary Measures

Results were summarized for each prognostic factor of three curve progression definitions over two types of follow-up intervals.

3.3.9. Synthesis of Results

Studies were classified based on the curve progression definition used and the follow-up interval duration. The curve progression categories were: i) increase in curve magnitude ≥5°, ii) curve progression to ≥30° or requiring surgery, iii) change in Cobb angle reported as °/year. A short-term follow-up interval was defined as measuring two radiographs captured within ≤ 1-year interval. A long-term follow-up interval was defined as any two radiographs captured at > 1-year interval. Levels of evidence were also qualified as strong, moderate, limited, unclear, conflicting, and no evidence based on the risk of bias and the consistency of the research findings for each article (adapted from Cornelius, et al.) (Table 3.1) [14].

Table 3.1 Rules for determining of the level of evidence when formulating summary statements about whether a variable was predictive of progression or not.

Level of Evidence	Description
Strong	Consistent results (≥80%) from at least 2 high-quality studies
Moderate	One high-quality study and consistent findings (≥80%) in 1 or more low-quality studies
Limited	Findings in 1 high-quality cohort or consistent results (≥80%) among low-quality studies
Unclear	Findings in only one study among low-quality studies
Conflicting	Inconsistent results irrespective of study quality
No	No study identified

Adapted from Cornelius et al. [14]

3.3.10. Additional Analyses

The inter-rater reliability was analyzed by using Kappa coefficients for the decisions during the full-text screening and for the Risk of bias (RoB) assessment [15].

3.4. Results

The PRISMA flowchart (Figure 3.1) shows a total of 1448 articles were acquired after duplicated articles were removed.

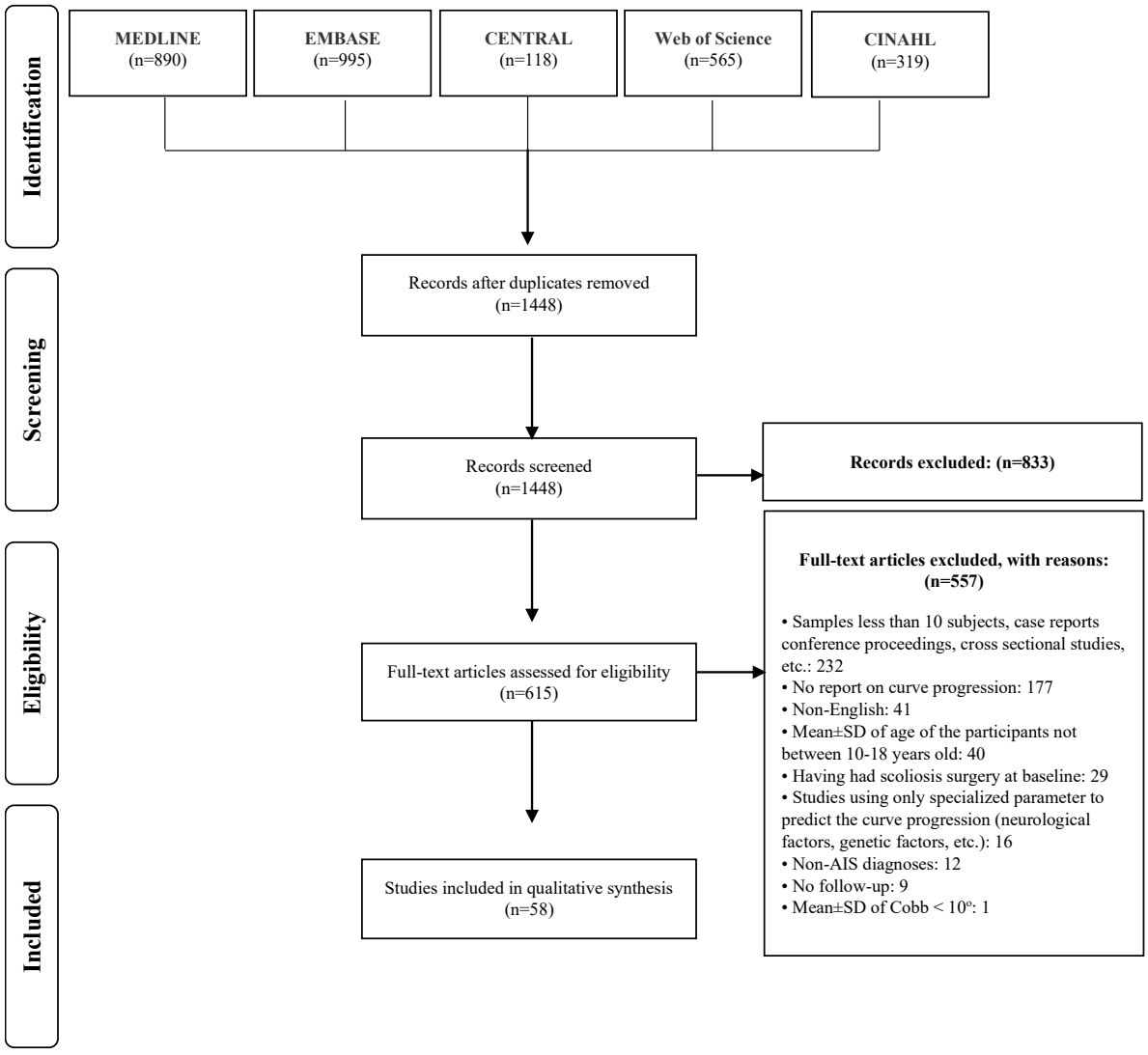


Figure 3.1 The PRSIMA flow chart

After screening, 58 full-text articles were included. Table 3.2 presents the included articles with their year of publication, country of origin, sample sizes and risk of bias score.

Table 3.2 Included articles and RoB assessments

Author	Country	Sample size	QUIPS 1	QUIPS 2	QUIPS 3	QUIPS 4	QUIPS 5	QUIPS 6	Overall RoB
Cheung et al, 2004 [16]	The Netherlands	30	M	N/A	L	L	H	L	L
Davis et al, 2018 [17]	USA	56	L	N/A	L	L	L	M	L
Hung, 2005 [4]	China	324	M	N/A	L	L	H	L	L
Lara et al, 2017 [18]	USA	295	L	H	L	L	M	M	L
Mao et al, 2016 [19]	Germany	95	L	N/A	L	M	M	L	L
O'Neill et al, 2005 [20]	USA	276	L	N/A	L	L	M	L	L
Ohrt-Nissen et al, 2016 [21]	Denmark	63	L	N/A	L	L	L	L	L
Sitoula et al, 2015 [22]	USA	161	L	N/A	L	L	L	M	L
Sun et al, 2013 [23]	China	68	L	N/A	L	M	L	L	L
Zaina et al, 2017 [24]	Italy	351	L	N/A	M	L	L	M	L
Duval-Beaupere, 1992 [25]	France	262	H	N/A	M	H	H	H	H
Konieczny et al, 2017 [26]	Germany	72	L	H	H	M	H	H	H
Kotwicki et al, 2008 [27]	Poland	158	H	N/A	L	M	H	H	H
Aulisa et al, 2009 [28]	Italy	50	H	N/A	L	M	H	M	M
Aulisa et al, 2014 [29]	Italy	522	M	N/A	M	M	M	M	M
Bohl et al, 2014 [30]	USA	34	H	N/A	M	M	M	M	M
Bunnell, 1986 [31]	USA	123	M	N/A	M	H	M	H	M
Charles et al, 2017 [32]	France	372	M	N/A	M	M	M	M	M
Cheung et al, 2018 [33]	China	318	L	N/A	L	M	L	H	M
Cheung, et al, 2018 [34]	China	513	L	N/A	M	M	M	M	M
D'Amato et al, 2001 [35]	USA	102	M	N/A	M	M	M	M	M
Danielsson et al, 2007 [36]	Sweden	92	L	L	L	M	M	M	M
Fang et al, 2015 [37]	China	32	H	N/A	M	M	H	M	M
Gepstein et al, 2002 [38]	Israel	122	M	N/A	M	M	L	M	M
Goldberg et al, 2001 [39]	Ireland	153	L	N/A	M	M	M	M	M
Goodbody et al, 2016 [40]	USA	182	L	N/A	M	L	L	H	M
Guo et al, 2012 [41]	China	60	M	N/A	L	M	M	M	M
Guo et al, 2014 [42]	China	38	M	H	L	M	M	M	M
Karol et al, 1993 [43]	USA	210	L	H	M	L	M	M	M
Karol et al, 2016 [44]	USA	168	M	L	M	M	M	M	M

Karol, 2001 [45]	USA	112	L	N/A	L	L	M	H	M
Katz et al, 2001 [46]	USA	51	M	H	M	M	M	M	M
Katz et al, 2010 [47]	USA	100	L	H	M	L	M	M	M
Kuroki et al, 2015 [48]	Japan	31	L	N/A	M	M	M	M	M
Lam et al, 2013 [49]	Hong Kong	294	M	N/A	M	M	M	L	M
LeBlanc, 1998 [50]	Canada	146	M	N/A	M	M	H	M	M
Lee et al, 2012 [51]	China	2308	M	H	M	M	M	M	M
Nault et al, 2013 [7]	Canada	37	L	N/A	M	M	M	M	M
Nault et al, 2014 [52]	Canada	133	M	N/A	M	M	L	M	M
Pasquini et al, 2016 [53]	Italy	67	M	M	M	H	M	M	M
Peterson et al, 1995 [10]	Sweden	159	L	M	M	M	M	L	M
Ploumis et al, 2018 [54]	USA	73	L	N/A	L	L	L	M	M
Ryan et al, 2007 [55]	USA	62	L	N/A	M	M	L	L	M
Shi et al, 2016 [56]	China	200	L	N/A	M	M	M	M	M
Sun et al, 2010 [57]	China	142	L	N/A	M	M	M	M	M
Tan et al, 2009 [9]	Singapore	186	L	M	M	M	H	L	M
Thompson et al, 2017 [58]	USA	168	L	H	M	L	M	M	M
Trivedi and Thomson, 2001 [59]	USA	42	M	M	M	M	H	L	M
Vijvermans et al, 2004 [60]	Belgium	151	L	N/A	M	H	M	M	M
Weiss, 1992 [61]	Germany	118	M	N/A	M	M	M	H	M
Wu et al, 2011 [62]	Canada	35	M	N/A	M	H	M	M	M
Yamauchi et al, 1988 [63]	Japan	122	H	N/A	M	M	M	M	M
Yip et al, 2016 [64]	Hong Kong	513	L	N/A	M	M	M	L	M
Ylikoski, 1993 [65]	Finland	110	L	N/A	L	M	L	H	M
Yrjonen and Ylikoski, 2006 [66]	Finland	80	L	N/A	L	M	M	M	M
Yrjonen et al, 2006 [67]	Finland	66	L	N/A	M	L	L	M	M
Zhang et al, 2015 [68]	China	89	M	N/A	M	M	L	L	M
Zhu et al, 2017 [69]	China	54	L	N/A	L	M	M	L	M

Abbreviations: L: Low, M: Moderate, H: High, N/A: not applicable, QUIPS1: Study Participation, QUIPS2: Study Attrition, QUIPS3: Prognostic Factor Measurement, QUIPS4: Outcome, QUIPS5: Study Confounding, QUIPS6: Statistical Analysis and Reporting

3.4.1. RoB Within Studies

Of the 58 included articles, only 10 (17%) showed low RoB, 45 (77%) presented moderate RoB, and 3 (5%) presented high RoB [16-18] (Table 3.2). The study participants RoB domain had the greatest number of articles with low RoB 32 (55%). The confounding and statistical analysis-reporting domains had the most articles presenting high RoB with 10 (17 %) and 9 (16%), respectively.

3.4.2. Study Characteristics

Most studies were retrospective [35 (60%)] and used an unknown [35 (60%)] or consecutive [18 (31%)] recruitment strategy (Table 3.3). Of the 58 included articles, 34 (59%) were cohort, 17 (29%) case series, 5 (9%) case-control, and 2 (3%) randomized controlled trial (RCT) studies. Most articles [31 (53%)] reported follow-up ≥2 years. For 8 (14%) articles, completion of bracing or having an age of at least 15 years old were used to determine the time for the follow-up.

Table 3.3 Study characteristic and baseline information summary

<table>
<tr><th colspan="10">Study Characteristics</th></tr>
<tr><th colspan="2">Recruitment timeline
n (%) of articles</th><th colspan="2">Recruitment Strategy
n (%) of articles</th><th colspan="2">Type of Study
n (%) of articles</th><th colspan="2">Range of the Mean Clinical FU duration
n of articles (%)</th></tr>
<tr><td rowspan="2">Prospective</td><td rowspan="2">15 (26%)</td><td rowspan="2">Consecutive</td><td rowspan="2">18 (31%)</td><td rowspan="2">Cohort</td><td rowspan="2">34 (59%)</td><td><2 years</td><td>5 (9%)</td></tr>
<tr><td>≥ 2 years</td><td>31 (5%)</td></tr>
<tr><td rowspan="2">Retrospective</td><td rowspan="2">35 (60%)</td><td>Randomized</td><td>3 (5%)</td><td>Case-series</td><td>17 (29%)</td><td>Skeletal maturity</td><td>11 (19%)</td></tr>
<tr><td>Non-randomized</td><td>1 (2%)</td><td>Case-control</td><td>5 (9%)</td><td>Beyond skeletal maturity</td><td>1 (2%)</td></tr>
<tr><td rowspan="2">Unknown</td><td rowspan="2">8 (14%)</td><td>Convenience</td><td>1 (2%)</td><td rowspan="2">Randomized controlled trial</td><td rowspan="2">2 (3%)</td><td>Others (completion of bracing or up to age at least 15 years old)</td><td>8 (14%)</td></tr>
<tr><td>Unknown</td><td>35 (60%)</td><td>Not specified</td><td>2 (3%)</td></tr>
<tr><th colspan="10">Sample Characteristics</th></tr>
<tr><th colspan="3">Total number of participants</th><th colspan="3">Menarche status, number of participants</th><th colspan="4">Risser sign Skeletal maturity, number of participants</th></tr>
<tr><td colspan="3">11,134</td><td colspan="3"></td><td colspan="4"></td></tr>
</table>

		N of participants (n of articles, %)		N of participants (n of articles, %)	
Range of the mean ages for participants (n of articles, %)				0	1334 (38, 66%)
11.8-14.9 (55, 95%)				1	339 (41, 71%)
Gender	**N of participants (n of articles, %)**	Pre-menarche	1988 (17, 29%)	2	463 (38, 66%)
Male	1980 (57, 98%)	Post-menarche	2130 (26, 45%)	3	302 (15, 26%)
Female	8986 (57, 98%)	Both Pre- and post- menarche reported	2821 (16, 28%)	4	273 (11, 19%)
Curve classification, N of participants (n of articles, %)		Not specified	31, 53%	5	98 (5, 9%)
				Others	136 (3, 5%)
Thoracic	1269 (37, 62%)	**Treatment, number of participants N of participants (n of articles, %)**		Not specified	13, 22%
Thoracolumbar	349 (34, 59%)	Observation /non-treated	1582 (12, 21%)	**Range of the mean Cobb angle (°) N of participants (n of articles, %)**	
Lumbar	361 (20, 34%)	Brace	4642 (42, 72%)		
Thoracolumbar/Lumbar	617 (12, 21%)	Surgery	475 (20, 34%)		
Double	873 (27, 43%)	Brace+ surgery	18 (1, 2%)	Initial, No of articles (%)	22-47 (54, 93%)
Triple	19 (4, 7%)	Exercise	118 (2, 3%)		
Others	1213 (6, 10%)	Electrical simulation	30 (1, 2%)	Follow-up, No articles (%)	15-49 (16, 28%)
Not specified	16, 28%	Not specified	8, 14%		

3.4.3. Sample Characteristics

The studies included a total of 11,134 participants (Table 3.3). Most participants were female 8986 (81%) (Table 3.3). The number of pre-and post-menarche female participants were 1988 vs 2130 participants reported in 17 (29%) vs 26 (45%) articles. Most participants had a thoracic curve type 1269 (37, 62%). Risser 0 was the most common skeletal maturity grade reported across the studies at baseline (38, 66%). The mean initial Cobb angles ranged 22 to 47 degrees.

3.4.4. Reviewer Agreement Analyses

The percentages of agreement were 84% and 59% for full-text screening and RoB ratings, respectively. The Kappa coefficients were 0.55 and 0.77 for full-text screening and RoB assessments, respectively.

3.4.5. Synthesis of the Results

Most studies defined curve progression as an increment of curve magnitude ≥5° [≥5° (26 studies, 45%), ≥6° (17, 29%), or ≥10° (3, 5%)] (Appendix 3.4). A second group of studies defined progression as curve magnitude increases to ≥30° or requiring surgery: ≥30° (2, 3%), ≥40° (12, 21%), ≥50° (5, 9%), and surgery (13, 22%) (Appendix 3.5). Four articles (7%) reported on change in Cobb angle as °/year (Appendix 3.6). Thirteen articles (22%) mentioned more than one progression criterion. Of the 58 articles, 20 (34%) articles studied progression over short-term follow-up interval and 34 (59%) over long-term intervals (Appendix 3.4-3.6). For 4 (7%) articles the follow-up interval studied was unclear (Appendix 3.4 and 3.5).

I)* Predictive factors for *curve progression ≥5° over short- and long-term follow-up intervals

Forty-six articles used ≥5° as the criteria of progression (Appendix 3.4). To predict progression ≥5°, a total of 32 predictive factors were studied over short-term and 87 over long-term follow-up intervals (Table 3.4).

Table 3.4 Levels of evidence summary statements about whether each predictive factor investigated does or does not predict curve progression ≥ 5° over short-term/long-term follow-up intervals

Level of Evidence	Number of studies with ROB (predictor+/ nonpredictor-)	Parameters	Predictor/Non-predictor	Follow-up Term
Strong	2+/0 Low, 4+/2- Moderate, 1+/0 Moderate*	High Cobb angle*	P	Short-term, unclear*
Strong	2+/0 Low, 2+/1- Moderate	Pre-menarche status	P	Short-term
Limited	3+/0 Moderate	Apex location (at higher vertebral levels)	P	Short-term
Limited	1+/0 Low, 0/1- Moderate	High spinal growth	P	Short-term
Limited	1+/0 Low	Low bone mineral density (BMD) of the femoral neck in concave-side hip	P	Short-term
Limited	1+/0 Low	Low BMD of the femoral neck in convex-side hip	P	Short-term

Limited	1+/0 Low	Low BMD of the Trochanter in concave-side hip	P	Short-term
Limited	1+/1- low, 6+/0 Moderate, 0/2- Moderate*	Low stages of Risser sign* (0-3)	P	Short-term, unclear*
Unclear	1+/0 Moderate	Body morphology (Anthropometric measurements and morphologic classification) [#]	P	Short-term
Unclear	1+/0 Moderate	High height	P	Short-term
Unclear	1+/0 Moderate	Initial apex lateral deviations	P	Short-term
Unclear	1+/0 Moderate	Low ASIS circumference (mm)	P	Short-term
Unclear	1+/0 Moderate	Low hip width (mm)	P	Short-term
Unclear	1+/0 Moderate	Low proportion of bone volume of body	P	Short-term
Unclear	1+/0 Moderate	Maximal apex lateral deviations	P	Short-term
Unclear	1+/0 Moderate	Maximal Cobb angle	P	Short-term
Unclear	1+/0 Moderate	Open Triradiate cartilage (TRC)	P	Short-term
Strong	0/2- Low, 2+/3- Moderate	Curve pattern	NP	Short-term
Moderate	0/1- Low, 0/1- Moderate, 0/1- High	Age at menarche	NP	Short-term
Moderate	0/1- Low, 0/1- Moderate, 0/1- High	Body mass index (BMI)	NP	Short-term
Limited	0/1- Low	BMD of the femoral neck on the non-dominant side	NP	Short-term
Limited	0/1- Low	BMD of the trochanter in convex-side hip	NP	Short-term
Limited	0/1- Low, 0/1- Moderate	Family history of scoliosis	NP	Short-term
Limited	0/2- Moderate	Kyphosis	NP	Short-term
Limited	0/1- Low, 0/1- Moderate	Weight	NP	Short-term
Unclear	0/1- Moderate	Apical vertebral rotation	NP	Short-term
Unclear	0/1- Moderate	Initial apex lateral deviations	NP	Short-term
Unclear	0/1- Moderate	Lordosis	NP	Short-term
Unclear	0/1- Moderate	Lumbosacral transitional abnormalities	NP	Short-term
Unclear	0/1- Moderate	Spinal balance (alignment of C7)	NP	Short-term
Unclear	0/1- Moderate	Rib hump	NP	Short-term
Conflicting	1+/1- Low	BMD in the spine	P/NP	Short-term
Conflicting	2+/2- Moderate	Gender	P/NP	Short-term
Conflicting	1+/-1 Low, 4+/3- Moderate	Initial age	P/NP	Short-term
Limited	1+/0 Low, 3+/2- Moderate	High apical vertebral rotation	P	Long-term
Limited	3+/0 Moderate	High torsion	P	Long-term
Limited	1+/0 Low, 0/1- Low*	High weight*	P	Long-term, Unclear*
Limited	1+/0 Low, 0/1- Moderate	Low curve flexibility	P	Long-term
Limited	2+/0 Moderate	Low slenderness (height/width ratio of regional T1–L5)	P	Long-term
Limited	2+/0 Moderate	Open Triradiate cartilage (TRC)	P	Long-term
Limited	1+/0 Low, 3+/4- Moderate	Pre-menarche status	P	Long-term
Limited	2+/0 Moderate	Spinopelvic inclination (T1≤ 3.5°, T9≤ 6.5°)	P	Long-term
Unclear	1+/0 Moderate	Apical intervertebral rotation (>2.4 °)	P	Long-term
Unclear	1+/0 Low *, 1+/0 Moderate	BMI (high [BMI (85th percentile) and low (<20th percentile)]	P	Long-term, unclear*
Unclear	1+/0 Moderate	High axial angle of the plane in which the Cobb angle is maximal	P	Long-term
Unclear	1+/0 Moderate	High axial rotation of lower junctional vertebra	P	Long-term
Unclear	1+/0 Moderate	High Cobb angle at brace weaning	P	Long-term
Unclear	1+/0 Moderate	High sacral takeoff angle (>5°)	P	Long-term
Unclear	1+/0 Moderate	Higher coronal rotation of lower junctional vertebra	P	Long-term
Unclear	1+/0 Moderate	Iliac crest height difference (>1 cm)	P	Long-term
Unclear	1+/0 Moderate	Low bone mineral density (BMD) of both hips	P	Long-term

Unclear	1+/0 Moderate	Low bone quality (broadband ultrasound attenuation (BUA))	P	Long-term
Unclear	1+/0 Moderate	Low bone quality (stiffness index (SI))	P	Long-term
Unclear	1+/0 Moderate	Low bone quality (velocity of sound (VoS))	P	Long-term
Unclear	1+/0 Moderate	Low kyphosis angle	P	Long-term
Unclear	1+/0 Moderate	Lower sagittal intervertebral rotation at the apical level	P	Long-term
Unclear	1+/0 Moderate	Lower slenderness (height/depth ratio of local L4)	P	Long-term
Unclear	1+/0 Moderate	Lower slenderness (height/depth ratio regional T1–L5)	P	Long-term
Unclear	1+/0 Moderate	Lower slenderness (height-depth ratio of local T12)	P	Long-term
Unclear	1+/0 Moderate	Lumbar pelvic relationship (LPR) (>12°)	P	Long-term
Unclear	1+/0 Moderate	Vertebral translations (at apical level)	P	Long-term
Moderate	1+/3- Low, 3+/16- Moderate	Age	NP	Long-term
Moderate	0/1- Low, 0/3- Moderate	Age at menarche	NP	Long-term
Moderate	0/1- Low, 0/2- Moderate	Apex location	NP	Long-term
Moderate	1+/2- Low, 2+/11- Moderate	Curve pattern	NP	Long-term
Moderate	0/1- Low, 0/2- Moderate	Height (standing)	NP	Long-term
Limited	0/2- Moderate	3D Cobb angle	NP	Long-term
Limited	1+/3- Low, 7+/14- Moderate	Cobb angle	NP	Long-term
Limited	1+/3- Low, 3+/3- Moderate,	Gender	NP	Long-term
Unclear	0/1- Moderate	Age at bracing	NP	Long-term
Unclear	0/1- Moderate	Age at maturity	NP	Long-term
Unclear	0/1- Moderate	Apical disk wedging	NP	Long-term
Unclear	0/1- Moderate	Apical vertebral translation (AVT) ratio (AVT-R)	NP	Long-term
Unclear	0/1- Moderate	Apical vertebral translation -lumbar (AVT-L)	NP	Long-term
Unclear	0/1- Moderate	Apical vertebral translation -thoracic (AVT-T)	NP	Long-term
Unclear	0/1- Moderate	Axial intervertebral rotation at the apical level	NP	Long-term
Unclear	0/1- Moderate	Axial rotation of upper junctional vertebra	NP	Long-term
Unclear	0/1- Moderate	Cobb ratio (thoracic Cobb/ lumbar Cobb)	NP	Long-term
Unclear	0/1- Moderate	Coronal decompensation	NP	Long-term
Unclear	0/1- Moderate	Coronal intervertebral Rotation at the apical level	NP	Long-term
Unclear	0/1- Moderate	Coronal rotation of upper junctional vertebra	NP	Long-term
Unclear	0/1- Moderate	Difference of inclination between the proximal and the distal vertebra	NP	Long-term
Unclear	0/1- Moderate	Disc index (wedging of the disk spaces in the curve)	NP	Long-term
Unclear	0/1- High	Educational level of the parents	NP	Long-term
Unclear	0/1- High	Educational level of the patients	NP	Long-term
Unclear	0/1- High	Family history of scoliosis	NP	Long-term
Unclear	0/1- Moderate	Femoral head height difference (mm)	NP	Long-term
Unclear	1-/0 Moderate	Height (sitting)	NP	Long-term
Unclear	0/1- High	Hours of self-training per week	NP	Long-term
Unclear	0/1- High	Hours of sports per week outside of the school	NP	Long-term
Unclear	0/1- Moderate	Lordosis	NP	Long-term
Unclear	0/1- Moderate	Low curve disk wedging	NP	Long-term
Unclear	0/1- Moderate	Lower curve intervertebral rotation	NP	Long-term

Unclear	0/1- High	Nutritional behavior	NP	Long-term
Unclear	0/1- Moderate	Pelvic incidence (PI)	NP	Long-term
Unclear	0/1- Moderate	Relative apical distance (RAD)	NP	Long-term
Unclear	0/1- Moderate	Rib–vertebra angle - concave side (RVA-cv)	NP	Long-term
Unclear	0/1- Moderate	Rib–vertebra angle- convex side (RVA-cx)	NP	Long-term
Unclear	0/1- Moderate	Rib–vertebra angle difference (RVAD)	NP	Long-term
Unclear	0/1- Moderate	Sacral slope (SS)	NP	Long-term
Unclear	0/1- Moderate	Sagittal rotation of lower junctional vertebra	NP	Long-term
Unclear	0/1- Moderate	Sagittal rotation of upper junctional vertebra	NP	Long-term
Unclear	0/1- Moderate	Slenderness (height/depth ratio of local T6)	NP	Long-term
Unclear	0/1- Moderate	Slenderness (height/width ratio of local T12)	NP	Long-term
Unclear	0/1- Moderate	T12–L1 intervertebral rotation	NP	Long-term
Unclear	0/1- Moderate	Trunk shift	NP	Long-term
Unclear	0/1- High	Type of school bag	NP	Long-term
Unclear	0/1- Moderate	Upper curve disk wedging	NP	Long-term
Unclear	0/1- Moderate	Upper curve intervertebral rotation	NP	Long-term
Unclear	0/1- Moderate	Vertebral tilt angles (VTA) for lumbar–inferior [VTA-L-I])	NP	Long-term
Unclear	0/1- Moderate	Vertebral tilt angles (VTA) for lumbar–superior [VTA-L-S	NP	Long-term
Unclear	0/1- Moderate	Vertebral tilt angles (VTA) for thoracic-inferior [VTA-T-I]	NP	Long-term
Unclear	0/1- Moderate	Vertebral tilt angles (VTA) for thoracic–superior [VTA-T-S]	NP	Long-term
Unclear	0/1- Moderate	Vertebral translations (at first thoracic level)	NP	Long-term
Conflicting	1+/1- Moderate	Apical vertebral body wedging	P/NP	Long-term
Conflicting	1+/1- Moderate	Low slenderness (height/width ratio of local L4)	P/NP	Long-term
Conflicting	1+/1- Moderate	Low slenderness (height/width ratio of local T6)	P/NP	Long-term
Conflicting	+1/1-Moderate	Pelvic tilt (PT)	P/NP	Long-term
Conflicting	2+/2- Low, 7+/8-Moderate	Risser sign	P/NP	Long-term
Conflicting	1+/1- Moderate	Spinal growth	P/NP	Long-term
Conflicting	1+/1- Moderate	Vertebral translation	P/NP	Long-term

***** indicates the unclear follow-up interval reported for that specific predictive factor. P: predictor, NP: non-predictor. [#] The parameters considered under body morphology were: Wrist thickness (mm), Deltoid circumference (mm), Under breast circumference (mm), Thigh circumference (mm), Arm circumference (mm), Fat (%), Muscle volume (%), Head, face, and neck ectomorphism score, Head, face, and neck mesomorphism score, Thorax ectomorphism score, Thorax mesomorphism score, Superior limbs ectomorphism score, Superior limbs mesomorphism score, Forearm length (mm)-All were significantly related with progression.

There were unclear follow-up intervals for 4 predictive factors.

The summary statements for prediction of progression ≥5° over a short-term interval are:

- Strong evidence that large Cobb angle and pre-menarche status were predictive.
- Strong evidence that curve pattern was not predictive.
- Moderate evidence that age at menarche for girls and BMI were not predictive.

- Limited evidence that apex location (at higher vertebral levels), high spinal growth, low BMD of the femoral neck in the hips and the trochanter in the concave-side hip, and low Risser sign were predictive.

The summary statements for prediction of progression ≥5° over a long-term interval are:

- Moderate evidence that age, age at menarche, curve pattern, apex location, and height were not predictive.
- Limited evidence that high apical/axial vertebral rotation, high torsion, high weight, low curve flexibility, low slenderness (height/width ratio of local T6, of regional T1-L5), open Triradiate cartilage (TRC), pre-menarche status, and spinopelvic inclination (T1≤ 3.5°, T9≤ 6.5°) were predictive.

II)* Predictive factors for *curve progression to a magnitude ≥30° or requiring surgery over short- and long-term follow-up intervals

Thirty-two articles used progression ≥30^{o} or surgical thresholds as a progression criterion (Appendix 3.5). There were 22 predictive factors studied over short-term, 13 for long-term and 4 for unclear follow-up intervals (Table 3.5).

Table 3.5 Levels of evidence summary statements about whether each predictive factor investigated does or does not predict curve progression when attempting to predict progression >30^{o} or surgery

Level of Evidence	Number of studies with ROB (predictor+/ nonpredictor-)	Parameters	Predictor/Non-predictor	Follow-up Term
Moderate	1+/0 Low, 2+/0 Moderate	Pre-menarche status	P	Short-term
Limited	4+/0 Moderate, 1+/0 Moderate*	High Cobb angle*	P	Short-term, Unclear*
Limited	2+/0 Moderate	Low age	P	Short-term
Limited	1+/0 Low	Sanders stages of maturity (SS1, SS2, and SS3)	P	Short-term
Unclear	1+/0 Moderate	Low areal bone mineral density (aBMD) at proximal of both femurs (zBMD < − 1)	P	Short-term
Unclear	1+/0 Moderate	Gender (female)	P	Short-term
Unclear	1+/0 Moderate	Low height (< 153.9 cm)	P	Short-term
Unclear	1+/0 Moderate	Low bone morphometry (cortical bone area, CrAr/ total bone area, TotAr (%)) at non-dominant distal radius	P	Short-term
Unclear	1+/0 Moderate	Low bone morphometry (cortical thickness, CtTh) at non-dominant distal radius	P	Short-term

Unclear	1+/0 Moderate	Low Olecranon stages of maturity	P	Short-term
Unclear	1+/0 Moderate	Low Risser sign (0-3)	P	Short-term
Unclear	1+/0 Moderate	Low trabecular bone micro-architecture (trabecular thickness, Tb.Th) at non-dominant distal radius	P	Short-term
Unclear	1+/0 Moderate	Low volumetric BMD (volumetric density of cortical bone measured at distal radius, Dcort) at non-dominant distal radius	P	Short-term
Unclear	1+/0 Moderate	Open Triradiate cartilage (TRC)	P	Short-term
Unclear	0/1- Moderate	Bone morphometry (cortical periosteal perimeter, (CtPm)) at non-dominant distal radius	NP	Short-term
Unclear	0/1- Moderate	Bone morphometry (total bone area, Tot Area (cm^2)) at non-dominant distal radius	NP	Short-term
Unclear	0/1- Moderate	Bone morphometry (trabecular bone area, Tb.Ar (cm^2)) at non-dominant distal radius	NP	Short-term
Unclear	0/1- High*	Hip joint asymmetries	NP	Unclear*
Unclear	0/1- Moderate	Trabecular bone micro-architecture (bone volume over total volume, BV/TV) at non-dominant distal radius	NP	Short-term
Unclear	0/1- Moderate	Trabecular bone micro-architecture (trabecular number, TrN) at non-dominant distal radius	NP	Short-term
Unclear	0/1- Moderate	Trabecular bone micro-architecture (trabecular spacing, Tb.Sp) at non-dominant distal radius	NP	Short-term
Unclear	0/1- Moderate	Volumetric BMD (overall volumetric density measured at distal radius, Dtot) at non-dominant distal radius	NP	Short-term
Unclear	0/1- Moderate	Volumetric BMD (volumetric density of trabecular bone measured at distal radius, Dtrab) at non-dominant distal radius	NP	Short-term
Moderate	2+/1- Low, 6+/0 Moderate	High Cobb angle	P	Long-term
Limited	1+/0 Low	Apex location (curve apex cephalad to T10)	P	Long-term
Limited	1+/0 Low	High weight	P	Long-term
Limited	1+/0 Low, 2+/3- Moderate	Low age	P	Long-term
Unclear	1+/0 Moderate	Body mass index [BMI (>85^{th} percentile) and <20^{th} percentile)]	P	Long-term
Unclear	1+/0 Moderate	High Cobb angles at brace weaning	P	Long-term
Unclear	1+/0 Moderate	Low grades of distal Radius and Ulna (DRU) classification (R7/U5)	P	Long-term
Limited	1+/2- Low, 0/1- Moderate	Gender	NP	Long-term
Unclear	0/1- Moderate	Age at menarche	NP	Longterm
Unclear	0/1- Moderate	Initial puberty status	NP	Long-term
Conflicting	1+/1- Low, 2+/1- Moderate, 1+/1- Moderate*	Curve Pattern	P/NP	Long-term, Unclear*
Conflicting	2+/2- Moderate	Menarche status	P/NP	Long-term
Conflicting	1+/2- Low, 3+/0 Moderate, 0/1- Moderate*	Risser sign	P/NP	Long-term, Unclear*

* indicates the unclear follow-up interval reported for that specific predictive factor. Abbreviations: #P: predictor, NP: non-predictor, #bone parameters: zBMD: z score of bone mineral density, CrAr: cortical bone area, TotAr (%): total bone area; CtTh: cortical thickness, Tb.Th: trabecular thickness, Dcort: volumetric density of cortical bone measured at distal radius, TRC: triradiate cartilage, CtPm: cortical periosteal perimeter, Tot Area: total bone area, Tb.Ar: trabecular bone area, BV/TV: bone volume over total volume, TrN: trabecular number, Tb.Sp: trabecular spacing, Dtot: overall volumetric density measured at distal radius, Dtrab: volumetric density of trabecular bone measured at distal radius.

The summary statements for prediction of progression ≥30° or requiring surgery over a short-term interval are:

- Moderate evidence that pre-menarche predicted progression.
- Limited evidence that large Cobb angle, low age, and Sanders stages of maturity (SS1-SS3) predicted progression.

The summary statements for prediction of progression ≥30° or requiring surgery over a long-term interval are:

- Moderate evidence that large Cobb angle predicted progression.
- Limited evidence that low age, high weight, and apex location cephalad to T10 predicted progression.

III) Predictive factors for *curve progression reported as change in Cobb angle (°/year) over short- and long-term follow-up intervals*

The degree of curve progression per year was reported in only 4 articles (Appendix 3.6). Nine predictors were studied for prediction of progression as change in Cobb angle (°/year) over short-term and 3 over long-term intervals (Table 3.6).

Table 3.6 Levels of evidence summary statements about whether each predictive factor investigated does or does not predict curve progression defined as change in Cobb angle (°/year) over short-term and long-term follow-up intervals

Level of Evidence	Number of studies with ROB (predictor+/ nonpredictor-)	Parameters	Predictive+/Non-predictive	Follow-up Term
Limited	2+/0 Moderate, 1+/0 High	Curve pattern (Thoracic, double, triple curves)	P	Short-term
Limited	1+/0 High, 1+/0 Moderate	High Cobb angle	P	Short-term
Limited	2+/0 Moderate	Low age	P	Short-term
Unclear	1+/0 Moderate	Growth velocity (≥ 4 cm/year)	P	Short-term
Unclear	1+/0 Moderate	High growth of the T4-L4 segment	P	Short-term
Unclear	1+/0 High	High rib hump	P	Short-term
Unclear	1+/0 Moderate	Pre-menarche	P	Short-term
Unclear	1+/0 High	State II of maturity (between start of puberty and menarche)	P	Short-term
Conflicting	1+/1- Moderate	Risser sign	P/NP	Short-term
Unclear	1+/0 Moderate	Distal Radius and Ulna classification (DRU) (R7/U5 stages)	P	Long-term
Unclear	1+/0 Moderate	High arm span	P	Long-term
Unclear	1+/0 Moderate	High height	P	Long-term

[#]Abbreviation: P: predictor, NP: non-predictor

For progression defined as change in Cobb Angle (°/year) the summary statements are:

- Limited evidence that curve pattern (thoracic, double, triple curves), large Cobb, and low age predicted progression over short-term follow-up intervals.

3.5. Discussion

Much of the evidence about prediction of curve progression is still limited or unclear and conflicting evidence is still present. The most cited parameters among studies were age, Cobb, Risser sign, menarche status, and gender. This emphasizes that these classical factors are still the most popular to use for prediction of progression for clinicians, which is probably due to their importance and feasibility to measure. However, our results showed that, of these factors, only large Cobb and premenarche were identified as predictive with moderate to strong evidence. The list of predictors with supporting evidence varied for each progression criteria and follow-up interval suggesting that research should use clear definitions and specific follow-up intervals.

The number of studies was insufficient to reach higher levels of evidence for most of the variables. The reason may be that some of these factors such as bone quality parameters have only recently been considered as potential prognostic predictors of progression with promising results from some studies [4], [5], [23]. The same may apply to 3D parameters of spine [7], [37], [52]. Those may also be important as a curve progression outcome since they could reflect the true 3D nature of the AIS.

In the review by Noshchenko et al., it was not explored whether predictors differed depending on progression definitions and follow-up durations which may limit our ability to rely on their results [8]. In their review, most parameters that were associated with progression were related to complex genetic, brain function and laboratory tests. However, clinicians require more convenient and simple prognostic tools if such clinical parameters can achieve good prediction accuracy. Nevertheless, our review shows that the current

literature suffers from lack of high quality studies for predicting progression which is consistent with the results of Noshchenko et al [8].

To standardize comparison on the predictive value of variables and avoid heterogeneity among studies, we recommend three key standard thresholds progression criteria which are consistent with the Scoliosis Research Society's (SRS) [1]:

i) Curve change >5° between two consecutive radiographs can be used to detect progression for short-term intervals (<1-year). Predicting curve progression for the next visit may guide treatment decision and could significantly reduce the number of radiographs required at upcoming visits.

ii) Progression to a magnitude of 25 to 40° can be considered for initiating brace treatment. Short-term prediction may help for timely initiating treatment or adjust the treatment plan for a more efficient outcome.

iii) Progression to a magnitude of >45° during growth or greater than 45° after growth stops can be considered as a threshold for prediction of progression to surgical treatment over long-term follow-up. Learning about predictors over long-term follow-up intervals may also help clinicians plan possible treatment options or discuss expectations at maturity.

Based on the RoB assessment, the study confounding, and statistical analysis domains had the most articles presenting high RoB bias. The potential key confounding factors including age, curve severity, curve type, skeletal maturity, gender, treatment, and menarche were often not appropriately accounted for increasing the risk of bias of the relationship between prognostic factor and outcome. Also, the lack of an appropriate conceptual framework or insufficient statistics to decide about predictors were evident. The ideal study design for conducting prognostic studies is a prospective cohort study. The most common method used for prediction of progression was linear regression analysis which is recommended due to simplicity and readability. It is suggested that studies report a robust step-by step approach from univariate to multivariate analysis and model development by reporting on level of significance, cut off values, coefficients, accuracy tests, and preferably a validity study afterwards.

In this review, only English language articles were included. Results showed moderate to good agreement between reviewers for full-text screening and RoB assessment, respectively. The agreement for full-text screening was (k=0.55) at first assessment which improved to 0.63 after adjusting the criteria and reassessing the articles. Data homogeneity is being examined to determine if a meta-analysis will be possible.

3.6. Conclusions

Our review showed that high Cobb angle and pre-menarche status were predictive of progression ≥5° over short-term intervals and for long-term intervals, only limited evidence was available for the predictive factors. For progression ≥30° or requiring surgery, pre-menarche was predictive over a short-term interval and large Cobb angle was predictive over the long-term. For progression in Cobb angle (°/year), only limited evidence showed that low age, high Cobb, and curve pattern were predictive over the short-term. More high-quality studies are required to conclude about majority of parameters presenting only limited, unclear or conflicting level of evidence.

3.7. Summary

The results of the systematic review study showed that only high Cobb angle and pre-menarche status were predictive of progression ≥5° over short-term intervals with a strong support from evidence. Other parameters with lower levels of evidence should be further investigated.

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Appendices

Appendix 3.1 The Search Strategy for the Selected Databases

Medline (n=890)
1. spinal curvatures/ or scoliosis/
2. (scolio* or spin* curvature).mp.
3. idiopathic.mp.
4. Adolescent/
5. (teen* or adolescen* or youth or youths or young people or young adult*).mp.
6. (1 or 2) and 3 and (4 or 5)
7. (radiograph* adj3 (indicat* or predict* or parameter* or factor*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. (clinical adj3 (indicat* or predict* or parameter* or factor*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. (demograph* adj3 (indicat* or predict* or parameter* or factor*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. (curve* adj3 (angle* or magnitude* or severity or thoracic or location or thoracolumbar or thoraco lumbar or lumbar or direction* or type* or mild or moderate or severe or pattern* or Lenke)).mp.
11. Cobb angle*.mp.
12. (lateral adj3 (curve* or curvature* or deviation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. (Apical adj3 (level* or vertebra* rotation* or location* or translation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. (Apex adj3 (level* or vertebra* rotation* or location* or translation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. AVR.mp.
16. axial rotation*.mp.
17. axial vertebra* rotation*.mp.
18. coronal balance.mp.
19. decompensation*.mp.
20. Rib* vertebra* angle*.mp.
21. coronal imbalance.mp.
22. frontal imbalance.mp.
23. radiograph* imbalance.mp.
24. (rib hump or rib prominence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25. shoulder asymmetry.mp.
26. height velocity.mp.
27. leg length discrepanc*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
28. spin* growth velocity.mp.
29. growing index.mp.
30. growth index.mp.
31. osteopenia.mp. or exp Bone Diseases, Metabolic/
32. bone mineral densit*.mp.
33. BMD.mp.
34. bone quality.mp.
35. bone densit*.mp.
36. bone stiffness.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
37. forward bend*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

38. surface topograph*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
39. Plumb line*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
40. Scoliomet*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
41. inclinomet*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
42. Moire topography.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
43. hypermobility.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
44. spin* flexibilit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
45. spin* movement*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
46. spin* morpholog*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
47. 3D spin* shape*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
48. kyphosis angle*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
49. kyphotic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
50. lordosis angle*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
51. lordotic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
52. spin* movement*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
53. spinopelvic balance.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
54. sagittal alignment*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
55. pelvi* incidence.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
56. sacr* slope.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
57. age.mp.
58. gender.mp.
59. sex.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
60. sexual maturity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
61. skeletal maturity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
62. Risser.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
63. Tri-radiate cartilage.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
64. wrist x-ray.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
65. Tanner stage*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
66. Sanders.ab.
67. menarche.mp.
68. premenarche.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
69. (wedg* adj3 vertebra*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
70. plane of maximal deformit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
71. or/7-70
72. disease progression/

73. progression.mp.
74. curve progression*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
75. scoliosis progression*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
76. (Cobb adj3 (increase* or change* or difference*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
77. curve angle change*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
78. curve deterioration*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
79. spin* deformit* progression*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
80. progressive adolescent idiopathic scoliosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
81. progressive AIS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
82. brac* prescription*.mp.
83. surgery* prescription*.mp.
84. or/72-83
85. (predict* or prognos* or risk factor*).ti.
86. model*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
87. (significant* adj6 (association* or relation* or predict* or prognos* or risk factor*)).mp.
88. predict* value of test*.mp.
89. progress*.mp.
90. (prognostic index or prognostic model*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
91. (predict* adj4 (outcome* or curve* or angle* or Cobb)).mp.
92. regression.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
93. (Fisher* adj exact).mp.
94. (regression analys* or logistic regression).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
95. Multiple logistic regression model*.mp.
96. multivari*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
97. Cox regression*.mp.
98. ((multivaria* or performance or cox or proportional hazards) adj3 (model or models)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
99. regression tree*.mp.
100. Kaplan-Meier Estimate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
101. Risk assessment*.mp.
102. risk ratio*.mp.
103. Odds ratio*.mp.
104. hazard ratio*.mp.
105. likelihood ratio*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
106. positive likelihood ratio*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
107. negative likelihood ratio*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
108. sensitivit*.mp.

109. specificit*.mp.
110. (receiver operating characteristic* or ROC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
111. (recalibration or receiver operating curve or roc).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
112. (scatter diagram* or scatter plot* or covariance decomposition or youden index).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
113. (area under curve or AUC or bootstrapping or Brier Score or "c index" or c-index).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
114. (calibration or CCR or concordance index or correct classification rate or cross validation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
115. ("D statistic" or D-statistic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
116. (Murphy's decomposition or Nagelkerke* or negative predictive value or npv or net reclassification improvement or nomogram*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
117. (positive predict* value* or PPV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
118. (negative predict* value* or NPV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
119. machine learning model*.mp.
120. cluster analys*.mp.
121. Discriminant analysis.mp. or exp Discriminant Analysis/
122. (decision curve analysis or discrimination or external validation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
123. ("goodness of fit" or Hosmer-Lemeshow test or internal validation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
124. (misclassification adj3 (probability or rate)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
125. or/85-124
126. 6 and 71 and 84 and 125

Embase (n=995)

1. exp scoliosis/

2. (scolio* or spin* curvature).mp.

3. idiopathic.mp.

4. adolescent/

5. (teen* or adolescen* or youth or youths or young people or young adult*).mp.

6. (1 or 2) and 3 and (4 or 5)

7. (radiograph* adj3 (indicat* or predict* or parameter* or factor*)).mp.

8. (clinical adj3 (indicat* or predict* or parameter* or factor*)).mp.

9. (demograph* adj3 (indicat* or predict* or parameter* or factor*)).mp.

10. (curve* adj3 (angle* or magnitude* or severity or thoracic or location or thoracolumbar or thoraco lumbar or lumbar or direction* or type* or mild or moderate or severe or pattern* or Lenke)).mp.

11. Cobb angle*.mp.

12. (lateral adj3 (curve* or curvature* or deviation*)).mp.

13. (Apical adj3 (level* or vertebra* rotation* or location* or translation*)).mp.

14. (Apex adj3 (level* or vertebra* rotation* or location* or translation*)).mp.

15. AVR.mp.
16. axial rotation*.mp.
17. axial vertebra* rotation*.mp.
18. coronal balance.mp.
19. decompensation*.mp.
20. Rib* vertebra* angle*.mp.
21. coronal imbalance.mp.
22. frontal imbalance.mp.
23. radiograph* imbalance.mp.
24. (rib hump or rib prominence).mp.
25. shoulder asymmetry.mp.
26. height velocity.mp.
27. leg length discrepanc*.mp.
28. spin* growth velocity.mp.
29. growing index.mp.
30. growth index.mp.
31. osteopenia.mp. or exp Bone Diseases, Metabolic/
32. bone mineral densit*.mp.
33. BMD.mp.
34. bone quality.mp.
35. bone densit*.mp.
36. bone stiffness.mp.
37. forward bend*.mp.
38. surface topograph*.mp.
39. Plumb line*.mp.
40. Scoliomet*.mp.
41. inclinomet*.mp.
42. Moire topography.mp.
43. hypermobility.mp.
44. spin* flexibilit*.mp.
45. spin* movement*.mp.
46. spin* morpholog*.mp.
47. 3D spin* shape*.mp.
48. kyphosis angle*.mp.
49. kyphotic.mp.
50. lordosis angle*.mp.
51. lordotic.mp.
52. spin* movement*.mp.
53. spinopelvic balance.mp.
54. sagittal alignment*.mp.
55. pelvi* incidence.mp.
56. sacr* slope.mp.
57. age.mp.

58. gender.mp.

59. sex.mp.

60. sexual maturity.mp.

61. skeletal maturity.mp.

62. Risser.mp.

63. Tri-radiate cartilage.mp.

64. wrist x-ray.mp.

65. Tanner stage*.mp.

66. Sanders.ab.

67. menarche.mp.

68. premenarche.mp.

69. (wedg* adj3 vertebra*).mp.

70. plane of maximal deformit*.mp.

71. or/7-70

72. disease progression/

73. progression.mp.

74. curve progression*.mp.

75. scoliosis progression*.mp.

76. (Cobb adj3 (increase* or change* or difference*)).mp.

77. curve angle change*.mp.

78. curve deterioration*.mp.

79. spin* deformit* progression*.mp.

80. progressive adolescent idiopathic scoliosis.mp.

81. progressive AIS.mp.

82. brac* prescription*.mp.

83. surgery* prescription*.mp.

84. or/72-83

85. (predict* or prognos* or risk factor*).ti.

86. model*.mp.

87. (significant* adj6 (association* or relation* or predict* or prognos* or risk factor*)).mp.

88. predict* value of test*.mp.

89. progress*.mp.

90. (prognostic index or prognostic model*).mp.

91. (predict* adj4 (outcome* or curve* or angle* or Cobb)).mp.

92. regression.mp.

93. (Fisher* adj exact).mp.

94. (regression analys* or logistic regression).mp.

95. Multiple logistic regression model*.mp.

96. multivari*.mp.

97. Cox regression*.mp.

98. ((multivaria* or performance or cox or proportional hazards) adj3 (model or models)).mp.

99. regression tree*.mp.

100. Kaplan-Meier Estimate.mp.

101. Risk assessment*.mp.

102. risk ratio*.mp.

103. Odds ratio*.mp.

104. hazard ratio*.mp.

105. likelihood ratio*.mp.

106. positive likelihood ratio*.mp.

107. negative likelihood ratio*.mp.

108. sensitivit*.mp.

109. specificit*.mp.

110. (receiver operating characteristic* or ROC).mp.

111. (recalibration or receiver operating curve or roc).mp.

112. (scatter diagram* or scatter plot* or covariance decomposition or youden index).mp.

113. (area under curve or AUC or bootstrapping or Brier Score or "c index" or c-index).mp.

114. (calibration or CCR or concordance index or correct classification rate or cross validation).mp.

115. ("D statistic" or D-statistic).mp.

116. (Murphy's decomposition or Nagelkerke* or negative predictive value or npv or net reclassification improvement or nomogram*).mp.

117. (positive predict* value* or PPV).mp.

118. (negative predict* value* or NPV).mp.

119. machine learning model*.mp.

120. cluster analys*.mp.

121. Discriminant analysis.mp. or exp Discriminant Analysis/

122. (decision curve analysis or discrimination or external validation).mp.

123. ("goodness of fit" or Hosmer-Lemeshow test or internal validation).mp.

124. (misclassification adj3 (probability or rate)).mp.

125. or/85-124

126. 6 and 71 and 84 and 125

CENTRAL (n=118)

ID	Search
#1	scolio* or spin* curvature*
#2	idiopathic
#3	Adolescent
#4	(teen* or adolescen* or youth or youths or young people or young adult*)
#5	#1 and #2 and (#3 or #4)
#6	(radiograph* AND (indicat* or predict* or parameter* or factor*))
#7	(clinical AND (indicat* or predict* or parameter* or factor*))
#8	(demograph* AND (indicat* or predict* or parameter* or factor*))
#9	(curve* AND (angle* or magnitude* or severity or thoracic or location or thoracolumbar or thoraco lumbar or lumbar or direction* or type* or mild or moderate or severe or pattern* or Lenke))
#10	Cobb angle*
#11	(lateral AND (curve* or curvature* or deviation*))
#12	(Apical AND (level* or vertebra* rotation* or location* or translation*))
#13	(Apex AND (level* or vertebra* rotation* or location* or translation*))
#14	AVR
#15	axial rotation*

#16	axial vertebra* rotation*
#17	coronal balance
#18	decompensation*
#19	Rib* vertebra* angle*
#20	coronal imbalance
#21	frontal imbalance
#22	radiograph* imbalance
#23	(rib hump or rib prominence)
#24	shoulder asymmetry
#25	height velocity
#26	leg length discrepanc*
#27	spin* growth velocity
#28	growing index
#29	growth index
#30	osteopenia or metabolic bone disease*
#31	bone mineral densit*
#32	BMD
#33	bone quality
#34	bone densit
#35	bone stiffness
#36	forward bend*
#37	surface topograph*
#38	Plumb line*
#39	Scoliomet*
#40	inclinomet*
#41	Moire topography
#42	hypermobility
#43	spin* flexibilit*
#44	spin* movement*
#45	spin* morpholog*
#46	3D spin* shape*
#47	kyphosis angle*
#48	kyphotic
#49	lordosis angle*
#50	lordotic
#51	spin* movement*
#52	spinopelvic balance
#53	sagittal alignment*
#54	pelvi* incidence
#55	sacr* slope
#56	age
#57	gender
#58	sex

#59 sexual maturity

#60 skeletal maturity

#61 Risser

#62 Tri-radiate cartilage

#63 wrist x-ray

#64 Tanner stage*

#65 Sanders:ab

#66 menarche

#67 premenarche

#68 (wedg* AND vertebra*)

#69 plane of maximal deformit*

#70 {OR #6-#69}

#71 disease progression

#72 progression

#73 curve progression*

#74 scoliosis progression*

#75 (Cobb AND (increase* or change* or difference*))

#76 curve angle change*

#77 curve deterioration*

#78 spin* deformit* progression*

#79 progressive adolescent idiopathic scoliosis

#80 progressive AIS

#81 brac* prescription*

#82 surgery* prescription*

#83 {OR #71-#82}

#84 (predict* or prognos* or risk factor*):ti

#85 model*

#86 (significant* AND (association* or relation* or predict* or prognos* or risk factor*))

#87 predict* value of test*

#88 progress*

#89 (prognostic index or prognostic model*)

#90 (predict* AND (outcome* or curve* or angle* or Cobb))

#91 regression

#92 (Fisher* AND exact)

#93 (regression analys* or logistic regression)

#94 Multiple logistic regression model*

#95 multivari*

#96 Cox regression*

#97 ((multivaria* or performance or cox or proportional hazards) AND (model or models))

#98 regression tree*

#99 Kaplan-Meier Estimate

#100 Risk assessment*

#101 risk ratio*

#102 Odds ratio*

#103 hazard ratio*

#104 likelihood ratio*

#105 positive likelihood ratio*

#106 negative likelihood ratio*

#107 sensitivit*

#108 specificit*

#109 (receiver operating characteristic* or ROC)

#110 (recalibration or receiver operating curve or roc)

#111 (scatter diagram* or scatter plot* or covariance decomposition or youden index)

#112 (area under curve or AUC or bootstrapping or Brier Score or "c index" or c-index)

#113 (calibration or CCR or concordance index or correct classification rate or cross validation)

#114 ("D statistic" or D-statistic)

#115 (Murphy's decomposition or Nagelkerke* or negative predictive value or npv or net reclassification improvement or nomogram*)

#116 (positive predict* value* or PPV)

#117 (negative predict* value* or NPV)

#118 machine learning model*

#119 cluster analys*

#120 Discriminant analysis

#121 (decision curve analysis or discrimination or external validation)

#122 ("goodness of fit" or Hosmer-Lemeshow test or internal validation)

#123 (misclassification AND (probability or rate))

#124 {OR #84-#123}

#125 #5 and #70 and #83 and #124

Web of Science (n=565)

TOPIC 1: TS=((scolio* OR "spin* curvature") AND (idiopathic) AND (teen* OR adolescen* OR youth OR youths OR "young people" OR "young adult*"))

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

TOPIC 2: TS=(((radiograph* OR clinical OR demograph*) NEAR/3 (indicat* OR predict* OR parameter* OR factor*)) OR (curve* NEAR/3 (angle* OR magnitude* OR severity OR thoracic OR location OR thoracolumbar OR thoraco-lumbar OR lumbar OR direction* OR type* OR mild OR moderate OR severe OR pattern* OR Lenke)) OR "Cobb angle*" OR (lateral NEAR/3 (curve* OR curvature* OR deviation*)) OR ((Apical OR Apex) NEAR/3 (level* OR "vertebra* rotation*" OR location* OR translation*)) OR AVR OR "axial rotation*" OR "axial rotation*" OR "coronal balance" OR decompensation* OR "Rib* vertebra* angle*" OR "coronal imbalance" OR "frontal imbalance" OR "radiograph* imbalance" OR "rib hump" OR "rib prominence" OR "shoulder asymmetry" OR "height velocity" OR "leg length discrepanc*" OR "spin* growth velocity" OR "growing index" OR "growth index" OR osteopenia OR "metabolic bone disease*" OR "bone mineral densit*" OR BMD OR "bone quality" OR "bone densit*" OR "bone stiffness" OR "forward bend*" OR "surface topograph*" OR "Plumb line*" OR Scoliomet* OR inclinomet* OR "Moire topography" OR hypermobility OR "spin* flexibilit*" OR "spin* movement*" OR "spin* morpholog*" OR "3D spin* shape*" OR "kyphosis angle*" OR kyphotic OR "lordosis angle*" OR lordotic OR "spin* movement*" OR "spinopelvic balance" OR "sagittal alignment*" OR "pelvi* incidence" OR "sacr* slope" OR age OR gender OR sex OR "sexual maturity" OR "skeletal maturity" OR Risser OR "Tri-radiate cartilage" OR "wrist x-ray" OR "Tanner stage*" OR Sanders OR menarche OR premenarche OR (wedg* NEAR/3 vertebra*) OR "plane of maximal deformit*")

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

TOPIC 3: TS=(progression OR (Cobb NEAR/3 (increase* OR change* OR difference*)) OR "curve angle change*" OR "curve deterioration*" OR "progressive adolescent idiopathic scoliosis" OR "progressive AIS" OR "brac* prescription*" OR "surgery* prescription*")

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

TOPIC 4: TI=(predict* OR prognos* OR "risk factor*") OR TS=(model* OR (significant* NEAR/6 (association* OR relation* OR predict* OR prognos* OR "risk factor*")) OR "predict* value of test*" OR progress* OR "prognostic index" OR "prognostic model*" OR (predict* NEAR/4 (outcome* OR curve* OR angle* OR Cobb)) OR regression OR (Fisher* NEAR exact) OR multivari* OR "Kaplan-Meier Estimate" OR "Risk assessment*" OR "risk ratio*" OR "Odds ratio*" OR "hazard ratio*" OR "likelihood ratio*" OR "positive likelihood ratio*" OR "negative likelihood ratio*" OR sensitivit* OR specificit* OR "receiver operating characteristic*" OR ROC OR recalibration OR "receiver operating curve" OR "scatter diagram*" OR "scatter plot*" OR "covariance decomposition" OR "youden index" OR "area under curve" OR AUC OR bootstrapping OR "Brier Score" OR "c index" OR "c-index" OR calibration OR CCR OR "concordance index" OR "correct classification rate" OR "cross validation" OR "D statistic" OR "Murphy's decomposition" OR

Nagelkerke* OR "negative predictive value" OR npv OR "net reclassification improvement" OR nomogram* OR "positive predict* value*" OR PPV OR "negative predict* value*" OR NPV OR "machine learning model*" OR "cluster analys*" OR "Discriminant analysis")

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

TOPIC 5: #1 AND #2 AND #3 AND #4

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

CINAHL (n=319)

Query	Limiters/Expanders
S15	S5 AND S8 AND S11 AND S14
S14	S12 OR S13
S13	(MH "Discriminant Analysis")
S12	TI ((predict* OR prognos* OR "risk factor*")) OR ((model* OR (significant* n6 (association* OR relation* OR predict* OR prognos* OR "risk factor*")) OR "predict* value of test*" OR progress* OR "prognostic index" OR "prognostic model*" OR (predict* n4 (outcome* OR curve* OR angle* OR Cobb)) OR regression OR (Fisher* n exact) OR multivari* OR "Kaplan-Meier Estimate" OR "Risk assessment*" OR "risk ratio*" OR "Odds ratio*" OR "hazard ratio*" OR "likelihood ratio*" OR "positive likelihood ratio*" OR "negative likelihood ratio*" OR sensitivit* OR specificit* OR "receiver operating characteristic*" OR ROC OR recalibration OR "receiver operating curve" OR "scatter diagram*" OR "scatter plot*" OR "covariance decomposition" OR "youden index" OR "area under curve" OR AUC OR bootstrapping OR "Brier Score" OR "c index" OR "c-index" OR calibration OR CCR OR "concordance index" OR "correct classification rate" OR "cross validation" OR "D statistic" OR "Murphy's decomposition" OR Nagelkerke* OR "negative predictive value" OR npv OR "net reclassification improvement" OR nomogram* OR "positive predict* value*" OR PPV OR "negative predict* value*" OR NPV OR "machine learning model*" OR "cluster analys*" OR "Discriminant analysis"))
S11	S9 OR S10
S10	(MH "Disease Progression")
S9	(progression OR (Cobb n3 (increase* OR change* OR difference*)) OR "curve angle change*" OR "curve deterioration*" OR "progressive adolescent idiopathic scoliosis" OR "progressive AIS" OR "brac* prescription*" OR "surgery* prescription*")
S8	S6 OR S7
S7	(MH "Bone Diseases, Metabolic+")
S6	(((radiograph* OR clinical OR demograph*) n3 (indicat* OR predict* OR parameter* OR factor*)) OR (curve* n3 (angle* OR magnitude* OR severity OR thoracic OR location OR thoracolumbar OR thoraco-lumbar OR lumbar OR direction* OR type* OR mild OR moderate OR severe OR pattern* OR Lenke)) OR "Cobb angle*" OR (lateral n3 (curve* OR curvature* OR deviation*)) OR ((Apical OR Apex) n3 (level* OR "vertebra* rotation*" OR location* OR translation*)) OR AVR OR "axial rotation*" OR "axial rotation*" OR "coronal balance" OR decompensation* OR "Rib* vertebra* angle*" OR "coronal imbalance" OR "frontal imbalance" OR "radiograph* imbalance" OR "rib hump" OR "rib prominence" OR "shoulder asymmetry" OR "height velocity" OR "leg length discrepanc*" OR "spin* growth velocity" OR "growing index" OR "growth index" OR osteopenia OR "metabolic bone disease*" OR "bone mineral densit*" OR BMD OR "bone quality" OR "bone densit*" OR "bone stiffness" OR "forward bend*" OR "surface topograph*" OR "Plumb line*" OR Scoliomet* OR inclinomet* OR "Moire topography" OR hypermobility OR "spin* flexibilit*" OR "spin* movement*" OR "spin* morpholog*" OR "3D spin* shape*" OR "kyphosis angle*" OR kyphotic OR "lordosis angle*" OR lordotic OR "spin* movement*" OR "spinopelvic balance" OR "sagittal alignment*" OR "pelvi* incidence" OR "sacr* slope" OR age OR gender OR sex OR "sexual maturity" OR "skeletal maturity" OR Risser OR "Tri-radiate cartilage" OR "wrist x-ray" OR "Tanner stage*" OR Sanders OR menarche OR premenarche OR (wedg* n3 vertebra*) OR "plane of maximal deformit*")
S5	((S1 OR S2) AND S3 AND S4) OR (MH "Scoliosis, Idiopathic, Adolescent")
S4	(teen* or adolescen* or youth or youths or young people or young adult*)
S3	idiopathic
S2	(scolio* OR "spin* curvature")
S1	(MH "Spinal Curvatures+") OR (MH "Scoliosis+")

Appendix 3.2 List of Excluded Articles with the Reason of Exclusion

Reasons for exclusion

1-Congenital, neuromuscular, syndrome related, and secondary reasons of scoliosis

2-Using only specialized parameter to predict the curve progression such as laboratory test results including level of enzymes or hormones, brain-function tests, genetic-related tests or analysis, electromyography, exercise

3-Using only non-radiographic imaging methods to assess curve progression such as in vitro studies, engineering methods (simulations, finite element method, and machine learning methods), magnetic resonance imaging (MRI), Computed tomography (CT), and questionnaires,

4-Having had scoliosis surgery at baseline

5-Samples less than 10 participants, case reports, conference proceedings, commentary and opinion letters, and reviews,

6-Non-English papers

7-Non-human subjects

8-Non AIS

9- The Mean±SD for age was more or less than 10 to 18 years old

10- The Mean±SD for the initial Cobb angle was < 10 degree

11-Study without follow-up

12-No radiographic/ultrasound follow-up of spine deformity

13-No report on prediction of curve progression

	Excluded Reference	Reason for Exclusion
1.	Lam, T.P., et al., *Vitamin D level and its correlation with bone mineral density in girls with adolescent idiopathic scoliosis (AIS).* Osteoporosis International, 2013. **24**(SUPPL. 4): p. S640.	5
2.	Carr, W.A., et al., *Treatment of idiopathic scoliosis in the Milwaukee brace. Long-term results.* Journal of Bone and Joint Surgery - Series A, 1980. **62**(4): p. 599-612.	13
3.	Kelly, J.J., et al., *Treatment of adolescent idiopathic scoliosis and evaluation of the adolescent patient.* Current Orthopaedic Practice, 2018. **29**(5): p. 424-429.	5
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Appendix 3.3 The Quality Appraisal Tailored for each Domain of the QUIPS Tool

Domains of the Quality Appraisal	Description of each domain
	Key Characteristics: Age, gender, curve Severity, curve type, skeletal maturity, and menarche,
1. Study Participation	Must describe key characteristics in population. (Complete score if 4+ of 6, partial if 2 of 6, 1 is no i.e. not enough)
	Must specify the recruitment type (consecutive, randomized, non-randomized) and the source of population (e.g.: database search), partial if only one
	Must describe time from beginning of recruitment for the study to end of recruitment in body of the article. No partial.
	Must either mention hospital/center in body of text, or for single center, have single address in contacts. No partial.
	Must include both inclusion and exclusion. Partial if only one. NOTE: must mention diagnosis, age, sex, in their criteria plus mention Surgery excluded.
	if <10 patients participated in the study per predictor considered, No.
	Must describe 4/6 key characteristics. Partial if 2/6
	Summary Study participation: The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome:
2. Study Attrition	**Key Characteristics: Age, gender, radiographic baseline: curve Severity, curve type, skeletal maturity, and menarche,**
	Must describe if any participants lost to follow up. If no attrition exists, then boxes are N/A
	If the participants lost to follow up, any attempts for follow-up must be described. No partial
	Must give one reason for the participants lost to follow up. No partial
	Must describe 2/6 characteristics of the participants lost to follow up
	If lost to follow up must account for 2/6 characteristics
	Study Attrition Summary: Loss to follow-up (baseline sample to study population analyzed) is not associated with key characteristics sufficient to limit potential bias to the observed relationship between PF and outcome:
3. Prognostic Factor Measurement: demographic	**Methods and Setting: Surgeon/researcher/rater/reader/reviewer/ clinician, Hospital/center**

factors (age, gender, etc.), radiographic factors (Cobb angle, Risser, sign etc.), bone quality, treatment (observation, bracing)	The PF must be described clearly (e.g., the Cobb method, the bone quality, skeletal maturity (Risser), curve type (Lenke, King) or cite a paper which described the methods clearly. No if only mentioned cobb method, Risser sign etc. NOTE: give partial if only good definition of some of the predictors studied.
	Must mention validity and reliability measures if multiple readers (surgeons/researchers), or if blinded. If a researcher did the measurements, his/her experience required). Partial if only 1/2 reliability measures. NOTE: Validity is supported by Citation to validity study or correlations with measurement gold standard or another measurement previously validated for the same goal.
	Need a justification for the choice of cut-off selected a priori. Could cite a paper to justify use of a cutoff.
	Must provide the description of the place (hospital, center), and the researcher…, If one described only, partial. NOTE: for self-reported variable we do not need to have rater information.
	At least 75% of the participants must have the data for PF (mark down if less than 75% had) NOTE: unsure if not reported.
	Must describe the methods used for the missing data (replaced by mean of the data, etc.) If no missing data, N/A
	PF Measurement Summary: PF is adequately measured in study participants to sufficiently limit potential bias.
4. Outcome Measurement: curve progression	**Methods and Setting: Surgeon/researcher/rater/reader/reviewer/ clinician, Hospital/center**
	Must define curve progression (e.g. curve change >6, etc.) / cite a paper that explained it clearly, must mention the method used to measure the curve progression (Cobb method), must mention the duration of the follow-ups to measure the curve progression if 1/3 , partial
	Need also validity data. Reliability measures if multiple readers (surgeons/researchers), or if blinded. If a researcher did the measurements, his/her experience required). Partial if only one of validity or reliability of measures provided.
	Must provide the description of the place (hospital, center), and the researcher, etc. If one described only, partial.
	Outcome Measurement Summary: Outcome of interest is adequately measured in study participants to sufficiently limit potential bias.
5. Study Confounding	**Key Confounders: Age, radiographic baseline: Curve Severity, curve type, skeletal maturity, gender, treatment (brace, observation) and menarche if not as the "PF"**
	Must mention 4/7 of the important confounders measured. If 3/7 measured, partial NOTE: Give yes reported adequately if recruited only one level or the confounders.
	Must clearly define the important confounders listed. If 3/7 measured, partial
	Must mention the reliable method of measurements for the curve type (Lenke, King) and skeletal maturity (Risser, sanders, tanner). If other methods without demonstrated reliability was used for either curve type/skeletal maturity, partial. if either blinded/multiple readers' reliability of X-ray information mentioned, partial
	Must provide the description of the place (hospital, center) and the surgeon. If one described only, partial.
	Must provide methods of imputation if certain patients missing data. If no missing data, N/A.

	For listed confounders, must either only include patients of those confounders, or separate patients in method.
	For listed confounders, if not accounted in study design, must analyze patients of each confounder separately.
	Study Confounding Summary: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome.
6. Statistical Analysis and Reporting	**Key statistics: name of analysis, the significant threshold, for multivariable analyses state the variable selection method**
	Must have sufficient statistics, partial if report only 1/3 for the listed statistics
	The model (regression) must provide appropriate conceptual framework. Otherwise, N/A.
	The developed model must have the appropriate statistics. Otherwise, N/A.
	If in methods describe reporting of data related to curve progression must report the results
	Statistical Analysis/Presentation Summary: The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.

Note: QUIPS is Quality in Prognostic Studies, red cells are the most important, yellow is moderate, and green is less critical. To determine the overall score for each article, the questions under each domain were prioritized based on their importance (the questions highlighted as red, yellow, and green based on the importance, respectively). Articles that were missing the information about those questions achieved lower scores.

Appendix 3.4 Summary of the Parameters for the Articles with Progression Criteria ≥5°

Predictive factors	Authors	Parameters	Non-pre	Pre	Univariate analysis	Multivariate analysis	ROB	Follow-up interval
Age (years)	Aulisa, et al. [1]	Age (mean ±SD=11.8 ± 0.5)	×		Spearman correlation=0.01, P=NS		M	L
	Aulisa, et al. [2]	Age at initial (mean=12.6)		✓		Reg, B=0.87, SE=0.25, R^2=0.48, P=0.001	M	S
	Bohl, et al. [3]	Age (mean=12.9, range=10-15)	×		Chi square, P=0.256		M	L
	Bunnell [4]	Age at initial (mean=12), Age at menarche (mean=12.5)	×	✓	Age at diagnosis reported to be a prognostic factor		M	S
	Danielsson, et al. [5]	Age at initial Age at maturity	× ×		Mann-Whitney, U test, P=0.82, U test, P=0.1		M	L
	Guo, et al. [6]	Initial Age in three bracing groups (SpineCor (pro during treatment) SpineCor (pro beyond maturity) (10-14) Rigid (pro beyond maturity),	×		Test: Unknown: SpineCor (pro during treatment), P=0.664, SpineCor (pro beyond maturity), P=0.616 Rigid (pro beyond maturity), P=0.322		M	L
	Guo, et al. [7]	Age (mean=pro:12-non-pro:13)	×		T-tests, P>0.05		M	L
	Hung [8]	initial age (range=11-13 yr)		✓	Model=SN=76% (95% CI, 69%-83%), SP=70% (95% CI, 62%-77%), (younger age at the time of diagnosis, higher risk)	Log reg, B=0.72, OR-=2.1 (95% CI,1.1-4), P=0.03, AUC=0.8 (95% CI, 0.75-0.85);	L	S
	Karol [9]	Age (range=10-16)	×		Fisher's exact test (two-tailed), P> 0.05		M	L
	Karol, et al. [10]	Age: categories=8-10, 11-12, 13-14, ≥15, age total (younger age, 8-10 to be as a high risk group)		✓	Kolmogorov-Smirnov test, P< 0.005		M	S
	Katz, et al.[11]	Age (mean=Pro: 12.6, Non-pro: 12.7)	×		T-test, P=0.68		M	L
	Konieczny, et al. [12]	Age at menarche (mean ±SD =12.3±0.2)	×		No correlation, P>0.05		H	S
	Kuroki, et al. [13]	Age (mean =12, range=10-14)	×		Difference test=NS		M	L

	LAM, et al. [14]	Age (≤13, >13)		✓	Chi, P<0.001, SN=0.874, SP=0.665	Log reg= -1.756, AOR=5.79 (95% CI,3.02-11.1), AUC=0.831 (95% CI, 0.785-0.877)	M	L
	Lara[15]	Age at initial (mean ±SD=14.1 ±1.8 (range, 10.0-18.7)	×			Log reg, P=0.342,	L	L
	LeBlanc [16]	Age (mean=14, range=9-20)	×		Discriminant analysis, P=0.1662		M	S
	Mao, et al. [17]	Age at initial visit, mean ±SD =Pro: 12.0 ± 1.1 and non-pro: 12.4± 1.0 (10-14) and Age at menarche, mean ±SD =Pro: 12.3 ± 1.1 and non-pro: 12.3 ± 1.0 (10-14)	× ×		T-test, P=0.132 T-test, P=0.974	Reg, B=-0.555, R^2= 0.043, OR=1.742 (age at initial visit)	L	L
	Nault, et al. [18]	Age (Pro: mean=13.3 (range=11-15), Non-pro: mean=12.5 (range=10-14))	×		T-test, P=0.49		M	L
	Nault, et al. [19]	Age (mean ±SD =Pro and Non-pro: 12.6 ± 1.2)	×		T-test, P=0.8		M	L
	O'Neill, et al. [20]	Age at initial (mean=12.8, range=11-17)	×		Cor Coef (r)=−0.118		L	L
	Ohrt-Nissen, et al. [21]	Age (mean ±SD =13.3±1.5)		✓*	Unpaired T-test=P <0.001, reg, B=-2.86(95% CI, -4.44- -1.28), P< <0.001	Reg, B= flexibility: -0.21 (-0.32 to -0.10), P<0.001, R2= 0.23; Premenarchal: 5.95 (0.44 to 11.54), P=0.035, R2= 0.39; Cobb (degrees): -0.24 (-0.77 to 0.29), P=0.366, R^2= 0.40; (all significant variables); age: -1.16 (-3.0 to 0.67), P=0.209, R^2=0.42	L	L
	Peterson, et al. [22]	Age (≤13, >13) (younger ages, ≤13)		✓*	SN, SP= 81%; +LR=82%, -LR= 80%;	B= 0.83, SE=0.67, P= 0.22	M	S
	Shi, et al. [23]	Age at initial visit (mean ±SD =12.1±1.2, range= 10-14), Age at menarche (mean ±SD	× ×		Chi square, P= 0.496, Chi square, P= 0.517		M	L

		=12.7±1.1, range=10-14)						
	Sun, et al. [24]	Age (mean ±SD: Pro=12.8±1.5, Non-pro=13.1±1.3) and Age at menarche (mean ±SD: Pro=12.8±1.2, Non-pro=12.6±1.2)	× ×		t- test, P=0.383 t- test, P= 0.521		L	S
	Sun, et al. [25]	Age at initial Age at menarche (years)	× ×		Chi square, P=0.118, SN=0.59, SP=0.57, ACC=0.57, OR=1.95, +LR=1.39, -LR=0.70, +PV=0.24, -PV=0.85 Chi, P=NS		M	L
	Vijvermans, et al. [26]	Age at initial Age at bracing Age at menarche	× ×	✓	Age at menarche and bracing did not significantly differ between pro and non pro	Age at initial: Reg, B=–0.160, SE=0.08, P=0.048, Age at bracing: Reg, B=0.003, SE= 0.137, P=0.98	M	L
	Weiss [27]	Age 10-15		✓	13 to 15: 23.8% progression rate between cobb 20-29 deg		M	L
	Wu, et al. [28]	Initial age (12.3, 8-12)	×		T-test, P=NS		M	S
	Yamauchi, et al. [29]	Age (Mean=12-13)		✓	Cor Coef=-0.42, (younger age (12 years at higher risk)	Partial Cor= -0.11	M	L
	Yrjonen, et al. [30]	Age (mean: 13.1-14.8)	×		T-test, P>0.05		M	L
	Zhang, et al. [31]	Age (≤13, >13)	×			Log reg= NS	M	L
	Zhu, et al. [32]	Initial age (13.7±1.8, 10-15)	×		P=0.1, OR= 1.02 (95%CI, 0.76-1.38)	Reg, B=0.03	M	S
Gender	Aulisa, et al. [2]	Gender	×			Reg, B=0.85, SE=1.11, R^2=0.48, P=0.44	M	S
	Bohl, et al. [3]	Gender (male)		✓	Chi= 0.01, SN=29%, SP=100%, ACC=65%, -LR=71%, +PV= 100%, -PV=59% (Male was considered as positive variable)		M	L
	Bunnell [4]	Gender		✓	Pro: M=53% F=35%,		M	S

					(when Cobb > 30 deg, F=M)			
	Davis, et al. [33]	Gender	×		Chi, P= 0.17		L	L
	Lara, et al. [15]	Gender	×		Bivariate analysis, P= 0.53	OR=1.54, (95% CI, 0.75-3.19), P=0.24	L	L
	Nault, et al. [19]	Gender	×		SN=10%, SP=89%, ACC=49%, OR=0.94, +LR=0.95, -LR=1, +PV= 0.5, -PV=0.48, (Male was considered as positive variable)		M	L
	Nault, et al. [18]	Gender	×		SN=17%, SP= 91%, ACC= 61%, OR=2.13, +LR= 1.94, -LR= 0.90, +PV=0.56, -PV=0.62 (Male was considered as positive variable)		M	L
	O'Neill, et al. [20]	Gender (male)		✓	Pearson's product moment=0.15	Reg, B=0.14, R^2=18%	L	L
	Ohrt-Nissen, et al. [21]	Gender	×		SN=3%, SP=93%, ACC=41%, OR=0.36, +LR=0.37, -LR= 1.05, +PV=33.33%, -PV=41.67% (Male was considered as positive variable)		L	L
	Vijvermans, et al. [26]	Gender	×			Reg, B= 0.46, SE, 0.43, P=0.28	M	L
	Wu, et al. [28]	Gender (male)		✓	5, ≥ 10: M=60%, 26%,5, ≥ 10: F=30%, 10%		M	S
	Yrjonen, et al. [30]	Gender (male)		✓	SN=40%, SP=47%, ACC=45%, OR=0.59, +LR= 0.75, -LR= 1.27, +PV= 18.18%, -PV= 72.73%, (Male was considered as positive variable)		M	L
	Zhu, et al. [32]	Gender	×		OR= 2.45 (95% CI, 0.47-7.48)	Log reg, B=0.89	M	S
Menarche Status	Bunnell [4]	Menarche status (premenarche)		✓	Pre menarche, Pro=53%, Non-Pro= 47%, Post menarche, Pro=11%, Non-Pro=89%		M	S
	Danielsson, et al. [5]	Premenarche at inclusion		✓	Chi square P=0.049		M	L

	Guo, et al. [6]	Menarche in three bracing groups (SpineCor, Rigid (Pro beyond maturity), SpineCor (pro beyond maturity)	×		Chi square, P= 0.675, 0.872, 0.178,		M	L
	Hung [8]	Menarche status (premenarche as high risk)		✓	SN=76% (95% CI, 69%-83%), SP=70% (95% CI, 62%-77%)	Log reg, B=0.91, OR=2.5 (95% CI, 1.00-6.00), P=0.04, AUC=0.8 (95% CI, 0.75-0.85);	L	S
	Katz, et al. [11]	Menarche status	×		Chi square, P=0.24, SN=28%, SP=55%, ACC=45%, OR=0.47, +LR=+0.62, -LR=1.31, +PV=27.77%, -PV=55.17% (post menarche was considered as positive test)		M	L
	LAM, et al. [21]	Menarche status (NM)		✓	Chi square, P< 0.001, SN=84%, SP=66%, AOR= 8.58 (95% CI, 3.86-19.06)	Log reg, B=2.15, AUC=0.83 (95% CI, 0.78-0.87),	M	L
	Ohrt-Nissen, et al. [21]	Menarche status (premenarche as high risk)		✓	Chi square, P<0.001, SN=47%, SP=29%, ACC=38%, OR=14.08 (95% CI, 2.87-95.26), P=0.002, +LR=0.65, -LR= 1.85, +PV= 42.86%, -LR=32%, (post menarche was considered as positive test) Reg, B=8.88 (95% CI, 3.92- 13.83), P< 0.001	Reg, B= 5.95 (95% CI, 0.44-11.54), R^2= 0.39, P=0.035	L	L
	Peterson, et al. [22]	Menarche status (premenarche as high risk)		✓*	Significant association with progression	Log reg, B=0.65, SE=0.69, P=0.34 (menarche not significant so didn't put not into the model)	M	S
	Shi, et al. [23]	Menarche status	×		Chi square, P=0.51		M	L
	Sun, et al. [24]	Menarche status (premenarche as high risk)		✓	SN=74.5%, SP=64.7%,	OR=6.67 (95% CI, 1.31-33.8), P=0.022	L	S

	Sun, et al. [25]	Menarche status (premenarche as high risk)		✓	Chi square, P<0.001, Fisher's exact, P< 0.001, SN=51%, SP=23%, ACC=27%, OR=0.21, +LR=0.53, -LR=2.52, +PV=0.11, -PV=0.63, (post menarche was considered as positive test)		M	L
	Zhang, et al. [31]	Menarche status	×			NS (not into the log reg model)	M	L
Risser Sign	Aulisa, et al. [1]	Risser sign (0 to 2)	×		Spearman= 0.07, P=NS		M	L
	Bohl, et al. [3]	Risser sign (0-2)	×		Chi square=P=0.10		M	L
	Bunnell [4]	Risser (0-4) (lower showed higher risk)		✓	Risser 0: Pro=68%, Non-pro=32%, Risser 1,2: Pro=52%, Non-pro: 48%, Risser 3,4: Pro=18%, Non-pro: 82%		M	S
	D'Amato, et al. [34]	Risser sign (≤1) (higher risk)		✓	Chi square=P=0.05 (Risser=2 associated with non-progression)		M	S
	Danielsson, et al. [5]	Risser sign (0-4)	×		Mann-Whitney nonparametric U test, P=0.25 (NS)		M	L
	Davis, et al. [33]	Risser sign (0, 1)		✓	Chi square=0.012 (Risser 0 associated with higher progression)		L	L
	Gepstein, et al. [35]	Charleston: (TH, TL, L+, Risser 0-2, (TH, TL, L)+ Risser 3-4, Boston: (TH, TL, L)+ Risser 0-2, (TH, TL, L)+ Risser 3-4,	×		Chi square, P= (0.79, NM ,0.75), (0.57, 0.51, 0.78); (0.79, NM ,0.75), (0.57, 0.51, 0.78), Risser (0-2) and (3–4) were not associated with success rate of both methods		M	L
	Guo, et al. [6]	Risser sign (0-2) in two bracing groups SpinCor (progressed during treatment, progressed beyond skeletal maturity), rigid (progressed beyond skeletal maturity)	×		Chi, square P=0.63, 0.09, and 0.36		M	L

	Guo, et al. [7]	Risser sign (0, 1, 2)		✓	T- tests, P< 0.05 (<1 was at higher risk versus ⩾1)		M	L
	Hung [8]	Lower Risser (0-1)		✓	Model=SN=76% (95% CI, 69%-83%), SP=70% (95% CI, 62%-77%),	Log Reg, B= 1.54, OR= 4.7 (95% CI, 2.2-9.9), P<0.001, AUC= 0.8 (95% CI, 0.75-0.85);	L	S
	Karol [9]	Risser sign (≤2)		✓	Fisher's exact test, P< 0.05		M	L
	Karol, et al. [10]	Risser (earlier stage 0, 1)		✓	Kolmogorov-Smirnov test= P< 0.002		M	S
	Karol, et al. [36]	Risser 0, 1, 2		✓	Chi square P<0.0001, 0.51, 0.51 (Risser 0 at higher risk)		M	S
	Katz, et al. [11]	Risser sign (0-2)	×		Chi square P= 0.30		M	L
	Katz, et al. [37]	Risser 0, 1, 2		✓	Risser stage 0 are at greatest risk for progression		M	L
	Kuroki, et al. [13]	Risser sign (0-2)	×		Chi square P=NS		M	L
	Lara, et al. [15]	Risser (0-5)+TRC (open/close)	×		Chi square P=0.141		L	L
	Mao, et al. [17]	Risser sign (0-2)	×		T-test, P= 0.426		L	L
	Nault, et al. [18]	Risser 0+open TRC, Risser 0+ closed TRC, Risser 1	×		Risser 0+open TRC, Pro=20%, Non-pro=16%, Risser 0+close TRC Pro=13%, Non-pro= 23%, Risser 1, Pro=7%, Non-pro21%		M	L
	O'Neill, et al. [20]	Lower Risser sign		✓	Pearson's product moment= −0.262, ($p < 0.05$) (n=276 patients)	Reg, B= −0.241, R^2=18%, P< 0.01	L	L
	Pasquini, et al. [38]	Risser (0-2)	×		Chi square P=0.643		M	U
	Peterson, et al. [22]	Risser sign (0, 1)		✓		Log reg, B=2.28, SE=0.69, P<0.001	M	S
	Sun, et al. [24]	Risser sign (<2)	×		T-test, P=0.054		L	S
	Sun, et al. [25]	Risser sign (0-1)		✓	Chi square, P<0.05, SN=51%, SP=64%, ACC=62%, OR=1.94, +LR= 1.45, -LR=0.75, +PV= 0.25, -PV= 0.85, (Risser 0-1 considered as positive test)		M	L

	Thompson, et al. [39]	Risser 0+TH, Risser 0+L, Risser 1,2+Th, R1,2+L	×		Chi square, P=0.21, 0.34		M	U
	Vijvermans, et al. [26]	Risser sign (≤2)		✓	Chi square, P <0.001	R0=Log reg, B= -0.39, SE=0.16, R^2=4.21%, P=0.017	M	L
	Yamauchi, et al. [29]	Risser sign (NM)		✓	Correlation: -0.47 (Low grades at higher risk) Partial correlation: -0.28		M	L
	Zhang, et al.[31]	Risser sign (≤2)		✓	OR=6.137	Log reg, B=1.814, SE=0.76, P=0.01	M	L
	Zhu, et al. [32]	Risser sign (0 or 1)		✓	Chi square, P=0.02, SN=51.20, SP-88.50%, OR=7.51 (95% CI, 1.27-24.43)	Log reg, B=0.82, AUC=1.2	M	S
Triradiate Cartilage (TRC)	Karol, et al. [36]	TRC, open (higher risk), closed+ Risser 0		✓	Open: Pro=13%, Non-pro=24%, close: Pro=23%, Non-pro=45%		M	S
	Katz, et al.[37]	Triradiate cartilage (TRC) closed open (higher risk)		✓	T- test, P= 0.004 (open)		M	L
	Ryan, et al. [40]	TRC, closed, open (higher risk)		✓	Chi square, P= 0.027 SN=68%, SP= 68%, OR=4.45, +LR= 2.09, -LR= 0.47, +PV= 53.57%, -PV= 79.41%, (TRC open considered as positive)		M	L
Body Mass Index (BMI) (kg/m^2)	Bunnell [4]	Height-weight ratio (NM)	×		Not significant		M	S
	Goodbody, et al. [41]	High-age group (BMI [85th percentile), mid-BMI group (BMI 20th–85th percentile), low-BMI group (BMI<20th percentile)		✓	High: OR=2.6 , P=0.02 , Low BMI: OR=3.2 , P< 0.01 (as compared to the mid-BMI group)	High: OR=1.2, P=0.71, Low: OR=2.8, P=0.03,	M	L
	Konieczny, et al. [12]	Body mass index (BMI) (at skeletal maturity) mean±SD= 20.9± 0.38	×		Pearson correlation, P=0.14		H	S
	Sun, et al. [24]	BMI, mean±SD= Pro: 16.9±1.5, Non-pro: 16.8±1.4	×		T-test, P= 0.90		L	S
	Zaina, et al. [42]	BMI, mean±SD= 27.2 ± 2.5, ≥85th percentile		✓	Correlation Coef=0.16, P=0.02		L	U

Body Morphology	LeBlanc [16]	Body shape/compositions (List provided in a footnote)		✓	Discriminant analysis, P< 0.0001-0.028, ACC=84%		M	S
Weight (kg)	O'Neill, et al. [20]	Overweight		✓	T-test, P< 0.01, Pearson's product moment= 0.203	Reg, B=0.153, R^2= 18%	L	L
	Sun, et al. [24]	Weight, mean±SD= Pro: 40.9±6, Non-pro: 41.4±5.5	×		T-Test, P=0.74		L	S
	Zaina, et al. [42]	Normal weight, mean±SD= 49 ± 8 and overweight BMI ≥85th percentile, 66 ± 11	×		Chi square, P=NS		L	U
	Zhu, et al. [32]	Weiht, mean±SD= Pro: 42.2±9.7 , Non-pro: 40.9±11.2	×		T-test, P=0.15		M	S
Height	Katz, et al.[11]	Peak height velocity ≥9, <9 cm/year)	×		Chi square, P=0.29, SN=58%, SP=59%, ACC=59%, OR=2.04, +LR= 1.43, -LR= 0.70, +PV=35%, -PV= 70.17% (Pre-PHV considered as positive test)		M	L
	LeBlanc [16]	Sitting height (mm), mean= Pro: 808.46, Non-pro: 823.06		✓	Discriminant analysis, P< 0.0001, 84%		M	S
	Mao, et al. [17]	Height at initial visit, Non-pro: 154.7 ± 7.2, Pro: 152.4 ± 7.8 (cm)	×		T- test, P=0.249		L	L
	Zhang, et al. [31]	Increasing velocity of standing height (≥30, <30), Increasing velocity of sitting height (mm/ year) ≥20, < 20	× ×			Log reg: P=NS Log reg: P=NS	M	L
Spinal Growth	Cheung, et al. [43]	Spinal Growth Velocity at start > 15 mm/year		✓	SN=79%, SP= 79%, +PV= 3.78, -PV= 0.26, correlation=0.40	Change in Cobb=1.177*ln (spinal growth velocity)	L	S
	Ryan, et al. [40]	Growth velocity cm/mo (range) 0.28 (0-1.2) with non-progression	×		T-test, P=0.14 (with non-progression or success rate)		M	L
	Wu, et al. [28]	Spinal growth in coronal and 3D, Maximal spinal length in coronal plane and 3D	× ×		High spinal growth velocity was not a clear cause for high incidence of progression.		M	S

					Spinal growth in coronal and 3D: Non-pro: (coronal: r = 0.0–0.38 and 3D: 0.09–0.43), Pro: (coronal: r = -0.64 to 0.59 and 3D: -0.52 to 0.01); Maximal spinal length in coronal plane and 3D: Non-pro: (coronal: r= 0.08–0.43, 3D:0.03–0.32), Pro: (coronal: 0.0–0.29, 3D: -0.07 to 0.2)			
	Zhang, et al. [31]	The spinal length increasing velocity (≥30, <30 mm/year)		✓		Log reg, B=1.808, SE= 0.77, P=0.02 OR=6.098 (higher length velocity higher risk)	M	L
Curve Flexibility	Kuroki, et al. [13]	Curve flexibility (upright Cobb vs hanging Cobb)	×		Chi square, P=NS		M	L
	Ohrt-Nissen, et al. [21]	Supine bending flexibility (lower flexibility higher progression)		✓	T- test, P<0.001, Reg, B= -0.22 (95% CI, -0.32- -0.11), P< 0.001	OR= 0.95 (95% CI, 0.9-0.98), P=0.013; Reg, AB= -0.21 (95%CI, -0.32- -0.1), R^2= 23% (for flexibility only, the overall R^2=42%) , P<0.001	L	L
Hip Parameters	LeBlanc [16]	Hip width, (mean, Pro=302.6, Non-pro=308.0 (mm)		✓	Discriminant analysis=0.0008, ACC=84%		M	S
	Ploumis, et al. [44]	Femoral head height difference (≤ 10, > 10 mm)	×		Chi, P>0.05		M	L
Cobb Angle (°)	Aulisa, et al. [1]	Initial Cobb, mean±SD=:29.30 ± 5.16, FU: 14.67 ± 7.56		✓	Kruskal-Wallis=111.902, P< 0.0001		M	L
	Aulisa, et al. [2]	Initial Cobb, mean±SD= 29.8 ± 7.5 and FU 17.1 ± 10.9		✓		Reg, B= -0.14, SE=0.04, R^2= 0.48, P=0.001	M	S
	Bohl, et al.[3]	Initial Cobb, range= 25-40	×		Chi square, P=0.31		M	L
	Bunnell [4]	Initial Cobb, mean (range)= 33 (10-49)		✓	Higher progression rate reported for cases with Cobb 40-50 (78%)		M	S
	D'Amato, et al. [34]	Cobb: 20-24; 25-34; 35-42 (> 35 high risk)		✓	Proportions: Pro :19%, Non-pro: 81%; Pro: 29%, Non-pro:		M	S

					71%; Pro: 37%, Non-pro: 63%			
	Danielsson, et al. [5]	Initial Cobb (range) 25-35	×		Mann-Whitney nonparametric U test, P=0.1 (NS)		M	L
	Davis, et al. [33]	Cobb >35 or < 35,	×		Chi square, P=0.95,		L	L
	Gepstein, et al. [35]	Charleston vs Boston success rates= Cobb < 25, 25-29, 30-39	×		Chi, P=0.73, 0.59, 0.62 (association with non-progression or brace success rate)		M	L
	Guo, et al.[6]	Primary Cobb 20–30 (in bracing groups as SpineCor (during treatment and beyond skeletal maturity), Rigid	×		Chi square, P=0.957,0.669; 1		M	L
	Guo, et al.[7]	Initial Cobb, mean±SD= Pro: 28.5 ± 6.4, Non-pro: 30.1 ± 5.1	×		T- test=NS		M	L
	Hung [8]	Initial Cobb (20-29, 30-39, ≥40) (A larger initial Cobb angle, higher risk)		✓	SN=76% (95% CI, 69%-83%), SP= 70% (95% CI, 62%-77%)	Log ref, B= 0.19, 1.56, 1.52; OR= 1.2 (95%CI, 0.6-2.6); 4.8 (95% CI, 1.9-11.9), P<0.01; 4.6 (95%CI, 1.3-15.9), P <0.017; AUC=0.8 (95%CI, 0.75-0.85)	L	S
	Karol, et al. [9]	Cobb (10-45)		✓	Fisher's exact test, P<0.05, Reported curves ≥30 at higher risk vs <30		M	L
	Karol, et al.[10]	Cobb (10-50) (larger curves higher risk) compared <25 Vs ≥25		✓	Chi, P=0.0147		M	S
	Katz, et al.[11]	Cobb angle (mean, Pro=39.9, Non-pro=39.2), Cobb ratio (thoracic Cobb/ lumbar Cobb, Mean, Pro, Non-pro=1.1)	× ×		T-test, P=0.35, T-test, P=0.77		M	L
	Kuroki, et al. [13]	Initial Cobb (20-29 vs 30-39)	×		Chi square, P=NS		M	L
	LAM, et al. [21]	Cobb (10 to 25, ≥26) (NM)		✓	Chi square, P= 0.17, SN=85%, SP=66%, AOR= 2.19 (95% CI, 1.22-3.91)	Log reg, B=0.782, AUC=0.83 (95%CI, 0.78-0.88), P=0.008	M	L
	Lara, et al. [15]	Initial Cobb, mean±SD=		✓		P=0.002, OR=1.03 (95% CI, 1.01- 1.04)	L	L

		28.01±13.46 (10-86)				(Larger curve magnitude at presentation)		
	Mao, et al. [17]	Cobb at initial visit (20-40)	×		T- test, P=0.263		L	L
	Nault, et al. [18]	Initial Cobb mean±SD= Pro: 23.4 ± 8.6, Non-pro: 21.3 ± 8.3	×		Comparison test (NM), P=0.2		M	L
	Nault, et al.[19]	Cobb angle at initial visit (11 to 40)	×		T- tests=0.99		M	L
	Ohrt-Nissen, et al. [21]	Initial Cobb mean±SD= Pro=34±4, Non-pro=33±4	×		T- test, P= 0.396; OR= 0.99 (95% CI, 0.83- 1.18), > 0.431; Reg, B= 0.19 (95% CI, -0.40-0.78), P=0.528,	Reg, B= -0.24 (95% CI, -0.77- 0.29), R^2= 0.40, P=0.366	L	L
	Pasquini, et al.[38]	Cobb (20-30 vs 30-40, (high risk))		✓	Chi square, P=0.022, SN=100%, SP=26%, ACC=31%, +LR= 1.35, -LR=0, +PV=9.80%, -PV= 100% (20-30 considered as positive)		M	U
	Peterson, et al. [22]	Initial Cobb angle (25 to 35)	×			Log reg, B= 0.37, SE=0.6, R^2=0.54	M	S
	Shi, et al. [23]	Initial Cobb, Cobb at brace weaning	×	✓	Chi square=, P= 0.95 Chi square, P= 0.033 (Cobb at brace weaning is significant)		M	L
	Sun, et al.[24]	Initial Cobb (31 to 40)		✓	T-test, P=0.047, Model, SN= 74.5%, SP=64.7%, +LR= 2.11, -LR= 1.54,	OR=6.73 (95% CI, 1.3-34.7), P=0.023	L	S
	Sun, et al.[25]	Curve magnitude >30, ≤30	×		Chi square, P=0.26, Cobb= SN= 67%, SP=45%, ACC=49%, OR= 1.65, +LR= 1.22, -LR= 0.73, +PV=0.22, -PV= 0.85 (>30 considered as positive)		M	L
	Trivedi and Thomson [45]	Cobb (< 30 vs 30-40)	×		T-test = P=0.23		M	L
	Vijvermans, et al. [26]	Initial Cobb (Mean: 29.51±6.71) (high Cobb)	×			Log reg, B= 0.03, SE= 0.023, P=0.203, R^2P= 1.17%	M	L

	Weiss [27]	Initial Cobb		✓	Greater Cobb showed more progressive curves		M	L
	Wu, et al. [28]	Initial Cobb Maximal Cobb angle		✓ ✓	Significantly different between Pro and Non-pro		M	S
	Yamauchi, et al. [29]	Cobb (20-45)		✓	Correlation, coef= -0.3, Partial correlation= -0.03	Reg, B=0.132	M	L
	Yrjonen, et al. [30]	Initial Cobb (mean range 33.1-32.4 in boys and girls)	×		T-test, P>0.05		M	L
	Zhang, et al. [31]	Cobb (≥35 (high risk), <35)		✓	OR=13.69	Log reg, B= 2.61, SE= 0.77, P=0.001	M	L
	Zhu, et al. [32]	Initial Cobb (40-50)	×		P=0.9, OR= 0.78 (95% CI, 0.59-1.02)	Reg, B= -0.25	M	S
Curve Pattern	Bohl, et al. [3]	Curve subtype (TH, TL/L, double)	×		Chi, P= 0.459		M	L
	Bunnell [4]	Curve pattern (TH, TL, L)		✓	TH: Pro=77%, Non-pro=23%; TL: Pro=67%, Non-pro=33%, L: Pro=30%, Non-pro=70%; Double: Pro=66%, Non-pro=34%		M	S
	D'Amato, et al.[34]	Curve type (TH, TL, L, double)		✓	TH: Pro=37%, Non-pro= 63%; TL: Pro=7%, Non-pro= 93%; L: Pro=6%, Non-pro= 94%; double: Pro=35%, Non-pro= 65% (TH and Double showed the highest rate of pro)		M	S
	Davis, et al. [33]	Curve classification (TH, TL/L, Double major)	×		Chi, P=0.31		L	L
	Fang, et al. [46]	Curve type (TH, TL, L, Double major)	×		F test, P=0.081		M	S
	Gepstein, et al.	TH, TL, L	×		Chi, P>0.05		M	L
	Guo, et al.[6]	Curve pattern in two bracing groups SpineCor (during treatment, beyond skeletal maturity), rigid	×		SpineCor, Chi=0.238, 0.626; Rigid= 0.828		M	L
	Hung [8]	Curve pattern (TH, TL, L, triple)	×		NS		L	S
	Karol [9]	King classification (1-5)	×		NS		M	L

	Katz, et al.[11]	Double curves (high risk) versus a single TH, or a L or TL		✓	Chi, P= significant		M	L
	Kuroki, et al.[13]	Curve pattern (TH, TL, L)	×		Chi, P=NS		M	L
	Lara, et al.[15]	Curve pattern (TH, L, TL, double TH, double L)	×		Fisher exact test, P=0.484		L	L
	Nault, et al.[18]	Curve type (TH, TL, L, double, triple)	×		NS		M	L
	Ohrt-Nissen, et al. [21]	Curve type (double, TH, TL, L)		✓	Curve type: Wilcoxon rank-sum test, P= 0.032,	Double: univariate reg, B= 9.2 (95%CI, -1.5-19.92), P=0.091; TH: 13.36 (95%CI, 4.2-22.52), P=0.005; TL: 6.29 (95% CI, -3.96- 16.5), P= 0.224; L (as reference)	L	L
	Shi, et al. [23]	Curve pattern (MT, TL/L, Double)	×		Chi, P= 0.321, 0.381, 0.822		M	L
	Sun, et al. [25]	Curve pattern (TH, TH+TL/L, TL/L)		✓	Chi square, P=0.044		M	L
	Sun, et al.[24]	Curve pattern (TH, TL, L)	×		SN=74.5%, SP=64.7%, OR= 11.25 (95% CI, 0.88-24.24), P=0.071		L	S
	Trivedi and Thomson [45]	Curve type (TH, TL+L)	×		Independent sample test, P= 1.00		M	L
	Vijvermans, et al.[26]	King classification (1-4)	×			Log reg, B= -0.028, SE=0.155, R^2P= 0.02%, P= 0.858	M	L
	Wu, et al.[28]	Curve pattern (double)	×		Double curves (Right TH-Left L) did not consistently progress in the same curve region (primary or minor)		M	S
	Yrjonen, et al.[30]	Curve pattern (TH, TL, L, double major)	×		curve pattern did not have statistical influence on the risk of progression (t -test, P > 0.05)		M	L
	Zhang, et al. [31]	Types of scoliosis (TH, double major)/ curve type (right or left)	×			Log reg=NS	M	L
	Zhu, et al. [32]	Curve pattern (TH, double, TL/L)	×		Chi, P=0.392		M	S

Sagittal Profile (°)	Bunnell [4]	Kyphosis Lordosis	× ×		Both are not prognostic		M	S
	Nault, et al.[18]	Kyphosis Lordosis	 ×	✓	Kyphosis, P=0.02 (S) (low values, higher risk) Lordosis, P=0.45 (NS)		M	L
	Peterson, et al.[22]	Kyphosis	×			Log reg, B= 0.37, SE=0.61, P=0.54 (NS)	M	S
Rib Vertebral Angle and Rib Hump	Katz, et al.[11]	Rib–vertebra angle- convex side [RVA-cx], Rib–vertebra angle - concave side [RVA-cv] Rib–vertebra angle difference [RVAD]	× × ×		T-test, P=0.11 T-test, P=0.75 T-test, P=0.21		M	L
	Peterson, et al.[22]	Rib hump	×			Log reg, B= -0.37, SE=0.83, P=0.66	M	S
	Yamauchi, et al. [29]	Rib-vertebral angle difference	×		Cor Coef=-0.17, Partial Cor Coef=-0.06		M	L
Pelvic Parameters	LeBlanc [16]	ASIS circumference (mm)		✓	Discriminant analysis, P=0.0039, ACC=84%		M	S
	Ploumis, et al.[44]	Iliac crest height difference		✓	Cor, Coef= 0.25, P<0.05		M	L
	Katz, et al.[11]	Lumbar pelvic relationship (LPR)		✓	T-test, p=0.1(S) (>12°)		M	L
	Guo, et al.[7]	Pelvic incidence (PI)	×		T- tests, P=NS		M	L
	Katz, et al.[11]	Pelvic tilt	×		T-test, P=0.88 (NS)		M	L
	Guo, et al.[7]	pelvic tilt (PT)		✓	T- tests, P=<0.01(<-0.5; PT: SN=64.30%, SP=83.30,	For sig ones, Log reg, B=-8.78, P= <0.01, AUC=0.76; P=<0.01; Cut-off=<=0.5	M	L
	Guo, et al.[7]	sacral slope (SS)	×		T- tests, P=NS		M	L
	Ploumis, et al.[44]	Sacral takeoff angle		✓	Cor, Coef= 0.23, P<0.05		M	L
	Guo, et al.[7]	Spinopelvic inclination (T1) Spinopelvic inclination (T9)		✓ ✓	T- tests, P= <0.05 (S), SPT1 (≤3.5) : SN=64.30%, SP=71.40%, T- tests, P= <0.05 (S); SPT9 (≤6.5°): SN=92.90%, SP=40.50%	For sig ones, Log reg, B: SPT1=-2.26, P<0.05, AUC=0.69, P<0.05, cut-off: ≤3.5 SPT9=-, -2.87; P<0.05, ,	M	L

						AUC=0.65; P=<0.05, Cut-off:≤6.5		
Spinal Alignment	Bunnell [4]	Spinal balance	×		Nonprognostic		M	S
	Katz, et al. [11]	Coronal decompensation, Lateral trunk shift	× ×		T-test, P=0.45 T-test, P=0.42		M	L
	Yamauchi, et al. [29]	Difference of inclination between the proximal and distal vertebra	×		Cor Coef=-0.16, Partial Cor Coef=0.08		M	L
Apical Vertebral Rotation	Katz, et al.[11]	Apical vertebral rotation thoracic apex [AVR-T] Apical vertebral rotation lumbar apex [AVR-L]	× ×		T-test, P=0.23 T-test, P=0.56		M	L
	Ohrt-Nissen, et al. [21]	Apical vertebra rotation (Nash and Moe grade 1 and 2)		✓	Reg, B= 10.64 (2.47-18.81), 12.86 (4.69-21.03); P= 0.012, 0.003 (high values)		L	L
	Peterson, et al.[22]	Apical vertebral rotation (Nash and Moe method)	×			Log reg, B= 1.15, SE=0.89, P= 0.19	M	S
	Vijvermans, et al.[26]	Apical vertebra rotation		✓		Reg, B= 0.295, P=0.135, R^2= 3.43%, P=0.031 (higher rotation)	M	L
	Yamauchi, et al. [29]	Apical vertebra rotation		✓	Cor Coef=-0.22, Partial Cor Coef=0.28 (higher rotation)		M	L
	Zhang, et al.[31]	Apical vertebral rotation		✓	(>grade III, high risk) OR=16.34	Log reg, B= 2.78, SE=0.93, P=0.003	M	L
Axial Vertebral Rotation	Nault, et al.[18]	Apical intervertebral rotation		✓	P=0.006 (S) (>2.4 °)		M	L
	Nault, et al.[18]	Upper curve intervertebral rotation	×		P=0.2 (NS)		M	L
	Nault, et al.[18]	Lower curve intervertebral rotation	×		0.3 (NS)		M	L
	Nault, et al.[18]	T12–L1 intervertebral rotation	×		0.6 (NS)		M	L
	Nault, et al. [19]	Axial rotation of upper junctional vertebra	×		Reg, P= 0.09,		M	L
	Nault, et al. [19]	Sagittal rotation of upper junctional vertebra	×		Reg, P= 0.6		M	L
	Nault, et al. [19]	Coronal rotation of upper junctional vertebra	×		Reg, P =0.2		M	L
	Nault, et al. [19]	Axial intervertebral rotation at apical level	×		Reg, P = 0.2		M	L

	Nault, et al. [19]	Sagittal intervertebral rotation at the apical level		✓	Reg, P = 0.01 (S) (a difference in the sagittal plane of 1.3 degrees) (lower values, higher risk)		M	L
	Nault, et al. [19]	Coronal intervertebral Rotation at the apical level	×		Reg, P = 0.5		M	L
	Nault, et al. [19]	Axial rotation of lower junctional vertebra		✓	Reg, P = 0.008 (S) (higher values of Lower junctional vertebra axial) vertebra coronal)		M	L
	Nault, et al. [19]	Sagittal rotation of lower junctional vertebra	×		Reg, P = 0.2		M	L
	Nault, et al. [19]	Coronal rotation of lower junctional vertebra		✓	Reg, P = 0.03 (higher values of Lower junctional vertebra coronal, S		M	L
Apex Location	Bohl, et al. [3]	Apex (T8 and cephalad Vs Caudal to T8)	×		Chi square, P= 0.163 (NS) SN=53%, SP=71%, ACC=62%, OR=2.7, +LR= 1.8, -LR= 0.67, +PV= 0.64, -PV=0.60; (T8 and cephalad considered positive)		M	L
	D'Amato, et al.[34]	Curve apex of T8: (higher vs lower)		✓	Chi square, P=0.034 (higher curve location more progressive)		M	S
	Danielsson, et al. [5]	Apex at T9 or above	×		NS (0.20)		M	L
	Davis, et al. [33]	Apex location (T6 -T9, T10-L3)	×		Chi square, P=0.081 (NS)		L	L
	Peterson, et al.[22]	Level of apex (T8-T11), (T12-L1)		✓	Apical level cephalad to 12th vertebra is significant	Log, re=2.73, SE=1.13, P=0.02, +PV=82%, -PV=80%, SP=81%, SN=81%	M	S
	Wu, et al.[28]	Apex Location		✓	P= Apex locations in the progressed group were significantly higher (*1.2 vertebra levels) than those in the stable group		M	S
Torsion	Aulisa, et al.[1]	Torsion of the apical vertebra measured by Pedriolle degrees		✓	Kruskal-Wallis= 16.9880, P< 0.01		M	L

	Nault, et al. [18]	Torsion		✓	T-test, P=0.02 (high torsion)		M	L
	Nault, et al.[19]	Torsion		✓	T-test, P= 0.049 (S) (high torsion, higher risk)		M	L
Lumbosacral Factors	Bunnell [4]	lumbosacral transitional anomalities	×		Non-prognostic		M	S
Vertebral Tilt	Katz, et al.[37]	Vertebral tilt angles (thoracic–superior [VTA-T-S], thoracic-inferior [VTA-T-I], lumbar–superior [VTA-L-S], lumbar–inferior [VTA-L-I])	× × × ×		T-test, P= 0.33, T-test, P= 0.08, T-test, P= 0.82, T-test, P=0.85		M	L
3D Cobb angle	Nault, et al. [18]	3D Cobb angle	×				M	L
	Nault, et al.[19]	3D Cobb angle	×		T-test, P= 0.08 (NS)		M	L
	Nault, et al. [18]	Cobb angle of plane of maximum deformity		✓	T-test, P= 0.001 (higher angle of plane of maximum curvature)		M	L
Vertebral Wedging	Nault, et al. [18]	3D apical vertebral body wedging	×		T-test, P=0.9 (NS)		M	L
	Nault, et al.[19]	3D wedging apical vertebrae	×		T-test, P= 0.9 (NS)		M	L
Slenderness	Nault, et al. [18]	T6 width slenderness	×		T-test, P=0.09 (NS)		M	L
	Nault, et al. [18]	T6 depth slenderness		✓	T-test, P=0.05 (S) (low values higher risk)		M	L
	Nault, et al.[19]	Slenderness T6 vertebra		✓	T-test, P= 0.05 (low values higher risk)		M	L
	Nault, et al. [18]	T12 width slenderness	×		T-test, P=0.1 (NS)		M	L
	Nault, et al. [18]	T12 depth slenderness		✓	T-test, P=0.03 (S) (low values higher risk)		M	L
	Nault, et al. [18]	L4 width slenderness		✓	T-test, P= 0.009 (S) (low values higher risk)		M	L
	Nault, et al. [18]	L4 depth slenderness		✓	T-test, P=0.007 (S) (low values higher risk)		M	L
	Nault, et al.[19]	Slenderness L4 vertebra	×		T-test, P= 0.5 (NS)		M	L
	Nault, et al. [18]	T1–L5 width slenderness		✓	T-test, P=0.05 (S) (low values higher risk)		M	L

	Nault, et al. [18]	T1–L5 depth slenderness		✓	T-test, P=0.005 (S) (low values higher risk)		M	L
	Nault, et al.[19]	Slenderness T1- L5 vertebra		✓	T-test, P= 0.046 (low values higher risk)		M	L
Disk Wedging	Nault, et al. [18]	Apical disk wedging	×		T-test, P=0.6 (NS)		M	L
	Nault, et al. [18]	Upper curve disk wedging	×		T-test, P=0.2 (NS)		M	L
	Nault, et al. [18]	Lower curve disk wedging	×		T-test, P=0.6 (NS)		M	L
	Nault, et al.[19]	Mean 3D wedging of apical disks		✓	T-test, P= 0.03 (S) (high values)		M	L
	Yamauchi, et al. [29]	Disc index (wedging of the disk spaces in the curve)	×		Cor Coef-=0.02, Partial Cor Coef= -0.04		M	L
Vertebral Translations	Katz, et al.[11]	Apical vertebral translation - thoracic [AVT-T] Apical vertebral translation-lumbar [AVT-L] AVT ratio [AVT-R] Relative apical distance [RAD]	× × × ×		T-test, P= 0.56 T-test, P=0.39 T-test, P=0.31 T-test, P=0.85		M	L
	Wu, et al.[28]	Initial apex lateral deviations, Maximal apex lateral deviations		✓ ✓	T-test,P= S, Maximal apex lateral deviation,T-test, P=S		M	S
	Yamauchi, et al. [29]	Deviation of the apical vertebra, first thoracic vertebra	×	✓	Cor Coef= Apical vertebra: -0.45 (S), first vertebra: 0.18 (NS); Partial Cor Coef= Apical vertebra: -0.25 (S), first vertebra: 0.03 (NS)	Apical vertebra: log reg, B= -0.258	M	L
Bone Density of Spine	Hung [8]	BMD (Z-score bone mineral density Spine (L2-L4)	×		T-test, P= 0.022, Chi, P=0.062,		L	S
	Sun, et al.[24]	BMD (lumbar spine from L2 to L4 (LSBMD) (g/cm2)		✓	T test, P=0.018, LSBMD, SN= 74.50%, SP=64.70%; +PV= 2.11, -PV=1.54; Reg, P= 0.003 (lower values, higher risk)	OR= 11.24 (95% CI, 12.36- 53.43), P=0.002	L	S

Bone Density of Hip	Hung [8]	BMD of femoral neck in convex-side hip		✓	T-test, P=0.013, Chi, P <0.05 (lower values considered as risk factors)		L	S
	Hung [8]	BMD of femoral neck in concave-side hip		✓	T-test, P=0.014, Chi, P <0.05 (lower values considered as risk factors)	Femoral neck in concave-side hip put into the model, Log reg, B= 0.81; OR= 2.3 (95% CI,1.1-4.5), P=0.02; AUC=0.8 (95% CI%, 0.75-0.85); Model: SN= 76% (95%CI, 69%-83%), SP= 70% (95% CI, 62%-77%); (lower values considered as risk factors)	L	S
	Hung [8]	BMD of Trochanter in convex-side hip	×		T-test, P=0.346, Chi, P=0.177		L	S
	Hung [8]	BMD of Trochanter in concave-side hip		✓	T-test, P=0.261, P<0.05 (low values, higher risk)		L	S
	LAM, et al. [21]	Bone Density (BMD) both hips		✓*	Chi square P= 0.002 (lower values as high risk) (level of sig P<0.2)		M	L
	Sun, et al.[24]	BMD of femoral neck on the nondominant side (FNBMD) (g/cm2)	×		P=0.129 (association test NS, test not specified)		L	S
Bone Quality	LAM, et al. [21]	Bone quality (broadband ultrasound attenuation (BUA)		✓*	Chi square P=0.057 (lower values had higher risk) (level of sig P<0.2)		M	L
	LAM, et al. [21]	velocity of sound (VoS)		✓*	Chi square P= 0.073 (S) (lower values had higher risk) (level of sig P<0.2)		M	L
	LAM, et al. [21]	Stiffness index (SI)		✓	Chi square P= 0.004 (S) (lower values had higher risk) (level of sig P<0.2); SN=85%, SP=66%; AOR= 2 (95% CI, 1.08-3.17)	Log reg, B= 0.694, AUC= 0.83 (95%CI, 0.78-0.87)	M	L
Bone Proportion	LeBlanc [16]	Bone volume (%) of whole body		✓	Discriminant analysis, P< 0.0001, ACC=84%		M	S

Other Factors	Bunnell [4]	Family history	×		Non-prognostic		M	S
	Hung [8]	Family history of scoliosis	×		Chi, P= 0.750		L	S
	Konieczny, et al.[12]	Family history of scoliosis	×			Binary logistic regression analysis (stepwise, backward), P=NS	H	S
	Konieczny, et al.[12]	Hours of sports per week outside of the school (< 1 hour, ≥ 1)	×		Hours of sport/w: Man-Whitney U test, P> 0.05	Binary logistic regression analysis (stepwise, backward), P=NS	H	S
	Konieczny, et al.[12]	Hours of self-training per week	×			Binary logistic regression analysis (stepwise, backward), P=NS	H	S
	Konieczny, et al.[12]	Educational level of parents	×			Binary logistic regression analysis (stepwise, backward), P=NS	H	S
	Konieczny, et al.[12]	Nutritional behavior	×			Binary logistic regression analysis (stepwise, backward), P=NS	H	S
	Konieczny, et al.[12]	Type of school bag	×			Binary logistic regression analysis (stepwise, backward), P=NS	H	S
	Konieczny, et al.[12]	Educational level of the patients	×			Binary logistic regression analysis (stepwise, backward), P=NS	H	S

abbreviations used in table were defined as follows: Non-pre: Non-predictor, Pre: Predictor, Pro: Progression, Non-pro: Non-progression, Cor Coef: Correlation coefficient, P: P value, NS: Not significant, NM: Not mentioned, CI: Confidence interval, Log reg: Logistic regression, B: Beta coefficient, SE: Standard error, AUC: Area under curve, OR: Odds ratio, AOR: Adjusted odds ratio, SN: Sensitivity, SP: Specificity, -PV: negative predictive value, +PV: Positive predictive value, -LR: Negative likelihood ratio, +LR: Positive likelihood ratio, ACC: Accuracy, AB: adjusted B coefficient, R^2P: quantifies the weight of importance of every variable in the model; the * denote that the variable was significantly associated with progression in univariate analysis but the p value of the model including that variable was not significant, cm:centimeter, TH: thoracic, TL: thoracolumbar, L: lumbar, kg=kilogram

Appendix 3.4 References

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Appendix 3.5 Summary of Articles for the Progression Criteria to a Magnitude ≥ 30° or Requiring Surgery

Predictors	Author	Parameters	Non-Pre	Pre	Univariate analysis	Multivariate analysis	RoB	FU intervals
Age (years)	Goldberg, et al. [1]	Age at initial (13.9±1.7)	×		T-test=1.37, P=0.11		M	L
	Karol [2]	Age (13.9, 10.6–16.9)		✓	Fisher's exact test (two-tailed), P< 0.05, (Age, < 13 yr is high risk for surgical thresholds)		M	L
	Lara, et al. [3]	Age at initial (14.2±1.9, 10-18.8		✓	Younger age at presentation showed higher risk of progression	OR=0.44 (95%CI, 0.27-0.72), P=0.0012	L	L
	Lee, et al. [4]	Age at the initial		✓	Unadjusted HR= 0.91 (95% CI, 0.84-0.97), HR= 0.008, (11.3 years as cutoff, risk of progression decreases as age increases)	Adjusted HR = 0.4 (95% CI, 0.26-0.6), P< 0.001	M	S
	Shi, et al. [5]	Age at the initial (≤ 45: 12.1±1.2 vs > 45: 12.5±1.3)	×		Chi square, P= 0.678		M	L
	Sun, et al. [6]	Age at initial (10.0–12.9 vs 13.0–15.9), Age at menarche	×	✓	Age at initial (younger age: 10.0–12.9 yr at higher risk of progression): Chi square, P <0.05, Age at menarche: NS		M	L
	Tan, et al. [7]	Age at initial	×		Chi, square P= 0.158		M	L
	Yip, et al. [8]	Age at initial		✓	HR=0.53 (95%CI, 0.41-0.96), P=0.00 (risk of progression decreased by age)	HR=0.53 (95%CI, 0.37-0.75), P=0.00	M	S
Gender	Davis, et al. [9]	Gender	×		Chi, P= 0.5		L	L
	Lara, et al. [3]	Gender	×		Chi, P=0.55	OR= 2.60 (95%CI, 0.56, 11.95), P=0.22	L	L
	Lee, et al. [4]	Gender		✓	Unadjusted HR= 0.81 (95%CI, 0.64-1.03), P= 0.805 for male (females showed higher risk of progression)	Adjusted HR=0.02 (95%CI, 0-0.24), P=0.002	M	S
	Sitoula, et al. [10]	Gender		✓	P=0.029, SN=27%, SP=86%, ACC=65%, OR=2.42, +LR= 2.02, -LR= 0.83, +PV= 0.53, -PV=0.68 (females showed a higher rate for progression)		L	L
	Tan, et al. [7]	Gender (females at higher risk)	×		Chi, P= 0.07, SN=5%, SP= 82%, ACC= 67%, OR= 3.8	Log reg, B= 0.931,	M	L

					(95%CI, 0.87-16.9),P=0.26, +LR=0.29, -LR= 1.14, +PV= 7.14%, -PV= 77.22% (Male was considered as positive test)			
Menarche/Pubertal Status	Cheung, et al. [11]	Menarche		✓	Chi, P<0.001, (higher risk for premenarche)		M	L
	Goldberg, et al. [1]	Menarche status		✓	Z score= 3.672, P< 0.01 (pre-menarche at diagnosis)		M	L
	Lee, et al. [4]	Initial menarche status		✓	Menarche status classified as an intermediate risk group for progression (pre-menarche at higher risk)		M	S
	Shi, et al. [5]	Menarche age	×		Chi, P=0.85		M	L
	Sun, et al. [12]	Menarche status		✓	Fisher's exact test, P< 0.001, (pre-menarche Status at higher risk)	Log reg, OR= 12.00 (95%CI, 3.73-47.25) (pre-menarche)	L	S
	Tan, et al. [7]	Initial pubertal status	×		Chi square, P= 0.48	Log, reg, P=0.129, OR=2.3 (95%CI, 0.8–6.6) (after puberty positive)	M	L
	Yip, et al. [8]	Initial menarche status		✓	Adjusted HR=0.21(95%CI, 0.11-0.38), P <0.001 (pre-menarche at higher risk)	Unadjusted HR= 0.41 (95%CI, 0.19-0.86), P=0.02	M	S
Risser Sign	Cheung, et al. [11]	Risser 0-3 for both		✓	Chi square, P<0.001 (Risser 0-3 have a significant risk for progression to surgical threshold))		M	L
	Davis, et al.	Risser classification (0, ⩾1)	×		Chi square, P= 0.13		L	L
	Karol [13]	Risser sign (0, 1, and 2)		✓	Progression to surgery was related to less Mature Risser sign		M	L
	Karol [2]	Risser 0 vs 1, 2; Risser 1 vs 2; Risser 0 open TRC vs Closed TRC		✓	Chi square, P< 0.001, 0.51, 0.005; Risser status (0) at the high risk for surgery		M	S
	Lara, et al. [3]	Risser (0-5)+TRC (open/close)	×		Chi, P=0.1093		L	L
	Sitoula, et al. [10]	Risser (0, 1, 2, 3)		✓	Chi square, P=0.005 (lower Risser grade have higher rate of progression)		L	L
	Sun, et al. [6]	Risser (0-1 vs 2-4) (surgical threshold)		✓	Fisher's exact test, P< 0.05, Chi square, P=0.002, (Lower Risser grade 0–1 at		M	L

					higher risk of progression to surgery			
	Thompson, et al. [14]	Risser 0 (MT, L); Risser 1, 2 (MT, L)	×		Chi, P>0.05		M	U
Triradiate Cartilage (TRC)	Karol, et al. [2]	TRC+ Risser 0 (open, close)		✓	Chi square, P=< 0.005 (open triradiate cartilage higher risk)		M	S
Distal Radius and Ulna Class (DRU)	Cheung, et al. [11]	Radius grade (5-10) and Ulna grade (4-8) for (≥40, ≥50 thresholds)		✓	≥40: Chi square, P< 0.001 and Chi square, P< 0.001; ≥50: Chi, P=0.002, Chi, P < 0.001; ACC= ≥40: 74.5% and 71.5%, ≥50: 85.6% and 86%; (R6/U5 showed a higher risk of progression)		M	L
Olecranon Stages of Maturity	Charles, et al. [15]	Olecranon process maturation for primary curve magnitude of 21–30° and >30°		✓	Chi square, P= 0.003 (higher risk during the accelerating pubertal growth phase for curves 21-30), P< 0.001 (higher risk at the onset of the accelerating growth phase for >30 curves)		M	S
Sanders Stages of Maturity	Sitoula, et al. [10]	Sanders (1-7)		✓	Chi square, P=0.0001, patients with SS1, SS2, and SS3 with curves > 20 ° or 25 at greatest risk for curve progression into the surgical range		L	L
Body Mass Index (BMI) (kg/m2)	Goodbody, et al. [16]	Low-BMI group (20th percentile), Mid-BMI group (20th–85th percentile) High-BMI group (85th percentile)		✓	Low BMI: For progression > 45: P < 0.01, OR=3.7, Need for surgery: P<0.01, OR=4.1, and for Orthotic failure P < 0.01, OR=3.7; Mid-BMI: NM; High BMI: For progression > 45: P=0.01, OR=3.4, Need for surgery=0.13, OR=2.2, and Orthotic failure=0.04, OR=2.4 (high and low BMI at higher risk of progression)		M	L
Weight (kg)	O'Neill, et al. [17]	Weight (Being overweight was a risk factor,≥ 85th percentile)		✓	T-test, P< 0.05; Pearson's product moment= 0.20	B=0.15, R^2=18%	L	L

Hip Parameters	Kotwicki, et al. [18]	Hip joint asymmetries derived parameters # (Including parameters for total range of rotation right and left hip)	×		Right: Mann-Whitney test, P> 0.05		H	U
Height (cm)	Lee, et al. [4]	Height (≥153.9 vs < 153.9)		✓	Unadjusted HR= 0.98 (95%CI, 0.97-0.99), HR, (P<0.001), Risk of progression decreases by increasing height	Adjusted HR= 0.98 (95%CI, 0.97-0.99), P=0.002	M	S
Cobb Angle (°)	Charles, et al. [15]	Primary curve magnitude 21–30° and >30°		✓ ✓	Chi square, P= 0.0034 Chi square, P= <0.001 (progression > 30 has higher risk versus ≤ 30)		M	S
	Cheung, et al. [11]	Initial Cobb		✓	Chi square, P <0.001, (≥ 35 showed a high risk)		M	L
	Davis, et al. [9]	Initial Cobb angle (< 35 vs > 35°)	×		Chi, P<=0.091		L	L
	Goldberg, et al. [1]	Initial Cobb angle		✓	Surgical: T- test= 9.16, P< 0.001, Unoperated: T test= 11.66, P< 0.001 (higher Cobb at presentation)		M	L
	Karol [13]	Curve magnitude		✓	Fisher's exact test (two-tailed), P< 0.0001 (initial Cobb ≥ 30 higher risk to progress to surgery)		M	L
	Karol [19]	Curve magnitude		✓	Chi, P<0.0001		M	S
	Lara, et al. [3]	Initial Cobb angle, 32.5 ±18.9 (10-104)		✓	Larger Curve magnitude at presentation was a significant risk factor	OR= 2.6 (95%CI, 0.56-11.95), P<0.0001	L	L
	Lee, et al. [4]	Cobb angle		✓*	Unadjusted HR =0.69 (95%CI, 1.16-1.21), P<0.001 (Initial Cobb angle > 25 and higher risk)	Adjusted HR= 0.84 (95%CI, 0.69-1.03), P=0.095	M	S
	Pasquini, et al. [20]	Initial curve magnitude 20-30 vs 30-40		✓	Two-way Chi, P=0.022 (30-40 ° higher risk of progression)		M	U
	Shi, et al. [5]	Initial Cobb angles, Cobb angles at brace weaning (≤45 vs > 45 groups)		✓ ✓	Chi, P< 0.001 (initial Cobb) Chi, P< 0.001 (at brace weaning) High values of Cobb associate with higher risk of progression after brace weaning)		M	L

	Sitoula, et al. [10]	Initial Cobb		✓	Initial Cobb, P=0.0001 (Cobb ≥ 25 had higher risk of progression)		L	L
	Sun, et al. [6]	Cobb before bracing (>30° vs ≤ 30)		✓	Chi, P= 0.002 (>30° was an independent risk factor for curve progression)	Cobb >30: 6.484 (95%CI, 1.302–32.289), P= 0.022	M	L
	Tan, et al. [7]	Initial Cobb angle < 25 vs ≥25		✓	Chi square, P< 0.001, SN= 68%, SP=92%, ACC=87%, OR=24.6 (95%CI, 9.9-60.06), +LR=8.43, -LR=0.34, +PV= 68.42%, -PV= 91.89%; (Cobb ≥25 has higher risk of progression)	P< 0.001, OR=27.5 (95%CI, 10.2-73.9)	M	L
	Yip, et al. [8]	Initial Cobb angle		✓	HR=1.11 (95%CI, 1.06-1.17), P< 0.001 (high risk group had a Cobb ≥24)	HR= 1.15 (95%CI, 1.1-1.2), P=0.000	M	S
Curve Pattern	Cheung, et al. [11]	Modified Lenke curve type (1-6)		✓	≥40: Chi square, P=0.006 (S) (TH and doubles curve at higher risk of progression) ≥50: Chi square, P=0.012 (NS)		M	L
	Davis, et al. [9]	Curve classification (TH, TH/L, Double major)	×		Chi square, P=0.07		L	L
	Lara, et al. [3]	Curve pattern (TH, L, TL, Double TH, Double L (reference))		✓*	Curve pattern: Fisher exact test, P=0.0014	TH: OR= 0.29 (95%CI, 0.03-2.79), P= 0.28; L: OR= 0.13(95%CI, <0.001-> 999), P= 0.83; TL: OR= 0.03 (95%CI, < 0.001-45.25), P= 0.34; Double TH OR= 1.51 (95%CI,0.18-12.32), P=0.70	L	L
	Pasquini, et al. [20]	Curve type (TH, TL, L, double major)	×		Chi square, P=0.312		M	U
	Shi, et al. [3]	Curve patterns (MT, TL, Double)	×		Chi square, P=1.00, 0.78, 0.21		M	L
	Sun, et al. [6]	Curve pattern (TH, Double TL/L)		✓	Chi square, P=0.278 (TH higher risk)	Log Reg, B=1.256, OR=2.671 (95%CI, 1.064–11.591, P= 0.039	M	L
	Thompson, et al. [14]	Modified Lenke (mLenke) classification system (I-VI), Curve type Main	×	✓	mLenke (I-VI) : Chi, P= 0.0866,		M	U

		TH (mLenke I-III) vs main L (mLenke V or VI)			Curve type TH vs L : Chi, P=0.0129 (main TH (mLenke I, II, or III) at higher risk)			
Apex Location	Davis, et al. [9]	Apex location (T6 - T9, T10-L3)		✓	Chi square, P=0.004, (apex cephalad to T10 at higher risk)	T10-L3: OR= 0.21 (95%CI, 0.06-0.75), P=0.016	L	L
Bone Density	Yip, et al. [8]	Osteopenia status (aBMD from DXA) of proximal of bilateral femurs		✓	Unadjusted value HR for osteopenia= 2.068 (95%CI, 1.202-3.561), P= 0.009; (Osteopenia high risk-(zBMD < − 1)	Adjusted value= HR= 2.245 (95%CI, 1.201- 4.198), P= 0.011; %	M	S
	Yip, et al. [8]	Bone Morphometry Tot Area (cm2), Tb.Ar (cm^2), CrAr/TotAr (%), CtPm, CtTh); at non-dominant distal radius	× × ×	 ✓* ✓*	 T-test: P=0.555 T-test: P=0.920 T-test: P=0.023 T-test: P=0.874 T-test: P=0.015		M	S
	Yip, et al. [8]	Volumetric BMD (SD) (Dtot(mgHA/cm3), Dcort (mgHA/cm3), Dtrab (mgHA/cm3)); at non-dominant distal radius	× ×	 ✓	T test, P=0.63, P=0.002, (Dcort < 570 mgHA/cm3 has high risk group), P=0.505);	(Dcort < 570 mgHA/cm3 high risk group) combined with Cobb angle ≥ 24° lead to SN=43%, SP=100%, PPV=100%, NPV=95	M	S
	Yip, et al. [8]	Trabecular Bone Micro-architecture (SD) TrN, BV/TV (%), Tb.Th, Tb.Sp); at non-dominant distal radius	 × × ×	 ✓*	 T test, P=0.178 T test, P=0.503 T test, P= 0.021 T test, P=0.415		M	S

Note that the abbreviations used in table described as: Non-pre: Non-predictor, Pre: Predictor, Progression, Non-pro: Non-progression, HR: Hazard ratio, P: P value, NS: Not significant, NM: Not mentioned, CI: Confidence interval, Log reg: Logistic regression, B: Beta coefficient, SE: Standard error, AUC: Area under curve, OR: Odds ratio, AOR: Adjusted odds ration, SN: Sensitivity, SP: Specificity, -PV: negative predictive value, +PV: Positive predictive value, -LR: Negative likelihood ratio, +LR: Positive likelihood ratio, ACC: Accuracy, Kg= kilogram, cm=centimeter, kg/m^2 =kilogram/square meter, aBMD= areal bone mineral density, DXA= dual-energy X-ray absorptiometry, BV/TV = bone volume over total volume, CrAr = cortical bone area, CtPm = cortical (periosteal) perimeter, CtTh = cortical thickness, Dcort = volumetric density of cortical bone measured at distal radius, Dtrab = volumetric density of trabecular, bone measured at distal radius, Dtot = overall volumetric density measured at distal radius, Tb.Ar = trabecular, bone area, Tb.Sp = trabecular spacing, Tb.Th = trabecular thickness, Tot Area = total bone area, TrN = trabecular number

* denotes that predictor is significant from univariate analysis but not from multivariate analysis

parameters included in this study: Internal rotation (R, L hip), External rotation (R, L hip), Total range rotation (R, L hip), Difference in IR: Right minus left, Difference in ER: Right minus left, Absolute difference left-right in IR, Absolute difference left-right in ER, Mid-point of rotation for right hip, Mid-point of rotation for left hip, Static rotational offset of the pelvis

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Appendix 3.6. Summary of Articles that Reported Change in Cobb Angle as °/year

Predictors	Authors	Parameters	Non-pre	Pre	Univariate analysis	ROB	FU intervals
Age (years)	Ylikoski [1]	Initial age (11-12 vs 13-16)		✓	Student's t T-test, P< 0.01 (higher risk for 11-12)	M	S
	Yrjonen and Ylikoski [2]	Initial age		✓	For age 12-13 had the highest risk of progression	M	S
Menarche Status	Ylikoski [1]	Menarche		✓	T- test, P< 0.001 (Premenarche showed higher risk)	M	S
Risser sign	Ylikoski [1]	Risser (0-2 vs 3-5)		✓	Student's t T-test, P< 0.001, (higher risk for Risser 0-2)	M	S
	Yrjonen and Ylikoski [2]	Risser (0-1 vs 2-3)	×		No significant difference between the two groups	M	S
Distal Radius and Ulna Classification	Cheung, et al. [3]	The distal radius (R4-R10) and ulna (U2-U8) (DRU) classification		✓	Peak curve progression matched with R7 (0.80±0.89 cm/month) and U5 stages (0.84±0.78 cm/month) (low grades have higher risk)	M	L
State of Maturity	Duval-Beaupere [4]	State of maturity (I-IV)		✓	F test, P<0.001. Risk is higher when first examination is between start of puberty and menarche (state II was at higher risk)	H	S
Growth Factors	Cheung, et al. [3]	Growth rate (body height)		✓	Height: Cor Coef=0.26, P<0.001, (higher values are risk factors)	M	L
	Cheung, et al. [3]	Growth rate (arm span)		✓	Arm span: Cor Coef=0.26, P<0.001 (higher values are risk factors)	M	L
	Ylikoski [1]	Growth of the T4-L4 segment		✓	Cor Coef=0.38, P< 0.001 (higher values are risk factors)	M	S
	Yrjonen and Ylikoski [2]	Growth velocity (standing heights between the last and the first visit were subtracted and divided by the follow-up time)		✓	Growth velocity ≥ 4 cm/year with curves ≥ 25° increased progression velocity, Student's t-test, P< 0.001	M	S
Cobb Angle (°)	Duval-Beaupere [4]	Supine Cobb angle		✓	Reg Coef= 0.59, P< 0.001	H	S

	Yrjonen and Ylikoski [2]	Cobb ≥25 and <25		✓	Curves with Cobb ≥25 and Growth velocity ≥ 4 cm/year are at higher risk, Student's t-test, P< 0.001	M	S
Curve Pattern	Duval-Beaupere [4]	TH, TL, L, double, triple		✓	TH, Double, and triple curves showed higher rate of progression	H	S
	Ylikoski [1]	TH, TL, L		✓	TH: Cor Coef= 0.56, P< 0.001, TL, L: Cor Coef=0.15 ((Correlation between the growth of the T4-L4 segment and the progression of curves in thoracic was more significant than TL and L)	M	S
	Yrjonen and Ylikoski [2]	Right and left TH, TL, L curves		✓	Right TH was most progressive, other curve types didn't significantly differ in progression velocity	M	S
Rib Hump	Duval-Beaupere [4]	Rib hump		✓	Reg Coef, r= 0.52 with annual increment of progression	H	S

Note that the abbreviations used in table described as: Non-pre: Non-predictor, Pre: Predictor, Cor Coef: Correlation coefficient, Reg Coef: Regression coefficient, TH: thoracic, TL: Thoracolumbar, L: Lumbar

Appendix 3.6 References

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Chapter 4: Ultrasound Reflection Coefficient (RC) Index

4.1. Overview

Based on the previous chapter regarding the study parameters suggesting the potential of measurement of bone quality to predict progression, a new ultrasound parameter called reflection coefficient (RC) index is introduced and described in this chapter. This novel index is considered to reflect the bone strength directly from the spine area. Section 4.2 includes a manuscript describing the theory behind the RC index including extraction, calculation, and validation of the RC index. Also, a correlation between the RC and the curve severity was also investigated. The title of the manuscript is "Investigation of Ultrasonic Soft Tissue-Bone Reflection Coefficients Correlating with Curve Severity in Children with Adolescent Idiopathic Scoliosis" and has been submitted to "Journal of Medicine and Engineering". Section 4.3 reports a clinical pilot study with the title of "Reliability of Measurements of a Reflection Coefficient Index to Indicate Spinal Bone Strength on Adolescents with Idiopathic Scoliosis (AIS): A Pilot Study". The manuscript was published in "European Spine Journal" in July 2021. Section 4.4 provides the summary of this chapter.

4.2. The Fundamentals of the Reflection Coefficient (RC) Index

4.2.1. Introduction

Scoliosis is a three-dimensional spinal deformity characterized by a lateral curvature of the spine. Adolescent idiopathic scoliosis (AIS) is the most commonly diagnosed form of scoliosis with unknown etiology [1], affecting 1–4% adolescent population especially children from 10 to 16 years old [2,3]. The curves with severe progression can have a negative impact not only on patients' psychosocial health but also on their physical well-being such as back pain, diminished pulmonary function, and increased mortality rate [4,5]. Understanding the etiopathogenesis of AIS can aid in providing more effective treatment to AIS patients.

Osteopenia or low bone density, quantified by bone mineral density (BMD) which means bone quantity or bone mass, is more commonly observed in children with AIS than normal children [6–9]. BMD measures the amount of calcium and is usually tested by dual-energy X-ray absorptiometry (DXA). Furthermore, children with AIS not only have lower BMD, but also have lower bone quality [10]. Bone quality, which is related to bone strength, describes microarchitecture, mineralization, turnover rate, and micro-fractures [11]. Bone quality can be assessed by radiographic methods [12]. Studies have revealed that the AIS groups have deteriorated bone quality and lower bone mass when compared with the control groups [10, 13–16]. Lee et al. also found that curve severity (Cobb angle) of scoliosis was inversely and independently associated with BMD [8].

On the other hand, quantitative ultrasound (QUS) is a non-invasive and ionizing radiation-free technique to evaluate bone quality. Lam et al. used the ultrasound transmission-through technique to measure bone properties at the calcanei in healthy group as well as in both mild and moderate AIS [10, 17]. Two measured QUS parameters, namely speed of sound (SOS) and broadband ultrasound attenuation (BUA), and a third derived stiffness index (SI), which is a combination of BUA and SOS, were found statistically lower in the group with AIS than in the healthy control group. Further, they suggested that SI was an independent and prognostic factor for curve progression and treatment planning [17]. Similar to the study of finding the relationship between BMD and severity of AIS [8], Du et al. attempted to correlate SOS with Cobb angles [18]. They found AIS subjects had lower SOS-values compared to non-scoliotic controls; however, they concluded there was no significant correlation between SOS and Cobb angles. So far, research findings have shown consistently that both bone quantity (BMD) and bone quality (SOS, BUA, and SI) could be found lower in AIS patients as compared to those of normal controls. However, a positive correlation between bone quantity or quality and curve severity has not been assertively established yet. In addition, quantitative US usually uses the transmission method to assess bone quality at peripheral sites other than the spine, namely calcaneus and radius [10, 18]. The use of reflected echoes from spinal scans to evaluate bone quality of the spines is limited.

When ultrasound propagates into the tissue, energy is reflected by any scatter which has a contrast of acoustic impedance with the surrounding tissue, and the strength of the echo mainly depends upon the magnitude of the contrast. Soft tissue–bone interface is an example of strong reflector [19, 20]. Given that the acoustic impedance of bone, which is a product of SOS and density, is related to the bone stiffness, and thus bone quality. Zheng et al. proposed to measure the ultrasound echoes directly from spines to assess bone quality and study if it correlated with the severity of AIS [21]. They introduced a reflection index (RI), which is a ratio of the received echo from the vertebra and a reference echo from a referenced phantom. The results showed that the RI decreased with the increase of curve severity; however, the correlation coefficient was small and the thickness of the soft tissue was ignored. Due to the limited fundamental work and theory in Zheng et al. study, we would like to develop a framework to explain the fundamental phenomenon of ultrasound echo from the spine to assess bone properties.

Therefore, this study aimed to a) develop the theoretical framework to explore the feasibility of determining a new parameter, called the reflection coefficient, from the ultrasound echoes acquired directly from the spine, and b) investigate if there are correlations between the reflection coefficient and the curve severity in children with AIS.

4.2.2. Materials and Methods

4.2.3. Theoretical Formulation

We consider a simple bone model with the cortex overlaid by soft tissue (Figure 4.1a). Both cortex and soft tissue are assumed to be homogeneous and isotropic. The thickness of soft tissue is h while the thickness of cortex is not relevant in this study. The cortical bone and soft tissue are characterized by the velocity (c), density (ρ), and the attenuation coefficient (α), where the subscripts b and s are used to denote bone and soft tissue, respectively.

A source signal of amplitude A_0 is generated by the transducer, travels through the soft tissue, and is reflected by the soft tissue–cortex interface. The recorded amplitude of the echo, A, can be described by

$$A = A_0 R_{sb} e^{-2\alpha_s h} \tag{4.1}$$

where R_{sb} is the reflection coefficient of the soft tissue–cortex interface, i.e.,

$$R_{sb} = \frac{Z_b - Z_s}{Z_b + Z_s} \tag{4.2}$$

$Z = \rho c$ is the acoustic impedance, and the factor $e^{-2\alpha_s h}$ accounts for the attenuation of the signal in the soft-tissue layer. The factor "2" in the exponent refers to the two-way travel within the soft tissue. In Equation 4.1, the unit of α_s is nepers/cm (np/cm) and $\alpha_s h$ is dimensionless.

The extraction of R_{sb} in Equation 4.1 requires the knowledge of A_0 of the source signal and the attenuation coefficient, α_s of the soft tissue. To estimate the two parameters, we utilize the multiple reflections or reverberation within a piece of soft-tissue mimic. Figure 4.1b shows one primary echo and two reverberations within the mimic, which can be respectively expressed by

$$\begin{aligned} A_1 &= A_0 R_{ta} e^{-2\alpha_t h} \\ A_2 &= A_0 (R_{ta})^2 R_{tm} e^{-4\alpha_t h} \\ A_3 &= A_0 (R_{ta})^3 (R_{tm})^2 e^{-6\alpha_t h} \end{aligned} \tag{4.3}$$

where the subscript t, a, and m refer to soft-tissue mimic, acrylic, and matching layer of the transducer respectively; α_t, R_{ta} and R_{tm} are respectively the attenuation coefficient of the soft-tissue mimic, the reflection coefficients of the soft-tissue mimic–acrylic, and soft-tissue mimic–matching layer interfaces.

By defining

$$A_1{}' = \frac{A_1}{R_{ta}} = A_0 e^{-2\alpha_t h},$$

$$A_2{}' = \frac{A_2}{(R_{ta})^2 R_{tm}} = A_0 e^{-4\alpha_t h}, \quad (4.4)$$

$$A_3{}' = \frac{A_3}{(R_{ta})^3 (R_{tm})^2} = A_0 e^{-6\alpha_t h},$$

Equation 4.4 can be generalized as

$$A_n{}' = A_0 e^{-2\alpha_t (nh)} \quad (n = 1, 2, 3) \quad (4.5)$$

Taking logarithm of both sides linearizes the equation

$$\ln(A_n{}') = -2\alpha_t (nh) + \ln(A_0) \quad (4.6)$$

where $-2\alpha_t$ and $\ln(A_0)$ are the slope and intercept of the best fitting line ($\ln(A_n{}')$ versus nh) by linear regression.

In this study, the clinical application of the reflection coefficient is to estimate the bone properties of spine. The elastic modulus of cortical bone, E, varies with its density ρ, through $E = 0.09\rho^{7.4}$[22]. Other forms of the relationship were provided in a review study by Hegason et al [23]. Elasticity is then associated with velocity through $c = \left(\frac{E(1-\nu)}{\rho(1+\nu)(1-2\nu)}\right)^{1/2}$, where ν is the Poisson's ratio [24]. Changes in bone properties such as density and velocity affect the acoustic impedance of the bone Z_b, and higher R_{sb} reflects larger acoustic impedance of the bone Z_b, thus implying better bone quality. From the

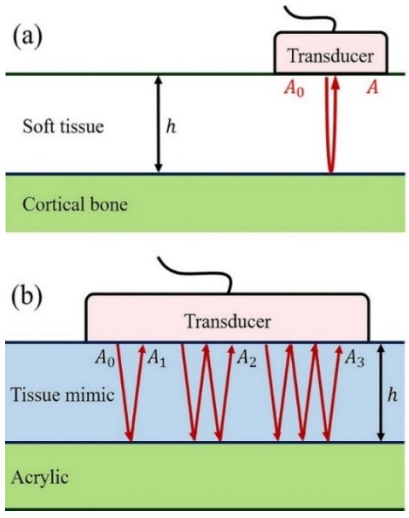


Figure 4.1 (a) A bone model. (b) The primary echo and multiple reflections within the tissue mimicking layer used to estimate A_0 and α_t.

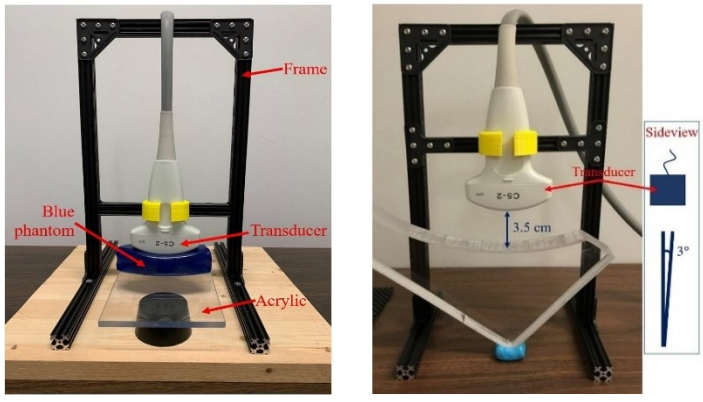
literature, the density of cortical bone in human ranges from 1800 to 2000 kg/m^3 [25, 26], and correspondingly velocity ranges from 2617 to 3666 m/s [27, 28], which corresponds to the impedance range of 4.7–7.3 Mrayls, and thus to a R_{sb}-range of 0.49–0.64.

4.2.4. Phantom Studies

The SonixTouch Q+ ultrasound system equipped with a 128-element C5-2/60 convex transducer (BK Medical, MA, USA) was employed for the study. The transducer has an adjustable center frequency including: 2, 2.5, 3.3, and 4 MHz. The center frequency was set at 3.3 MHz for the whole study unless otherwise stated.

Determine the Magnitude of the Source of the Ultrasound Transmission Signal (A_0), the Velocity of Sound (c_t) and the Attenuation Coefficient (α_t) of the Soft-Tissue Mimic (Blue Phantom)

As shown in Figure 4.2a, the transducer was mounted on an aluminum frame and placed in contact with a piece of 2.9-cm thick blue phantom (BP) (CAE Healthcare, FL, USA) overlying an acrylic plate, which was supported by two rubber corks. BP was used because it has ultrasound properties similar to those of soft tissue. Ultrasonic gel (Parker Laboratories, NJ, USA) was applied to all contacting surfaces between the transducer and the BP as well as between the BP and the plate to ensure good coupling. The thickness of BP after being compressed by the transducer was slightly under 2.9 cm, i.e., 2.2 cm. The



a) b)

Figure 4.2 (a) Experimental setup to measure the ultrasound properties of Blue Phantom and plates, and to estimate the subsequent reflection coefficients. (b) Experimental setup to measure the reflection from a rough curved surface. The surface is also tilted about 3 degrees in a direction (out of the page) perpendicular to the long axis of the transducer array.

received RF ultrasound signal was recorded and used to determine the c_t, α_t and A_0 based on Equation 4.6.

Determine the Reflection Coefficient (R) of Five Different Materials

Based on the previous experimental setup, the acrylic plate was also replaced by different metal plates such as aluminum, brass, copper, and steel to estimate their reflection coefficients with BP. The stiffness of the tested materials ranged from soft to hardest (related to density) while the acoustic impedance of bone should be between that of acrylic and aluminum. To determine the reflection coefficient of the five materials based on measurements, the measured ultrasound signals with Equation 4.1 was used.

The determination of theoretical reflection coefficients is based on Equation 4.2 and requires the predetermined densities, velocities, or acoustic impedance. The density of the BP was measured by the Archimedes' principle while the densities of the five plates were referenced from the literature. The velocities of the used materials, i.e. BP and five plates, were measured by the ultrasonic pulse-echo method using the previous described framework. Regarding the matching layer of the transducer, its acoustic impedance is pooled from references. These values used for the calculation of reflection coefficients are listed in Table 4.1.

Table 4.1 Properties of the materials used in the study.

Material	Density (kg/m3)	Velocity (m/s)	Impedance (Mrayls)
Water [29]	1000	1480	1.48
Blue Phantom (BP)[a]	900	1485	1.34
Soft tissue [30, 31]	1050	1540	1.62
Cortical bone [32–34]	1930	3250	6.27
Acrylic [35]	1180	2720	3.21
Aluminum [35, 36]	2700	6150	16.61
Brass [36]	8415	4275	35.97
Copper [35, 36]	8900	4515	40.18
Steel [36]	8030	5700	45.77
PZT [37]	-	-	33.00
Matching layer[b]	-	-	7.30[c]

[a]Both density and velocity were experimentally determined.
[b]$Z_{matching} = (Z_s Z_{PZT})^{1/2}$ [37]
[c]The value falls within the range given by the literature [38, 39].

Estimate the Effect of Surface Roughness and Inclination upon the Echo-amplitude

Beside the plate study, a 2.4-cm thick acrylic plate with a 19-cm diameter arc on one side (Figure 4.2b) was used to mimic the posterior arch of a vertebra. The surface of the arc was rough, which was caused by the circular-saw cutting. The transducer was placed at 3.5 cm from the rough surface of the phantom, which was similar to a normal distance from an ultrasound transducer to a lamina when the ultrasound was used to scan a scoliotic patient. To investigate the influence of the surface roughness, three scans were performed on: a) a smooth flat surface (SFS), b) rough curved surface (RCS), and c) a smooth curved surface (SCS) which was created by sanding the rough curved surface (RCS). The phantom with the RCS was also tilted at about 3 and 5 degrees in the direction perpendicular to the long axis of the transducer array, named RCIS, to examine the effect of inclination on the recorded echo amplitudes (Figure 4.2b). The experiments were carried out in a water tank with both the transducer and the phantom immersed in water.

Study a Vertebral Phantom

A second phantom study was performed on a cadaveric dry lumbar vertebra. The vertebra phantom was fixed to the bottom of the water tank with LePage® Fun-Tak® mounting putty (Lepage, Canada). Similar to the acrylic arch phantom experiment, the vertebra was submerged in water with the transducer set at 3.5 cm from the laminae. Again, the reflection coefficient of the cortical bone surface was calculated using Equation 4.1 with the ultrasound measurement signals.

4.2.5. In-vivo Pilot Study

Study Participants

Thirty-seven children (9 M; 28 F), aged 14.0 $\pm$ 1.6 years old (ranged between 11 and 17), were recruited from the local scoliosis clinic. Ethics approval was obtained from the University of Alberta Research Ethics Board. All participants signed the written consents prior to participation. The inclusion criteria were participants who 1) were diagnosed with

AIS, 2) had the age ranging from 10 to 18 years old, 3) the Cobb angle was between 10° to 45° (mild to moderate cases) and 4) had no prior surgeries.

Data Acquisition

The same ultrasound system described in the phantom study with the convex transducer was used for this in-vivo study. The scanning parameters used were: −15 dB power, 6-cm imaging depth, and 50% gain with linear time gain compensation (TGC). These parameters were selected based on the previous studies with some minor adjustments to ensure optimal image quality [40]. Data was obtained by an operator with two-years experience in using the US system to scan AIS subjects. The participants were asked to stand in a standard upright posture (Figure 4.3a) within a frame to prevent twisting of the body. The ultrasound gel was applied to their backs prior to scanning. During scanning, the transducer was positioned perpendicular to the sagittal profile of the subjects and moved along the spinal curve. Transverse B-mode images (cross-section image of a vertebra) (Figure 4.3b) were displayed in real-time, this allowed the operator to ensure the transducer was almost perpendicular to the lamina region. In this study, we used the low lumbar region (either L4 or L5) for analyses because these two vertebrae usually had little axial rotation in the spinal axis. Approximately 50 to 100 B-mode images and the corresponding radio-frequency (RF) data were exported for further analysis.

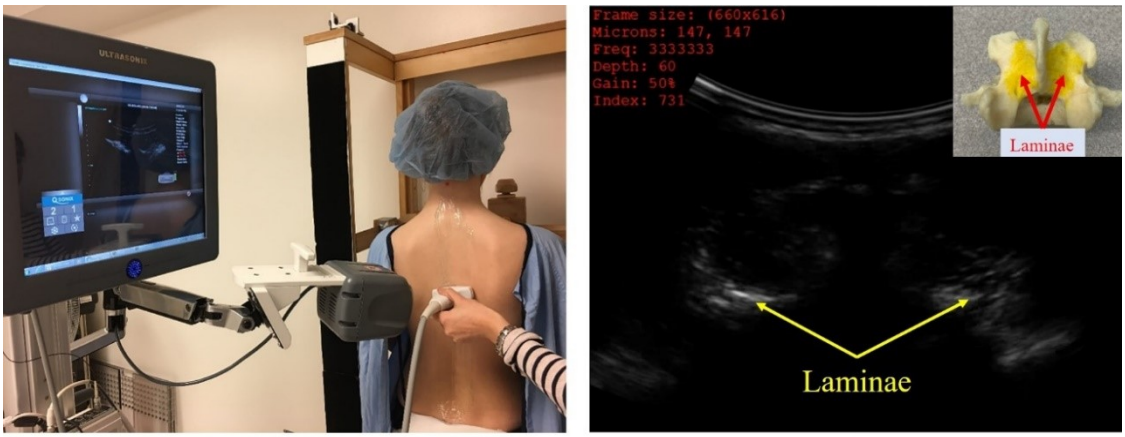


Figure 4.3 (a) The ultrasound scan of children with AIS in standing position. (b) A B-mode image of a vertebra. A cadaver vertebra is shown in the inset.

Selection of B-mode Frames

The lamina has been identified as a strong ultrasound reflector because the lamina area is usually a relatively flat surface [19]. This was similar to the arch phantom and the linear plate studies. The middle of the lumbar vertebra L5 was first identified. If the quality of image on L5 was poor, L4 was then used. Five consecutive B-mode frames around the middle of the vertebra with the most levelled pair of laminae were used.

4.2.6. Signal Processing

The RF data thus acquired was exported by Matlab software (R2019a, MathWorks, MA, USA). Each frame had 256 time series (A-lines). In the selected frames, the series with the largest reflected amplitudes from the laminae were selected for the analysis. Hilbert transform was applied to the series to obtain the envelopes of the signals [41]. The peaks of the envelopes were used as amplitudes to calculate the reflection coefficients. The envelope technique has been shown to be robust in facilitating the detection of the peaks of noisy signals, thereby yielding more consistent and stable results. Three recording with maximum amplitudes from the center of the transducer were used for the measurements in the experiments with plate phantoms. In the vertebral phantom and in-vivo studies about three to five recording of maximum echo-magnitudes corresponding to each lamina were exploited to measure the R. The measured R is the result of averaging the R from both laminae.

4.2.7. Results

4.2.8. Phantom Studies

Determination of A_0, c_t, and α_t

The primary echo and two reverberations traveling within the BP are shown in Figure 4.4a with the envelope peaks (the A_n) being 15,863, 2,120, and 274 respectively, which were the average of the three time series at locations corresponding to the center of the transducer. By means of Equation 4.4, the A_n are converted to $A_n{}'$ with R_{tm} and R_{ta} from Table 4.2. The best fitting line goes through the three points (Figure 4.4b) with a r^2 close

to unity, indicating the perfect fit between the data and the line. The source amplitude, A_0 was calculated to be 84,000. The best-fitted α_t is 0.18 np/cm or 1.53 dB/cm, which is compatible to the results obtained by transmission-through measurements with the correction for transmission loss through the water–BP interfaces [42]. The determined α_t thus can be considered the intrinsic absorption coefficient of BP. Further, using the echo and multiples, the velocity of the BP (c_t) was estimated to be 1,485 m/s.

Reflection Coefficient (R) of Five Different Materials

Based on the received reflection signals and Equation 4.1, the measured reflection coefficients, R, of the BP–plate interfaces are shown in Table 4.2. The velocity measurements used for the reference reflection coefficients fall within the ranges provided in literature (Table 4.1). The discrepancies of the measured R versus the calculated R ranged from 1.60% to 6.68%. Figure 4.4c also shows the measured reflection coefficients versus the calculated for the five plates.

Table 4.2 The calculated and measured reflection coefficients of the interfaces involved in this study. ϵ is given by the absolute value of the difference (calculated - measured) × 100% divided by the calculated value.

Reflection coefficients	Calculated	Measured	ϵ (%)
BP/Acrylic (R_{ta})	0.41	0.38 ± 0.02	6.68
BP/Aluminum	0.85	0.84 ± 0.06	1.60
BP/Brass	0.93	0.94 ± 0.07	1.73
BP/Copper	0.94	0.98 ± 0.11	4.41
BP/Steel	0.94	0.96 ± 0.02	2.14

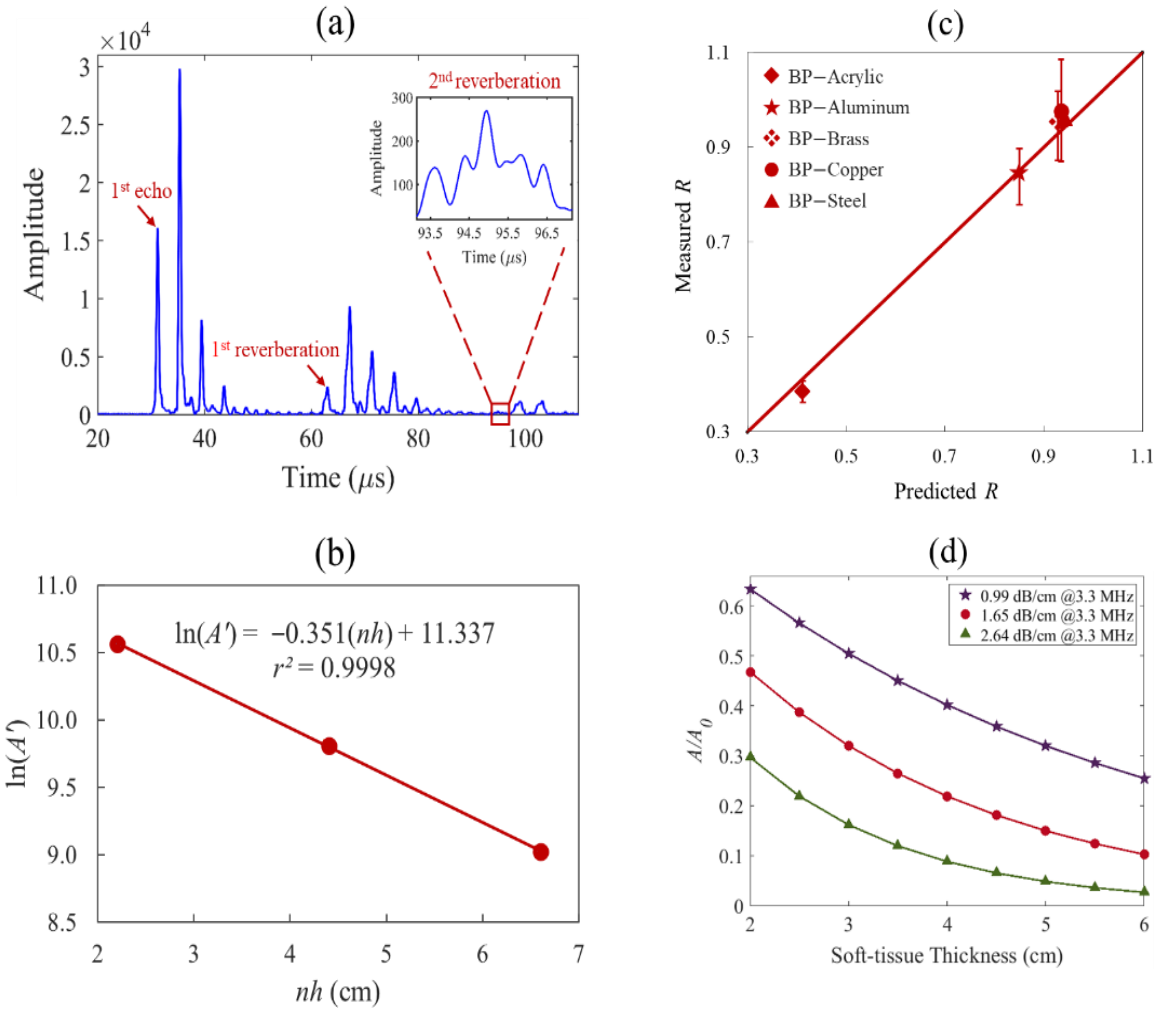


Figure 4.4: (a) Envelopes of the recorded echo and two reverberations within the BP. The amplitude of the 2nd reverberation is small and the zoomed signal is shown in the inset. (b) The linear regression line of the three data points. (c) Comparison between the measured and predicted reflection coefficients. Error bars denote the standard deviations (see Table 4.2). (d) The simulated amplitude ratio with change of soft-tissue thickness for three α_s-values.

Influence of Surface Roughness and Inclination

Using the signals from the smooth flat surface (SFS) as the reference, the measured R_{wa} from the SFS, RCS, and SCS are 0.37, 0.28, and 0.33, respectively. The signal loss due to surface roughness is observed when the R_{wa} measured from the RCS is 85% of that of the SCS. Comparison between the acquired signals on the SFS and RCIS at 3 degrees is displayed in Figure 4.5a–b.

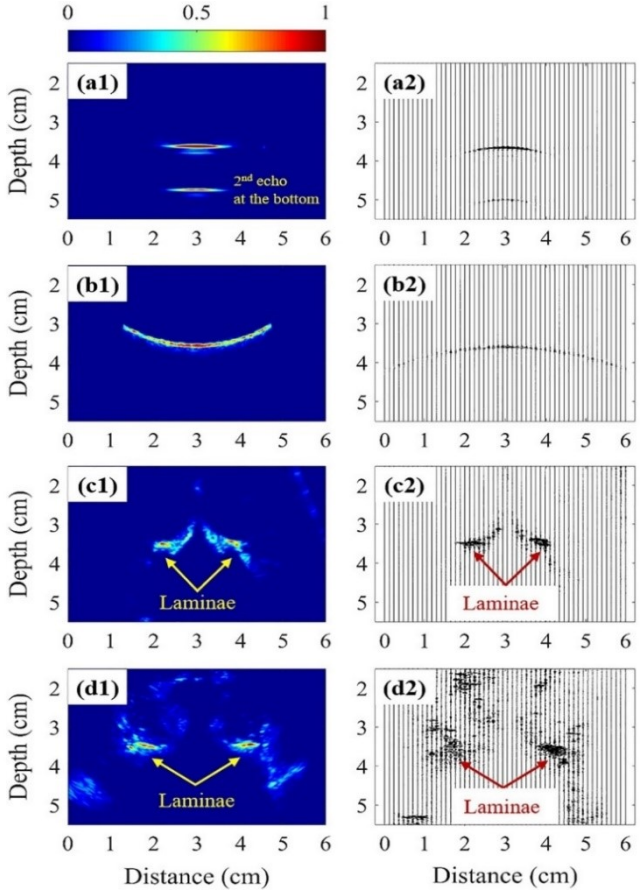


Figure 4.5 The ultrasonographs (Left) and the corresponding RF data (Right) of the following target: (a) acrylic phantom with the SFS, (b) acrylic phantom with the RCIS, (c) lumbar vertebra phantom, and (d) lumbar vertebra of a subject.

The RCIS signals (Figure 4.5b) show weaker intensity and amplitude in the ultrasound image and the corresponding RF plot than those of the SFS signals (Figure 4.5a). While the R_{wa} of the RCS accounts for about 76% of the reference R_{wa} (SFS), further loss due

to 3-degree inclination reduces the R_{wa} recovered from the RCIS signal (Figure 4.5b) to 0.23, just 62% of the reference. As the inclination increases to 5 degrees, the R_{wa} is reduced to just 0.12 or 32% of that from the SFS. The image of the cadaveric lumbar vertebra is shown in Figure 4.5c1–c2. The predicted R_{wb} is about 0.62 while the recovered coefficient is 0.23. Figure 4.5d1–d2 shows an example of the in-vivo ultrasound image of the lumbar vertebra and the corresponding RF data.

4.2.9. In-vivo Study

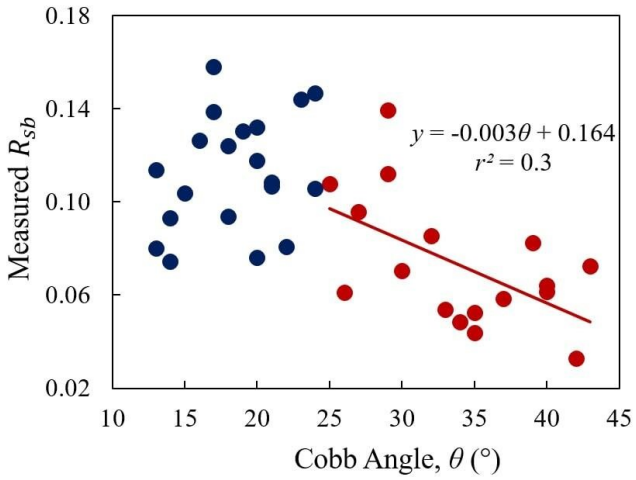


Figure 4.6 The correlation between the R_{sb} and Cobb angle.

The decay in echo-amplitude due to the attenuation of ultrasound in the soft tissue was compensated using an α_s-value of 1.65 dB/cm at 3.3 MHz. The measured R_{sb} of the 37 AIS patients ranges from 0.03 to 0.16. For example, the R_{sb} recovered from Figure 4.5d2 is 0.07. Based on the magnitude of the curves (Cobb angle – CA), the data was divided into two groups, mild ($10° < CA \leq 24°$) and moderate ($25° \leq CA < 45°$) curves. Figure 4.6 plots the measured R_{sb} versus CA; the mild curve group is colored with blue and the latter is shaded with red. The average R_{sb} values for the mild and moderate scoliosis regions are 0.11 ± 0.02 (n = 20) and 0.07 ± 0.03 (n = 17), respectively. Independent T-test analysis was performed to compare the measurements of the two groups (alpha of 0.05). The result shows that the measured R_{sb} values between the two groups are significantly different

between the two groups (p-value = 0.0001 < 0.05). There was also a trend observed in the moderate curve region with r^2 = 0.3. The best fitting line shows the reflection coefficient declines with the increasing CA, i.e., with the severity of the scoliosis.

4.2.10. Discussion

The theoretical calculation of the reflection coefficients of the BP and five different materials' interfaces (acrylic, aluminum, brass, copper, and steel) was matched to the measured values and maximum discrepancy was 6.7% (Table 4.2). As the stiffness of cortical bone is in between acrylic and aluminum, it is expected that the reflection coefficient of BP-cortical bone interface is between 0.38 to 0.84.

From the surface roughness and inclination studies, the roughness of the surface demonstrated approximately 25% of the signal loss. When the surface was smoothened again, the received signal was back to nearly 90% of the original. The small curve on the surface (SCS) had a small effect when compared to the flat surface (SFS). Furthermore, the effect of the tilt angle was actually more significant. Together with the surface roughness, a 3-degree tilt demonstrated about 40% loss while a 5-degree tilt demonstrated a nearly 70% signal loss. These experiments demonstrated that a significant amount of energy loss was expected due to both the inclination and roughness of the surface.

From the cadaveric vertebra study, the recovered coefficient is 0.23 $\pm$ 0.06, only 33% of the predicted R_{wb} (0.62). Besides, these factors affect the signal loss, the thickness of the human soft tissue may also have effects. Figure 4.4d shows the simulated responses of the amplitude ratio with soft-tissue thickness for three values of α_s. With a constant source amplitude A_0 and a fixed tissue thickness, the amplitude of the echo decreases with increasing α_s-value while for a fixed α_s, the amplitude decreases exponentially with thickness. The attenuation coefficient of soft tissue, α_s, in human ranges from 0.3 to 0.8 dB/cm at 1 MHz with an average of about 0.50 dB/cm [31, 43]. Since the relationship between α_s and frequency is linear [30, 44], α_s was extrapolated to be 1.65 dB/cm at 3.3 MHz, which is similar to α_t obtained by the best fitting regression and transmission-

through experiments. Ultrasound energy decreases with distance exponentially as it propagates through the absorptive soft tissue. The absorption mechanism dissipates energy within the tissue as heat, reducing the energy and magnitude of the signal. Using the ultrasound images of the 37 AIS subjects, the thickness of soft tissue, measured from the lamina to the skin surface, ranged from 2 to 6 cm with an average of about 3.5 cm. At 3.5 cm soft tissue thickness, the simulated echo-amplitude is only 26% of the source amplitude for α_s = 1.65 dB/cm. Therefore, the effect of soft tissue on the echo-amplitude cannot be ignored.

The effect of absorption upon the reflection coefficient was also studied. The first-order approximation of the amplitude acoustic reflection coefficient for two lossy biological tissues is given by [45]

$$R_{lossy} = R_{lossless} + i\frac{\Delta}{2} \tag{4.7}$$

And

$$\Delta = \frac{\alpha_s}{k_{\alpha_s}} - \frac{\alpha_b}{k_{\alpha_b}} \tag{4.8}$$

where $i^2 = -1$, $R_{lossless}$ is the lossless acoustic reflection coefficient, and Δ is the change of α/k (absorption coefficient per wavenumber) across the tissue interface. Assuming cortical bone has an attenuation coefficient of 45 dB/cm at 3.3 MHz [46], the absorption term (imaginary component) accounts for less than 10% or precisely 6.8% of the $|R_{lossy}|$. For the simplicity, we ignore the attenuation effect on the reflection coefficient and only consider the lossless reflection coefficient in this study.

After an approximate compensation of the attenuation in the soft tissue, the measured R_{sb} was in range of 0.03–0.16, lower than the expected values of 0.49–0.64 due to the mentioned loss factors. This loss is challenging to measure to fully recover the R_{sb}. However, by assuming the loss is similar in each AIS subject, meaningful conclusion could be drawn from the measured R_{sb}. The average R_{sb} value for the moderate curve was lower than that of the mild curve region (0.07 vs 0.11). There was also a mild tendency of decreasing R_{sb} when the curve was larger. A moderate correlation between the R_{sb} and CA was found with r^2 of 0.3.

4.2.11. Conclusion

This preliminary study has demonstrated the feasibility of using ultrasonic reflection coefficients for the estimation of material properties and its application in estimating bone properties of AIS patient groups. The total loss in echo amplitude due to the absorptive soft tissue layer, surface roughness and inclination is significant and difficult to quantify. However, although these losses hinder the recovery of true bone properties, the average R_{sb} on the mild curve region was larger than that of the moderate curve region. An inverse relationship between the R_{sb} and CA is found in the AIS group with moderate curves, indicating that bone properties may decrease with the severity of scoliosis. Future investigation of the change of R_{sb} on individual person should be performed to track the risk of progression.

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4.3. Test-retest and Reliability Analyses of the Reflection Coefficient (RC) Index

4.3.1. Introduction

Adolescent idiopathic scoliosis (AIS) is a lateral curvature of spine coupled with axial vertebral rotation (AVR). The Cobb angle measure on posteroanterior (PA) radiographs is the gold standard to quantify the severity of scoliosis [1]. Children with AIS are usually monitored every 6 to 12 months to check if curve progresses (Cobb change >5°) [2]. Families and patients are concerned about the ionization radiation exposure and the risk of cancer [3, 4]. A study showed that the cancer rate in children with AIS was 4.3% which was five times higher than the age-matched population [5]. According to the literature, 27% to 38% of children with AIS suffer from osteopenia [6, 7], which means these children have lower bone mineral density (BMD) than normal. Dual x-ray absorptiometry (DXA) is the gold standard method to assess BMD, but it also exposes patients to ionizing radiation [8]. The BMD measured by DXA is also costly and rarely available in scoliosis clinics [8]. Other than the term bone density, bone quality is a better explanation when referring to all the bone properties which include the internal structure, geometry and the mechanical properties [9]. Quantitative Ultrasound (QUS) has been introduced to assess bone quality. The advantages of using ultrasound (US) are no exposure to ionizing radiation, low cost, and portability. More importantly, the elastic nature of the US waves provides an ideal method to evaluate the bone quality [10]. The main QUS parameters associated with the bone quality or bone strength are broadband ultrasound attenuation (BUA), the velocity of sound (VOS) and the stiffness index (SI) [11, 12]. The BUA is a measure of the ultrasound attenuation at different frequencies. It provides information about the cortical bone thickness, elasticity, and micro-architecture of bone. The VOS indicates the transmission velocity of ultrasound passing through bone which can evaluate the bone elasticity and density. Furthermore, the SI is a composite of BUA and VOS parameters and reflects bone elasticity. Langton et al. [13] conducted a study and showed that BUA was a good predictor of elasticity (R^2=75%) and bone strength (R^2=73%). In the 1990s a transmission method

which used US signals passing through the heel area to obtain QUS parameters was introduced. Lam et al. [14] used this transmission method to evaluate the bone quality in children with AIS. They found that the QUS parameters were correlated with the BMD value measured with DXA at the femoral neck, and these parameters were smaller than in a control group without scoliosis. Another study [12] also showed that the SI value measured at the heel area reflected low bone quality in children with AIS. This SI value was a prognostic factor of curve progression for AIS with an odds ratio of 2 (1.0–3.7, 95% CI) while BUA and VOS were not. However, none of these studies measured the bone quality of the spine directly. The transmission technique is not suitable for assessing the spine. Literatures [15-17] also reported that the speed of ultrasound and the reflection coefficient parameters were correlated with the stiffness and mechanical strength of cortical bones. Zheng et al. used an US pulse echo technique to measure the US reflection signals directly from spine [18]. In their preliminary study, they introduced a parameter called the frequency amplitude index (FAI) which reflected the cortical bone stiffness of spine. Their index, however, ignored the soft tissue attenuation effect and only showed a mild correlation with curve severity on children with AIS. In the present study, a modified FAI parameter called the reflection coefficient (RC) index was introduced. This ultrasound RC index accounts for soft tissue effect and reflectsbone stiffness. The objectives of this study were to investigate the test-retest, intra-rater and inter-rater reliabilities of the RC index measured from the lowest lumbar vertebra to reflect bone strength of the spine in children with AIS.

4.3.2. Methods

4.3.3. Clinical Participants

Ethics approval was granted from the local health research ethics board. Fifty-eight children were recruited. Participants signed written consents before data collection. The inclusion criteria were participants who a) were diagnosed with AIS, b) were aged between 10-18 years old, c) had major Cobb angle <55° and d) had no prior surgical treatment.

Among these 58 participants, 37 (64%) were under observation and 21 (36%) were under brace treatment.

4.3.4. Equipment

A SonixTouch Q+ ultrasound system equipped with a 128-element C5-2/60 convex transducer and a position sensor (BK Medical, MA, USA) was used. The US parameters were set at: frequency 3.3MHz, gain 50%, power -15dB and the imaging depth of 6 cm. These parameters were verified through *in-vivo* experiments to ensure the quality of the US image and raw data for measurements.

4.3.5. Data Collection

Each participant was scanned in a standardized standing posture (Figure 4.7). Prior to scanning, the spinous processes of C7, L5 and all vertebrae in between were palpated, identified, and marked on the skin. All scans started from the vertebral level C7 and terminated at L5. The US system captured both the spine image and the raw data. The raw data consisted of the amplitude of the US reflection signal at specific locations. Repeated scans were acquired on the first 24 participants during a single session. After the first scan, the operator told the participant to relax and then instructed him/her to hold the same posture as before again. A second scan was then performed.

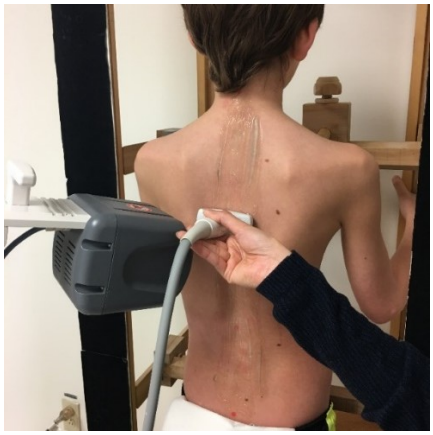

Figure 4.7 Acquisition of ultrasound data from a particpant with AIS in a standardized standing position with feet shoulder-width apart, hands holding the wooden frame, looking straight ahead, standing still and breathing normally.

4.3.6. Data Measurements

Two raters (R1, R2), both with 2+ years of experience measuring US images but novice on RC index measurements were involved. Both raters measured 10 practice images (not included in the analysis) and discussed any disagreement to ensure both raters were consistent and confident to measure the RC. For the test-retest study, rater 1 measured the RC for both scans (24 images) one week apart to minimize memory bias. For the reliability study, both raters measured all 58 images twice one week apart. Both raters were blinded to all participants' information and the other rater's measurements before measurements.

4.3.7. Reflection Coefficient (RC)

Equation (4.9) shows the calculation of the RC based on the US waves propagate through soft tissue with thickness (h), hitting the surface of the cortical bone and reflect back to the transducer. The magnitude of the US source signal (A_0) was determined in an *in-vitro* study prior to this study. A portion of the US transmitted signals was absorbed by the soft tissue due to attenuation. The magnitude of the reflected signal (A) was related to the stiffness and elasticity of the cortical bone [17]. Since the acoustic impedance of bone is significantly higher than that of soft tissue, most of the US signals hitting the soft tissue-bone interface are bounced back to the transducer if the surface is flat. The reflection signal is stronger if the bone is stiffer.

$$RC = \frac{Ae^{-2\alpha_s h}}{A_0} \tag{4.9}$$

where RC is the Reflection Coefficient of the soft tissue-bone interface; A is the amplitude of the echo; α_s is the attenuation coefficient of the soft tissue (1.65dB/cm at 3.3 MHz); h is the thickness of soft tissue, and A_0 is the amplitude of the source signal.

4.3.8. Measurement of the Reflection Coefficient (RC)

An in-house software was developed to semi-automatic measure the RC index. Figure 4.8 shows the procedures after the US image was reconstructed. The reconstruction process was described in [18]. Step 1) placing a red box around the L5 vertebra on the US image

(Figure 4.8a). Step 2) selecting the US frames around the centers of laminae of L5 on the transverse view (Figure 4.8b and c). Step 3) measuring the soft tissue thickness (h) from the surface of the skin to the point where the peak signal occurs from the laminae (Figure 4.8d and e). The magnitude of the maximal reflection signal A was extracted from the raw data based on the selected location. Then, the software automatically calculated the RC value using equation (4.9). Four other US frames, 2 above and 2 below were also selected to repeat the RC measurements (Figure 4.8b). Each selected US frame had 5 frames in between to ensure the RC measurements covered the entire region of the laminae.

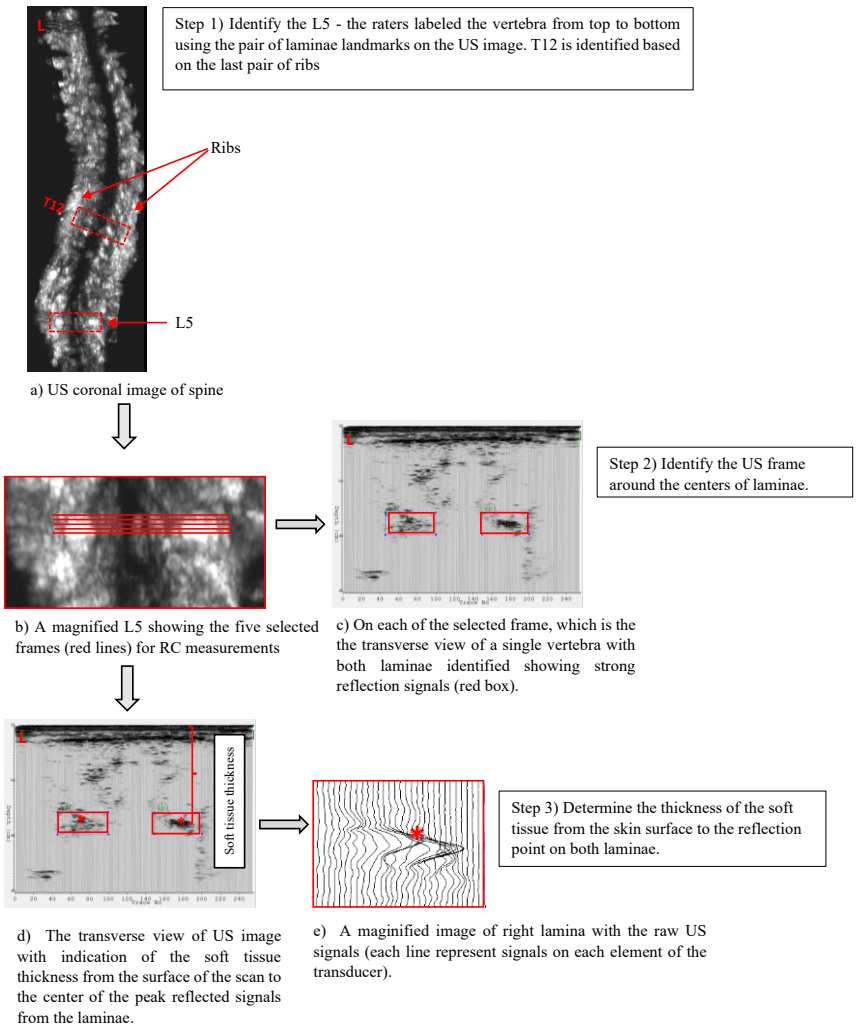

Figure 4.8a-e The 3 steps process to measure the reflection coefficient (RC) from a reconstructed ultrasound images

4.3.9. Data Analysis

Three different methods with a total of 5 RC measurements were investigated: i) the maximum RC (MRC) on the left and right laminae among the 5 selected frames, ii) the average RC (ARC) values on the left and right laminae among the 5 selected frames, and iii) the combined average RC (CARC) value on both left and right laminae. The soft-tissue thickness h was measured for each method.

For the test-retest, the two-way mixed model and consistency ICC [3,1] was used. For the reliabilities analyses, a two-way random model and absolute agreement ICC [2,1] was calculated. The reliability was interpreted as; poor: ICC< 0.5, moderate: $0.5 \leq ICC < 0.75$, good: $0.75 \leq ICC \leq 0.9$, and excellent: ICC> 0.90 [19]. The mean absolute difference (MAD) and the standard error of mean (SEM) [20] were reported. All statistical analyses were performed using the IBM SPSS v23 software (IBM, Armonk, New York, USA).

4.3.10. Results

Fifty-eight participants (47F, 11M) were included with age 14.0±1.57 (10.3 - 16.9) years old and the major Cobb angle ranging from 12° to 48° (24.3°±8.6°) identified on both radiographs and US images without missing any data or measurements.

4.3.11. Test-retest Reliability Analysis

Table 4.3a reports the average RC values from scan 1 versus scan 2 on all 5 measurements. The average RC values was similar between left and right laminae for the same method. However, the overall range of the Left-MRC (0.03-0.34) was smaller than the Right-MRC (0.04-0.45). The difference was not significant ($p<0.05$). Also, the ARC was not significantly different from the CARC. Table 4.3b shows the ICC [3,1] for the test-retest between scan 1 and 2, and all five measurements show good reliability (range: 0.77 to 0.83). Table 4.3c shows the comparison of the h measurements with all methods. The overall variation was less than 0.54 cm (13% of average thickness) which was approximately 9 US frames (distance between each frame is 0.59 mm).

Table 4.3a The average RC values for scan 1 and 2 from rater 1.

	Left Lamina		Right Lamina		CARC
	MRC	ARC	MRC	ARC	
Scan 1	0.16±0.08 (0.06-0.34)	0.08±0.04 (0.04-0.18)	0.17±0.11 (0.07-0.45)	0.09±0.04 (0.04-0.22)	0.08±0.04 (0.04-0.18)
Scan 2	0.16±0.07 (0.03-0.3)	0.09±0.04 (0.04-0.2)	0.18±0.11 (0.04-0.45)	0.09±0.05 (0.02-0.22)	0.09±0.03 (0.04-0.18)

Note: MRC = maximum reflection coefficient, ARC = average reflection coefficient, CARC = combined average reflection coefficient,

Table 4.3b The test-retest reliability of RC values between scan 1 and 2 from rater 1.

	Left Lamina		Right Lamina		CARC	
	ICC [3,1] (95% CI)	SEM	ICC [3,1] (95% CI)	SEM	ICC [3,1] (95% CI)	SEM
MRC	0.77 (0.54-0.89)	0.01	0.83 (0.66-0.92)	0.01	N/A	
ARC	0.81 (0.61-0.91)	0.01	0.81 (0.62-0.91)	0.01		
CARC	N/A				0.82 (0.62-0.92)	0.01

Note: MRC = maximum reflection coefficient, ARC = average reflection coefficient, CARC = combined average reflection coefficient, M1 = measurement 1, M2 = measurement 2, R1 = rater 1, R2 = rater 2, CI= confidence interval, ICC= intraclass correlation coefficient, SEM= standard error of measurements.

Table 4.3c The MAD of soft tissue thickness h (cm) measured by the MRC, ARC and CARC methods on the first 24 images from rater 1.

Categories	Method	Left Lamina	Right Lamina	Average of Left & Right
		MAD (cm)	MAD (cm)	MAD (cm)
Soft tissue thickness (h)	**MRC**	0.54±0.43	0.48±0.43	N/A
	ARC	0.46±0.39	0.43±0.36	
	CARC	N/A		0.44±0.37

Note: MRC = maximum reflection coefficient, ARC = average reflection coefficient, CARC = combined average reflection coefficient, MAD = mean absolute difference between measurements from scan 1 vs scan 2.

4.3.12. Intra-rater Reliabilities

Table 4.4a shows the RC values of both the left and right MRC and ARC for repeated measurements from raters 1 and 2. The right RC measurements were higher than the left. Table 4.4b shows the intra-rater reliabilities of the left and right MRC and ARC. Rater 2

showed an excellent reliability, but rater 1 only showed moderate and good reliability with left and right measurements, respectively. Between the ARC and MRC, ARC showed better reliability. Also, the right measurement was more reliable for both raters. Table 4.4c shows the intra-rater reliability for CARC with ICC [2, 1] ≥ 0.84 and the SEM was ≤0.01 for both raters. Among the 3 methods, the CARC showed the best reliability.

Table 4.4a The average RC measurements on the first and second measurements (M1 and M2) on the same 58 images using MRC and ARC methods from rater 1 (R1) and rater 2 (R2).

		Left Lamina		Right Lamina	
		M1	**M2**	**M1**	**M2**
MRC	**R1**	0.14±0.07 (0.04-0.32)	0.14±0.08 (0.05-0.41)	0.17±0.12 (0.03-0.78)	0.16±0.12 (0.03-0.86)
	R2	0.12±0.06 (0.05-0.31)	0.12±0.06 (0.04-0.32)	0.13±0.10 (0.03-0.67)	0.14±0.11 (0.03-0.72)
ARC	**R1**	0.07±0.03 (0.03-0.17)	0.08±0.03 (0.03-0.18)	0.09±0.05 (0.02-0.38)	0.08±0.05 (0.02-0.36)
	R2	0.07±0.03 (0.03-0.14)	0.07±0.03 (0.02-0.14)	0.07±0.04 (0.02-0.27)	0.08±0.04 (0.02-0.28)

Table 4.4b The intra-rater reliability on RC measurements from R1 and R2 on the same 58 images using the MRC and ARC methods.

		Left Lamina		Right Lamina	
		SEM	**ICC [2,1] (95% CI range)**	**SEM**	**ICC [2,1] (95% CI range)**
MRC	**R1**	0.04	0.53 (0.31-0.69)	0.03	0.75 (0.62-0.84)
	R2	<0.01	0.93 (0.88-0.95)	<0.01	0.96 (0.93-0.97)
ARC	**R1**	0.01	0.71 (0.55-0.81)	0.01	0.86 (0.78-0.91)
	R2	<0.01	0.97 (0.95-0.97)	<0.01	0.98 (0.97-0.99)

Table 4.4c The mean±SD and intra-rater reliability for RC measurements from R1 and R2 on the same 58 images using the CARC method.

		M1	M2	SEM	ICC [2,1] (95% CI range)
CARC	**R1**	0.08±0.04 (range 0.03-0.22)	0.08±0.03 (range 0.03-0.20)	0.01	0.84 (0.73-0.90)
	R2	0.070±0.03 (range 0.03-0.17)	0.07±0.03 (range 0.03-0.17)	<0.01	0.98 (0.97-0.99)

4.3.13. Inter-rater Reliabilities

Table 4.5a shows the inter-rater reliability of the RC measurements for MRC and ARC. Again, the ARC was more reliable than MRC, and the first measurements from both raters had better agreement. Table 4.5b shows the inter-rater reliability for CARC with ICC [2, 1] ≥ 0.85 for both measurements and an SEM of 0.00. The MAD of the thickness h for the CARC method between raters 1 and 2 was almost the same for both measurements. In terms of the frame selection variation, there was maximum 10 frames difference between raters 1 and 2.

Table 4.5a The inter-rater reliability for RC measurements from R1 and R2 on the same 58 images using the MRC and ARC methods.

		Left Lamina		Right Lamina	
	Measurements	**SEM**	**ICC [2,1] (95% CI)**	**SEM**	**ICC [2,1] (95% CI)**
MRC	**M1**	0.02	0.70 (0.50-0.82)	0.02	0.82 (0.60-0.91)
	M2	0.04	0.54 (0.32-0.70)	0.02	0.81 (0.70-0.88)
ARC	**M1**	0.01	0.83 (0.69-0.90)	0.01	0.86 (0.66-0.93)
	M2	0.01	0.79 (0.66-0.87)	0.01	0.85 (0.76-0.91)

Table 4.5b The inter-rater reliability for RC measurements on the same 58 images using the CARC method, the soft tissue thickness (h) measurement difference and the frame number selection differences between R1 and R2.

	Measurements	MAD±SD	SEM	ICC [2,1] (95% CI range)
CARC	**M1**	0.01±0.01	<0.01	0.86 (0.56-0.94)
	M2	0.01±0.01	<0.01	0.85 (0.73-0.91)
Soft tissue thickness (h) (cm) difference	**M1**	0.20±0.07		
	M2	0.21±0.08		N/A
Frame selected difference	**M1**	7.47±7.29		
	M2	9.18±11.46		

4.3.14. Discussion

This is the first study to investigate the reliabilities of the RC index. According to US theory, when the sound wave hits a tilted surface, the echo will reflect away from the transducer. The lamina at L5 is a relatively flat area with minimum rotation and should reflect most of the signals. In this study, the vertebral rotation on L5 was 2.8° ± 1.8° (n=58), which was in a small magnitude range.

The test-retest study showed that the RC measurements are repeatable for each method. However, the RC value on the right lamina was slightly higher than left, this indicated that the right side of the vertebral bone was slightly stronger than the left. This phenomenon might be related to the curve direction. Among the 58 participants, 31 had major curves on right side. Fourteen of these had major curves > 25°. On the other hand, 27 subjects had left major curves but only 9 of their curves were > 25°. From a biomechanical point of view, the lumbar vertebra supports most of the body weight [23]. The Wolff's law stated that when the loading on a particular bone increase, that bone remodels itself over time and becomes stiffer [23, 24]. The soft-tissue thickness measured on the left lamina was also slightly bigger than that on the right. This might relate to more L5 rotation toward the right. The overall AVR for the 24 participants involved in the test-retest study was 2.7°±1.7°. The average AVR toward the right was 3.0°±2.0° (ranged 0.6 to 8.4) while toward the left was -2.1°±1.0° (ranged -3.3° to -0.6°). For the intra-rater, the reliability on the right side

was better than on the left side. This was due to the RC value being smaller on the left side, hence it was more difficult to identify the peak value from the image. As shown in Figure 4.8c, the image is darker on the right which means signals are stronger. Also, R2 seems to measure the RC index more reliably. R1 had more deviations on cases when AVR was > 5°. There were five outliers on R1-MRC measurements. If these 5 cases were excluded, the intra-rater on the left RC improved from 0.53 to 0.70. The CARC presented better inter-rater reliability than both the MRC and ARC. Again, by excluding those five R1 outliers, the MRC inter-rater for left lamina improved from 0.54 to 0.66 for the second measurement. Also, the maximum average inter-rater difference for the soft tissue thickness h and for the number of frames were 2.1 mm and 9, respectively. Since the spacing between each frame was 0.59 mm, the 9 frames difference was equivalent to 5.4mm, which was smaller than the height of a single vertebra. In addition, the CARC showed the best reliability among the methods while the MRC had the least. This may be due to a single extreme value in MRC might affect the result significantly. To highlight the clinical significance, a preliminary association of the RC value and curve progression was investigated. Figure 4.9 shows the distribution of the CARC on all 58 participants. Eighteen out of 58 cases showed curve progression and their RC values were captured within 7 months of the RC data collection visit. The overall average of the CARC for all participants was 0.07±0.03. If we use the threshold of 0.07 (dashed line), 19 participants were above the average. Among those, 13/19 cases (68%) showed no progression. If we use 0.08 as the threshold, 12/15 cases (80%) showed no progression. Furthermore, there are 7 cases with values above 0.10 (mean + 1 SD) and all of those showed no progression. Hence, the stronger the bone, the less likely the curve is to progress.

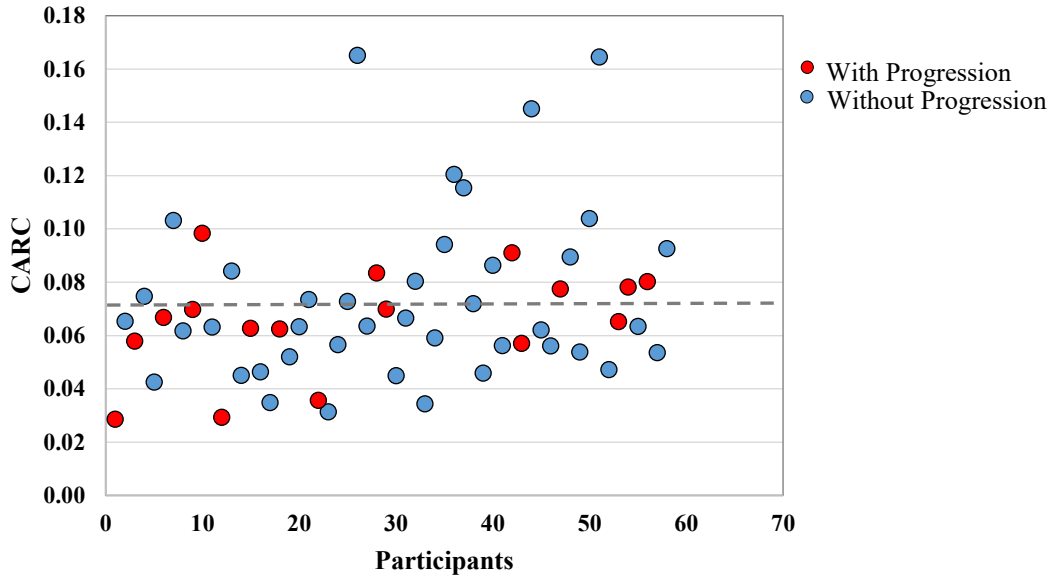

Figure 4.9 Distribution of the participants with and without progression based on the CARC measurements (n=58)

4.3.15. Conclusions

The reflection coefficient (RC) index can be measured repeatably and reliably. The CARC method provided the best reliability (ICC [2, 1] ≥ 0.77 and SEM ≤0.01). A RC value above the average already indicate a lower chance of curve progression. Future studies can consider using the RC index and other risk factors to predict curve progression.

4.4. Summary

This chapter reviewed a new ultrasound index called reflection coefficient (RC) which showed that this index is linearly related with the stiffness of the study materials. Based on the experimental results, the stiffer the bone, the higher the RC value. A moderate Correlation between RC and the curve severity was observed (R^2=0.3). The factors that affected the RC value and could cause signal loss were the absorption by soft tissue layer, surface roughness, and the inclination which are difficult to quantify. A pilot study was also conducted to test the repeatability and reliability of this index. In summary, the CARC

which was the combined average RC value on both the left and right laminae was the most repeatable and reliable to measure the RC index. The reliability for CARC method was good (ICC [2, 1] ≥ 0.82 and SEM ≤0.01). Clinical application of this index was discussed, and our findings showed that 68% children who had the RC value above the average (RC = 0.07) showed a lower chance of curve progression.

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Chapter 5: Ultrasound Kyphotic Angle (KA)

5.1. Overview

This chapter describes a new US measurement method of the kyphotic angle (KA) on sagittal US images. The materials of this chapter are based on two studies which have been submitted to refereed journals. In section 5.2, a pilot study with the title "Intra- and Inter-rater Reliabilities and Differences of Kyphotic Angle Measurements on Ultrasound Images versus Radiographs for Children with Adolescent Idiopathic Scoliosis – A Preliminary Study" is presented. This study has been submitted to "Journal of Spine Deformity". The section 5.3 presents a research study with the title" Factors Influencing Kyphotic Angle Measurements on Ultrasound Spinal Images in Children with Adolescent Idiopathic Scoliosis (AIS)" which has been submitted to "European Spine Journal". Section 5.4 provides the summary of this chapter.

5.2. Reliabilities and Differences of Kyphotic Angle Measurements on Ultrasound Images versus Radiographs

5.2.1. Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional (3D) spinal condition characterized by lateral curvature and vertebral rotation. It has no known cause and primarily affects girls aged 10 to 18 years old. The current gold standard to diagnose and monitor AIS is to measure the Cobb angle on standing posteroanterior (PA) radiographs [1]. Currently, the clinically accepted error for the Cobb angle measurement is 5° and the definition of curve progression is indicated by an increase of 6° or more [2] of the Cobb angle. According to the Scoliosis Research Society, the recommended treatments are observation, orthotic treatment (bracing), and surgery [2]–[4], and most scoliosis centers use the value of the Cobb angle to inform treatment recommendations. However, treatment decision based solely on the Cobb angle measured on PA radiographs may fail to account for the 3D nature of AIS, an issue which is only recently being addressed according to the

International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment (SOSORT) guidelines.

Sagittal parameters such as the kyphotic angle (KA), lumbar lordosis, and pelvic incidence have been identified as important factors according to newer SOSORT guidelines on the treatment of AIS as a 3D spinal disorder [4]. Thoracic hypokyphosis in particular is prevalent in patients with AIS [5]–[9]. Mac-Thiong et al. found a correlation between the thoracic curve type and the degree of the KA, and additionally suggested that inadequate sagittal biomechanics could alter the loading of the spine, affecting the progression of AIS [6]. Furthermore, Van Loon et al. have demonstrated that the correction of a flattening sagittal spine via the introduction of a wedge at the thoracolumbar junction in the supine position worked to reduce the Cobb angle on PA radiographs. This approach suggested a role for the correction of thoracic hypokyphosis in the conservative treatment of AIS [10].

Scoliotic and kyphotic angles are generally measured from standing radiographs. There are only few studies have addressed the reliability and repeatability of KA measurements. This is due to the inconsistencies in vertebral selection, making comparisons between measurements difficult. Among all the KA measurement approaches, there were studies using the Cobb method to measure the kyphosis between superior endplate of T1 and inferior endplate of T12 [5], [11]–[16]. A study by Carman et al. measuring KA found that an 11° difference in KA was accepted to rule out measurement error with 95% confidence [13]. Ohrt-Nissen et al. found an intra-rater reproducibility of 9° and inter-rater reliability of 13° [16].

However, the frequency of taking lateral (LAT) radiographs exposes children with AIS to higher ionizing radiation than PA radiographs, which increases lifetime cancer risk [17]. Even though the EOS Imaging machine is recently available in many scoliosis centers and the ionizing radiation dosage is reduced, the clarity of identifying the endplates of vertebrae at the upper thoracic region is still a challenge. Ultrasound (US) imaging is a radiation-free alternative that has been used to successfully measure the Cobb angle and the axial vertebral rotation (AVR) on standing PA and transverse views [18], [19], respectively. As

a single US scan of the spine can provide information on all 3 planes: PA (Cobb), transverse (AVR) and lateral (KA), it may help to measure the KA more reliably. Recently, Lee et al. also used US to measure the sagittal curvature. However, their method only used the sagittal information. Similar to the US PA view, the endplates of vertebrae are invisible in the lateral view, and so an alternate method to measure sagittal angles must be developed. The objectives of this study were to 1) present a new method to measure KA based on 3D US images, 2) determine the intra-rater and inter-rater reliabilities of the KA measurement, and 3) determine the inter-method accuracy in comparison to the Cobb method measured from radiographs.

5.2.2. Methods

5.2.3. Clinical Participants

Twenty subjects (17F, 3M, aged 13.7±2.2 years old, range 10-17 years old) were recruited in this study from a local scoliosis clinic. The inclusion criteria were subjects who were 1) diagnosed with AIS, 2) Cobb angle ≤50°, 3) required out of brace PA and sagittal radiographs, and 4) had no prior surgical treatment. The Cobb angle of ≤50° was chosen, which can eliminate patients who have large axial vertebral rotation, to make sure laminae are visible on the ultrasound images. Ethics approval was obtained from the local health research ethics board and written consents were obtained from all subjects prior to data acquisition.

5.2.4. Data Acquisition

Standing out of brace PA and LAT radiographs and an US scan were obtained from each subject on the same day, with the US scan following the radiographs within 1 hour. The PA and LAT radiographs were acquired simultaneously using the EOS system (EOS Imaging, Paris, France) with subjects standing in a standard posture: subjects looked forward without tilting their heads and their hands were placed on the front chamber wall of the EOS system. US images were acquired using the Sonix TABLET medical US system equipped with a 128-element C5-2/60 GPS convex transducer (Analogic Ultrasound – BK

Medical, Peabody, Massachusetts, USA). This system recorded the orientation and location of the transducer to capture the 3D information of the spine. Each US scan started at the C7 vertebra and terminated at L5, with the transducer positioned perpendicular to the subject's back and moved along the path of the curve. During the scan, each subject was positioned in a standing frame in a position similar to that used in the EOS chamber with the hands placed at chest height against the opposite wall of the standing frame. The hips and the shoulders were also positioned in the same plane in a neutral standing position to minimize movement of the subject during the scan. Each US scan lasted for less than 1 minute. The US operator had 3 years of experience to acquire good US spinal images. An in-house developed program, called the Medical Imaging Analysis System (MIAS), was used to compile and process the acquired US data to produce coronal, transverse and sagittal plane images of the spine. This software allows users to zoom in and out the image, adjust the contrast and brightness.

5.2.5. Raters

Two raters (R1 and R2) performed ultrasound KA measurements from US images. R1 had 2 years of experience measuring KA on both radiographs and US LAT images and R2 had 4 years of experience measuring KA on LAT radiographs, but less than 1-year experience on US images. R3 who had over 20 years of experience on radiographs measurement measured the KA on the corresponding radiographs. Prior to the study, both R1 and R2 measured an extra 10 LAT US images from previous patients' records as a training set to obtain a mutual measurement agreement. These 10 measurements were not used for analysis.

5.2.6. Data Measurements

The KA on both radiographs and US images were measured using the MIAS program. All raters were blinded to the clinical information and R3 measured the KA from the radiographs once while R1 and R2 measured the KA from the US images twice. The radiographs and US images were randomly coded with numbers. The second US

measurement (M2) was measured one-week apart from the first measurement (M1) to minimize recall bias. On LAT radiographs, the Cobb method was applied. During the measurements, all raters were permitted to adjust contrast, brightness and magnification. For the radiography measurement, two lines were then drawn parallel to the top endplate of T1 and bottom endplate of T12, and the MIAS program displayed the value automatically.

On US images, the centers of lamina (COL) of the T1-T3 and T10–T12 vertebrae are first identified on the PA view (Figure 5.1a). The tips of the 6 spinous processes (SP) were then identified in the transverse views (Figure 5.1b) which was more precise than the PA view. The SP would automatically display in the sagittal view, where its location could be fine-tuned (Figure 5.1c). The identification of T3 and T10 were only used to confirm the trend of the spinal curve. The MIAS program also automatically displayed the KA calculated using the intersection of a line connecting the SP of T1 and T2 and another line connecting the SP of T11 and T12. The program calculated the acute angle formed by the intersection of these two lines, which was taken to represent the proxy KA.

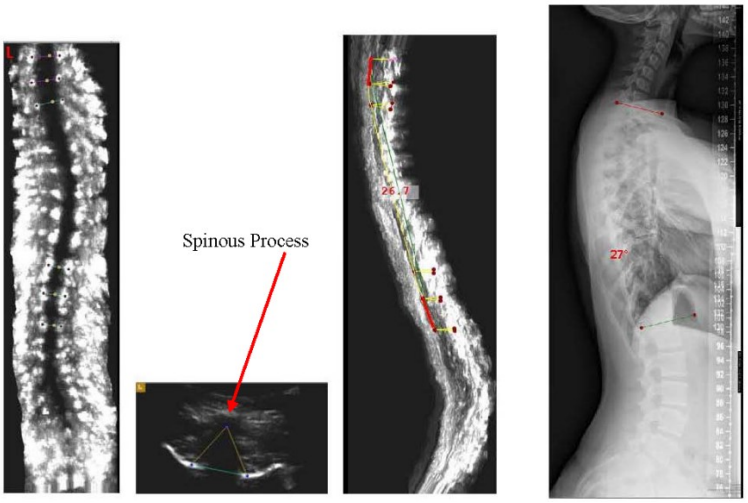

Figure 5.1 (a) An ultrasound image showing a coronal PA view of spine with T1-T3 and T10-T12 identified on the image, (b) an US transverse view of T1 with the laminas identified and joined using a line and the midpoint of the line as the spinous process, (c) US sagittal view of spine and the kyphotic angle measured 27 ° using the slope of a line joining spinous process of T1 and T2 at the top to T11 and T12 at the bottom, d) the sagittal view X-ray of the spine correspond to the same patient and the kyphotic angle measured using the Cobb method as 27°.

5.2.7. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics v23 software (IBM, Armonk, New York, USA). The mean and standard deviation (SD) of the KA measurements on both radiographs and US images from both raters were reported. The intra- and inter-rater reliabilities of the US KA measurements were calculated using the intraclass correlation coefficient [ICC (2,1)] with a 2-way random model and absolute agreement with a confidence interval of 95%. The inter-rater reliability was determined by comparing the measurements made by both raters (R1 and R2) with 2 different measurements (M1, M2). The accuracy of the US measurements was analyzed by comparing the radiographic measurements with US measurements. The ICC value was considered excellent (≥0.90), good (0.75-0.90), moderate (0.5-0.75), or poor (<0.5) reliability based on Koo's report [20]. The mean absolute difference (MAD) and standard error of the mean (SEM) [21]were determined for the intra-rater, inter-rater and inter-method analyses. The inter-method of inter-rater comparison was calculated to report the measurement differences. Bland-Altman analyses were also performed. A regression equation between the US KA and the radiographic KA value was generated based on all rater 1 and 2 US measurements.

5.2.8. Results

Among the 20 subjects, 10 subjects were under observation and they were in their initial visits. Another 10 subjects were under brace treatment and they were in those clinics that their braces were first prescribed. The major Cobb angle of the subjects ranged from 13° to 41° (25°±8°) and KA from radiography ranged from 16º to 56º (38°±10°). A total of 20 KAs were measured on both radiographs and US images. Table 5.1 summarizes the mean, standard deviation, and the range of the KA measurements by each rater.

Table 5.1 KA measurement means, standard deviations, and range on radiographs and US images (n = 20)

	M1 (°)	M2 (°)
R1 (US)	40±10 (22-56)	37±12 (11-58)
R2 (US)	41±11 (18-59)	39±13 (17-60)
R3 (Radiograph)	38±10 (16-56)	N/A

R -Rater, M - Measurements

Table 5.2 shows the MAD±SD, SEM and the intra-rater reliability (ICC[2,1]) of the US KA measurements of R1 and R2. Both raters have excellent reliability.

Table 5.2 The intra-rater reliability of the US KA measurements (n = 20)

	MAD±SD (°)	SEM (°)	ICC [2,1]
R1	3.1±1.7	0.4	0.94
R2	3.2±2.3	0.5	0.95

R - Rater; MAD - mean absolute difference; SD - standard deviation; SEM - standard error of the mean; ICC - intraclass correlation coefficient

Table 5.3 compares the inter-rater reliability on both US KA measurements. The ICC values showed good reliability (>0.85), and there was no statistically significant difference on the measurements ($P < 0.05$).

Table 5.3 The inter-rater reliability for KA measurements on both US and radiographs (n = 20)

Image Modality	MAD±SD (°)	SEM (°)	ICC [2,1]
M1 US	4.2±4.6	1.8	0.85
M2 US	4.8±4.2	1.6	0.86

Table 5.4 shows the inter-method comparison of R1 and R2. The results from both raters on KA measurements from radiographic measurements, US-M1 and US-M2 showed similar as all the SEM values were under 1.7º and the ICC[2,1] values were >0.84.

Table 5.4 The inter-method comparison and reliability of the KA measurements from both raters (n=20)

Variable	MAD±SD (°)	SEM (°)	ICC [2,1]
R1 (M1 vs X-ray)	4.2±3.0	1.1	0.87
R1 (M2 vs X-ray)	3.9±2.9	0.9	0.90
R2 (M1 vs X-ray)	5.0±4.1	1.7	0.84
R2 (M2 vs X-ray)	4.1±3.9	1.3	0.88

Figure 5.2 shows a comparison between the US M2 vs. the radiographic measurements for both R1 and R2. Both R1 and R2 showed the US KA always overestimated. The variability was smaller when the KA values were larger. The US measurements of both raters were averaged and plotted against the average radiographic KA measurements by both raters. A linear equation of the radiographic KA = 0.82° x US KA + 5.60° was generated, which can be used to convert the US KA to its radiographic equivalent. When using this equation to assess the accuracy of the US measurements, the overall MAD between US and radiographic KA was 2.9±1.6°.

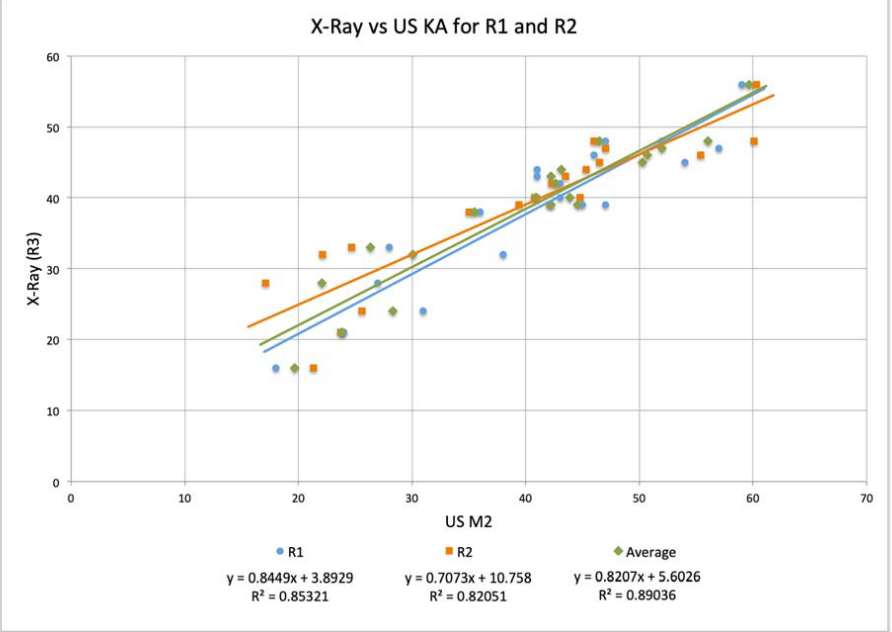

Figure 5.2 Inter-method comparison between the radiographic measurements and US measurements from both raters (R1 and R2) and the average of both raters with R2 indicating the percent of variance explained by the regression.

Figure 5.3 shows the Bland-Altman analyses for R1 x-ray versus the second US measurement and the same repeated for R2. R1 demonstrates less bias than R2 between the two types of measurements, with a scatter that indicates moderate overestimation but all points within 1.96 standard deviations about the mean. R2 showed a systematic overestimation of larger values of KA than R1, confirming the results found in Figure 5.2.

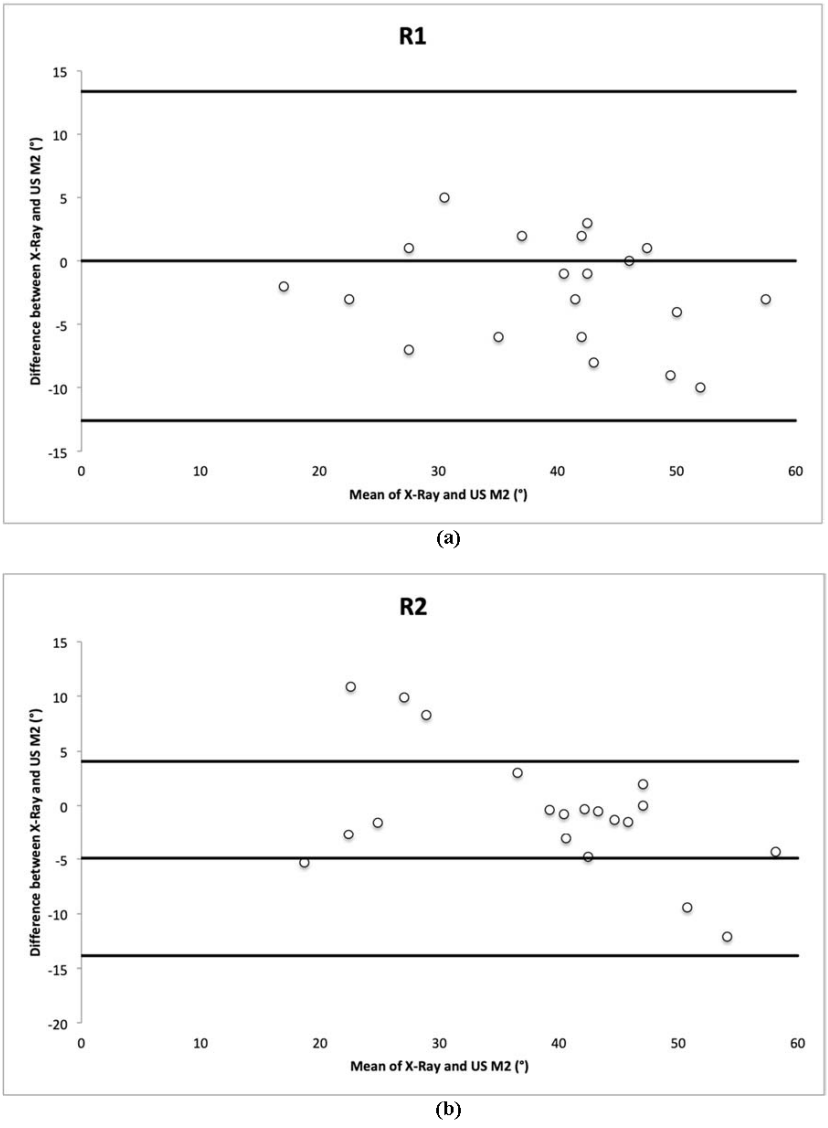

Figure 5.3 The Bland-Altman plot of mean and ±1.96 standard deviations of the mean of radiographic and US measurements versus the differences between the radiographic and US measurements for (a) Rater 1 and (b) Rater 2.

5.2.9. Discussion

Scoliosis is a three-dimensional problem which may include abnormal spinal curvature in all 3 planes. Besides the Cobb angle on the coronal view and the axial vertebral rotation on the transverse view, the KA on the sagittal view is also an important parameter to be measured. However, due to the increase of cancer risk in taking an extra radiograph, most orthopedic surgeons decide not to take the LAT radiograph in the follow-up clinic unless patients complain about back pain. Although the low dose x-ray system (EOS) has become common, clinicians and parents are still concerned about the accumulated ionizing radiation. The US method has been introduced and it has been demonstrated that it can measure the Cobb angle and vertebral rotation reliably, but it has not been developed for kyphotic measurement using the available 3D information. From the literature, Carman et al. reported that, without fixing the end vertebrae to measure the KA, the measurement difference could be as large as an 11° difference in between consecutive measurements of the same subject [13]. Also, there is no standard clinically accepted error in KA measurements. The KA measurement differences between the inter-rater and the inter-method of both raters (Tables 5.3 and 5.4) ranged from 3.9^{o} to 4.8^{o}, which showed very little difference, indicating that kyphotic angle measurements from both radiographs and US images are similar.

A limitation in assessing the relevance of the data acquired in this study is the wide variety of methodology used in determining thoracic kyphosis (TK), including but not limited to a range of radiographic parameters (T1-T12, T2-T12, T5-T12, and nonfixed endplate methods), computer assisted methods, and surface topography [5], [12], [16], [22], [23]. While the T1-T12 method is the most commonly reported, for both ease of comparison of the degree of kyphosis between subjects, and also for its relevance in capturing the entirety of the global TK. Of course, it has some radiograph-specific drawbacks such as the difficulty in visualizing the T1 vertebra due to the overlap of the shoulder girdle in some subjects [5], [11]–[14], [16]. This limitation does not exist in US images because the vertebral selection and the COL identification on both coronal and transverse planes are

shown clearly. This makes T1 clearly visible in every US image, and this highlights a key strength of using US images for kyphotic measurements. Additionally, a study [24] has compared different methods based on plumbline measures, using correlation of plumbline distance, or based on video rasterstereography methods to measure kyphosis. These studies only provided fair to good results on reliability, but no direct measurements were reported.

In addition to the lack of consistency in terms of measurement method for TK, there are only two studies reported the standard intra-rater and inter-rater reliabilities of the KA measurement based on T1-T12 [15], [16]. Among the two studies, Ilharreborde et al. [15] reported an average intra-operator difference of three experienced raters was 6° and an inter-operator reproducibility of 7°. The current study demonstrates similar results. Furthermore, Ilharreborde et al. already used 3D EOS system to capture the TK, which may have more reliable images. Ohrt-Nissen et al. [16] reported the intra-rater and inter-rater reliabilities of 0.87 and 0.82, respectively. Our results reported similar or better results on both intra-rater and inter-rater reliabilities while using the US images.

Limitations of our study include a) the US image quality, which may depend on the skill of the US operator, and b) the identification of the lamina, which requires experience to identify COL on US images. However, the advantage of the US images is the ability to view the spinal images in all three-dimensional views (coronal, transverse, and sagittal). This eliminates the difficulty of only observing on the sagittal view. Furthermore, as this is the only known study to measure KA directly from US images, the reduction of exposing children to extra ionizing radiation can be made.

5.2.10. Conclusions

The intra-rater and inter-rater reliabilities of the KA measurements on US images can be performed reliably and the measurement differences are within the clinical accepted range. Also, the average differences of the KA measurements between the US images and radiographs is 4^{o}, which shows no significant difference on repeat KA measurements from radiographs. However, since the number of study cases is small, a larger clinical trial is needed to validate the US method can be applied to scoliosis clinics.

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5.3. Factors Influencing Kyphotic Angle Measurements on Ultrasound images

5.3.1. Introduction

Adolescent idiopathic scoliosis (AIS) is a 3D structural spinal disorder which includes lateral curvatures in the coronal plane, vertebral rotation in axial plane, and may have abnormal curvatures in the sagittal plane. The current imaging standard to measure the severity of scoliosis is radiography. Children with AIS usually take an X-ray every 6 months to monitor curve progression and review treatment decision [1, 2]. Traditionally, a posterioanterior (PA) and a lateral (LAT) radiograph are taken at the initial visit. Then, for children under observation, LAT radiographs are only requested when patients have abnormal sagittal curvature or complain of back pain. For brace candidates, LAT radiographs are only obtained at the in-brace follow-up. Since the EOS X-ray system (EOS Imaging, Paris, France), a low dose ionizing radiation system, has become more common, more clinicians prescribe PA and LAT radiographs at every follow-up clinic. Surgeons can thus review the 3D alignment of the spine. In addition to the Cobb angle measured on the PA radiograph [2], the kyphotic angle (KA) and the lordotic angle are measured on the LAT radiograph.

The KA value is especially important for children with AIS undergoing brace treatment or planning surgery. Orthotists and surgeons need to consider the sagittal profile while they design the brace or plan to operate the spine to ensure that the sagittal balance and alignment are optimized. Inappropriate treatment planning may reduce the treatment effectiveness or lead to undesirable changes in sagittal profile such as hypokyphosis or flattening of the thoracic kyphosis. Flattening of the spine increases the risk of death related to scoliosis because it may cause a reduction of the lung function [3]. In addition, the KA has also been considered as a parameter associated with curve progression. Studies reported that children who had curve progression showed a significantly lower KA versus the cases without progression [4, 5].

The KA can be measured using different top vertebral levels along the curve. Researchers have reported using T1-T12 [6, 7], T3-T12 [8], T4-T12 [9], T5-T12 [10] for KA measurements. The most common method to measure KA is the Cobb method and the angle is formed between the superior endplate of T1 and inferior endplate of T12 [11]. Carmen et al. used the Cobb method from T1 to T12 on 20 radiographs and the measurement error reported was 11 degrees [6]. Ohrt-Nissen et al. reported kyphotic angle measurements from different levels and showed a variability in intra- and inter-rater results from 8° to 13°[9] with the best intra- and inter-rater reproducibility for T4–T12 and T5–T12 levels.

Taking the LAT radiographs in addition to PA radiographs adds ionizing radiation to children with AIS. This is a worrisome issue since children with AIS have to undergo multiple visits and this excessive radiation may increase the incidence of cancer [12, 13]. Even though the EOS system uses lower ionizing radiation, the cumulative radiation is still a concern to children's families [12, 13]. Ultrasound (US) is a non-ionizing radiation imaging modality. An US imaging method had been introduced which could be used to measure the Cobb angle and the axial vertebral rotation reliably and accurately [14-16]. Recently, our group conducted a pilot study on 20 subjects to evaluate the intra-rater and inter-rater reliabilities for measuring the KA from US spinal images and the results showed good reliability ((ICC) [2, 1] $\geq$ 0.84). However, this pilot study did not explore which factors can affect the accuracy of KA measurements. Therefore, this study aimed to further validate the accuracy and reliability of the US KA measurements based on a larger data set and to investigate how curve severity, X-ray imaging comparisons and curve type could influence the accuracy and reliability of KA measurements on US images in children with AIS.

5.3.2. Methodology

5.3.3. Clinical Participants

Sixty participants (53 F, 7 M, aged 13.4±1.6 years old) were consecutively recruited and scanned using our US scanner. The inclusion criteria were participants who a) were

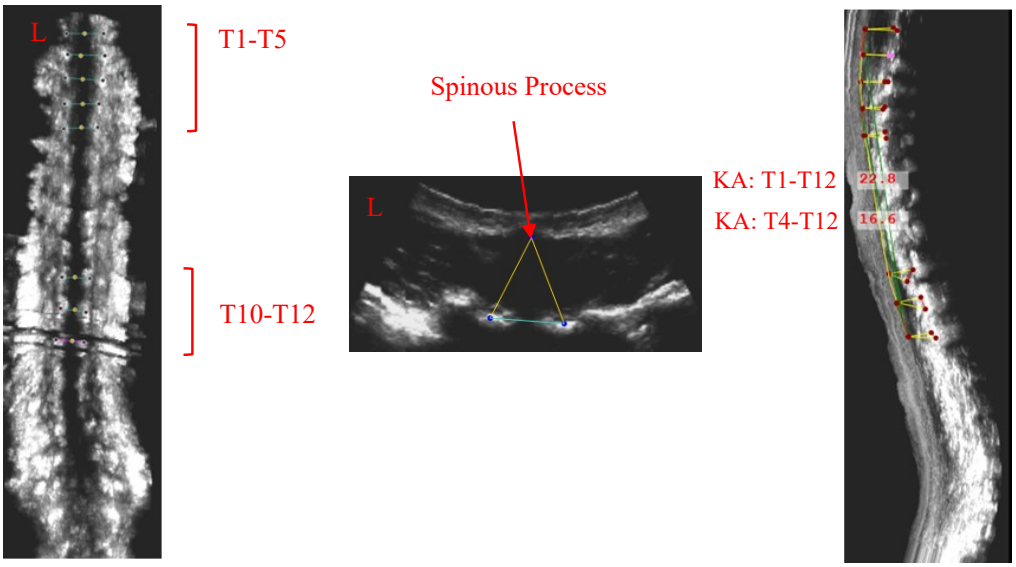
diagnosed with AIS, b) had a major Cobb angle <55°, c) had no prior surgical treatment, d) had an out of brace radiograph at the recruitment clinic, and e) required PA and LAT radiographs. Among the 60 cases, 32/60 (53%) were undergoing brace treatment and 28/60 (47%) were under observation. The ethics approval was obtained from the local health research ethics board and all participants consented prior to participation.

5.3.4. Data Acquisition

There were 34/60 participants where the EOS X-ray system was used and 26/60 where a conventional X-ray system was used. All X-ray and US images were acquired in a standard standing position. During EOS acquisition, the PA and LAT radiographs were taken simultaneously, but for the conventional X-ray system, the LAT radiograph was taken independently after repositioning the patient. During the LAT radiographs, the participants were asked to stand in an upright position, without tilting the head and looking forward, hands placed at chest height against the opposite wall and without leaning forward or backward. US images were acquired using the Sonix TABLET which is equipped with a 128-element C5-2/60 GPS convex transducer (Analogic Ultrasound – BK Medical, Peabody, Massachusetts, USA). During the US data acquisition, participants stood in a frame devised to stabilize them in their natural position. They stood with feet shoulder-width apart, looking straight and without tilting the head, with both hands held on the poles of the frame at around chest height to ensure the arms were not overlapping the spine. The operator then identified and marked the C7 and L5 vertebrae as the starting and end points of the scan. Both US and X-ray were performed in the same day, but two different rooms and the US images were acquired blind to the X-ray acquisition. One operator with 4+ years of experience performed the US scanning. Among the 60 participants, 40 had a second US acquisition at their subsequent follow-up visits within 7.0±3.1 months from their first visit. An in-house custom software was used to reconstruct the US images in coronal, axial and sagittal planes and measure the KA.

5.3.5. Data Measurement

Two raters, R1 and R2, were involved in this study. R1 had 20+ years of experience doing radiographic measurement and measured the KA on the LAT radiographs. R2 had 2+ years of experience measuring the KA on US images. Both raters measured all images twice one week apart to reduce memory bias. R1 measured the KA using the Cobb method using the T1/T12 and T4/T12 approaches. The procedures for using 3D US information to measure the KA measurements on US images are shown in Figure 5.4. The rater first identified the center of laminae (COL) for the vertebral levels from T1 to T5 and T10 to T12 on the PA images (Figure 5.4a). When the vertebra was selected on the PA image, the corresponding axial view was displayed. The operator then labelled the tip of the spinous process at that level (Figure 5.4b). Once all the center of laminae and spinous processes were labelled, the sagittal view with all labelled points were displayed automatically (Figure 5.4c). Labelling the T3 and T10 vertebrae helps confirm the curve trend of the spine on the sagittal view. The rater then drew a line manually to join the spinous processes of T1 and T2 and joining the spinous processes of T11 and T12 to measure the KA between these segments for the T1/T12 level measurement method (Figure 5.4c). The same procedure was repeated to measure the KA angle from T4/T12.



a) b) c)

Figure 5.4 The process of measuring KA on US images. a) The center of the laminae of T1 to T5 and of T10 to T12 are first identified on the coronal US image. b) Then, the two centers of laminae and the tips of spinous process are identified in the axial view of the 3D US image at the level passing horizontally by both laminae. c) The spinous processes locations are then displayed in the sagittal view and used to measure the KA. The T1/T12 KA is obtained by measuring the angle between segments connecting T1T2 and T11/T12. The T4/T12 KA is obtained by measuring the angle between segments connecting T4T5 and T11/T12.

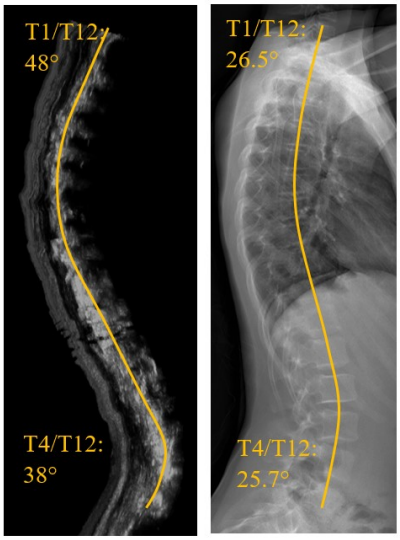
5.3.6. Data Analysis

The mean and standard deviation (SD) for both X-ray and ultrasound KA measurements at different occasions, measurement 1 and 2 (M1 and M2) for reanalysis of baseline images were reported. The intra-rater (M1 vs M2) and inter-method (X-ray vs US for both levels of measurements) reliabilities were calculated using the intraclass correlation coefficient ICC [2, 1] with a 2-way random model and absolute agreement with 95% confidence interval. The mean absolute difference (MAD) and standard error of measurements (SEM) between first and second measurements (M1 and M2) on each the US and the X-ray imaging modalities were reported. The Pearson correlation coefficient between US and X-ray measurements were calculated. The bias analysis and limits of agreement between US and X-ray was plotted using the Bland-Altman method. The independent Student t-test was

used to compare the X-ray and US measurements in terms of the KA severity. Also, the Chi square analysis was used to investigate the association of MAD thresholds (5° and 7°) with the X-ray acquisition systems and the curve type including number of scoliotic curves and apex location at upper thoracic (UT), main thoracic (MT), thoracolumbar (TL) and lumbar (L) regions. For the Chi square analysis, the X-ray acquisition systems coded as conventional (0) and EOS (1) and the number of coronal curves was coded to single (0) and double or multiple as (1). The number of curves and apex location were extracted from our scoliosis database which were measured by the clinical staff with 10+ years of experience. The alpha level < 0.05 was used to determine statistical significance.

5.3.7. Results

Ten of the 60 cases were excluded after comparison. Even though we tried to standardize the standing posture, the excluded 10 cases had adopted a standing posture that was significantly different between X-ray and US images because during x-ray acquisition the standardized instructions were not followed. Figure 5.5 shows an example in which the subject placed the hands above the head during the X-ray acquisition. Hence, fifty participants (43 F, 7 M, aged 13.4±1.9 years old) were analyzed. There were 83 coronal scoliosis curves, and the average of all curves was 23.1°±8.2° (10° to 44°).



a) b)

Figure 5.5 Comparison between the KA measurements on US and X-ray images for the same subject. The orange line shows the sagittal curve for a subject who has an arm flexion of around 60° during US data acquisition and >90° during X-ray data acquisition. a) The US KA are 48° and 38° when using T1/T12 and T4/T12 measurement, respectively. b) The corresponding X-ray KA values are 26° and 25°, respectively.

5.3.8. Reliability and Agreement Analysis

Table 5.5 shows the mean, standard deviation, MAD, SEM and the intra-rater reliability (ICC [2,1]) of KA measurements of the first and second intra-rater measurements when using the two different levels measurement method for the US and for the x-ray images, respectively.

The intra-rater MAD of X-ray KA was slightly bigger than the MAD of US KA, but there was no difference between level measurement method for a given imaging system. When comparing the different levels measurement method, T1/T12 showed a better intra-rater reliability. Overall, the intra-rater reliability results of KA measurements on both X-ray image types combined and on US images were excellent with ICC [2,1] >0.9, MAD ≤3.1° and SEM ≤0.79° when using the guidelines from Koo et al. [17]. (Table 5.5)

Table 5.5 The average, standard deviation, SEM and intra-rater reliability of the KA measurements for both vertebral levels measurement methods on the X-ray and US images.

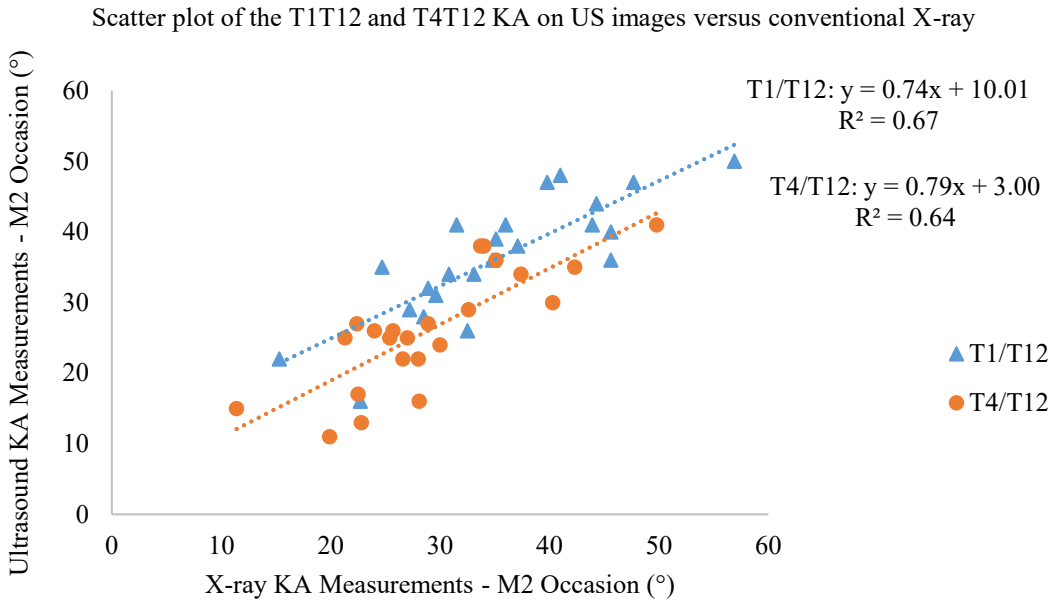
	Measurement Levels	Mean±SD (range) At the Baseline		Intra-rater Reliability Results		
		M1 (°)	M2 (°)	MAD±SD (°)	SEM (°)	ICC [2,1] (95%CI, range)
X-ray (combining both systems)	R1 (T1/T12)	32.6±11.0 (9 to 59)	32.7±10.0 (8 to 57)	2.5±2.2	0.52	0.95 (0.91 to 0.97)
	R1 (T4/T12)	26.4±10.8 (2 to 51)	26.4±10.1 (2 to 50)	3.1±2.7	0.79	0.92 (0.86 to 0.95)
Ultrasound	R2 (T1/T12)	35.9±9.6 (13 to 54)	35.5±9.6 (8 to 58)	2.2±1.9	0.43	0.95 (0.92 to 0.97)
	R2 (T4/T12)	25.7±10.3 (1 to 51)	25.9±9.5 (4 to 46)	2.8±2.5	0.67	0.93 (0.88 to 0.96)

Table 5.6 shows the inter-method reliability in which measurements for both set of vertebral levels show good reliability (ICC [2,1] ≥0.82). The maximum MAD±SD and the SEM of the differences between X-ray KA and US KA were 5.0°±3.8° and 1.6°, respectively.

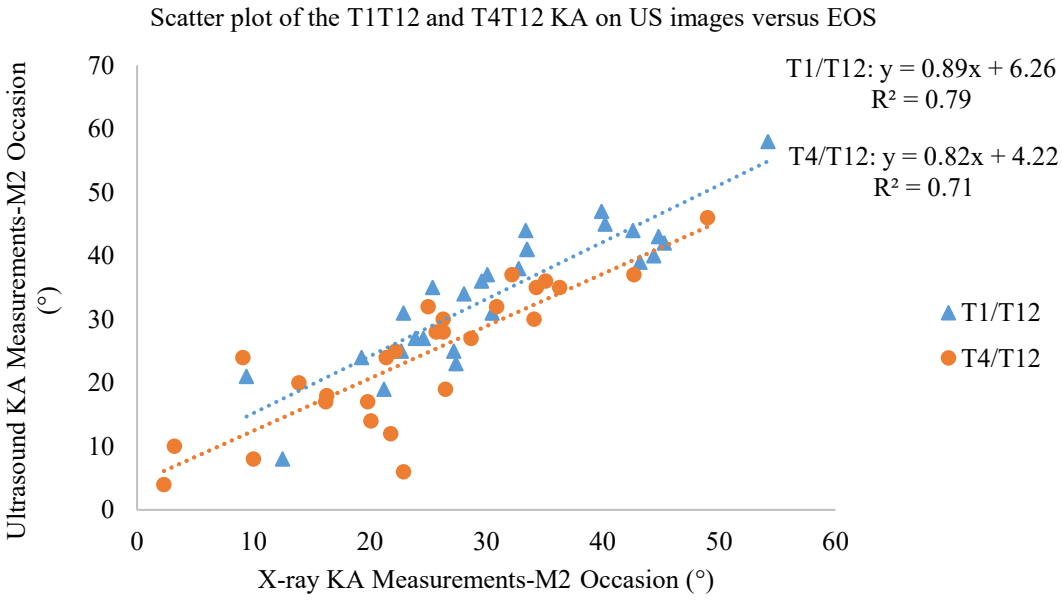
Table 5.6 The comparison of inter-method differences and reliabilities at different occasions (M1, M2) and for different levels measurement methods as T1/T12 and T4/T12.

	Measurement Levels	MAD±SD (°)	SEM (°)	ICC [2,1] (95%CI, range)
T1/T12	US (M1) vs X-ray (M1)	4.8±3.2	1.30	0.84 (0.67 to 0.92)
	US (M2) vs X-ray (M2)	4.6±3.1	1.23	0.84 (0.69 to 0.91)
T4/T12	US (M1) vs X-ray (M1)	5.0±3.8	1.24	0.82 (0.71 to 0.90)
	US (M2) vs X-ray (M2)	4.6±3.7	1.56	0.82 (0.70 to 0.89)

Overall, the US KA had a linear correlation with X-ray KA for both different levels measurement method (T1/T12 and T4/T12). (Figure 5.6) The T1T12 X-ray KA from the EOS X-ray predicted the corresponding US KA (R^2 = 0.79) better than the conventional X-ray (R^2 = 0.67). For the EOS system, when the X-ray T1/T12 KA values were small (<15°), the variation was bigger.



(a)



(b)

Figure 5.6 Scatter plots of the US KA versus the X-ray KA from the second measurement occasion (M2) for both different levels measurement method (T1/T12 and T4/T12) when using data from comparisons to (a) the conventional X-ray system and (b) the EOS X-ray system.

Figure 5.7 shows the Bland-Altman plot of the inter-method measurement difference in KA versus the average of the US and X-ray measurements at the second occasion (M2) using the T1/T12 level measurement method. On average, there was a -2.4º bias, which means US measurements were larger than X-ray and there was no correlation between the severity of the KA and the differences in measurements. The 95% limits of agreement were from 12.4 to 7.4 degrees suggesting that X-ray measurements corresponding to US measurement can be expected to be 12.4 degrees smaller and up to 7.4 degrees bigger with 95% confidence.

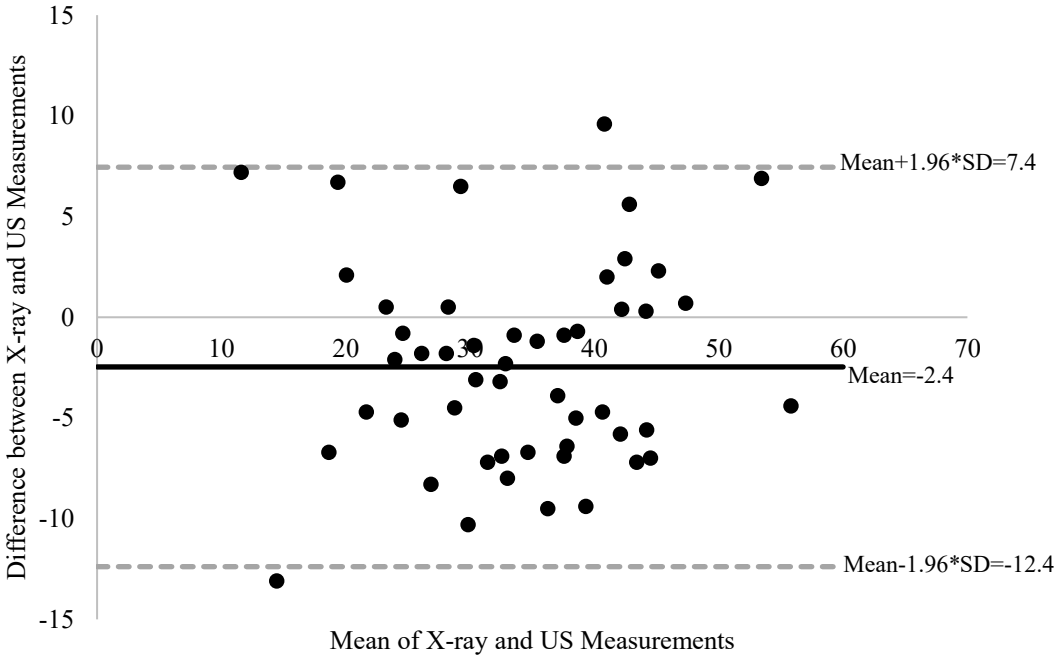


Figure 5.7 Bland-Altman plot of the inter-method differences between the X-ray T1/T12 KA – US T1/T12 KA versus the average KA.

5.3.9. Factors Influencing the Accuracy and Reliability

Table 5.7 shows the association of measurement difference (MAD) with the X-ray KA severity, the X-ray systems and curve type for the T1/T12 level measurement method since it showed a better reliability. Two thresholds of MADs were tested and compared. The 5-degree threshold was selected based on the maximum MAD observed from inter-method

analysis (Table 5.7a). Also, the 7-degree threshold was selected based on the minimum threshold reported on inter-rater reliability analysis on KA from literature [18] (Table 5.7b). Table 5.8 shows the distribution of the curve type based on apex location for both thresholds.

Table 5.7 Test of association between the magnitude of the absolute measurement difference and the KA severity, the X-ray system and the curve type for the T1/T12 measurements using a) a 5º MAD threshold, and b) for a 7º MAD threshold.

T1/T12 Level of Measurements			MAD (°) (between X-ray (M2) and of US KA (M2)		Statistic value	P value
			≤5.0 (n=27)	>5.0 (n=23)		
X-ray KA Severity		Mean±SD	33.7±8.9	31.4±11.2	t=0.80	0.42
X-ray System	Conventional (n=23)	Number n (%)	13 (57%)	10 (43%)	Chi square=0.10	0.74
	EOS (n=27)		14 (63%)	13 (37%)		
Curve type		Single (n=19)	10 (53%)	9 (47%)	Chi square=0.02	0.87
		Others (n=31)	17 (55%)	14 (45%)		

(a)

T1/T12 Level of Measurements			MAD (°) (X-ray KA - US KA) (M2)		Statistic value	P value
			≤7.0 (n=40)	>7.0 (n=10)		
X-ray KA		Mean±SD	33.9±9.5	27.8±11.1	t=1.74	0.08
X-ray System	Conventional (n=23)	Number n (%)	19 (83%)	4 (17%)	Chi square=0.18	0.67
	EOS (n=27)		21 (78%)	6 (22%)		
Curve type		Single (n=19)	15 (79%)	4 (21%)	Chi square=0.02	0.88
		Others (n=31)	25 (81%)	6 (45%)		

(b)

MAD= mean absolute difference, KA= kyphotic angle, M2= measurement 2, US= ultrasound

Kyphotic Angle Severity

The average X-ray KA value did not differ significantly between patients with large inter-method differences or not for both thresholds. (Table 5.7, p = 0.42 vs. p = 0.08.)

X-ray System

The number of cases with a MAD ≤ 5° when comparing the US KA to the conventional or the EOS X-ray were 57% vs 63%. However, the number of cases with a MAD ≤ 7° when comparing the US KA to the conventional or the EOS X-ray were 83% vs 78%, respectively. There was no statically significant difference in frequency of error above and below either large MAD threshold based on the X-ray acquisition system used in the comparison with US KA (Table 5.7).

Curve Type

There also was no significant difference between the number with single or more than single curve among those with larger errors based on MAD thresholds of 5° and 7° when comparing US KA to Xray KA, with 53% vs 55% and 79% vs 81%, respectively. (Table 5.8) Among 83 scoliotic curves in total, 50/83 (60%) were within 5º threshold, but 68/83 (82%) were within 7º threshold. For MT curve, accuracy increased significantly when comparing the 5º to 7º thresholds while the number of cases increased from 22/33 (67%) to 30/33 (90%). Similar trend occurred on the TL/L, it increased from 24/43 (56%) to 35/43 (81%).

Table 5.8 The association between the magnitude of the absolute errors of measurements (5° and 7° thresholds) and the apex location of the scoliotic curves.

Curve type (Total n = 83)	MAD ≤ 5.0° (n = 50)	MAD > 5.0° (n = 33)	MAD ≤ 7.0° (n = 68)	MAD > 7.0° (n = 15)
UT (n = 7)	4 (8%)	3 (9%)	3 (4%)	4 (27%)
MT (n = 33)	22 (44%)	11 (33%)	30 (44%)	3 (20%)
TL/L (n = 43)	24 (48%)	19 (58%)	35 (51%)	8 (53%)

Abbreviations: UT= Upper Thoracic, MT= Main Thoracic, TL= Thoracolumbar, L= Lumbar

5.3.10. Discussion

The current gold standard to measure the KA is to use the Cobb method on LAT radiograph. Apart from the ionizing radiation issue, the X-ray modality is a projection

method which means when axial vertebral rotation exists, it may introduce error in KA measurements. Also, if the pelvis rotates in the axial plane while standing it may add errors on the projection. Therefore, the true KA measurement may not be obtained. In contrast, during the US imaging acquisition, the operator captures the information along the curve. The sagittal US images can capture the vertebral rotation aspect information. Hence, the X-ray KA and US KA may have more discrepancy when vertebral rotation is significant.

The X-ray KA and US KA showed higher correlation when using measurements from the EOS X-ray than the conventional X-ray. This result may be explained by better image quality from the EOS system than the conventional X-ray. The conventional X-ray system uses divergent X-ray beam for exposure in which the X-ray photons need to travel longer distance to expose the upper level of vertebra. This may lead to lower penetration energy on the upper level, which affects the image quality [19]. In addition, T1/T12 level measurement method may have higher correlation because it has less chance to have vertebral rotation on the T1 level than T4.

In this study, 10 cases we excluded due to posture variations. The MAD between X-ray KA and US KA measurements ranged from 11 to 21 degrees in these 10 cases. The major reason was the arm flexion. Using an ImageJ (NIH, USA) angle measurement tool, the measured arm flexion on LAT radiographs ranged from 20° to 162° for these participants. Normally, if the subject follows the X-ray technician's instructions, the arm flexion should be approximately 60°. Of these 10 cases, 8 had arm flexion >60°, one <40° and one within 40 to 60 degrees. In Figure 5.5, the arm flexion for that subject is over 90° during the X-ray acquisition and was 60° during the US acquisition, respectively. This patient presented a 22° difference on the KA measurement. Based on the literature, the arm position could affect the sagittal alignment [20, 21]. In addition, among these 10 cases, differences in head position as well as pelvic tilt were noticed. The hyper extension or flexion of the head may affect the KA especially when using the T1/T12 level measurement method. Among the 10 excluded cases, 4 also showed hyper extension of the head. Also, since there is no support to stabilize the hips and pelvis while acquiring X-ray images, children may lean their abdomen forward which make their lower body closer to the opposite wall. This could

affect the bottom endplates of T11 or T12; hence affecting the KA measurements. This was also observed in 2/10 cases. Therefore, standardization of the posture during data acquisition is important. Overall, the US data acquisition seems more consistent while all participants stood in a frame that supports the shoulder and hips and while offering support for the arms flexed at an angle between 40° to 60°. The same operator scanned all the participants, and she ensured all patients stood properly. However, X-ray data acquisitions were performed by a number of technicians. An unrestricted technician might allow participants with slightly more variable positioning.

Among the 50 cases analysed, 40 had a second US data at the consecutive follow-up clinic . Figure 5.8 shows a comparison of US KA measurements (T1/T12 method) with 23 under brace treatment and 17 under observation for both measurements. The participants with bracing have lower mean value of the KA versus the ones who were under observation; however, the difference is not statistically significant (1st visit - brace vs observation: 33.2°±9.9° vs 38.0±10.0; 2nd visit 33.5°±11.5° vs 37.5°±11.4°). There is no significant change on the KA values between the first and the follow-up visits. A longer follow-up period may require.

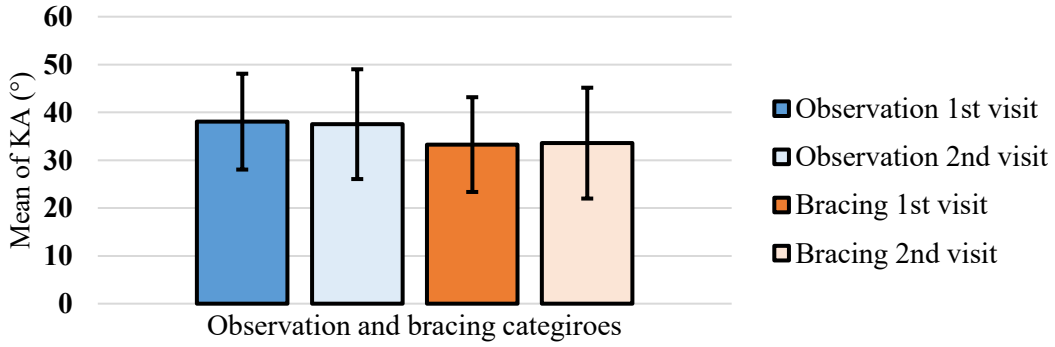


Figure 5.8 Comparison of the US KA (M2) between the observation and bracing group (n=40) as well as the changes of the KA between the first and second US visits for both groups

The intra-rater reliability and measurement error of the X-ray KA (ICC [2,1] ≥ 0.92 ≤ 3.1°±2.7 °) were better in this study than others [6,18]. The rater experience is important. This is the only study to compare the US KA with X-ray KA on a large data set. The ICC [2,1] of the US KA and measurement error was slightly lower than the X-ray method, but

the US rater had only 2+ year of experience. However, the result is still compatible to other X-ray measurement studies in which the intra-rater measurement error ranged between 6° to 11° [6, 18] and inter-rater errors ranged from 7° to 13° [9, 18]. Approximately 80% of the US KA measurements were within 7° differences with the X-ray KA.

In term of limitation, the US scan is operator dependent. A good image quality must be acquired to ensure an acceptable sagittal reconstruction of the spine. Moreover, US data acquisition usually takes 30 seconds to 1 minute to scan a spine, which is longer than the X-ray acquisition (6 seconds). This may increase chances of body movements and may affect the body alignment. Also, a test-retest analysis could be performed to investigate the repeatability of the KA measurements.

5.3.11. Conclusions

US imaging is a reliable and safe method to capture KA measurements from a sagittal image. The US KA measurement is reliable and accurate enough and can be used in every clinic. The standing posture must be standardized and enforced while acquiring images no matter which imaging modality is used.

5.4. Summary

The sagittal X-ray images are not often acquired due to concerns related with radiation. This chapter reported a new US method to measure kyphotic angle on US sagittal images. The results showed that KA can be measured reliably on US images and the maximum measurement differences was 4.0° when compared with X-ray KA. Furthermore, the intra-rater and inter-method reliability coefficients were high (ICC > 0.84) when using the T1/T12 method to measure the KA, and 80% of KA measurements were within the clinical acceptance error (7°). None of the 3 investigated factors showed a significant influence on the measurement error. However, the standing posture during image acquisition was the only factor which might influence the measurement difference of the KA measurements. Since KA can be measured reliably, this parameter will be considered as a potential prognostic factor for prediction of curve progression.

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Chapter 6: Reliability and Factors Influencing the Measurement Variation of Ultrasound Axial Vertebral Rotation (AVR)

6.1. Overview

This chapter reports a study to investigate the intra-rater, inter-method reliability coefficients and factors influencing the measurement variation of ultrasound (US) axial vertebral rotation (AVR) when compares with Stokes' method on radiographs in AIS. Section 6.2 is the manuscript entitled "Investigation of Factors Influencing the Reliability and Measurement Variation of Ultrasound Axial Vertebral Rotation on Adolescents with Idiopathic Scoliosis" which has been submitted to "The Spine Journal". Section 6.6 provides a summary of this chapter.

6.2. Introduction

Idiopathic scoliosis is the most common type of scoliosis among adolescents [1]. The standard of care for scoliosis is taking radiographs every 6 months to evaluate this spine disorder. As per Scoliosis Research Society (SRS) guidelines, the three treatment options available for the adolescent idiopathic scoliosis (AIS) are observation, bracing and surgical interventions. The treatment option is selected based on the severity of curvature, the maturity status of the patients, the patients' self-image and the risk of curve progression [2], [3]. However, to recommend an appropriate management, the spinal curvature in coronal, axial and sagittal planes must be reviewed, as AIS is a three-dimensional (3D) spinal disorder.

Besides the Cobb angle in the coronal plane, axial vertebral rotation (AVR) is another important curve characteristics on AIS which is defined as the rotation of the vertebra along the longitudinal axis and projected in the axial plane [4]. A spinal curvature with large AVR could cause the thoracic rib hump which is an asymmetry due to prominence of one side of rib cage [5]. Also, AVR is considered as a potential predictor that could be used to predict curve progression [6].

A few 2D and 3D methods have been suggested to measure the AVR [7]–[13]. The challenge about 2D methods is that the AVR measurements are not directly measured on axial plane which may affect the accuracy of measurements. Of the 3D methods, computed tomography (CT) [11] , magnetic resonance imaging (MRI) [14], and the EOS 3D reconstruction [15] modalities have also been suggested to measure the AVR. The AVR measurements are performed in axial plane for CT and MRI; however, there are some limitations about these two methods. Both of imaging methods require a long data acquisition time and are relatively costly when comparing with radiography. They acquire the images in supine position which may affect the curvature characteristics, hence influencing the rotation severity. Lastly, the CT method, uses even higher level of radiation versus conventional X-ray which is not desirable [16]. Another 3D method is using the 3D EOS system which applies low level of radiation and capture a posteroanterior (PA) and lateral (LAT) spinal radiographs simultaneously. However, the EOS 3D reconstruction of spine is a timely process which could last up to an hour for severe idiopathic scoliosis cases [17]. Also, for EOS 3D reconstruction, two acquisitions including PA and LAT are required. The accumulated radiation with both PA and LAT radiographs may increase the health risk to these children. Therefore, most of the orthopedic surgeons use the landmark features to estimate the AVR without actual measurements.

Another option that can measure AVR directly and fast is to acquire spinal ultrasonography. Suzuki et al. [18] was the first group using an ultrasound system combined with an inclinometer to measure the AVR in a prone posture. However, no reliability analysis of the AVR was reported from their study. Burwell *et al.* was another group [19] who applied ultrasound to measure rib rotation and lamina rotation in the prone position. The reduction of curve severity due to the prone posture may happen. Recently, Vo et al. used a freehand 3D ultrasound system to scan children with AIS in upright position. A single scan of ultrasound from top to bottom along the lateral spinal curvature on the coronal view allows a 3D reconstruction of spine. An *in-vitro* study was conducted to investigate the reliability of the 3D ultrasound method for AVR measurements using laminae. The results showed an excellent intra- and inter-rater reliabilities. However, no

clinical participants and no comparison with X-ray measurements were included for this study [20]. Chen et al reported on the center of lamina (COL) method to measure AVR in both *in-vitro* and *in-vivo* studies [21], the results showed high intra-rater and inter-rater reliability coefficients for both *in-vitro* and *in-vivo* studies (ICCs > 0.91, MAD < 1.4°) [21]. They also compared their measurements with Stokes' method and showed a good inter-method reliability for the *in-vitro* study (ICC = 0.84-0.85) with the mean absolute difference (MAD) within 4.5°-5.0°; while the agreement for the *in-vivo* study was poor to moderate (ICC = 0.49-0.54, MAD = 2.7°-3.5°). Another study compared and validated the AVR measurements using 3D US measurements COL method and an MRI method. Even though their US measurements were reliable, both MRI and US scans were acquired in supine position [22]. These two studies [21, 22] only focused on the apical AVR measurements and did not investigate the US measurement reliability on the entire spine. Also, no investigations were reported on which factors might influence the US AVR measurements. Therefore, this study aimed to determine the reliability and variation of US AVR measurements at vertebrae levels T4 to L4 and what factors might affect the measurement.

6.3. Methods

6.3.1. Clinical Participants

Twenty-four participants (20 F, 4 M, aged 13.6±1.6 years old) were randomly selected from our US database. The ethics approval was obtained from the local health research ethics board and all participants consented prior to participation. The inclusion criteria were participants who were diagnosed with AIS, had a Cobb angle <55 degree, and had no prior surgical treatments.

6.3.2. Data Acquisition

All participants were scanned by an US imager in addition to the X-ray acquisition as the standard of care. The US images were acquired using the Sonix TABLET medical US

system equipped with a 128-element C5-2/60 GPS convex transducer (Analogic Ultrasound – BK Medical, Peabody, Massachusetts, USA). The X-ray data acquisition was performed while participants were positioned in an upright standing position. For the conventional X-ray, the chest was against the metal plate of X-ray machine and the hands grabbed on the side bars at a height around chest level. For the EOS system, the patients placed their hands at chest level and touching in front of them. During the US data acquisition, participants were asked to stand in an upright position, look straight and no tilt head in a frame devised to stabilize them. Both hands grabbed on the frame poles around chest height. One operator with 4+ years of experience performed the scanning. An in-house software was used to reconstruct the US images. The coronal and sagittal views looked like PA and LAT radiographs. The axial view showed a single US B-mode image of a slice of vertebra on transverse view.

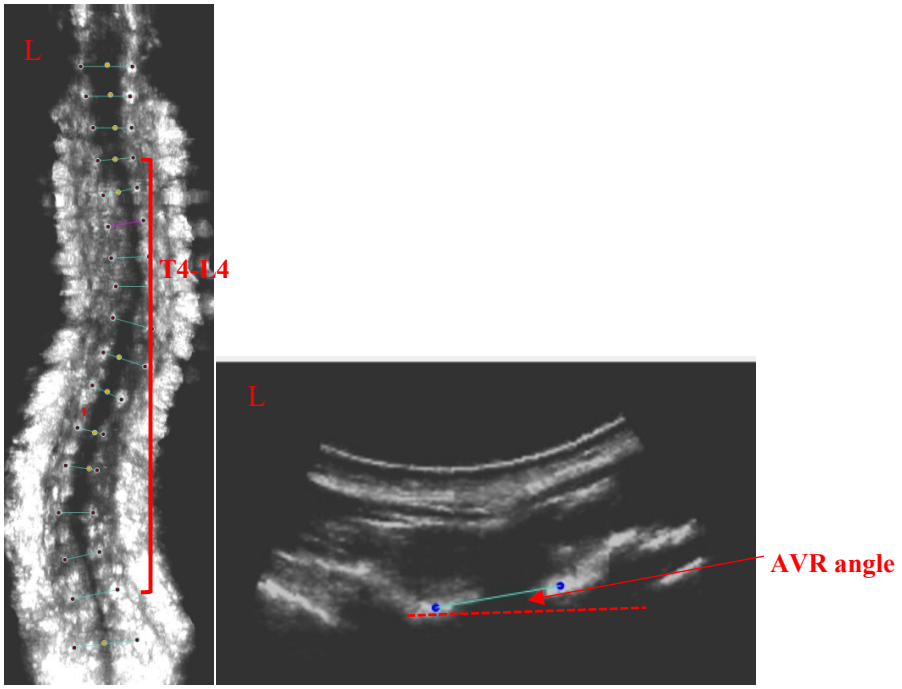
6.3.3. Raters

Rater 1 who had over 20+ years of scoliosis experience measured the AVR on the radiographs from T4 to L4 vertebrae using Stokes' method [5] (X-ray AVR). Rater 2 who had around 5 years of US measurement experience measured the AVR using COL [21] at the same level on the US images (US AVR). Rater 1 only measured the AVR once since he had demonstrated good reliability and repeatability for AVR measurements in the study [21]. Rater 2 measured the US images twice in two measurement occasions (M1 and M2) with one week apart to reduce the memory bias.

6.3.4. AVR Measurements

Both measurements methods were performed using a custom semi-automatic software. On a coronal radiograph, R1 first identified and outlined the pedicles on a selected vertebra. The software then automatically estimated the centers of the pedicles. R1 then placed a line across the minimum distance of the vertebral body and selected the vertebral level. The program then calculated the AVR automatically based on Stokes' method [23]. For the US measurement, R2 first identified the center of laminae at each vertebral level on the

coronal view as shown in Figure 6.1a. The rater then selected the vertebral level to perform a fine adjustment of the COL locations in the corresponding transverse view. Once selected, the program would display the axial view (Figure 6.1b). Rater 2 could make COL adjustment in the axial view; afterwards, the software would then display the AVR for each level.



a) b)

Figure 6.1 The process of AVR measurement starting from coronal to axial US images. a) The center of laminae are identified on the coronal view, and at each of the vertebra levels (T4 to L4) a line is automatically drawn and joined the COL. b) On the axial view, the selected vertebra (T6), the center of the laminae can be fine-tuned, and the AVR angle forms between the line which joins the COL and a horizontal reference line (dashed line).

6.3.5. Data Analysis

The mean and standard deviation (SD) for each set of measurement including X-ray AVR and US AVR (M1 and M2) were reported. The intra-rater reliability of the US AVR and the inter-method reliability coefficients were analyzed using the intraclass correlation coefficient ICC [2,1] with a 2-way random model and absolute agreement with 95% confidence interval. The mean absolute difference (MAD) and standard error of

measurements (SEM) between X-ray AVR and US AVR measurements were reported. The agreement between two methods measurements was also plotted using the Bland-Altman's method. An independent Student t-test was performed to compare the difference between the AVR measurements from different subgroups defined by factors of interest: a) the apical region (inferior apical, apical and superior apical vertebral levels) versus the non-apical region, b) the curve severity (Cobb angle between 10° to 25° (mild), and Cobb angle between 25° to 45°(moderate)), and c) curve type either upper thoracic (UT)/main thoracic (MT) and thoracolumbar (TL)/lumbar (L). Also, a one-way ANOVA test was performed to compare the effect of AVR severity: mild (0° to 5°), moderate (6° to 10°) and severe (>10°) on differences of measurements between the US and x-ray imaging methods, followed by post-hoc Bonferroni test to investigate the differences between these three categories. An alpha level <0.05 was considered as a statically significant difference.

6.3.6. Results

Forty-two curves were identified in these 24 radiographs, and the average of the Cobb angle was 24.4°±9.0° (10° to 43°). In total, 312 (24 spine x 13) AVR were measured in which 125 were within the apical regions and 187 were outside. For one case, the apex level was at L4 therefore, only two vertebrae including the superior and apical vertebral levels were available.

Table 6.1 shows the X-ray and the US AVR measurements including the mean±SD from both raters, the MAD, SEM and intra-rater reliability between M1 and M2. The intra-rater reliability on US measurements was excellent with an ICC [2,1] = 0.93, the MAD was 1.7°±1.7° and the SEM was 0.46°.

Table 6.1 The average, standard deviation, SEM and intra-rater results of the AVR measurements on both X-ray and US images

Measurements	M1 (°)	M2 (°)	MAD±SD (°)	SEM (°)	ICC [2,1] (95%CI, range)
X-ray Measurements	-0.4±4.3 (-17.0 to 12.1)	N/A			
US Measurements	1.1±6.5 (-14.8 to 20.5)	1.1±6.0 (-14.8 to 17.3)	1.7±1.7	0.46	0.93 (0.91 to 0.94)

MAD: Mean absolute difference, SD: Standard deviation, SEM: Standard error of measurement, ICC: Intra-class correlation coefficient, US: Ultrasound

Table 6.2 shows the MAD, SEM and inter-method reliability results of the AVR measurements between X-ray and US methods. The MADs were calculated based on differences between X-ray and US measurements and the results on both measurement occasions were consistent (< 4.6°). The SEM was less than 2.4° and the ICC [2,1] was poor to moderate (ICC [2,1] ≥0.49) as per interpretation guidelines provided by Koo et al [24].

Table 6.2 The MAD, SEM and inter-method reliability results of the AVR measurements between X-ray and US methods

Measurements	MAD±SD (°)	SEM (°)	ICC [2,1] (95%CI, range)
X-ray vs US (M1)	4.6±3.3	2.4	0.49 (0.38 to 0.57)
X-ray vs US (M2)	4.3±3.2	2.2	0.50 (0.39 to 0.59)

Figure 6.2 shows the Bland-Altman plot of the AVR difference of the inter-method measurement versus the average of US (M2) and X-ray measurements. Majority of the measurements 278/312 (89%) were within the lower and upper boundaries of 95% confidence interval. A slight positive correlation (R^2=0.13) was observed between AVR severity and the differences of the measurement indicating larger AVR severity, larger variations of the measurements.

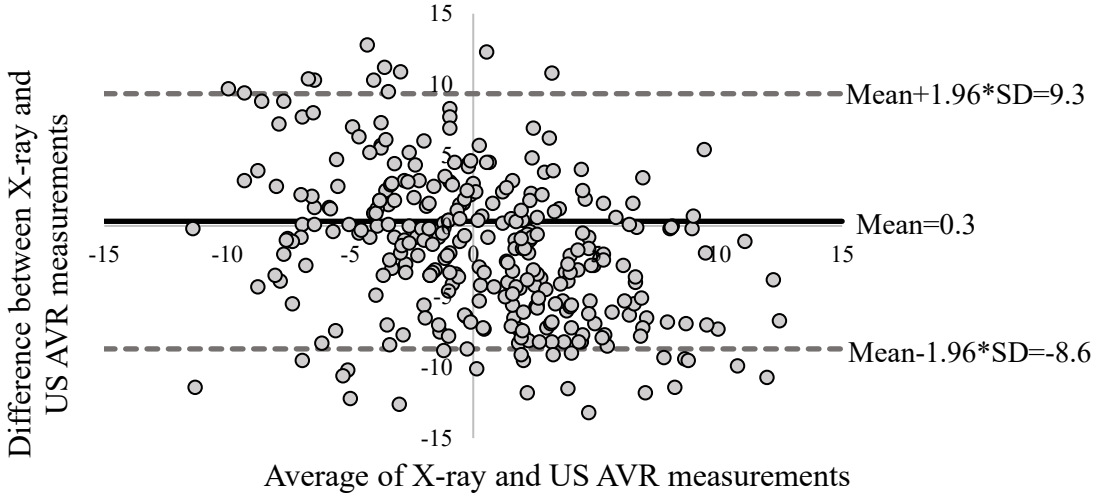


Figure 6.2 Bland-Altman plot of the differences between the X-ray and US AVR versus the average of the AVR from the X-ray and US(M2) measurements

6.3.1. Factors Influencing the AVR Measurement Difference

Apical vs Non-Apical Regions

The average of AVR measurement difference between US (M2) and radiographic methods at both apical and non-apical regions were compared, and the results were statistically significant ($p<0.05$). The mean of AVR measurement difference at the apical region was larger than non-apical region (4.0°±3.3° vs 2.9°±2.2°) (Table 6.3).

Curve Severity

Table 6.3 also shows the MAD±SD of inter-method measurements was not statically significant different between mild and moderate groups ($p=.97$). The average MAD in both curve severity groups was approximately 4°.

Curve Type

There was no statically significant difference ($p=.29$) between the inter-method measurement difference between UT/MT and TL/L curve types (Table 6.3). In general, the inter-method measurement difference TL/L was slightly smaller 3.7° vs 4.3° when compared to the UT/MT curves.

Table 6.3 Comparison of the AVR measurement difference (MAD) in terms of region of measurement, curve severity and curve type

Average of difference between X-ray and US (M2) (MAD±SD)	**Apical Regions (N=125)**	**Non-apical Regions (N=187)**	**t test**	**P value**
	4.0±3.3	2.9±2.2	-3.4	**.001**
MAD±SD at apical region	**Mild curve (n=78)**	**Moderate curve (n=47)**	0.02	.97
	4.1±3.2	4.0±3.2		
MAD±SD at apical region	**UT/MT (n=60)**	**TL/L (n=65)**	1.0	.29
	4.3±3.7	3.7±3.0		

MAD: Mean absolute difference, SD: Standard deviation, US: Ultrasound, M2: Measurement 2, UT: Upper thoracic, MT: Main thoracic, TL: Thoracolumbar, L: Lumbar

AVR Severity

Table 6.4 shows the average of MAD among the three AVR severity categories for the apical region. As the results show, there is a significant difference among the three categories. The largest mean of measurement difference between X-ray and US was observed for the largest severity category (X-ray AVR >10°). Further analysis showed that mean of MAD±SD for the largest severity category was significantly larger versus the second category ($p<0.05$), while it was not significant when compared with first category.

Table 6.4 Comparison between the average of the inter-method difference in AVR severity

AVR Severity (°)	MAD±SD (°)	F value	P value	Comparisons	P value
Mild: (0 to 5) (n=88)	4.1±3.0	4.03	**.02**	1 vs 2	.35
Moderate: (6 to 10) (n=27)	3.0±3.2			1 vs 3	0.16
Severe: >10 (n=10)	6.3±4.2			2 vs 3	**.017**

AVR: Axial vertebral rotation

6.4. Discussion

The intra-rater and the inter-method reliability coefficient ICC [2,1] of the US AVR measurement in the current study was similar to the results from the previous study [21]. The US AVR can be reliably measured (ICC [2,1] > 0.9), but it is in the poor to moderate range (ICC[2,1] = 0.49 to 0.5) when compared with Stokes' method. This means that the US method cannot directly compare with the X-ray estimation method. As Stokes' method uses the pedicle shadows projected on the 2D X-ray image, the AVR value is always underestimated using Stokes' method. The overall US AVR is 4.45° higher than Stokes' method.

The average of AVR measurement difference between X-ray and US method at the apical region was statistically larger than non-apical region. However, there were 88/125 (70%) of the AVR differences are within 5°, the majority is still within the measurement error. When the X-ray AVR is larger, the more difference occurs. This phenomenon may either due to the underestimation of the X-ray AVR from Stokes' method or the poor US image quality which makes the US AVR inaccurate. When a large AVR exists, it causes more

uneven back surface which makes the US probe more difficult to contact the surface of skin properly. Since the majority of the X-ray AVR is within 5° at the apical region, the overall inter-method reliability (ICC [2,1]) for apical and non-apical region groups was 0.6 and 0.41, respectively.

There was no correlation between the curve severity and the difference of the X-ray AVR and US AVR measurements (Figure 6.3). It may be due to the mild curve is more dominant.

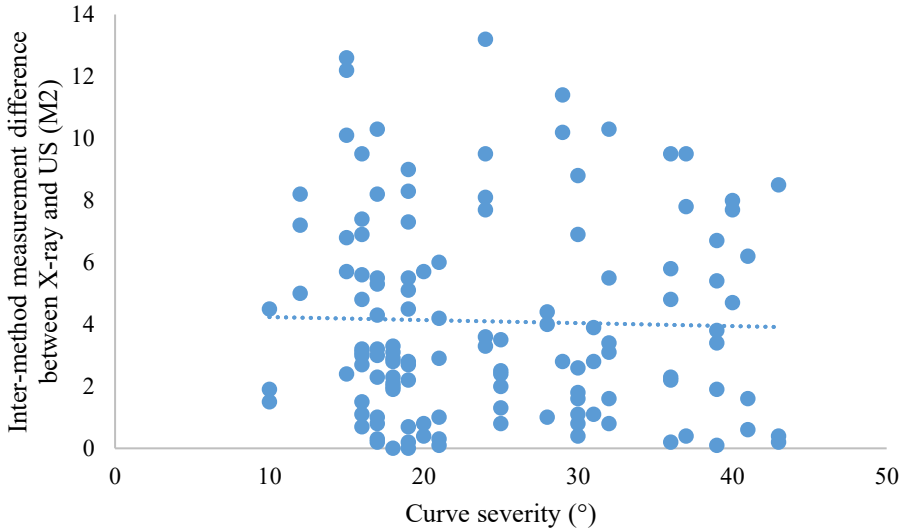


Figure 6.3 Scatter plot of the inter-method measurement difference and curve severity

Furthermore, the MAD of inter-method measurements was not significantly different between UT/MT and TL/L curve types, the error of measurements at UT/MT was almost the same as TL/L region (0.6° different). Although the COL is more difficult to identify on the lumbar region in the coronal view [25], using the axial view can ensure the rater can determine the COL more precisely. Hence, the advantage of using the US method is the 3D information. Also, another advantage of using US was the time required to obtain the AVR measurements using the COL method versus Stokes' method. The COL method was significantly faster than Stokes' method (5 seconds versus 45 seconds per vertebra).

In terms of limitations, the US data acquisition could take more time particularly for the cases with large AVR. To scan cases with large AVR, the operator needs to make sure there is an appropriate contact for imaging of the laminae. Longer scan could increase chances of body movements which may affect the curvature characteristics. Also, the standing posture instructions is very important during data acquisition particularly for X-ray imaging. For x-ray data acquisition, if the patient's body tilts, it may cause other vertebra features such as spinous process to overlap pedicles and project over them which could make identifications of the pedicles difficult.

To further verify the accuracy of the US COL method for the AVR measurements, the AVR acquired from the EOS 3D reconstruction measurements in a standing position should be conducted.

6.5. Conclusion

The results of the study showed an excellent US intra-rater reliability with the average of difference 1.7° and a moderate inter-method reliability of ICC [2,1] ≥0.49. Overall, 89% of the measurements were within the lower and upper boundaries of 95% confidence interval. The error measurement was larger when AVR severity was larger. The curve severity and curve type were not factors influencing the difference between the X-ray AVR and US AVR measurements. The apical region and AVR severity were the influencing factors.

6.6. Summary

This chapter shows a high intra-rater reliability of the AVR measurements on US images. However, the inter-method reported a moderate reliability. The discrepancy between the two methods could be related to AVR measurement on a 2D X-ray using Stokes' method versus COL method. The US AVR is measured directly in the axial plane whereas the X-ray AVR is measured on a projected 2D radiographic image. Also, the inter-method AVR measurement difference at the apical region was also significantly larger than non-apical. The inter-method measurement difference was significantly larger when AVR severity was

>10° versus 6° to 10° at the apical region. As a result, the US AVR can be investigated as a potential prognostic factor of progression for model development.

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Chapter 7: Development of Detection Models for Curve Progression

7.1. Overview

This chapter overviews two studies focusing on model development for curve progression. The first study is a pilot study and the second one is a large clinical study. Section 7.2 covers a brief description of the pilot study. The result of that pilot study has been reported in the manuscript entitled "Development and Validation of a Model to Predict X-ray Progression at a Follow-up Visit Based on Ultrasound and Clinical Parameters for Adolescent Idiopathic Scoliosis (AIS)" which has been submitted to the "Journal of Spine Deformity". It also has been presented in 56th Annual Meeting of Scoliosis Research Society (SRS) in 2021. The section 7.3 presents the large clinical study that is used to investigate the association of baseline, radiographic and US parameters with curve progression. The materials of the section 7.3 are taken from the manuscript entitled "Identifying Prognostic Parameters to Develop a Detection Model of Curve Progression with Clinical Validation on Adolescents with Idiopathic Scoliosis" which has been submitted to the "European Spine Journal". Section 7.4 provides a summary of this chapter.

7.2. A Preliminary Analysis on Development and Validation of a Model to Detect Progression

Prior to conduct a large study on development of detection model, multiple models were developed and tested. One of the preliminary study models based on four baseline parameters including a) the X-ray Cobb, b) a novel US parameter called reflection coefficient (RC) as an index of bone strength, c) chronological age, and d) the menarche status plus an extra parameter of the US Cobb change measured from ultrasonographs at the baseline and follow-up visits are reported in this section. In this study, seventy-five female participants with AIS aged 13.9 ± 1.5 years old were recruited and consented from a single center. All participants were followed 8.5±5.3 months away from the baseline visit

and had the US scans during the baseline and follow-up visits plus the standard of care. Among the 75 participants, 56 (75%) (age 13.6±1.6yr) were randomly selected for model development and 19 (25%) (age 13.5±2.1yr) were used for model validation. The curve progression cases for the model development and validation groups with the consecutive Cobb angle increase >5^{o} were 25 and 7, respectively. The results showed that only US Cobb change and RC index were the final predictors, and the model achieved the sensitivity=85.7%, specificity=91.7% and accuracy=89.5%. However, a larger study was required to investigate more prognostic factors, use those potential parameters for model development and validate the model which is explained in detail in section 7.3.

7.3. Identifying Prognostic Parameters to Develop a Detection Model of Curve Progression with Clinical Validation

7.3.1. Introduction

Adolescents with idiopathic scoliosis (AIS) mainly present lateral deviations of spine which typically also include rotations, and twists in their spine. Children with AIS need to be monitored by consecutive posterioanterior (PA) and sometimes lateral (LAT) radiographs every six months to measure the curve severity using the Cobb method [1]. Ronckers et al. reported that on average 22.9 radiographs per person were acquired during treatment and follow-up of scoliosis after following 5,513 females [2]. On the other hands, approximately 15% of children with AIS showed progression defined as a Cobb angle change over 5°at the 6 months follow-up visit [3].

Exposing children to ionizing radiation may increase the risk of cancer incidence [4]–[6]. Also, the long-term negative effects because of cumulative radiation may appear years after for the exposed person or even in the next generations [4]–[6]. One recommendation would be using a safe non-ionizing imaging modality, ultrasound (US), to image spine. From the literature, few parameters measured from US images have shown reliable and accurate results with both intra- and inter-rater and inter-method reliabilities were good (ICCs>0.82) when compared from radiographic measurements [7]–[11]. The measured parameters

included the Cobb angle [7], axial vertebra rotation (AVR) [9], Cobb angle at the plane of maximum curvature (PMC) [10], and kyphotic angle (KA) [11]. Recently, a new US parameter called the reflection coefficient index (RC), which was proposed to provide spinal stiffness information. This parameter can be extracted and measured reliably from US images [12]. However, US cannot replace X-ray because radiography is needed for the diagnosis of scoliosis. However, it is possible to reduce the follow-up X-rays for children without progression if we could predict risk and detect curve progression.

From the literature, a list of baseline, clinical, radiographic and physiologic parameters have been associated with curve progression [13]–[18]. The most cited parameters that were linked with curve progression were a) the severity of the Cobb angle, b) AVR, c) curve type, d) Risser sign, and growth-related factors such as e) gender, f) age, and g) menarche status [13]–[17]. In 2005, Hung et al. put forward a new parameter, osteopenia, as a new potential predictor. Their study showed that younger age at the time of diagnosis, premenarchal status in females, low Risser sign (0-1) and presence of osteopenia could be used to predict curve progression [13]. They used dual X-ray absorptiometry (DXA) to measure the bone mineral density (BMD) of the hip which exposed these children to extra ionizing radiation. Their prediction model had the sensitivity and specificity of 76% and 70%, respectively. Another study by Lam et al. showed that a lower ultrasound stiffness index - a bone quality assessment index acquired at calcaneus, younger age, pre-menarche status, and larger Cobb angle were associated with a higher risk of curve progression with a sensitivity of 85% and a specificity of 66% [19]. Also, progressive, and non-progressive groups were compared in terms of the sagittal parameters including kyphotic and lordotic angles and the results showed that the progressive group had a significantly lower kyphotic angle. However, no prediction model was developed in that study [20].

Based on a systematic review that we conducted recently, the level of evidence is limited or conflicting for most of the parameters reported in the literature. To develop a prediction model, clinicians are always looking for parameters which can be captured from their regular scoliosis clinic. Therefore, a larger and rigorous study is needed to further confirm the prognostic parameters to predict curve progression.

This study aimed to identify different baseline, radiographic and US parameters to develop a detection model on curve progression and to validate the model based on clinical data for children with AIS.

7.3.2. Materials and Methods

7.3.3. Clinical Participants

One hundred and sixty-two female participants with AIS were consecutively recruited and signed informed consent. Ethics approval was obtained from the local research ethics board. The inclusion criteria were participants who a) were diagnosed with AIS, b) were aged between 10-18 years old, c) had major Cobb angle <55° and d) had no surgical treatment during or prior to the study. Among the 162, 94 were under conservative treatment (bracing and Schroth's exercises), and 68 were under observation. All participants were followed-up 8.0±4.1 months away from their baseline visit. All participants had the US scans during their baseline and follow-up visits in addition to the standard care. One-hundred participants (13.6 ±1.6 yr) were randomly selected for development of detection model and the rest of 62 (13.4 ±1.7 yr) were used for model validation. Among the model development and validation, 25 and 11 cases had curve progression (Cobb angle change >5 degrees) as per the Scoliosis Research Society guidelines [21], respectively.

7.3.4. US Data Acquisition

The participants were scanned by an US system (Sonix TABLET with SonixGPS system, BK Medical, MA, USA), in a standard standing position as described in our previous studies [22] for both visits. The US system is equipped with a 128-element C5-2/60 GPS convex transducer. The parameters that were set for imaging were: 2.5 MHz center frequency, focus on the imaging depth at 6 cm, and the signal gain of 15%. During data acquisition, the B mode images that included the US reflection signals as well as position

and orientation information were acquired. Then, a custom software was used to reconstruct the US images in 3D and display on coronal, axial and sagittal planes.

7.3.5. Investigated Parameters & Data Measurements

a) Demographic Parameters

- ***Chronological Age, Body Mass Index (BMI), Menarche Status***

The demographic information of each participant including the age, BMI and menarche status were extracted from our local clinic database.

b) Radiographic Parameters

- ***X-ray Cobb Angle, Number of Curves, Risser Sign at Baseline***

The X-ray Cobb angle, number of curves (NOC) and Risser sign which were measured and recorded by the clinical staff who had at least 10+ years of experience. This radiographic data was extracted from the database as well.

c) Ultrasound Parameters

Raters Involved in US Parameters Measurements

The US parameters were measured by three raters. R1 and R2 had over 2 years of experience measuring the US parameters. Rater 3 was a novice. For the training R3 first practiced on 10 practice files apart from study files and compared her measurements with R1 and discussed the discrepancies. Once she was confident, she measured study cases. All the US parameters were measured using a custom software. Fig 7.1 shows the measurements of the Cobb angle, AVR, KA and RC index on US images.

- ***Ultrasound Cobb Change***

The US Cobb was measured at both the baseline and follow-up visits using the center of lamina (COL) method [7] on the US coronal view image (Fig 7.1a). Then, the difference of the US Cobb angle between the two visits was calculated for each participant.

- ***Maximal Axial Vertebral Rotation (AVR)***

The COL method was used to measure the AVR on transverse view US images (Fig 7.1b). The maximum AVR among the apical vertebra, the superior and inferior of the apical level was used.

- ***Plane of Maximum Curvature (PMC) Curve Angle***

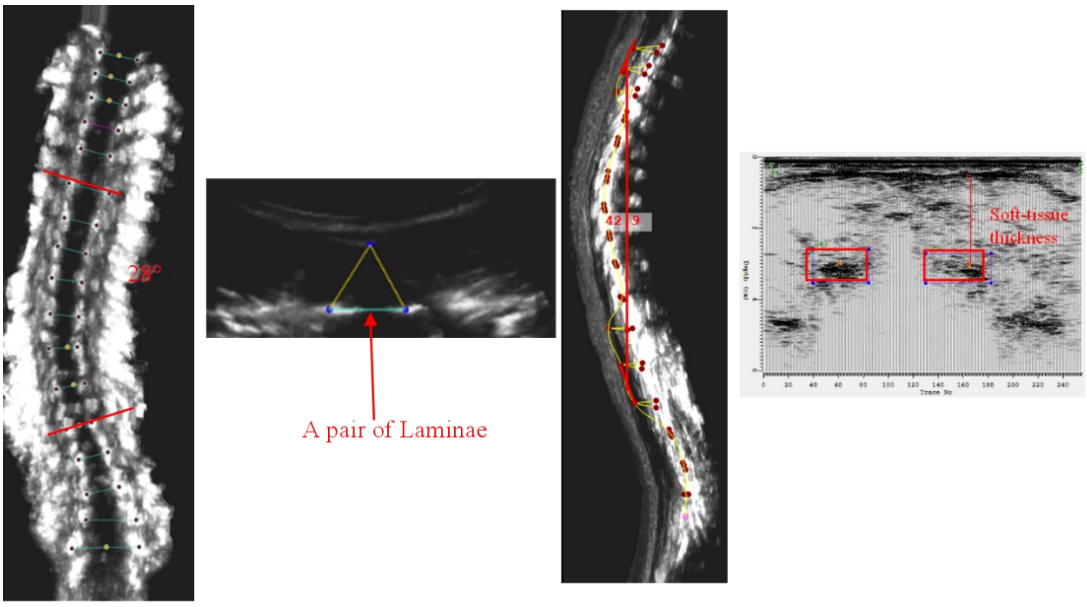
The Curve angle in the PMC usually occurs in the maximum axial rotation plane. Similar to the study in [10], to calculate the maximum Curve angle in the plane of PMC, the Curve angles in the maximum AVR at the apical region with five AVR offsets values -4°, -2°, 0°, +2°, +4° were recorded.

- ***Kyphotic angle (KA)***

The centers of the laminae for T1 and T2 and T11 and T12 were determined on US coronal view (Fig 7.1a). Then, the tips of spinous process for each of those vertebrae were identified in the transverse view at the skin level (Fig 7.1b). The angle between the line joining the spinous process of T1 and T2 and the line joining the spinous process of T11 and T12 in the sagittal plane was measured as US KA angle (Fig 7.1c).

- ***US Reflection Coefficient (RC) Index***

To measure the RC index, the L5 vertebra was identified on coronal US image (Fig 7.1a). The B-mode US image around the center of the laminae was selected on the coronal view. The transverse view image was then displayed, and the operator marked the laminae on the transverse image. The distances from the surface of the skin to the center of left and right laminae which visualized as the maximum US reflection signals in Fig 7.1d were determined. A custom developed software was then used to calculate the RC index. Four more B-mode US images, 2 above and 2 below of the center B-mode image were used to calculate the corresponding RC values at these levels. The average of the 5 left and 5 right RC values called as combined average reflection coefficient (CARC) method, which was described in [12], was used as the investigated parameter. The method of measurement was selected because it showed a good reliability.



a) b) c) d)

Figure 7.1 The measurements of US parameters including. a) US Cobb angle, b) AVR, c) KA and d) RC index on US images. a) US Cobb angle measured 28° on a coronal US image using the center of laminae method, b) the US AVR is measured on the transverse view US image using the center of laminae, c) to measure the KA, the angle between the two line that joins the spinous process of T1 and T2 and T11 and T12 is measured d) the RC index is measured based on the magnitude of the US refection from the laminae at L5 level by accounting the thickness of the soft tissue from the skin to laminae.

7.3.6. Statistical Analysis

The univariate analysis including Student's t test was conducted to investigate the difference between cases with and without progression with an alpha level of $p<0.05$ for our continuous variables. The association of the categorical variable i.e., menarche status, NOC and Risser sign with curve progression were tested using Chi square analysis with an alpha level of $p<0.05$. The dependent variable *curve progression* was coded into "1" for participants "with progression" and "0" for participants "without progression". To develop the detection model, logistic regression analysis was used. The *forward selection* method was chosen for analysis. Three classification cut-offs set 0.4, 0.5 and 0.6 were tested. The model statistics including sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were reported. The receiver operating characteristic curve (ROC) was also performed to compare different threshold values for significant

continuous parameters and area under the curve (AUC) was reported. All statistical analyses were performed using the IBM SPSS v23 software (IBM, Armonk, New York, USA).

7.3.7. Results

Univariate Analysis

Table 7.1 presents the demographic information of the 100 participants used for model development into two categories: with progression and without progression. The average values of the BMI, X-ray Cobb angle, max AVR, PMC Cobb, KA and RC index were smaller in cases with progression versus those without progression. The US Cobb change was higher among the cases with progression versus without progression. Age was about the same among the two groups. Among these parameters only the US Cobb change and RC index were significantly different between the two groups ($p<0.05$).

Table 7.1 The mean±SD for age, BMI, X-ray Cobb and US parameters for the cases with and without progression and the statistical t-test values on the described parameters between the two groups.

Variables	With progression (n=25)	Without progression (n=75)	t-test (p value)
Age (yr)	13.7±1.5	13.5±1.7	-0.44 (0.66)
Body Mass Index (BMI) (kg/m^2)	18.9±2.7	19.5±3.8	0.73 (0.46)
X-ray Cobb (°)	22.6±9.7	25.7±9.8	1.38 (0.17)
US Cobb change (°)	6.6±5.0	-2.4±6.5	**-6.39 (0.00*)**
Max AVR (°)	3.4±9.9	5.2±9.4	0.82 (0.41)
PMC (°)	24.5±10.5	27.1±10.4	1.09 (0.27)
Kyphotic Angle (KA) (°)	32.0±11.2	35.1±11.6	1.18 (0.24)
Reflection Coefficient (RC)	0.05±0.02	0.07±0.02	**3.95 (<0.01*)**

US= Ultrasound, PMC=Plane of maximum curvature, AVR=Axial Vertebra Rotation, the asteroid indicates significant difference ($p<0.05$)

Table 7.2 indicates the association of the categorical parameters with curve progression. The majority of the participants already had menarche (70% vs 30%). Also, 56% of the participants had Risser sign >1. In addition, only 46% of the participants had a single curve. Of these 3 parameters, only the NOC was statistically associated with curve progression ($p<0.05$).

Table 7.2 The association between categorical parameters with curve progression

Parameters	Parameters division	Coding	With Progression (n=25)	Without Progression (n=75)	Chi square (p value)
Menarche Status	**Pre-menarche**	**1**	7 (28%)	23 (31%)	0.063 (0.80)
	Menarche	**0**	18 (72%)	52 (69%)	
Risser sign	**≤1**	**1**	12 (48%)	32 (43%)	0.21 (0.64)
	>1	**0**	13 (52%)	43 (57%)	
NOC	**Single**	**0**	6 (24%)	40 (53%)	**6.49 (0.011*)**
	Double or more	**1**	19 (76%)	35 (47%)	

NOC= Number of curves, the asterisk indicates significant difference ($p<0.05$)

Multivariate analysis

Table 7.3 shows the developed model specifications and statistics. The curve progression detection model was: Logit (p) = Log (p/1-p) =-1.40+0.28(US Cobb change)-39.45(RC)+1.36 (NOC). The participants who had higher values of US Cobb Change and NOC, and lower values of RC were at a higher probability to have curve progression using 0.4 cut-off threshold. The statistical values of the model development data were sensitivity=68.0% (95% CI, 46.5 to 85.0), specificity= 89% (95%CI, 80.6 to 95.2) and accuracy=84% (95%CI, 75.3 to 90.5).

Table 7.3 The final predictors and the statistics of the developed model

Predictors	B	Standard error	Level of significance	EXP (B) 95% CI	Logistic regression model
NOC	1.36	0.68	0.04	3.90 (1.02 to 14.84)	Log (p/1-p) =-1.40+0.28(US Cobb change)-39.45(RC)+1.36 (NOC)
RC	-39.45	17.27	0.02	0.00 (0.000 to 0.004)	
US Cobb Change	0.28	0.07	<0.01	1.33 (1.14 to 1.55)	
Constant	-1.40	1.62	0.38	0.24	
Model Characteristics	Sensitivity= 68% (95%CI, 46.5 to 85.0)		Specificity= 89% (95%CI, 80.6 to 95.2)		Accuracy=84% (95%CI, 75.3 to 90.5)

RC=reflection coefficient; NOC= Number of curve, B= Beta coefficient, EXP (B): Odds ratios for the predictors which are exponentiation of coefficients; CI=Confidence interval; P= Probability of progression

Model Validation

Of the three tested probability cut-off thresholds, 0.4 classification results were the best and presented in Table 7.4. The accuracy of the developed model was tested in 62 new participants and the probability of curve progression was calculated for each participant.

The following accuracy statistics achieved: the sensitivity=90.9%, specificity=90% and accuracy=90% (Table 7.4).

Table 7.4 The validation results from the test data set

N = 62	Actual progression	Actual non-progression	
Predicted progression	10	5	Positive Predictive value = 10/15 = 67.0%
Predicted non-progression	1	46	Negative Predictive value = 46/47 = 97.8%
	Sensitivity= 10/11 = 90.9%	Specificity= 46/51 = 90.1%	Accuracy = 56/62 = 90.3%

Thresholds for US Cobb change and RC

- ***US Cobb change***

The ROC analysis on US Cobb change resulted in the AUC= 0.89 which was significant. Figure 7.2 compares three different threshold values of US Cobb change as 4°, 5° and 6° versus the percentage of sensitivity and specificity. As the results show, the 4° threshold provides the best sensitivity (78%), but the lowest specificity. On the other hand, the 6° threshold provides the reverse result, the lowest sensitivity and the highest specificity. Using the 5° threshold provides the middle values for both sensitivity and specificity.

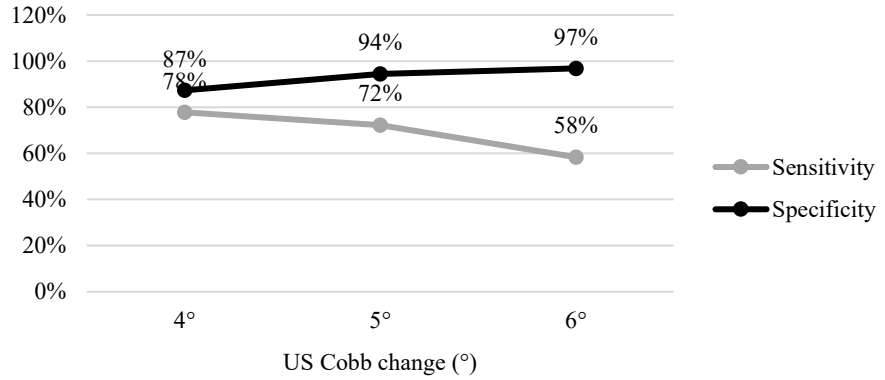


Figure 7.2 Compares three different thresholds of US Cobb change as 4°, 5° and 6° in terms of their sensitivity and specificity

- ***Reflection Coefficient (RC) Index***

The AUC for the RC index was 0.66 which was also significant ($p<0.05$). Fig 7.3 shows the comparison of 3 different threshold values for the RC index from 0.05 – 0.07 versus the sensitivity and specificity. The best sensitivity was achieved when RC was equal to 0.07 (83%); however, the specificity was the lowest (40%). The 0.05 threshold shows the highest specificity (73%); however, its sensitivity is lower for the 0.06 threshold (56% vs 69%). Using the 0.06 threshold provides a middle value on both sensitivity and specificity.

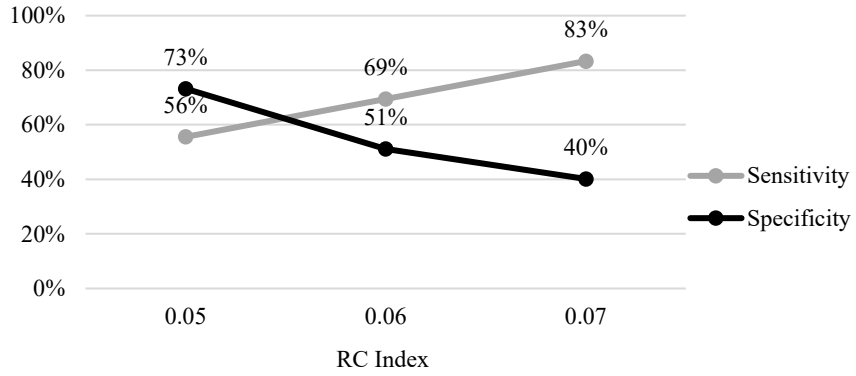


Figure 7.3 The comparison of different threshold values for the RC index to discriminate the cases with and without progression

7.3.8. Discussion

Based on the literature, for majority of the prognostic factor of curve progression the evidence is insufficient in quantity or quality to formulate conclusive statements. In this study, we conducted a comprehensive step-by step analysis to identify the prognostic factors which associate with curve progression on children with AIS. Using our detection model 90% of accuracy was achieved. Our model was able to avoid unnecessary radiographs for 74% of similar cases. Even though by using our model there was only one missing progressive case as false negative (NPV= 98%), the positive predictive value was 67%. This shows that there were 5 false positive cases that were wrongly classified as progression cases. It should be noted in clinical practice, all children, even those without progression would need to take radiographs if requested. Even though there is a 6/62 (10%)

chance of misclassification, using our model, it is possible to recommend skipping x-rays for the majority of children predicted to be without progression. Among the 6 misclassification cases, 1 was from the progression group, but 5 from the non-progression group. For the missed progression case, the participant had the RC index of 0.11 which is above the average of the RC measured for the progression group (0.05±0.02). Also, this case was already mature with a Risser sign of 4 and one year had passed her menarche at the time of data acquisition which may explain high RC value for her.

Table 7.5 shows the information on the predictors (US Cobb change, RC and NOC) as well as the predicted probability of progression for the 5 cases misclassified as progression cases. Even though these cases were misclassified as progression by using our model, their probability is not significantly larger than the 0.4 threshold used to identify as progression. This means that most of the measurements for the US Cobb change (5° to 8°) and particularly RC (0.04 to 0.06) were close to marginal values that may overlap between progression and non-progression group. More accurate measurements could reduce the risk of misclassifications.

Table 7.5 Predictors values (US Cobb change, RC and NOC) as well as the predicted probability of progression for the 5 cases misclassified as progression cases.

Cases	Ultrasound (US) Cobb change	Reflection coefficient (RC) index	Number of curve (NOC)	Predicted probability of progression
1	5	0.04	0	0.48
2	6	0.04	0	0.52
3	5	0.06	1	0.59
4	8	0.05	0	0.58
5	5	0.04	0	0.46

Note that the predicted probability >0.4 was considered as threshold to identify those with progression

Figure 7.4 shows the participants with and without progression in terms of their US Cobb change and RC index. The region outlined with the red box indicates the high-risk area for curve progression. Of the cases in this region, 28/36=77% had an US Cobb change ≥5°, 25/36=69% had RC≤0.06 and 26/36=72% had multiple curvatures. Within this region, there are 9 cases without progression as well. These cases showed RC ≤0.06 and US Cobb

change ≥5° while 7/9 of them had only a single curvature. Nevertheless, they still meet the progression criteria for two of our predictors and are still at risk of showing curve progression. When these cases were tracked in our data base, we found that 3/9 showed curve progression within a year or 2 from their study scan visit.

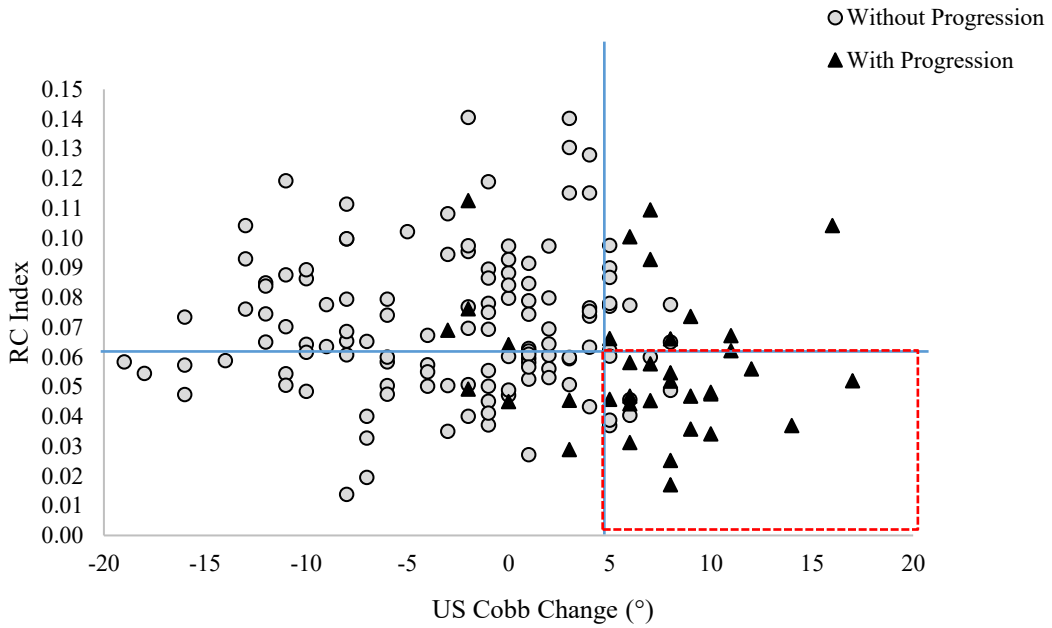


Figure 7.4 Illustration of the RC index versus US cobb changes for 162 cases with and without progression

In our study we focused on female participants to maintain the homogeneity of the data. However, we also tested our model on 29 boys with AIS. Of these 29 cases 6 showed curve progression and 23 no progression. The validity results showed a sensitivity=68%, specificity=87% and accuracy=83%. Since the number of male cases was small, no conclusive statement could be made.

To compare the results of our model with existing models [18] the sensitivity reported from literature is within 60% [23] to 85% [24] and specificity from 48% [24] to 81% [25]. The most cited parameters were low age, low Risser sign (0-1), pre-menarche status, large Cobb angle and presence of osteopenia [18]. Our results using US Cobb angle change in addition

to these promising candidate variables showed better accuracy results to detect curve progression at follow-up without use of x-ray radiation. Also, in our study we introduced new parameters extracted from US which is a safe method. There are some limitations regarding our study. Our sample size does not include large group of progression cases. Larger study may help to improve the validation results. Another issue is about heterogeneity of the baseline parameters. Our participants were recruited at different timeline in their growth which may generate some heterogeneities. It is suggested to follow participants prospectively from the initial visit after diagnosis to control for the effect of confounders and check one variable at a time. Lastly, our sample included participants under observation and conservative treatment which could affect the results. It is suggested to examine the predictability of parameters for each group separately. Nevertheless, this study showed promising results for the detection of progression, and improvemed predictability could be achieved by including a larger sample and a homogenous dataset.

7.3.9. Conclusion

The final model of curve progression was associated with US Cobb change, RC index and NOC. A large US Cobb change, small RC value and presenting multiple curves increases the risk of presenting curve progression at the follow-up visit. The developed model was validated with sensitivity, specificity, and accuracy all over 90%. Future study should include a greater number of participants to provide better validation of the model.

7.4. Summary

This chapter described two studies to develop a detection model for curve progression and validated with clinical data. The first study was a pilot study that investigated development of detection model using some baseline, clinical, radiographic data and US parameters from both the baseline and follow-up visit. The results showed that the probability of presenting curve progression at time of follow-up for girls with AIS was higher when the US Cobb change was bigger, and the RC value was lower (weaker bone). The 2nd study included more participants for model development and validation. Also, more parameters,

particularly US parameters extracted from coronal, axial and sagittal planes, were investigated. The model achieved sensitivity, specificity, and accuracy of 90%. The results indicated that participants with lower RC (weaker bone, RC ≤0.06), larger US Cobb change (≥5°) and multiple curvatures (NOC>1) were at higher risk of curve progression. Using the predicted model, it may possible to reduce radiographs at that follow-up visit for 74% of children which were predicted to not present progression.

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Chapter 8: Conclusions and Recommendations

8.1. Overview

This chapter provides a summary of this PhD work and reports major contributions, the clinical significance, limitations, and future recommendations. Section 8.2 summarizes the final findings from each study leading to the answers to the objectives of my thesis. Section 8.3 outlines the major contributions of this thesis. In section 8.4, the clinical significance of this thesis work is presented. Limitations and future recommendations are described in Section 8.5.

8.2. Summary of Thesis Work

This thesis has outlined the process of developing a detection model for curve progression for children with AIS. To begin, a comprehensive systematic review was conducted to identify potential prognostic predictors of curve progression. The results showed that only a large Cobb angle and pre-menarche status were strongly supported by the literature to predict curve progression >5° during a short-term follow-up. However, conflicting results and limited evidence were reported for most parameters. Further investigations were required for many of these parameters. The potential baseline parameters that were selected based on that systematic review were age, body mass index (BMI), menarche status, X-ray Cobb angle, number of curve (NOC), Risser sign. Also, the ultrasound (US) reflection coefficient (RC) which is related to bone quality was selected.

A new US parameter called US RC index was derived based on the fundamentals of ultrasound imaging physics. To learn about the theory, extract the RC index, and calculate its value, both *in-vitro* and *in-vivo* experiments were conducted. From the *in-vitro* experiments, the RC index was found to be linearly correlated with the stiffness of the scanning materials which also applied to the bone in the *in-vivo* study. Also, in a pilot clinical study, the RC index was moderately correlated with the curve severity of 37 participants (R^2=0.3) suggesting this parameter may have value to predict curve progression.

Then, a study was conducted to evaluate the repeatability and reliability of RC. Different methods of measurements were tested throughout this study and the most repeatable and reliable was the average of the RC index measured on each lamina for five consecutive frames at L5 with intra-rater and inter-rater reliabilities of ICC [2,1] ≥ 0.84 and SEM ≤ 0.01. The results showed 68% of children who had a larger RC value (stronger bone) than the average of the study participants (0.07) showed no curve progression. However, it was a pilot study and the ability of the RC index to predict curve progression required further evaluation.

The US parameters that were considered for investigation as predictors of progression consisted of US Cobb change, plus the US parameters at baseline including US maximum axial vertebral rotations (AVR), Curve angle in the plane of maximum curvature (PMC), US kyphotic angle (KA), and US RC index.

Two studies were conducted to evaluate the reliability and validity of the KA on US images. The first pilot study (n=20) showed US KA was a reliable measurement with an ICC [2, 1] ≥ 0.85 for the intra-rater, inter-rater, and inter-method analyses. The average difference between US and X-ray measurements was within 5°. Then, a large clinical study (n=50) was conducted to further evaluate the intra-rater and inter-method reliabilities of the KA as well as to investigate factors that might affect the accuracy of the measurements. The results showed good intra-rater and inter-method reliability ICC [2, 1] ≥ 0.84 using the T1/T12 level measurement method. In addition, 80% of the measurements were within the clinically accepted error (7°). The position of the arms during standing posture was the only factor that might affect the measurement difference of the KA measurements.

The factors influencing the reliability and variation measurement of the US AVR were investigated. The ultrasound AVR measurement using the center of laminae (COL) method was compared with Stokes' method on radiographs. The intra-rater result was excellent (ICC [2,1] =0.9); however, the inter-method reliability was poor to moderate (ICC [2,1] ≥0.49) and the maximum average difference in AVR measurement between X-ray and US

was 4.6°. The factors that showed a significant influence on the differences in the measurements were AVR measurements at the apical region and AVR severity.

Next, a pilot study with 56 cases was conducted to develop a detection model of curve progression using the following parameters age, menarche status, X-ray Cobb angle, RC index that all acquired at the baseline visit except the US Cobb change. Of these, only the RC index and then US Cobb change were the final predictors of curve progression. Then, the model was validated in 19 new participants including 8 progression cases and the results showed sensitivity, specificity, and accuracy of 86%, 92%, and 90% during validation, respectively. This preliminary study showed promising results for developing a model to predict curve progression using US parameters. However, since the number of cases used to develop the model and validate it was small, a larger clinical study was conducted.

Finally, a large clinical study with 162 girls with AIS was conducted. Among those, 100 participants including 25 progression cases were used for model development. The parameters were demographic extracted at baseline: age, body mass index (BMI), and menarche status; radiographic extracted at baseline: X-ray Cobb angle, NOC, and Risser sign; and ultrasonic: US Cobb change, and baseline US parameters including max AVR, PMC Cobb angle, KA, and RC index. After a step-by-step analysis, the significant parameters were US Cobb change, RC index, and NOC. The generated model was Log (p/1-p) =-1.40+0.28(US Cobb change)-39.45(RC)+1.36 (NOC). Then, the model was validated on 62 cases. The sensitivity, specificity, and accuracy results were over 90% which is promising. Using our model at the follow-up visit, we were able to reduce radiographs for 74% of non-progressive cases.

8.3. Major Contributions

The main contributions of this PhD thesis are:

- Introduction of a new US parameter called RC index, *in-vitro* validation of the index and demonstration of the reliable measurements from the developed method

- Introduction of a new method to measure KA on US images, presenting the reliability of measurements, validation of the measurement in a large study, and reporting on factors that may affect the accuracy of the US KA measurements
- Development of a new curve progression detection model based on my proposed parameters, and accurate up to 90%.

8.4. Clinical Significance

The developed model focuses on the detection of curve progression as measured on radiograph at a follow-up visit for children with AIS (Figure 8.1). At the initial visit, PA and LAT radiographs are requested as well as an ultrasound scan. After the patient is diagnosed with AIS, the number of curves (NOC) is determined based on an X-ray image. From the US image, the RC index as well as the first-visit US Curve angle are measured and recorded. Then, for the next follow-up visit, an ultrasonography is acquired. The US Cobb change is calculated. The parameters including the US Cobb change, the baseline RC index, and the baseline NOC are used to calculate the probability of the curve progression on the radiograph based on the equation: Log (p/1-p) =-1.40+0.28(US Cobb change)-39.45(RC)+1.36 (NOC). If the value is > 0.4, the case is considered as high-risk of showing progression. A radiograph is then requested to confirm the Cobb angle change and for planning the course of treatment. Following this approach, it is possible to reduce the number of radiographs at the second visit for the cases that are considered to have a low risk of progression.

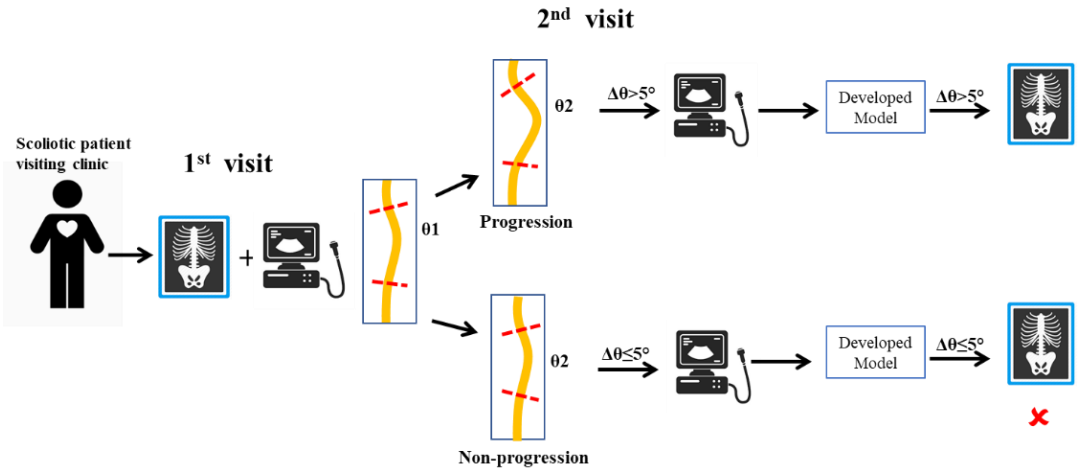

Figure 8.1 Clinical application of the detection model to detect cases with progression in clinical practice

8.5. Limitations and Future Recommendations

The main limitation of this study is the number of participants used to develop and validate the model. The total number is smaller than the sample size required to provide 80% power, 500 participants including 72 progression cases. The lack of a larger sample size is due to the COVID-19 pandemic which affected the recruitment and follow-up testing in clinical study.

Another point is the heterogeneities that exist in our data set. The children were recruited at different timelines in their care path; more specifically, they were also at different growth stages. Even though we tried to focus on only female cases and reduce the heterogeneities to some level with our selection criteria excluding larger curves and those treated with surgeries, the baseline information varied between participants.

The next limitation is regarding the treatment status of the participants included in our study. The children were either under observation or conservative treatment during data acquisition. The interventions could have affected the outcome of progression. Also, since the number of cases under each category was not large, it was difficult to run the analysis for each category during the model development.

The following recommendations have been provided for consideration in future investigations:

- Continue recruiting subjects for the study so that a larger data sample and more homogenous data can be used to develop and validate the model.
- Use all participants' data at their first visit to the scoliosis clinic.
- Apply different machine learning algorithms to develop the prediction models and to help choose the most accurate model for clinics.
- In terms of treatment status, develop the model for observation and treatment groups separately in order to investigate whether treatment has any effect on the results.
- Consider other progression criteria, as well as a short-term or long-term follow-up interval for developing the prediction model rather than solely focusing on prediction of curve progression at the follow-up visit.
- Develop a program to automatically measure all the US parameters instead of manual measurement and extraction to minimize measurement errors.

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Chapters 1 and 2

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Chapter 3

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