

Title: Using Ultrasound for Screening Scoliosis to Reduce Unnecessary Radiographic Radiation - A Prospective Diagnostic Accuracy Study on 442 Schoolchildren

(Title's word count: 19 out of 20)

Author names and affiliations

Henry PANG¹, Yi-shun WONG¹, Benjamin Hon-kei YIP², Alec Lik-hang HUNG¹, Winnie Chiu-wing CHU³, Kelly Ka-lee LAI⁴, Yong-ping ZHENG⁴, Thomas Wai-hung CHUNG⁵, Geeta SHARMA⁵, Jack Chun-yiu CHENG⁶, Tsz-ping LAM^{6*}

¹ Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR;

² Division of Family Medicine and Primary Health Care, The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR;

³ Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR;

⁴ Department of Biomedical Engineering, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR;

⁵ Student Health Service, Department of Health, Hong Kong SAR;

⁶ SH Ho Scoliosis Research Lab, Joint Scoliosis Research Center of the Chinese University of Hong Kong and Nanjing University, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong

*Corresponding author: Tsz-ping Lam, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, 5/F., Clinical Science Building, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR. E-mail: tplam@cuhk.edu.hk. Phone: (852) 3505-3309

Abstract: (200 / 200 words)

Scoliosis screening is important for timely initiation of brace treatment to mitigate curve progression. Scoliosis screening programs including the one in Hong Kong refer schoolchildren for confirmatory radiography if children are screened positive with Scoliometer and Moiré Topography. Despite being highly sensitive (88%) for detecting those who require specialist referral, this screening program has more than 50% false positive rate, thereby subjecting schoolchildren to unnecessary radiation.

Radiation-free ultrasound has been reported to be valid and reliable for quantitative assessment of curve severity in scoliosis patients. The aim of this prospective diagnostic accuracy study was to determine if ultrasound was accurate in determining the referral status on scoliosis screening after being screened positive by Scoliometer and Moiré Topography. Our study recruited 442 schoolchildren with mean Cobb angle of $14.0 \pm 6.6^\circ$. The sensitivity and specificity of ultrasound in predicting the correct referral status, confirmed by X-ray, were 92.3% and 51.6%, while the positive and negative predictive values were 29.0% and 96.9% respectively. ROC curve analysis showed the area under curve was 0.735 and 0.832 for ultrasound alone and in combination with ATR measurement respectively. This indicates ultrasound is accurate resulting in more than 50% reduction of unnecessary radiation for scoliosis screening.

Using Ultrasound for Screening Scoliosis to Reduce Unnecessary Radiographic Radiation - A Prospective Diagnostic Accuracy Study on 442 Schoolchildren

Main text (2910 out of 4500 words)

Introduction:

Scoliosis is a complex three-dimensional spinal deformity affecting 1-3% of the general population^{1,2}. If left untreated, scoliosis can progress and be associated with serious health problems including back degeneration^{3,4}, cardiopulmonary compromises⁵, negative body images and psychosocial disorders arising out of grossly deformed torso⁶. Spinal deformity in scoliosis is quantitatively assessed with radiological Cobb angle⁷. In general, observation with close monitoring until skeletal maturity is recommended for Cobb angle $< 20^\circ$. For skeletally immature patients with Cobb angle $\geq 20^\circ$ to 25° , bracing is indicated^{8,9}. The effectiveness of bracing has been reported in the literature including a randomized controlled trial conducted by Weinstein¹⁰. For scoliosis with severe curves, surgery is indicated typically in the form of spinal fusion for the scoliotic curves resulting in permanent loss of motion of the fused spinal segment¹¹. Surgery is a major invasive procedure carrying significant risks including blood loss, wound infections, implant failures, spinal cord injuries and even mortality¹². In view of the invasive nature of surgical procedures and the significant morbidities with severe scoliosis, it is important to diagnose scoliosis early so that bracing can be started to control the curve from progressing to surgical thresholds¹³. As scoliosis is asymptomatic at its initial phase, the key for successful treatment is by screening to detect scoliosis among asymptomatic immature subjects¹⁴.

Current scoliosis screening programs including that employed in Hong Kong were mostly developed back in the 1980s and rely on Angle of Trunk Rotation (ATR) measured with forward bending of the spine with or without Moiré Topography^{15,16}. Schoolchildren will receive confirmatory X-ray examination of the whole spine if screening results are positive (Figure 1). A recent scientific review by Fong et al concluded that the scoliosis screening program in Hong Kong is clinically effective with a sensitivity of 88% in detecting those with curve severity greater than the specialist referral threshold, i.e. Cobb angle $\geq 20^\circ$ ¹⁵. One issue, however, is that there are schoolchildren suspected to have scoliosis at the initial screening, but later shown to be either free from the disease or with Cobb angle $< 20^\circ$. They are thus subjected to unnecessary radiation exposure from x-ray examination. In one of our reports capturing the data between 1995-97, a total of 2894 schoolchildren received x-ray with 1406(48.6%) having Cobb angle $\geq 20^\circ$, i.e. the referral threshold requiring specialist care. On the other hand, 1488(51.4%) had either no scoliosis or with Cobb angle $< 20^\circ$ ¹⁵. They did not need specialist referral and could be managed conservatively with follow up evaluation at the primary care level. This issue of unnecessary x-ray exposure is not unique to Hong Kong as programs in other countries are also affected with similar problems¹⁷⁻¹⁹. Taking x-ray is not without risks. Radiation may increase the risk of breast cancer in girls with scoliosis²⁰. In addition, radiographic diagnostics in childhood contributes significantly to leukemia and prostate cancer²¹. As echoed in 2012 SOSORT Consensus paper, reducing radiation exposure in one of the goals for treating scoliosis patients²².

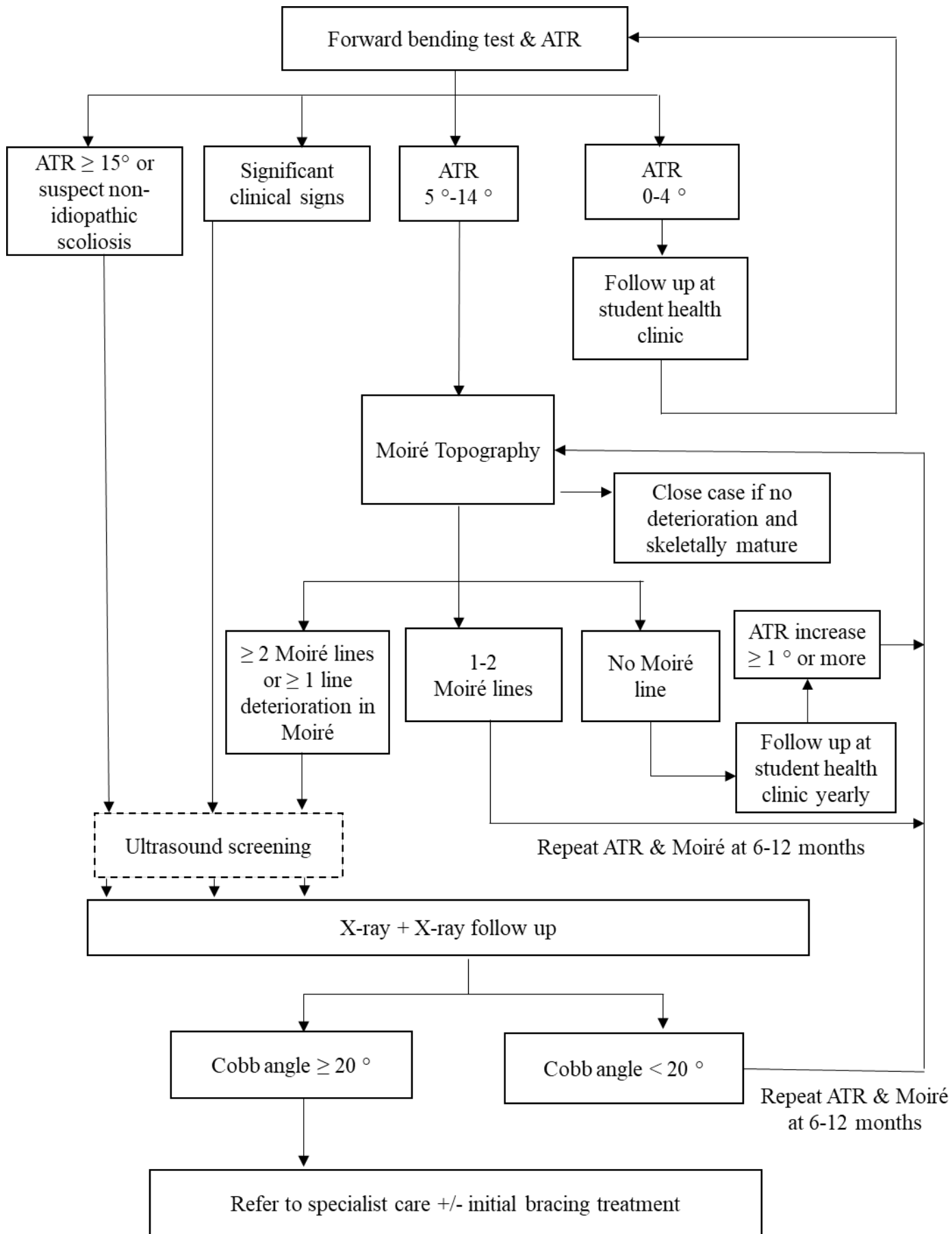


Figure 1: The algorithm of Scoliosis Screening Program in Hong Kong. Box with dotted line indicates the proposed usage of ultrasound for screening after positive ATR and Moiré Topography, and before confirmatory X-ray.

Given the health concerns with radiation exposure, ultrasound has recently received attention for quantitative assessment of spinal deformity²³⁻²⁵. In addition to being radiation-free, ultrasound is generally regarded as an inexpensive, dynamic and highly portable modality of investigation frequently used in medical diagnostics²⁶. Previous studies on ultrasound assessment for back deformity, including a recent one by our study group on 952 scoliosis patients, have validated the accuracy of ultrasound for proven cases of scoliosis^{27,28}. Nevertheless, previous studies were confined to those with confirmed diagnosis of scoliosis. To the best of our knowledge, no study has been reported focusing on the role of ultrasound in screening scoliosis for determination of the referral status on whether the subject needs specialist referral or not, i.e. those with scoliosis above the referral threshold of Cobb angle $\geq 20^\circ$ as distinct from those with milder curves or no scoliosis at all.

We therefore proposed to carry out this scientific study with the primary objective of evaluating the sensitivity and specificity of ultrasound in determining the referral status, i.e. “for specialist referral” or “not for specialist referral”, through predicting whether the Cobb angle was beyond the referral threshold of $\geq 20^\circ$ or not in scoliosis screening. The secondary objective was to evaluate if Angle of Trunk Rotation (ATR) of the scoliotic curve as measured with the Scoliometer during the Adam’s Forward Bending Test could increase the accuracy of ultrasound assessment in the primary objective .

Results:

Study population and curves characteristics

As shown in the Study Flow Diagram in Figure 3, 442 subjects (243 females and 199 males, mean age 13.2 ± 1.8 years) with various degrees of coronal curvatures (mean Cobb angle of major curve $14.0^\circ \pm 6.6^\circ$, range $0-39.0^\circ$) were studied. Detailed demographics and curve characteristics are depicted in Table 1. 29.6% female subjects were in their premenarche state. Distribution of the Cobb angle of major curves is shown in Table 2, with major curves defined as the largest scoliosis curves with Cobb angle $\geq 10^\circ$ in an individual subject. Out of 442 subjects, it was noted that 326 subjects (73.7%) had Cobb angle $\geq 10^\circ$, and 78 subjects (17.6%) had Cobb angles $\geq 20^\circ$. Majority of curves (56%) belonged to mild scoliosis defined as those with Cobb angle between 10 to 20° . Distribution of the apical location of major curves is shown in Figure 4. Curve convexity distribution of major curves was 55% towards the left side (n=179), and 45% towards the right (n =147).

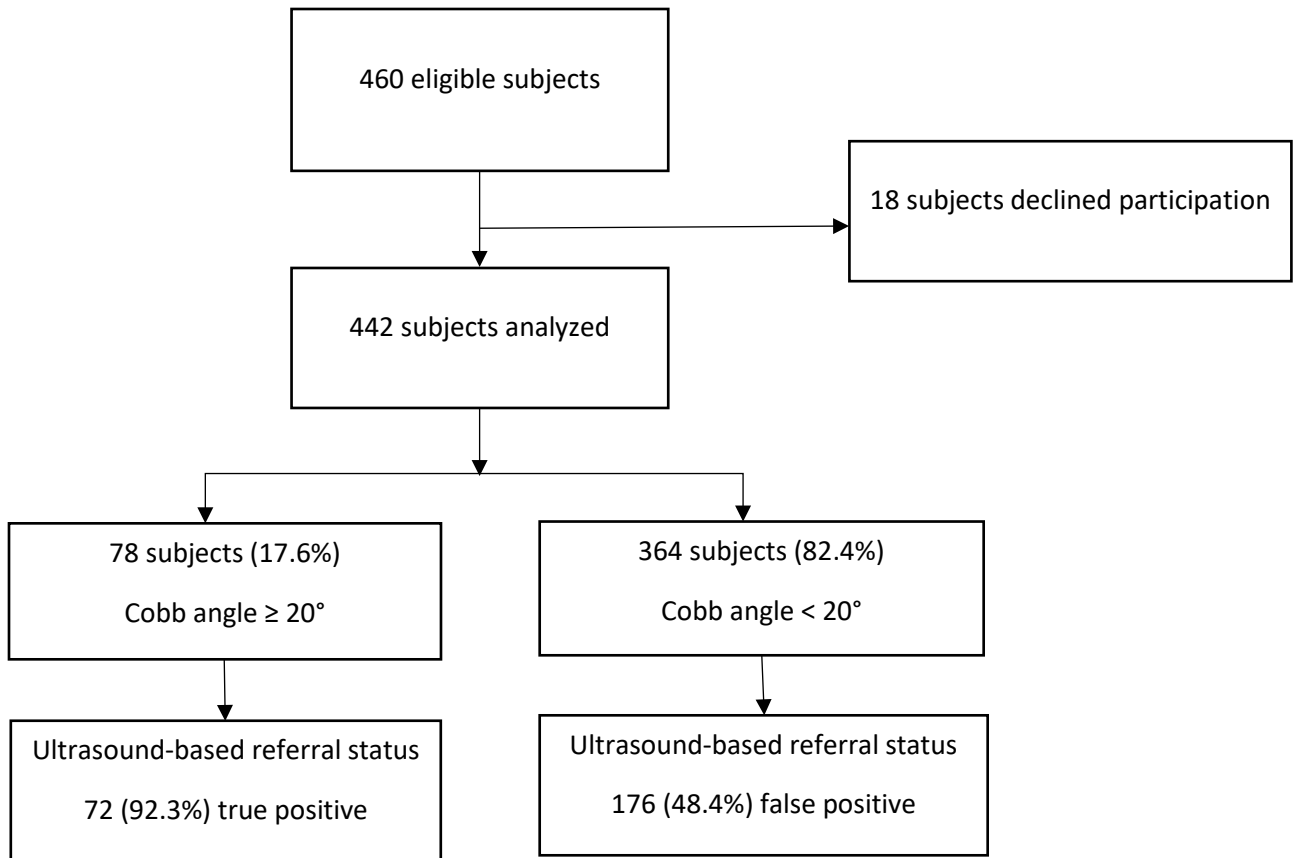


Figure 3: The study flow diagram

Subject	Mean	SD
Age (year)	13.2	1.8
Years since menarche (year)*	1.29	1.2
BMI (kg/m ²)	18	2.4
Weight (kg)	45.1	9.4
Height (m)	157.5	10.4
Max. Cobb (°)	14.0	6.6
Max. SPA (°)	11.4	5.0
Max. ATR (°)	5.7	2.4

Table 1: Basic characteristics of study subjects. *Year since menarche was calculated based on female subjects who had their first menstruation. SPA: spinous process angle

Cobb angle	Frequency	Percentage frequency
10-14	145	44.5%
15-19	103	31.6%
20-24	42	12.9%
25-29	26	8.0%
30-34	6	1.8%
35-39	4	1.2%

Table 2: Frequency distribution table of the Cobb angle of major curves

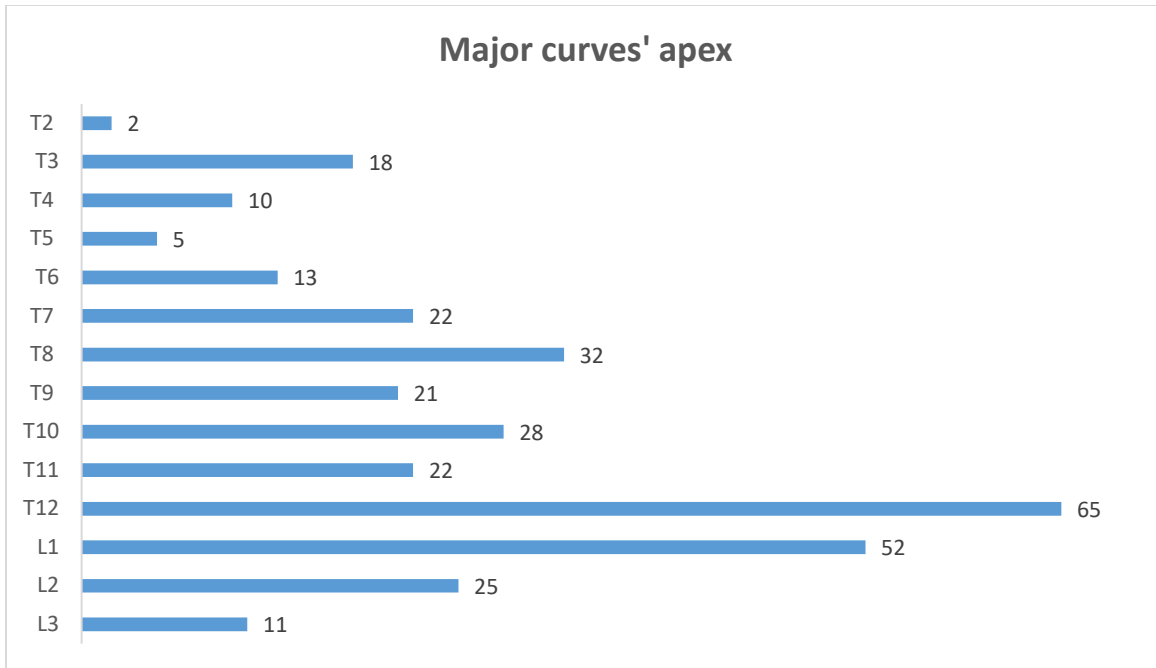


Figure 4: Distribution of apical vertebra location for the major curves

Ultrasound findings

Logistic regression analysis showed the logistic predictive equation was $\log(\text{prob}/1-\text{prob}) = -3.533 + 0.159 \cdot \text{SPA}$ for SPA alone, where SPA refers to spinous process angle, the curve severity measured by ultrasound as an estimation of Cobbs angle, and will be further elaborated in the methodology part. The logistic predictive equation was $\log(\text{prob}/1-\text{prob}) = -4.74 + 0.137 \cdot \text{SPA} + 0.336 \cdot \text{ATR}$ for SPA with ATR respectively. Here, prob in these equations refers to the probability of having a predicted positive ultrasound-based referral status.

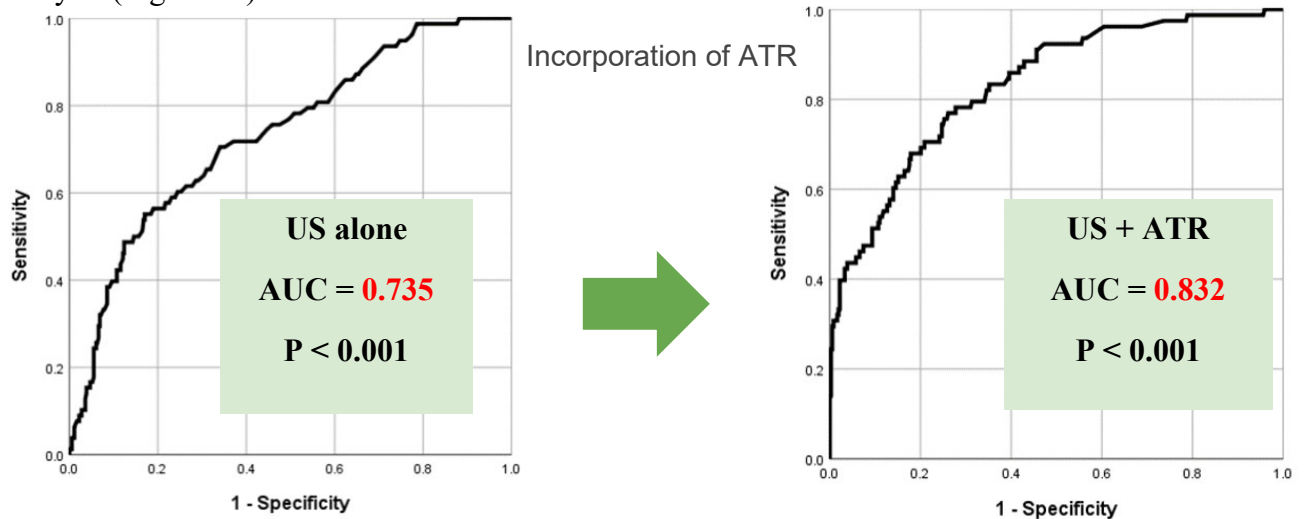
The optimal probability cut-off for the logistic predictive equation combining SPA and ATR was determined by two factors. Firstly, the optimal cut-off had to fulfill its clinical significance, and only probability cut-offs with sensitivity $\geq 90\%$ were selected as it is undesirable to miss a case of scoliosis during screening who required specialist referral and bracing treatment. Secondly, for those cut-offs with sensitivity $\geq 90\%$, Youden indices were calculated based on their sensitivity and specificity. The optimal cut-off was selected with the greatest Youden index. At the optimal probability cut-off of 0.11, the sensitivity and specificity for determining the referral status were 92.3% and 51.6% respectively, whereas the positive and negative predictive values were 29.0% and 96.9% respectively (Table 3). Thus, in using ultrasound for determining the referral status, ultrasound can correctly identify 72 out of 78 subjects with Cobb angle $\geq 20^\circ$, and 188 out of 364 subjects with Cobb angle $< 20^\circ$. Using the same cut-off threshold, the positive likelihood ratio was 1.91, while the negative likelihood ratio was 0.15. Six subjects (1.4% of the whole cohort of 442 subjects) who reached the referral threshold of 20° had false negative results with ultrasound. The median of the major Cobb angles of these 6 false negative subjects was 25.5° (range $20\text{-}35^\circ$), among whom 3 (0.7%, out of 442 subjects) had major curves Cobb angles $\leq 25^\circ$.

	X-ray-based referral status			
Ultrasound-based referral status	Yes	No	Total	
Yes	72	176	248	PPV :29.0%
No	6	188	194	NPV: 96.9%
Total	78	364	442	
	Sensitivity: 92.3%	Specificity: 51.6%		

Table 3: Accuracy of ultrasound together with ATR in determining referral status. X-ray-based or ultrasound-based referral status is positive if Cobb angle measured / predicted is $\geq 20^\circ$. PPV: positive predictive value, NPV: negative predictive value

ROC Curve analysis

Patient-based analysis showed that area under the ROC curve was 0.735 ($p < 0.001$) with ultrasound-derived spinous process angle (SPA) alone for predicting the referral status and increased to 0.832 ($p < 0.001$) when the angle of trunk rotation (ATR) was incorporated into the prediction model (Figure 5a). Similar findings were noted with curve-based analysis (Figure 5b).



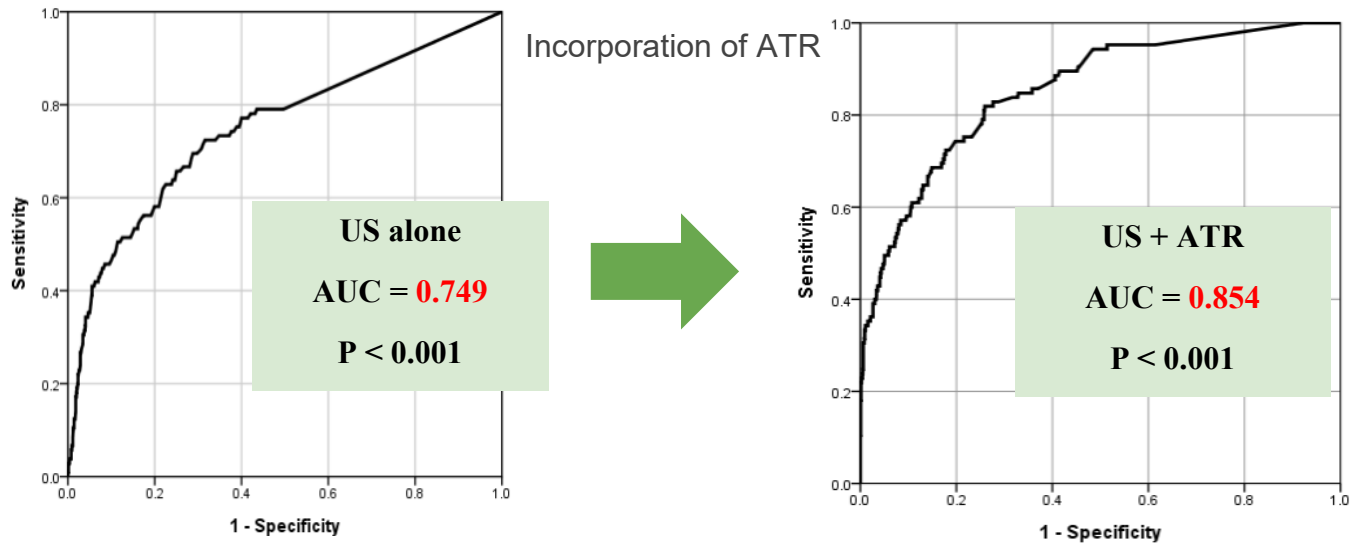


Figure 5: Receiver operating characteristic (ROC) curve analysis for SPA without and with ATR. X-ray-based referral status is the dependent variable, and ultrasound(US)-based referral status \pm Angle of Trunk Rotation are the independent variable. Figure 5a (Top): ROC curves obtained from patient-based analysis. The area under the ROC curve was 0.735 ($p < 0.001$) with ultrasound-derived SPA alone for predicting the referral status and increased to 0.832 ($p < 0.001$) when ATR was incorporated into the prediction model. Figure 5b (Bottom): Curve-based ROC curve of predictive power of SPA without and with ATR, showing similar findings with improvement after incorporating ATR into the prediction equation.

Discussion:

As mentioned earlier, population screening program is essential for early detection of asymptomatic scoliosis for timely diagnosis and treatment to prevent curve progression¹⁵. In Hong Kong, screening for scoliosis was launched in 1995 as part of the annual health assessment program under the Student Health Service²⁹. More than 1 million schoolchildren have been screened since its inception. At Student Health Service Centres, children starting from Primary 5 or aged 10 years are screened according to an algorithm utilizing Angle of Trunk Rotation (ATR) and the Moiré Topography (Figure 1). ATR is measured with a Scoliometer during the Adam's Forward Bending Test. Students with ATR between 5° to 14° together with positive results with Moiré Topography, or those with $ATR \geq 15^{\circ}$ will be referred for confirmatory radiological examination. Students with radiological Cobb angle $\geq 20^{\circ}$ will be referred to an orthopaedic unit for specialist management. Otherwise, the students will remain to be followed up at Student Health Service Centres with observation, regular re-assessment with or without X-ray according to the algorithm.

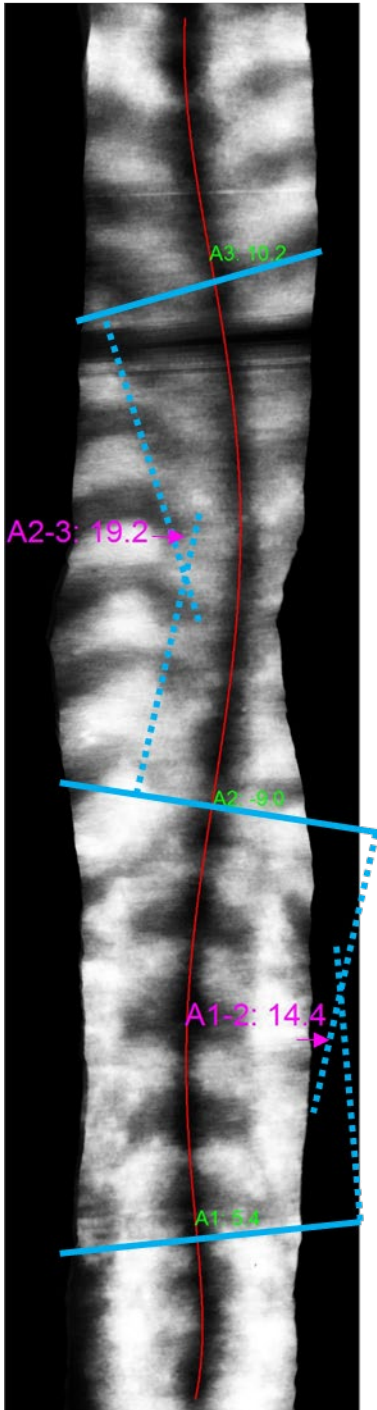
Although recognized as being highly sensitive for identifying schoolchildren who require specialist referral (88 %) & treatment (80%), the screening program in Hong Kong has false positive rate of 50%¹⁶. These children have either no scoliosis or with Cobb angle $< 20^{\circ}$. It follows that they only require conservative management with primary care follow up and are thus subjected to unnecessary x-ray exposure. Although

advanced systems such as the recently available EOS radiographic system is characterized by lower dose of irradiation, given the potential health hazards with repeated radiation exposure especially for growing children, it remains highly desirable if unnecessary radiographic investigation can be avoided, in particular for those with no scoliosis or with only mild curves, i.e. with Cobb angle $< 20^{\circ}$ ³⁰.

With recent technological advancement in body imaging or contour evaluation, several radiation-free modalities for scoliosis assessment have been proposed. One such modality is surface topography (also known as Rasterstereography), including Moiré Topography which is an assessment item of the screening program in Hong Kong³¹. Other surface topography assessment systems include Jenoptik Formetric system (Aesculap meditec GmbH, Germany)³², Inspeck System (Vivid 910, Konica Minolta, Japan)³³, Integrated Shape Imaging System (Oxford Metrics, Ltd., Oxford, UK)³⁴ and the Quantec Spinal Imaging System (Quantec Inc., Lancashire, England)³⁵. All these are based on the principle of detecting deformed projected lines on scoliotic back of patients, with 3D sectioned images reconstructed by the triangulation method³⁶. A recent systematic review of twelve studies evaluating the validity of surface topography showed that the accuracy of this method varied, and surface topography did not enable measurement of Cobb angle^{37,38}. Chowanska et al. investigated the use of surface topography as a screening tool for scoliosis, quoting the sensitivity was 64.5% and the specificity was 88% for $ATR \geq 5^{\circ}$ and the sensitivity was 77.4% and the specificity was 71.1% for $ATR \geq 4^{\circ}$. Their study concluded that surface topography is not suitable for scoliosis screening³⁹.

Similar to rasterstereography, Ortelius800TM system (Orthoscan Technologies Inc., MA, USA) is another technology that detects scoliosis curve with surface topography. This system utilizes electromagnetic spatial sensing technology to record the surface position of spinous processes tips location through palpation by trained examiners. Conflicting results were reported by different research groups with regards to the accuracy of this system. Knott et al reported only 55% of the predicted curves were within acceptable range, and Zabka et al reported an average difference in measurement of up to 6.7 degree.⁴⁰⁻⁴². Another modality proposed is infrared thermography based on the asymmetrical paraspinal muscle activity of scoliotic patients. Higher muscle activity is observed in the convex side, leading to higher temperature and infrared emission as detected by an infrared camera. Nevertheless, infrared thermography for screening spinal deformity is still under development and related researches remain limited to feasibility studies⁴³.

Out of all the recently developed imaging and topographical investigation for scoliosis, ultrasound is characterized as being inexpensive, radiation-free and highly portable and is frequently used in medical diagnostics^{44,45}. 2-dimensional(2D) B-mode ultrasound has been used for examining spinal morphology while 3D spinal images can be reconstructed with addition of a position-tracking transducer^{23,24,26}. Vertebral landmarks, notably the spinous processes, can be visualized in spine volume projection images (Figure 6) with which SPA can be measured. For proven cases of scoliosis, the intra- and inter-rater reliability of ultrasound assessments have been reported to be satisfactory as being respectively greater than 0.94 and 0.88 that are comparable to that with traditional radiographs⁴⁶.



- Red line : line of spinous processes
- A1,A2,A3 : curve inflection points
- A1-A2 : lumbar curve, SPA = 14.4.
Corresponding X-ray Cobbs angle = 14.9
- A2-3 : thoracic curve, SPA = 19.2.
Corresponding X-ray Cobbs angle = 19.5
- Continuous blue line : line perpendicular to tangential to the line of spinous process at curve infection point

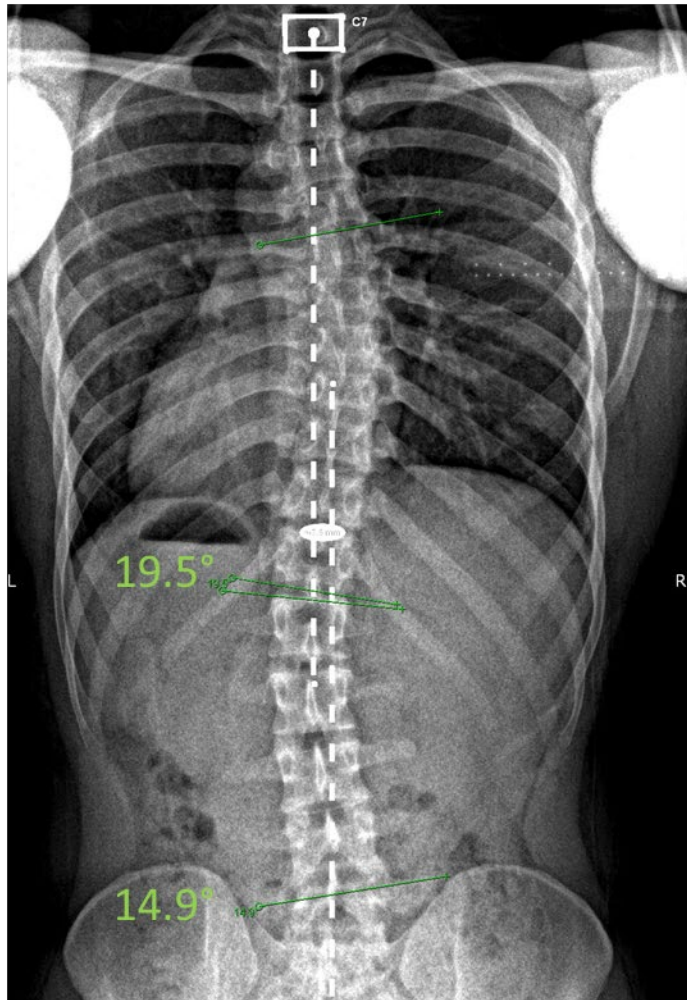


Figure 6: Measurement of SPA: along the line of spinous processes (in red), the curve inflection point corresponds to the most tilted vertebra which can be identified manually, or with an automatic computer program for spinal curvature measurement in a way similar to the Cobb method.

SPA measured from ultrasound scanning was investigated in this study for its role in scoliosis screening. For schoolchildren initially screened positive for suspected scoliosis, the results of this study demonstrate that ultrasound-based SPA measurement is accurate

in determining the referral status, i.e. “for specialist referral” or “not for specialist referral”, through predicting whether the Cobb angle is beyond the referral threshold of $\geq 20^\circ$ or not in scoliosis screening. A sensitivity of 92.3% and a specificity of 51.6% were noted at the probability cutoff at 0.11. In other words, if incorporated as an integral part of the scoliosis screening program when the schoolchildren were screened positive but before confirmative radiographic examination, ultrasound can avoid unnecessary radiation from confirmatory radiography in around 50% of cases for those with radiological Cobb angle below the specialist referral threshold of 20° .

While ultrasound can be useful to identify subjects who do not need specialist referral, there are 6 cases with false negative results having Cobb $\geq 20^\circ$ but are screened negative with ultrasound. They account for 1.4% of the entire cohort of this study, with three of them (50%) having major Cobb angle $\leq 25^\circ$. Our team has investigated the underlying causes by looking into the raw ultrasound images and data, with two major issues were identified. Firstly, the scanning algorithm used in this study can only detect two scoliosis curves at most in the same patient. Therefore, the SPA from 3 subjects with triple curves were averaged out and missed by the system as having SPA $< 20^\circ$. The second issue was the scanner’s low sensitivity at either end of spinal curves, leading to missing out of 3 curves with Cobbs angle $\geq 20^\circ$ in upper thoracic or lower lumbar region.

There were limitations with this study. Firstly, our study was conducted at a single centre. Secondly, subgroup analysis with respect to curve levels, curve types, body height, gender and stages of skeletal maturity was not conducted due to limited sample sizes. Immature female subjects have the highest risk of curve progression hence requiring more stringent screening and monitoring for back deformity⁴⁷. In this study, only 31 % subjects were skeletally immature females who are either pre-menarche or with menarche less than 9 months ago. In another large-scale scientific study for a total of 952 scoliotic patients on the accuracy of ultrasound, it was shown the accuracy for female patients with years since menarche less than 9 months was not as accurate as that for the mature.²⁸ In order to gather the necessary scientific information for evidence-based clinical application of ultrasound for screening scoliosis, further studies adopting a multi-center design investigating a larger sample size are warranted so that its use in screening scoliosis with various curve types from different ethnic groups especially for immature female subjects can be evaluated.

In addition to determining the referral status, one may extend the use of ultrasound for scoliosis by establishing a prediction model of Cobbs angle based on SPA. The current study only focuses on whether ultrasound is useful for screening of scoliosis, but for prediction of Cobbs angle, it would require another formal study with linear regression based on SPA and Cobbs angle. Nevertheless, the dataset from this study can provide a training set for such purpose, while another formal study can collect relevant data as validation set and test sets to generate the aforementioned predictive model.

Latest but not least, further improvement of the ultrasound machines and its algorithm are desirable. For instance, the first issue of detecting a maximal of two scoliosis curves can be tackled by modifying the scanner algorithm to detect more than two curves. For the second issue with low sensitivity over either ends of spinal curve, one can extend the scanning region to include the lower cervical region and sacral area (c.f. the protocol used in this study with scanner steered from L5 to T1). Our team has provided feedbacks to the inventor of the ultrasound machine, and believe further improvement for the ultrasound system could be made in reducing false negative outcomes from ultrasound

assessment. This would in turn further improve the sensitivity of the ultrasound, and therefore allowing us to select a better probability cutoff with higher specificity and Youden index.

Conclusion

This study provided strong evidences that ultrasound together with ATR measurement were useful for identifying schoolchildren who do not require specialist referral with Cobb angle $< 20^\circ$, thus reducing unnecessary X-ray exposure in the referral workflow of the scoliosis screening program. Ultrasound could therefore be considered for incorporation into the scoliosis screening program for keeping radiation exposure As Low As Reasonably Achievable (the ALARA principle of radiation safety) especially for immature subjects⁴⁸.

Materials and Methods: (917/1500 words)

Study design & subjects' recruitment

This was a prospective diagnostic accuracy study on 442 schoolchildren referred for radiological investigation after being screened positive for suspected scoliosis in a governmental Scoliosis Screening Program (Figure 1). Suitable subjects seen at Student Health Service Centres from Oct 2017-Nov 2018 were invited to participate according to the following criteria:

Inclusion criteria

School children of both genders recommended for radiographic assessment of spinal deformity at the Scoliosis Screening Program (Figure 1)

Exclusion criteria

- i. Patients with standing height < 1 m, or > 2 m
- ii. Patients with body mass index (BMI) ≥ 25 kg/m²
- iii. Subjects with skin diseases
- iv. Subjects with fracture or wound that affects ultrasound scanning
- v. Subjects with ferromagnetic implants
- vi. Subjects with surgery done for the spine
- vii. Subjects with winged scapula or other irregularity of back contour that affects ultrasound scanning
- viii. Subjects who cannot stand steadily during scanning
- ix. Subjects with allergy to ultrasound gel

Detailed explanation of the study was given. Any question was answered up to the subjects' and guardians' satisfaction. Informed written consent was obtained from both the subjects and the guardians before enrolment into the study. Ethical approval was granted from local IRB (Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee, CREC, Ref no. 2016.658).

Radiographic examination

Postero-anterior standing views of the whole spine were taken using the EOS radiographic system according to a standard protocol³⁰. Subjects stood with shoulders in forward flexion at 90 degrees and forearms kept in vertical position with hands fisted. Respiration was kept as shallow as possible during EOS scanning. Spinal curvatures and their severity were measured according to the Cobb Method⁷.

Ultrasound measurement

Ultrasound scanning of the spine from L5 up to T1 vertebra was independently done on the same day as the EOS radiographic investigation. The ultrasound investigators were kept blinded to the radiographic examination. Scolioscan (Telefield Medical Imaging Ltd, Hong Kong), the ultrasound system reported to be reliable and valid for spinal deformity assessment with intra- and inter-observer reliability at 0.988 and 0.949 respectively was used²⁷. The system composed of an ultrasound scanner with a linear probe of 100 mm in width and a frequency range of 4-10MHz, a frame structure and a spatial sensor attached to the ultrasound probe for spatial data capture. Daily calibration was

performed using a phantom to assure the accuracy of spine image formation and subsequent angle measurement.

The ultrasound scanning procedure has been described elsewhere.²⁸ In brief, subjects stood on the Scolioscan platform with a standardized posture kept stable with pegs throughout the scanning process. Ultrasound frequency was set at 7.5 MHz, the focus and scanning depth were set at 3.5 units and 7.1 cm respectively based on previous study as the optimal setting. After adjusting the ultrasound scanner setting, the probe was steered from L5 to T1 along the line of spinous processes (corresponding to the red line in Figure 6). The working principles of the software for automatic measurement of spinal curvatures have been reported by Cheung et al, where the curve inflection point corresponding to the end vertebra could be identified with an automatic computer program for measurement of the Spinous Process Angle (SPA) as illustrated in Figure 6²⁶. 10 to 30 seconds were required for data processing, and the whole ultrasound assessment process including data entry and patient positioning took around 5-10 minutes, which was comparable to that for EOS radiographic assessment.

Clinical measurement of ATR

ATR was measured clinically with a Scoliometer. The subject was instructed to bend forward. A scoliometer was steered along the longitudinal path of the spine centering at the spinous processes for measurement of ATR.

Data collection and statistical analysis

Subjects' characteristics of gender, age, body weight and height were recorded. The cut-off threshold for specialist referral was defined as radiographic Cobb angle $\geq 20^\circ$ as stipulated in the current algorithm of the Scoliosis Screening Program in Hong Kong (Figure 1). Conventional x-ray evaluation was used as the gold standard in determining the x-ray-based referral status (i.e. "for specialist referral with radiographic Cobb angle $\geq 20^\circ$ " or "not for specialist referral with radiographic Cobb angle $< 20^\circ$ "). Ultrasound-based referral status was determined according to the SPA of the subjects for predicting whether the Cobb angles were beyond the referral threshold of 20° or not with the use of the binary logistic regression model. The x-ray-based referral status was the dependent dichotomous variable whereas the SPA and the ATR were analyzed as independent variables. Receiver Operating Characteristic (ROC) curve analysis was performed and the sensitivity and specificity of ultrasound in determining the referral status under curve-based and patient-based data were calculated. Curve-based analysis was performed with each curve being treated as an individual record. Patient-based analysis was performed with each subject being handled as an individual record according to the following: (1) for the primary objective, the major curve Cobb angle of an individual subject was used to determine the x-ray-based referral status analyzed as the dichotomous dependent variable whereas the maximum SPA for that individual subject was analyzed as the independent variable and (2) for the secondary objective, the probability from the curve-based logistic regression equation incorporating both the SPA and ATR for each curve of an individual subject was determined first, the maximum probability for the individual subject was then identified and analyzed as the independent variable. Level of significance was set at $p < 0.05$. SPSS Version 20.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis.

Acknowledgements:

The authors thank the contribution of Echo Ka Ling Tsang, Heidi Lau, Lyn Wong, Josephine Wing Lam Yau and colleagues in the Student Health Service for their assistance in conducting the study.

Additional information**Declaration of competing interest**

YPZ was an inventor of a number of patents related to the Scolioscan system, which have been licensed to Telefield Medical Imaging Limited through the Hong Kong Polytechnic University. YPZ also served as the consultant to Telefield Medical Imaging Limited to improve the function of the Scolioscan system.

TPL's institute Department of Orthopaedics and Traumatology of the Chinese University of Hong Kong received an unconditional donation for supporting scoliosis-related research and education from Telefield Medical Imaging Ltd.

All other authors declare no conflict of interest.

The study was an investigator-initiated study. The donor was not involved in the collection, analysis, interpretation of the data and the decision to approve publication of the finished manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

This study is funded by The HMRF grant (Health and Medical Research Fund of the Hong Kong S.A.R., China, Project no: 04152896)

Data availability: The data that support the findings of this study are available from corresponding author upon reasonable request.

References (48/60)

- 1 Stokes, I. A., Bigalow, L. C. & Moreland, M. S. J. J. o. O. R. Three-dimensional spinal curvature in idiopathic scoliosis. **5**, 102-113 (1987).
- 2 Hattori, T. *et al.* In vivo three-dimensional segmental analysis of adolescent idiopathic scoliosis. **20**, 1745-1750 (2011).
- 3 Danielsson, A. J. & Nachemson, A. L. J. S. Back pain and function 22 years after brace treatment for adolescent idiopathic scoliosis: a case-control study—part I. **28**, 2078-2085 (2003).
- 4 Weinstein, S. L. *et al.* Health and function of patients with untreated idiopathic scoliosis: a 50-year natural history study. **289**, 559-567 (2003).
- 5 Weinstein, S., Zavala, D. & Ponseti, I. J. J. B. J. S. A. Idiopathic scoliosis: long-term follow-up and prognosis in untreated. **63**, 702-712 (1981).
- 6 Fowles, J. V. *et al.* Untreated scoliosis in the adult. 212-217 (1978).
- 7 Cobb, J. R. J. J. The problem of the primary curve. **42**, 1413-1425 (1960).
- 8 Rowe, D. J. M., WI: Scoliosis Research Society. The Scoliosis Research Society Brace Manual. 1-9 (1998).
- 9 Negrini, S. *et al.* 2016 SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth. **13**, 3 (2018).
- 10 Weinstein, S. L., Dolan, L. A., Wright, J. G. & Dobbs, M. B. J. N. E. J. o. M. Effects of bracing in adolescents with idiopathic scoliosis. **369**, 1512-1521 (2013).
- 11 Moskowitz, A., Moe, J., Winter, R., Binner, H. J. T. J. o. b. & volume, j. s. A. Long-term follow-up of scoliosis fusion. **62**, 364-376 (1980).
- 12 Coe, J. D. *et al.* Complications in spinal fusion for adolescent idiopathic scoliosis in the new millennium. A report of the Scoliosis Research Society Morbidity and Mortality Committee. **31**, 345-349 (2006).
- 13 Cheng, J. C. *et al.* Adolescent idiopathic scoliosis. **1**, 15030 (2015).
- 14 Hresko, M. T., Talwalkar, V. R. & Schwend, R. M. Position Statement-Screening for the Early Detection for Idiopathic Scoliosis in Adolescents SRS/POSNA/AAOS/AAP Position Statement. (2015).
- 15 Luk, K. D. *et al.* Clinical effectiveness of school screening for adolescent idiopathic scoliosis: a large population-based retrospective cohort study. **35**, 1607-1614 (2010).
- 16 Lee, C. *et al.* Referral criteria for school scoliosis screening: assessment and recommendations based on a large longitudinally followed cohort. **35**, E1492-E1498 (2010).
- 17 Karachalios, T. *et al.* Ten-year follow-up evaluation of a school screening program for scoliosis: is the forward-bending test an accurate diagnostic criterion for the screening of scoliosis? **24**, 2318 (1999).
- 18 Yawn, B. P. *et al.* A population-based study of school scoliosis screening. **282**, 1427-1432 (1999).
- 19 Goldberg, C., Dowling, F., Hall, J. & Emans, J. J. S. A statistical comparison between natural history of idiopathic scoliosis and brace treatment in skeletally immature adolescent girls. **18**, 902-908 (1993).
- 20 Hoffman, D. A. *et al.* Breast cancer in women with scoliosis exposed to multiple diagnostic x rays. **81**, 1307-1312 (1989).

- 21 Schmitz-Feuerhake, I. & Pflugbeil, S. J. R. p. d. 'Lifestyle' and cancer rates in former East and West Germany: the possible contribution of diagnostic radiation exposures. **147**, 310-313 (2011).
- 22 Knott, P. *et al.* SOSORT 2012 consensus paper: reducing x-ray exposure in pediatric patients with scoliosis. **9**, 4 (2014).
- 23 Suzuki, S. *et al.* Ultrasound measurement of vertebral rotation in idiopathic scoliosis. **71**, 252-255 (1989).
- 24 Huang, Q.-H., Zheng, Y.-P., Lu, M.-H. & Chi, Z. J. U. Development of a portable 3D ultrasound imaging system for musculoskeletal tissues. **43**, 153-163 (2005).
- 25 Cheung, C.-W. J., Law, S.-Y. & Zheng, Y.-P. in *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. 6474-6477 (IEEE).
- 26 Cheung, C.-W. J. *et al.* Ultrasound volume projection imaging for assessment of scoliosis. **34**, 1760-1768 (2015).
- 27 Zheng, Y.-P. *et al.* A reliability and validity study for Scolioscan: a radiation-free scoliosis assessment system using 3D ultrasound imaging. **11**, 13 (2016).
- 28 Wong, Y.-s. *et al.* Is Radiation-Free Ultrasound Accurate for Quantitative Assessment of Spinal Deformity in Idiopathic Scoliosis (IS): A Detailed Analysis With EOS Radiography on 952 Patients. **45**, 2866-2877 (2019).
- 29 Lee, C. *et al.* Costs of school scoliosis screening: a large, population-based study. **35**, 2266-2272 (2010).
- 30 Wade, R. *et al.* A systematic review of the clinical effectiveness of EOS 2D/3D X-ray imaging system. **22**, 296-304 (2013).
- 31 Takasaki, H. J. A. o. Moiré topography. **9**, 1467-1472 (1970).
- 32 Frobin, W., Hierholzer, E. J. P. e. & sensing, r. Video rasterstereography: a method for on-line measurement of body surfaces. **57**, 1341-1345 (1991).
- 33 Song, L., Bourassa, Y., Beauchamp, D. & Lemelin, G. (Google Patents, 2002).
- 34 Turner-Smith, A. R. J. J. o. b. A television/computer three-dimensional surface shape measurement system. **21**, 515-529 (1988).
- 35 Groves, D. & Curran, P. Proceedings of the 6th international symposium on surface topography and spinal deformity. (1992).
- 36 Drerup, B. J. S. Rasterstereographic measurement of scoliotic deformity. **9**, 22 (2014).
- 37 Mohokum, M., Schülein, S. & Skwara, A. J. O. r. The validity of rasterstereography: a systematic review. **7** (2015).
- 38 Knott, P. *et al.* Multicenter comparison of 3D spinal measurements using surface topography with those from conventional radiography. **4**, 98-103 (2016).
- 39 Chowanska, J., Kotwicki, T., Rosadzinski, K. & Sliwinski, Z. J. S. School screening for scoliosis: can surface topography replace examination with scoliometer? **7**, 9 (2012).
- 40 Filo, O. *et al.* in *Orthopaedic Proceedings*. 430-430 (The British Editorial Society of Bone & Joint Surgery).
- 41 Knott, P., Mardjetko, S., Nance, D. & Dunn, M. Electromagnetic topographical technique of curve evaluation for adolescent idiopathic scoliosis. *Spine* **31**, E911-E915 (2006).
- 42 Zabka, M., Rehak, L. & Uhrin, T. Accuracy and clinical usefulness of scoliosis measurement with magnetic spine mapping--Ortelius. *Bratislavske lekarske listy* **116**, 469-474 (2015).
- 43 Kwok, G. *et al.* Postural screening for adolescent idiopathic scoliosis with infrared thermography. *Scientific reports* **7**, 1-8 (2017).
- 44 Kane, D., Grassi, W., Sturrock, R. & Balint, P. J. R. Musculoskeletal ultrasound—a state of the art review in rheumatology. Part 2: clinical indications for musculoskeletal ultrasound in rheumatology. **43**, 829-838 (2004).

- 45 Wakefield, R. J. *et al.* Musculoskeletal ultrasound including definitions for ultrasonographic pathology. **32**, 2485-2487 (2005).
- 46 Li, M. *et al.* A preliminary study of estimation of cobb's angle from the spinous process angle using a clinical ultrasound method. **3**, 476-482 (2015).
- 47 Noshchenko, A. *et al.* Predictors of spine deformity progression in adolescent idiopathic scoliosis: A systematic review with meta-analysis. **6**, 537 (2015).
- 48 Hendee, W. R. & Edwards, F. M. in *Seminars in nuclear medicine*. 142-150 (Elsevier).