Ultrasound *vs.* x-ray: a new way for clinicians to track scoliosis progression?

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Abstract

This retrospective study, utilising prospectively collected data, investigates the use of spine ultrasound as an alternative method for assessing scoliosis, with the aim of reducing radiation exposure. We included 92 patients aged 10 to 16 years with suspected idiopathic scoliosis. Exclusion criteria were weight over 150 kg, metal implants, pre-existing conditions, secondary deformities, and cognitive impairments. Each patient underwent clinical assessment and full spine radiographs, followed by spine ultrasound using the Scolioscan® system. Unprocessed B-mode ultrasound images were analysed using automatic measurements. The correlation between Ultrasound Coronal Angle (UCA) and Radiographic Cobb Angle (RCA) was evaluated at initial and follow-up visits. Strong correlations were found between UCA and RCA, with correlation coefficients ranging from 0.786 to 0.903 ($p<0.001$). The regression formula showed good predictive accuracy for curve progression on follow-up radiographs. The best results were observed in females and in primary thoracic curves ($r = 0.936$, $p<0.001$). Although only four patients exhibited true progression (≥5° increase in Cobb angle), changes in scoliotic angles were effectively detected using ultrasound. This study confirms the feasibility of unprocessed spine ultrasound for scoliosis monitoring in clinical settings. Automatic measurements without 3D reconstruction make ultrasound a practical tool for tracking progression. The regression model shows potential for predicting curve progression, although further validation is needed. These findings suggest spine ultrasound could reduce the need for radiographs, benefiting patients by minimising radiation exposure while providing reliable monitoring of scoliosis progression and treatment outcomes.

Key Words: scoliosis; adolescent; ultrasound; spine.

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Idiopathic Scoliosis (IS) represents a structural 3D deformity of the spine and thoracic cage in healthy children of any age with multifactorial, yet unclarified etiology.[1] During the rapid growth spurts, the scoliotic curve can progress, perpetuating a "vicious cycle".[2] The severity of the curve is measured using the Cobb method.[3,4] According to the Scoliosis Research Society (SRS), a Cobb angle greater than 10° with rotational aspects on a spine radiograph is required to diagnose IS. Currently, the Cobb angle remains the most reliable criterion for defining and monitoring patients with IS and is directly correlated with all treatment decisions.[5] Due to the described measurement error in the Cobb angle, a change of more than 5° is considered a progression of the scoliotic curve.[6] Among the different types of IS, Adolescent Idiopathic Scoliosis (AIS) is the most common and has the highest risk of progression.[7,8]

Early detection and prevention of scoliosis progression during growth is a primary goal of conservative treatment, using 3D correction principles.[5] Full spine radiography in PA or AP projection remains the gold standard for diagnosing and monitoring of IS.[5] However, repeated exposure to ionizing radiation poses a significant risk. Studies indicate that these patients undergo an average of

16 radiographic exams, increasing the risk of certain cancers, particularly breast cancer in women, by fivefold.[9,10,11] To reduce radiation exposure, the EOS® imaging system was developed, offering significantly lower radiation levels with comparable image quality to conventional radiographs.[12,13] However, its high-cost limits accessibility, prompting the need for more affordable alternatives. The ultimate goal is to replace spine radiography as the primary tool for diagnosing and monitoring scoliosis.

A recent report[14] highlights the postural-motor challenges and caregiving burden associated with scoliosis in individuals with Prader-Willi Syndrome (PWS). By identifying delays in postural-motor milestones and significant differences in lumbar extension, it emphasizes the necessity for tailored interventions. Additionally, the findings stress the increased caregiving demands linked to scoliosis, demonstrating the importance of ongoing monitoring to ensure timely interventions and support for both individuals with PWS and their caregivers. Another previous systematic review[15] highlights the neurophysiological, balance, and motion abnormalities linked to AIS. It emphasises the critical need for standardized testing to improve treatment approaches and advance understanding of the complex aetiology of AIS.

In recent years, non-invasive methods like spine ultrasound and surface topography have gained attention as potential alternatives.[16,17,18] These methods are radiation-free, making them safe for unlimited use. Although ultrasound measurements show smaller angles compared to radiography due to differences in anatomical landmarks used, studies have demonstrated a strong correlation between the two.[19] The Scolioscan® device allows for simple, fast, and pain-free spine ultrasound scanning, with studies demonstrating its potential for diagnosing and monitoring IS.[20-23] Recent studies confirmed its reliability and validity and suggest ultrasound could replace radiography in monitoring scoliosis progression and treatment effects.[24-26] The new portable Scolioscan® Air has also shown comparable accuracy to the standard device, expanding its usability.[25]

In previous research,[19-26] ultrasound image analysis required 3D reconstruction in the Scoliostudio® software for precise visualization of anatomical landmarks. Manual measurements were used for greater accuracy, with no significant differences in reliability between using Spinous (SP) and Transverse Processes (TP) for coronal ultrasound angle assessment.[17] Despite its benefits and supporting research, spine ultrasound is not widely used in clinical practice due to the time-consuming nature of 3D software reconstruction and limited staff availability. To integrate ultrasound as a viable alternative to radiography in routine practice, B-mode imaging (without any post-processing) and automatic measurements were compared to spine radiography. Although B-mode only visualises the coronal angle, it offers a quick and efficient way to assess spinal deformities, which is crucial since most treatment decisions are based on frontal plane measurements.[5] This study aimed to determine whether basic ultrasound can reliably track AIS progression, potentially reducing the need for repeated radiographic exposure.

Matarials and Methods

Study design and setting

This retrospective study was conducted at the Institute for Physical Medicine, Rehabilitation and Orthopedic Surgery "Dr Miroslav Zotovic", Banja Luka, Bosnia and Herzegovina, from July 2021 to August 2023, with Ethics Committee approval (No. 21-01-7947-2/24).

Participants

The study included 92 patients (aged 10-16, both genders) referred as suspected IS, with no prior treatment. Clinical assessment and Scoliometer readings indicated the need for full spine radiography. Patients with a Cobb angle ≥10° were diagnosed with AIS,[27] while those with <10° were classified as having no scoliosis/bad posture. Treatment varied from PSSE alone to PSSE combined with bracing, following SOSORT guidelines.[5] Braced AIS patients were advised to wear the brace full-time (18-23 hours/day) based on curve severity and progression risk. Follow-up radiographs were performed for patients with clinical worsening or six months after brace adaptation. For radiographs, brace wear time was adjusted to avoid the "concertina effect".[28] Patients with pre-existing conditions, secondary deformities, or cognitive impairments were excluded.

Data collection

The US examination was performed using the Scolioscan® system (model SCN801) manufactured by Telefield Medical Imaging Ltd, Hong Kong.[22] It includes hardware that enables the scanning process and software (Scoliostudio®) for additional adjustments and 3D reconstruction of the spine. Contraindications for Scolioscan® are weight over 150 kg and the presence of metal and magnet implantants (*i.e.*, pacemaker, defibrillator, cochlear implant).

Five trained technicians with similar experience conducted standardized scans. B-mode ultrasound images with clear visualisation of TP's were used without 3D reconstruction or software adjustments. The same technician couldn't scan the same patient during the initial and follow-up visits, due to organisational challenges of the outpatient department which encompasses several outpatient clinics. The technicians performing the scans had completed specialized training for the use of the ultrasound system. The positioning of the patients and the scanning process were standardised.

The scanning process is fast and easy for the patient, who needs to maintain a stable posture during 45 seconds to 1 minute of scanning. The device is adjustable to the height and width of the patient. After scanning, the ultrasound images (B-mode) were utilized without additional adjustments or use of the 3D reconstruction and analysis software integrated into the Scolioscan® system (Scoliostudio®). Automatic measurements, generated by the system, were employed on the ultrasound images, representing the fastest and most efficient method for measurement. These automatic measurements displayed the tilt angle of each vertebra from the T1 to the L5 level relative to the horizontal plane. Two raters (physicians) selected the end vertebrae of the primary curve, identifying the most tilted vertebrae

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without prior review of the X-ray image for the same patient, to avoid subjectivity and measurement bias. Following the selection of end vertebrae and using the transverse processes as measurement reference points, the ultrasound angle (Scolio-angle) of the primary curve was expressed in degrees, calculated as the sum of the angles of the end vertebrae. This way, the ultrasound (Scolio) angle didn't necessarily display the same end vertebrae as the radiological (Cobb) angle.

Two physicians independently selected the most tilted end vertebrae of the primary curve, avoiding prior X-ray review to prevent bias, following which the US Coronal Angle (UCA) was calculated automatically.

Data extraction

The patient data were extracted from the Institute's health information system. Demographic and anthropometric data covered gender, age, Body Weight (BW), Body Height (BH), and Body Mass Index (BMI) in kg/m² and percentiles. AP full spine standing radiographs and US scans were performed on the same day within one hour. Primary scoliotic curve was the focus of the measurement. A standardised protocol was followed using the GE PROTEUS XR with the "Care Stream Classic CR" imaging system. Digital measurements were made using the "TraumCad®" software. Radiological parameters included the Cobb angle, primary curve location and Vertebral Rotation (VR) at the curve apex, using Raimondi method.

Statistical analysis

Results were presented as frequencies (percentages) or means ± standard deviations. Pearson's correlation analysis was used to assess the relationship's direction and strength. Linear correlation between RCA and UCA was evaluated, and the difference between them (US measurement error) was calculated. This difference was then analysed against other variables. Variables significantly correlated with the measurement error were included in a regression model to predict the RCA on follow-up X-rays. A p-value<0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 29.0 (IBM Corp, 2022).

Results

The study included 92 patients (41% boys and 59% girls) with primary curves ranging from 3° to 45° Cobb angle. Of these, 83 were diagnosed with AIS and 9 with bad posture. After initial clinical and radiological evaluation, 37 patients received bracing. For those with bad posture or mild AIS follow-up radiographs were conducted after an average (Median) of 12.1 months (Interquartile Range: 5 months). Table 1 displays the distribution of patients based on anthropometric characteristics, radiological, and ultrasound findings.

A statistically significant linear correlation between RCA and UCA measurements was observed in all patients, with correlation coefficients (r) ranging from 0.786 to 0.903. The correlation between RCA and UCA, according to the technician who performed US diagnostics, is shown in Table 2.

Table 1. *Basic characteristics of the examined sample.*

	Total (n=92)	Male (n=38)	Female (n=54)	p value
Age	12.9±1.6	13.0±1.6	12.8±1.7	0.571[a]
Height	163.4±10.8	167.5±12.0	160.5±8.8	0.004[a]
Weight	49.7±9.0	51.9±9.3	48.1±8.5	0.043[a]
BMI	18.5±2.1	18.4±2.0	18.5±2.3	0.784[a]
BMI (percentil)	44.2±25.9	42.7±28.0	45.2±24.5	0.655[a]
Thoracic curve (%)	48 (52.2)	22 (57.9)	26 (48.1)	0.478[b]
Lumbar curve (%)	44 (47.8)	16 (42.1)	28 (51.9)	
RCA1	19.2±9.9	15.9±8.6	21.5±10.1	0.007[a]
UCA1	15.8±8.2	12.7±6.1	17.9±8.9	0.003[a]
RCA2	16.0±7.9	13.7±6.9	17.6±8.2	0.018[a]
UCA2	13.9±6.1	11.2±4.5	15.8±6.4	0.000[a]
VR1	10.2±8.8	9.3±7.6	10.7±9.6	0.455[a]
VR2	9.2±7.9	10.1±7.3	8.6±8.3	0.380[a]

[a]*t test;* [b]*Chi-Square.*

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Furthermore, the correlation between RCA and UCA at the initial and follow-up assessment was presented in total sample, as well as in groups according to gender and location of the primary curve, which is shown in Table 3.
The best correlation can be observed in females with primary thoracic curves, as well as males with primary lumbar curves.

The error in US measurement of the spinal curvature angle was calculated as the difference between UCA and RCA. The correlation matrix of the ultrasound measurement error and sociodemographic and anthropometric parameters as well as the location of the curvature is presented in Table 4.
No statistically significant linear correlation of the US

Table 2. *Correlation between RCA and UCA by technicians*

	r (p)	Unstand. B (CI 95%)
Technician 1 (n=64)	0.786 (<0.001)	0.916 (0.733-1.100)
Technician 2 (n=75)	0.823 (<0.001)	1.100 (0.923-1.277)
Technician 3 (n=10)	0.903 (<0.001)	1.696 (1.036-2.356)
Technician 4 (n=25)	0.863 (<0.001)	0.912 (0.682-1.143)
Technician 5 (n=10)	0.853 (<0.001)	1.318 (0.661-1.975)

Table 3. *Correlation between RCA and UCA*

	Total	Male	Female	Thoracic	Lumbar	Thoracic male	Thoracic female	Lumbar male	Lumbar female
Initial	0.825	0.776	0.827	0.869	0.705	0.711	0.898	0.933	0.553
Follow-up	0.796	0.650	0.841	0.879	0.605	0.632	0.936	0.720	0.518

All p values are <0.001.

Table 4. *Correlation matrix of difference between UCA-RCA (follow-up) – US error.*

	Total	Male	Female	Thoracic	Lumbar
Age	0.059 (0.575)	0.126 (0.451)	0.001 (0.995)	0.073 (0.622)	0.055 (0.722)
Gender	-0.074 (0.571)	-	-	0.035 (0.814)	-0.198 (0.197)
T or L	0.101 (0.336)	0.237 (0.152)	0.006 (0.963)	-	-
Weight	-0.044 (0.678)	-0.066 (0.695)	-0.057 (0.683)	0.086 (0.560)	-0.171 (0.268)
Height	0.008 (0.940)	0.015 (0.928)	-0.051 (0.712)	-0.021 (0.885)	0.058 (0.710)
BMI	-0.098 (0.352)	-0.166 (0.319)	-0.048 (0.732)	0.181 (0.218)	-0.317 (0.036)
BMI percentile	-0.083 (0.430)	-0.200 (0.229)	0.032(0.819)	0.124 (0.402)	-0.257 (0.092)
VR	0.260 (0.012)	0.334 (0.040)	0.231 (0.092)	0.326 (0.024)	0.204 (0.183)

Results are presented as correlation coefficient and p value in bracket.

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measurement error was observed according to age, gender, curvature location, weight and height. BMI (kg/m²) has shown a significant correlation in the group with primary lumbar curves and VR measured on the apex of the primary curve on the initial spine radiograph.

In groups divided by gender and primary curve location, a significant correlation between US error and VR was observed among males and primary thoracic curves, while in females significance is close to conventional level of significance. In the group of primary lumbar curves, no significant correlation between US error and VR is observed.

In order to predict the RCA value of the spinal curvature on the follow-up spine radiograph, statistically significant predictors in the regression model included VR on the initial spine radiograph and the UCA value measured on the follow-up ultrasound (Table 5).

According to the model incorporating these two independent variables, the regression equation for predicting the curvature magnitude on the follow-up spine radiograph is: Predicted RCA = 1.391+0.933xUCA+0.160xVR. The predictive power of this model in clinical settings is acceptable; based on the R^2 value, this model explains 66% of the variability of the curvature in the follow-up spine radiograph.

To test the agreement between the two measurement methods, RCA and UCA measurements, the Bland-Altman method was used (Figure 1). The range of agreement is defined as the mean difference between the UCA and RCA measurements ± 2 Standard Deviations (SD). The measurement agreement is satisfactory under outpatient clinical conditions, with an average difference of 1.00° according to Cobb's method.

The predictive RCA value (pRCA) calculated using the regression formula significantly correlates with the RCA value measured on the spine radiograph. The average change in RCA for 1° is accompanied by an average change in pRCA for 1°, with smallest deviations in individual measurements observed in girls and in thoracic curves (see Figure 2). Minimal deviation in individual measurements of RCA compared to pRCA was observed in girls with thoracic curves (see Figure 3).

Discussion

Our study was conducted in a clinical setting without additional staff or technical adjustments, making it more practical for daily use compared to other studies. Unlike previous studies that required 3D-reconstructed ultrasound images for analysis,[19-26] ours is the first to assess unprocessed (B-mode) ultrasound images and compare them to radiographs for detecting curve progression.

Similar to other studies, we found that UCA measurements were generally lower than RCA, due to the use of different anatomical landmarks in ultrasound[19] compared to radiography.[29] This difference occurs because ultrasound cannot penetrate bones, making posterior spinal structures like vertebral bodies and intervertebral discs invisible.[30] Despite these variations, the difference between UCA and RCA was clinically insignificant (<5°), consistent with previous findings[19,24,31] and within the typical measurement error range for the Cobb angle.[32] Studies with a wider Cobb angle range showed more pronounced differences between UCA and RCA.[19,31] While no significant differences in reliability and validity were observed between various US measurement methods, the TP angle showed the closest alignment with the Cobb angle.[19] We found only one study[33] utilising automatic TP measurements, similar to our approach.

Our study showed a strong correlation between UCA and RCA measurements, with best correlation in thoracic

Table 5. *Regression models.*

Model	n	R^2 adj.	SE	Intercept	Beta (95% CI) US	Beta (95% CI) VR	Mean diff
Total	92	0.652	4.652	1.391	0.933 (0.761 – 1.105)**	0.160 (0.040 – 0.280)*	2.080 (1.091-3.070)
Male	38	0.464	5.042	1.575	0.873 (0.484 – 1.261)**	0.252 (0.021 – 0.482)*	2.497 (0.777-4.218)
Female	54	0.709	4.421	0.589	1.003 (0.791 – 1.215)**	0.107 (-0.305 – 0.249)	1.787 (0.570-3.004)
L	44	0.383	5.073	4.238	0.740 (0.389 – 1.092)**	0.145 (-0.021 – 0.310)	2.584 (1.005-4.164)
Th	48	0.779	4.217	-0.411	1.026 (0.810 – 1.241)**	0.173 (-0.023 – 0.370)	1.619 (0.351-2.887)
L Male	16	0.583	4.826	2.706	0.699 (0.003 – 1.396)*	0.362 (-0.015 – 0.740)	3.931 (1.156-6.706)
L Female	28	0.222	5.175	5.165	0.710 (0.190 – 1.230)**	0.061 (-0.138 – 0.260)	1.814 (-0.172-3.800)
Th Male	22	0.347	5.342	0.659	1.000 (0.409 – 1.591)**	0.104 (-0.299 – 0.507)	1.455 (-0.816-3.725)
Th Female	26	0.887	3.283	-1.132	1.026 (0.785 – 1.266)**	0.215 (-0.002 – 0.432)	1.814 (0.257-3.258)

** p<0.05, **p<0.01; SE reg. – Std. error of the Es.*

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curves, consistent with previous research.[19,23,24] This difference may be due to the greater thickness of muscles and fat tissue in the lumbar area,[30] which complicates ultrasound penetration. Additionally, TPs are positioned more posteriorly in the lumbar region, making them less visible, especially with VR.[30] Using TPs as landmarks in both regions for automatic measurements may have also affected correlation. Previous studies have shown that relying solely on TPs in the lumbar area, without including superior articular processes, reduces the correlation between UCA and RCA.[20,21] This is likely because the distance between vertebral landmarks and the skin surface varies at different vertebral levels.[34,35] Analysis by gender showed a stronger correlation between UCA and RCA in females than in males, independent of curve severity, location, or vertebral rotation. This may be due to the relatively small curve size in our sample, up to 45° of Cobb angle. No gender-based differences have been reported in other studies, suggesting the need for further research. We could not assess factors like sagittal profile, leg length discrepancy, or adapted scanning positions, which might have influenced results.[30] The best correlation was seen in girls with primary thoracic curves and boys with primary lumbar curves, though the latter finding is limited by a small sample size of 16 patients. First-braced patients were included to evaluate US potential for monitoring brace treatment effectiveness, as they typically require more radiographs during treatment compared to non-braced patients.[36,37]

A previous study by our team[38] showed lower correlation between UCA and RCA on unedited images with manually measured angles. This may be attributed to the less experienced technicians and doctors, which affected image quality and measurement precision. The spine ultrasound can also essential for monitoring progression, which has been previously confirmed.[39] In the present study, only four patients (as shown in Table 6) showed true progression (Cobb angle

Table 6. *Patients with progression.*

No.	Age	Gender	T/L	BMI	RCA	AVR	RCA control	UCA	UCA control
1	11	Female	Lumbar	18.2	13	2	26	13.7	10.2
2	11	Female	Lumbar	16.4	11	0	21	11.9	12.8
3	12	Female	Lumbar	19.9	10	20	20	10.3	11.3
4	11	Female	Thoracic	18.7	15	6	21	11.1	12.2

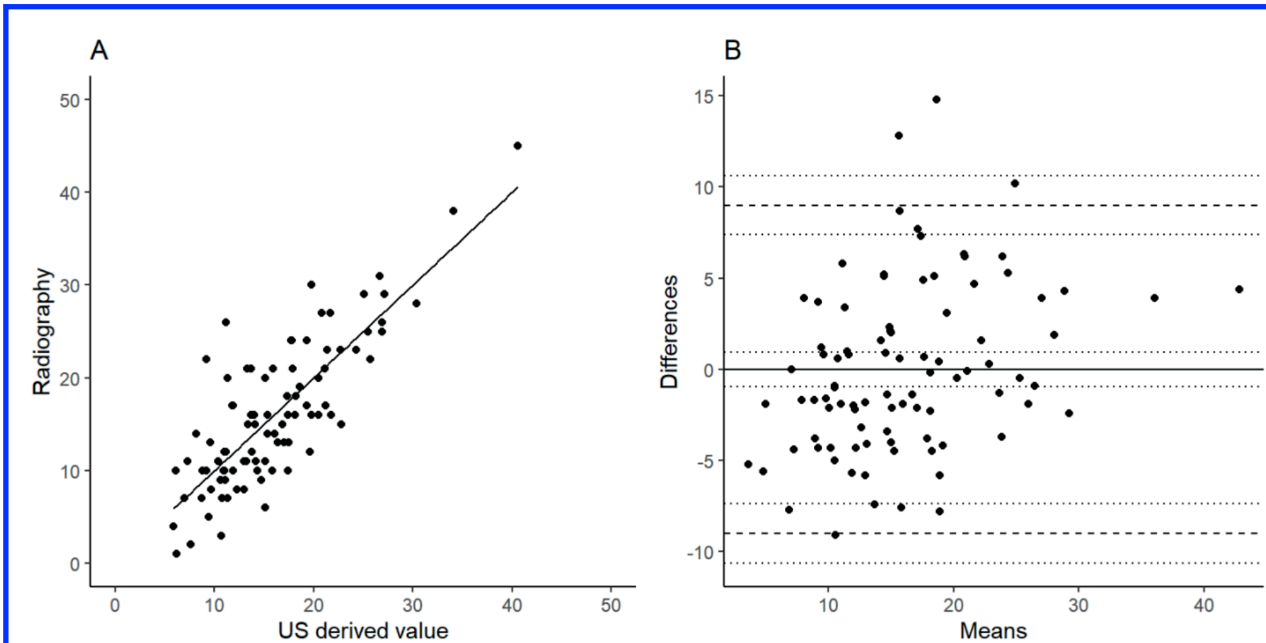

Figure 1. *Prediction in total.*

worsening ≥5°). Therefore, we refer to "progression" as any detectable change in scoliotic angle between two US assessments compared to radiographs. Although we need a larger sample of progressive cases to substantiate the reported results, we have shown promising results using unprocessed US images combined with automatic TP measurements and developed a regression formula to predict the RCA on follow-up radiographs. The best prediction was observed in girls and in primary thoracic curves, with the smallest measurement deviations. Previous studies[24,31] have presented similar formulas with comparable prediction accuracy. The only study to report automatic TP measurements[33] showed higher correlation coefficients between UCA and RCA. However, their analysis was based on reconstructed US images.

These findings highlight the potential of ultrasound as a viable alternative to spine radiography for screening, diagnosis, and follow-up of patients with bad posture and AIS in clinical practice. Studies have shown that ultrasound can reduce the need for spine radiographs by up to 50% in school screenings.[40] Unprocessed US images don't capture scoliotic deformity in 3D. However, since treatment decisions still largely depend on Cobb angle measurements in the frontal plane,[28] ultrasound as a practical tool could be

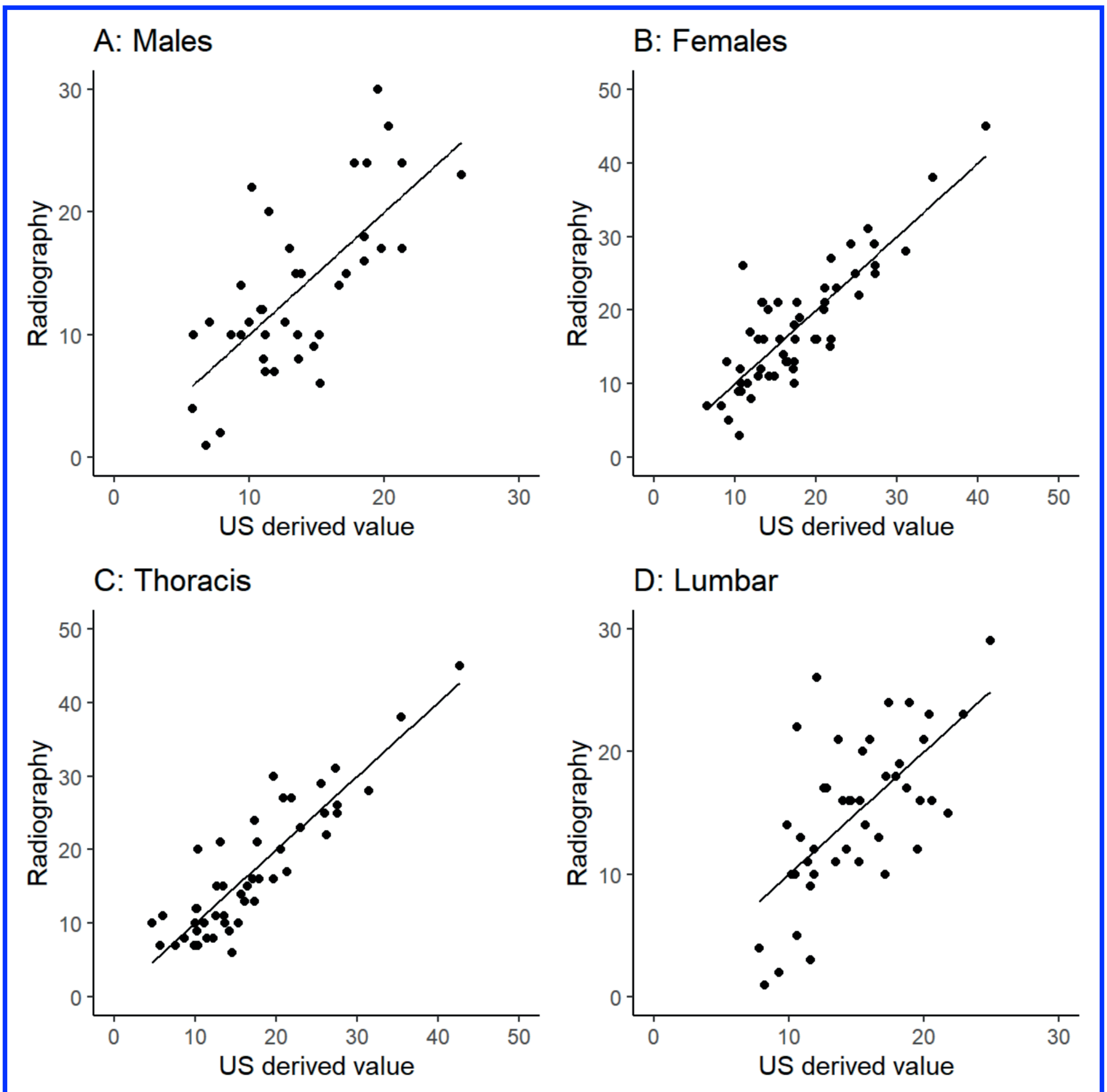

Figure 2. *Scater of Predicted Ro* vs. *Real Ro by location and gender.*

used for monitoring progression in this dimension, while changes in other two dimensions could be tracked with combined clinical and surface topography assessment. Although spine radiography remains the gold standard for diagnosing of scoliosis, treatment decisions are based on a range of diagnostic tools.[5] Thus, the frequency of radiographs and associated radiation exposure for monitoring of progression can be significantly reduced. However, ultrasound has limitations for curves with apices above T6,[41] as well as in obese and mentally challenged patients. Further prospective studies with larger patient samples and more controlled clinical settings are needed to validate and refine our proposed regression formula. Demonstrating that automatic measurements on unprocessed US images are sufficiently accurate to track progression in children with AIS will enhance the appeal of spine ultrasound for clinicians to utilize it in routine clinical practice. This could lead to a significant reduction in the number of spine radiographs, ultimately benefiting patients by minimising radiation exposure.

The findings of this study contribute significantly to the existing body of knowledge and clinical practice by demonstrating the practicality and reliability of unprocessed ultrasound images combined with automatic TP measure-

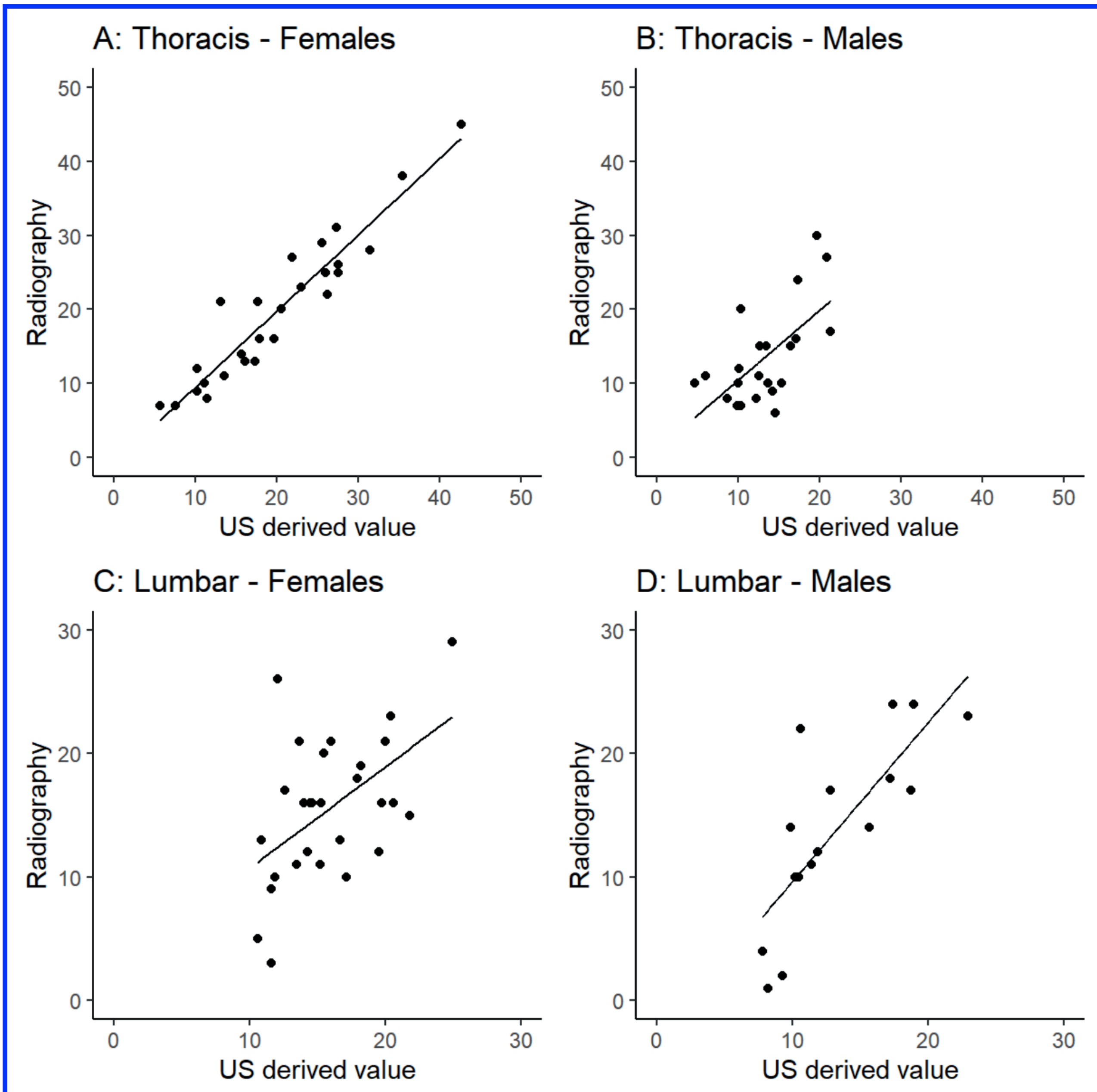

Figure 3. Scater of Predicted CA vs. *Real CA by location x gender.*

ments for monitoring scoliosis progression. This approach addresses a critical gap in the literature by validating a less resource-intensive alternative to radiographs, particularly for detecting curve progression in clinical settings. Unlike previous studies that relied on 3D-reconstructed images, this study highlights the feasibility of using standard B-mode ultrasound, making it more accessible for routine use. The strong correlation between Ultrasound Curve Angle (UCA) and Radiographic Cobb Angle (RCA), especially in thoracic curves and female patients, supports its utility in specific patient populations. Moreover, the proposed regression formula for predicting RCA offers a valuable tool for clinicians to monitor scoliosis progression with reduced reliance on radiography, thereby minimizing radiation exposure. These advancements align with current clinical priorities to improve patient safety and streamline care, paving the way for wider adoption of ultrasound in scoliosis management. This integration could significantly enhance diagnostic efficiency, reduce healthcare costs, and improve patient outcomes.

Conclusions

This retrospective study establishes ultrasound as a practical and effective tool for routine monitoring of AIS in clinical settings. The use of automatic measurements on unprocessed images demonstrated consistent reliability, simplifying the evaluation process for clinicians. The regression formula introduced offers a promising method for predicting curve progression on follow-up radiographs, with further prospective validation needed to confirm its applicability. These findings advocate for the integration of ultrasound into scoliosis care, enabling reduced reliance on radiographic exams, lowering radiation exposure, and enhancing patient safety while maintaining accurate monitoring of disease progression and treatment outcomes.

Confict of interest

All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have had an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Author statement

SP was responsible for the conception of the work, with all authors contributing to study design. IS and FG completed the data acquisition and analysis, with all authors involved in the interpretation of data. SP was responsible for the original drafting of the work with all authors revising it critically for important intellectual content. All authors had final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SP is the manuscript's guarantor.

Ethics approval

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Patient and public involvement statement

No patients/public were involved in the design, implementation or analysis of results of this work.

Availability of data and materials

All data ara available in the present article.

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