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# Adolescent idiopathic scoliosis: advances and new perspectives

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# Adolescent idiopathic scoliosis: advances and new perspectives

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# Handgrip strength assessment at baseline in addition to bone parameters could potentially predict the risk of curve progression in adolescent idiopathic scoliosis

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**Introduction:** Adolescent idiopathic scoliosis (AIS) is characterized by deranged bone and muscle qualities, which are important prognostic factors for curve progression. This retrospective case–control study aims to investigate whether the baseline muscle parameters, in addition to the bone parameters, could predict curve progression in AIS.

**Methods:** The study included a cohort of 126 female patients diagnosed with AIS who were between the ages of 12 and 14 years old at their initial clinical visit. These patients were longitudinally followed up every 6 months (average 4.08 years) until they reached skeletal maturity. The records of these patients were thoroughly reviewed as part of the study. The participants were categorized into two subgroups: the progressive AIS group (increase in Cobb angle of ≥6°) and the stable AIS group (increase in Cobb angle <6°). Clinical and radiological assessments were conducted on each group.

**Results:** Cobb angle increase of ≥6° was observed in 44 AIS patients (34.9%) prior to skeletal maturity. A progressive AIS was associated with decreased skeletal maturity and weight, lower trunk lean mass (5.7%, $p = 0.027$) and arm lean mass (8.9%, $p < 0.050$), weaker dominant handgrip strength (8.8%, $p = 0.027$), deranged cortical compartment [lower volumetric bone mineral density (vBMD) by 6.5%, $p = 0.002$], and lower bone mechanical properties [stiffness and estimated failure load lowered by 13.2% ($p = 0.005$) and 12.5% ($p = 0.004$)]. The best cut-off threshold of maximum dominant handgrip strength is 19.75 kg for distinguishing progressive AIS from stable AIS (75% sensitivity and 52.4% specificity, $p = 0.011$).

**Discussion:** Patients with progressive AIS had poorer muscle and bone parameters than patients with stable AIS. The implementation of a cut-off threshold in the baseline dominant handgrip strength could potentially be used as an additional predictor, in addition to bone parameters, for identifying individuals with AIS who are at higher risk of experiencing curve progression.

KEYWORDS

adolescent idiopathic scoliosis, handgrip, strength, bone, curve progression

# 1. Introduction

Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional spinal deformity (1). AIS is a multifactorial disease, and its etiology and pathogenesis are not fully understood (1). Systemic low areal bone mineral density (aBMD) in 30% of AIS girls was identified using dual energy x-ray absorptiometry (DXA) (2). Over 80% of AIS patients with low BMD at baseline are associated with persistent osteopenia in their early adulthood (3). Recent studies utilizing high-resolution peripheral quantitative computed tomography (HR-pQCT) to assess the true volumetric bone mineral density (vBMD) and micro-architecture of bone revealed that individuals with AIS exhibited deranged bone qualities including bone macro- and microstructure and lower bone mechanical properties at the distal radius when compared with normal female adolescents (4, 5). It is speculated that systemic low bone mass tends to increase the chance of vertebral bone wedging and contributes to the increase of spinal curvature (6). Low aBMD at the femoral neck (7) and cortical vBMD at the distal radius (8) were identified to be important and independent prognostic factors for curve progression in AIS. However, the underlying cause of systemic low bone mass in AIS is not fully understood. Emerging evidence showed that AIS patients presented abnormal bone turnover and mineralization (9, 10).

Abnormal muscle qualities such as lower skeletal muscle mass were also observed in AIS patients (11). AIS girls with a right thoracic curve had higher T2-weighted signal intensity in magnetic resonance imaging (MRI) and a greater fatty component in the multifidus muscle on the concave side when compared with the age-matched controls without scoliosis (12). The muscle volume was also larger in the convex side, while the concave side displayed higher levels of endomysial and perimysial fibrosis and fatty infiltration (13, 14). The electromyographic activity at the convex side exhibited an increase, accompanied by more type I muscle fiber, which was positively correlated with the curve severity in AIS patients (15).

The bone and muscle closely interact with each other via both biochemical and mechanical pathways (16). The skeletal growth is regulated and modulated by mechanical loading through a mechanotransduction process that involves paracrine and endocrine signaling (17). The muscle serves as the primary source of mechanical stimuli necessary for the bone to develop its strength and mass. From a mechanical perspective, the accelerated skeletal growth with lower bone density observed in AIS patients may indicate that they probably experience less mechanical loading compared with healthy controls due to reduced muscle mass and strength (18). The differential growth of bone and muscle tissues could be a possible mechanism contributing to the development and progression of AIS (18). The association between muscle and bone qualities has been investigated in normal children (19), elderly (20, 21), and patients with type 2 diabetes mellitus (22), but this is poorly understood among patients with AIS. To the best of our knowledge, no study focused on the association between bone qualities, muscle mass and strength, and curve progression in AIS patients. This retrospective case–control study aims to investigate whether baseline muscle and bone parameters in AIS could predict curve progression.

# 2. Materials and methods

## 2.1. Subjects

The medical records of a scoliosis clinic in a local hospital were retrieved and reviewed between the period 2019 and 2022. The study included 126 subjects who met the following inclusion criteria: (1) female aged between 12 and 14 when first diagnosed with AIS, which was confirmed through clinical examination and standard standing posteroanterior radiograph of the entire spine (23), (2) available data on baseline hand grip strength and bone parameters, (3) without prior treatment such as brace and physiotherapeutic scoliosis specific exercises at their first visit, and (4) with longitudinal follow-up every 6 months and reaching skeletal maturity (defined as age ≥16 years old and year since menarche of ≥2) before 2018. All subjects exhibited an average maximum Cobb angle of 21.7° ± 6.64° at the first clinical visit. The median of follow-up duration was 4.08 years. The exclusion criteria included Cobb angle of <10° or ≥40° at first visit, scoliosis with any known etiology such as congenital scoliosis, neuromuscular scoliosis, scoliosis of metabolic etiology, scoliosis with skeletal dysplasia, known endocrine and connective tissue abnormalities, known heart condition or other diseases that could affect the safety of exercise, eating disorders or gastrointestinal malabsorption disorders, and currently taking medication that affects bone or muscle metabolism. The subjects were categorized into two groups, namely the progressive AIS (increase in Cobb angle ≥6°) group and the stable AIS (increase in Cobb angle <6°) group, according to the criteria established by the Scoliosis Research Society (SRS). All procedures performed in studies involving human participants were in accordance with the ethical standards of The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (reference no.: CREC-2009.491 and CREC-2009.020) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all subjects included in this study and their guardians before undertaking the evaluations.

## 2.2. Handgrip strength

Handgrip strength was measured using the standard dynamometer (T.K.K. 5401 Grip-D; Takei Scientific Instruments Co., Ltd., Japan) during the first visit prior to any intervention. The subjects were instructed to hold the dynamometer and position their arm aligning with the trunk, pointing downward. Three trials to evaluate maximal isometric contraction in both hands were measured (24). The highest value at each hand was used for analysis. Previous studies have indicated a high level of reliability and validity of handgrip strength result among untrained adolescents (25).

## 2.3. Arm lean mass

The body composition was evaluated using a standardized protocol by bioelectric impedance analysis (BIA) (InBody 720, Biospace, Korea), which utilized an eight-polar bioimpedance method using a multi-frequency current (11). The skeletal muscle mass was computed based on the muscle mass of the limbs, which predominantly consists of skeletal muscle and accounts for 70% of the total skeletal muscle mass in the body. The estimated whole body, arm, and leg lean mass were reported.

## 2.4. Bone qualities and bone mechanical properties of the distal radius

The bone parameters of the non-dominant distal radius of the subjects were measured using HR-pQCT (XtremeCT I; Scanco Medical AG, Switzerland). A fixed offset at 5 mm proximal to the most proximal limit of the inner aspect of epiphyseal growth plate of the radius was used to define the region of interests (5). A total of 110 slices were acquired, with a voxel size of 82 $\mu m^3$ and a thickness of 9.02 mm. An image that exhibited severe motion artifact was excluded from the analysis. The periosteal surface of the radius was contoured by a single technician to minimize the inter-operator variation. A Gaussian filter was used to remove the noise signal (26). An automated threshold-based algorithm was used to segment the cortical bone and trabecular bone (26). The total area, cortical area, and trabecular area of the bone were measured. The cortical thickness was calculated as the mean cortical volume divided by the outer cortical surface area (27). The total, cortical, and trabecular vBMD were calculated in whole bone envelope, cortical bone, and trabecular bone, respectively.

Bone mechanical properties, including stiffness and estimated failure load, were calculated by finite element analysis using the software provided by the manufacturer (μFEA Solver v.1.15; Scanco Medical, Switzerland). The finite element model contained eight-node brick elements with a volume of 82 $\mu m^3$ and assumed that bone tissue is an isotropic and elastic material characterized by a Young's modulus of 10 GPa and a Poisson's ratio of 0.3 (28). A uniaxial compression test was conducted, applying a 1% strain along the axial direction. The estimated failure load was determined when the effective strain of the 1 $mm^3$ elements in the model exceeded 7,000 microstrain (29).

## 2.5. Areal bone mineral density of the femoral neck

aBMD of the non-dominant femoral neck ($g/cm^2$) was measured using dual energy x-ray absorptiometry (DXA, XR-46; Norland Medical Systems, Fort Atkinson, WI, USA). The details of DXA measurement was presented in a study conducted by Cheng et al. (30). The z-score was calculated with reference to a normative dataset consisting of local ethnic Chinese girls.

## 2.6. Anthropometric and maturity assessment

Body weight and arm span were measured. Given that AIS patients had a reduction of body height due to spinal deformity, measuring of arm span was used as a means of calculating body mass index (BMI) (BMI by arm span = body weight/arm $span^2$). The self-reported age of menarche corrected to the nearest month was recorded. Skeletal age was evaluated using the Thumb Ossification Composite Index (TOCI) (range 1–8) on a left hand radiograph. TOCI is a validated staging system reflecting the ossification pattern of the thumb epiphyses and the adductor sesamoid bone with high accuracy for predicting skeletal maturity and comparable with the Sanders simplified maturity system (31). A longitudinal study has shown that peak height velocity in AIS girls can be predicted by TOCI, and majority attained their peak height velocity at TOCI stage 5 (31).

## 2.7. Dietary calcium intake and physical activity level

The subjects were required to provide the details regarding their usual consumption habits and frequency in the past 1 year using a modified version of the Chinese Food Frequency Questionnaire for evaluating the dietary calcium (Ca) intake. The assessment of dietary nutrient intake was conducted using the Food Processor Nutrition Analysis and Fitness software version 7.9 (Esha Research, Salem, OR, USA), and the composition of some local foods was determined based on the China Food Composition Table (Institute of Nutrition and Food Safety, 2002) (32). The physical activity level of the past 1 year was assessed using the Chinese version of the Modified Baecke Questionnaire (33).

# 3. Statistical analysis

Data were tested using the Kolmogorov–Smirnov test for normality, and normally distributed data were presented as mean ± SD. Student's *t*-test was used to compare the difference on parameters between the progressive and stable AIS groups. Skewed data was presented as medians (range), and Mann–Whitney *U* test was used for comparison between groups. Body weight was not included as the covariates in the regression model since it was highly correlated with the lean mass ($r = 0.891$ and 0.931 in AIS and the controls, respectively). SPSS statistic software (version 24; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The analyses were two-tailed. $P$-values <0.05 were considered statistically significant.

## 4. Results

All patients with AIS were clinically followed up until they reach skeletal maturity. A total of 44 AIS patients (34.9%) had curve progression with a change of Cobb angle ≥6° prior to skeletal maturity. At baseline, it was observed that progressive AIS patients had similar age, curve severity, and lifestyle parameters, but lower weight and TOCI as compared with stable AIS. The initial maximum Cobb angle and Cobb angle at maturity were similar between the progressive and stable AIS groups at baseline (22.5 ± 7.5 vs. 21.3 ± 6.1, $p = 0.309$), but both angles were significantly higher at maturity for the progressive AIS group (32.8 ± 11.5 vs. 20.9 ± 6.5, $p < 0.001$). For muscle parameters, the progressive AIS group had lower trunk (5.7%, $p = 0.027$) and arm lean mass at both the dominant (9.2%, $p = 0.035$) and non-dominant (8.6%, $p = 0.041$) sides, and a weaker handgrip strength at the dominant side (8.8%, $p = 0.027$). For bone parameters, the progressive AIS group showed a reduced femoral neck aBMD (6.3%, $p = 0.007$), deranged cortical compartment [29.1% smaller area ($p = 0.003$) and 6.5% lower vBMD ($p = 0.002$)], and lower bone mechanical properties [13.2% lower stiffness ($p = 0.005$) and 12.5% lower estimated failure load ($p = 0.004$)] when compared with the stable AIS group. More patients with progressive AIS (75%) when compared with patients with stable AIS (36.6%) received either bracing or surgical intervention between baseline and until skeletal maturity. Basic characteristics, lifestyle, and muscle and bone parameters in progressive and stable AIS are shown in **Table 1**.

The predictive power of dominant handgrip strength in the curve progression was estimated using receiver operating characteristic (ROC) analysis. The best cut-off threshold of maximum dominant handgrip strength was 19.75 kg for distinguishing progressive AIS from stable AIS, with a sensitivity of 75.0%, specificity of 52.4%, and area under curve of 0.637 (**Figure 1**). When applying dichotomous result of maximum dominant handgrip strength into a backward logistic regression with all the significant predictors, the handgrip strength and estimated failure load were remained in the last step of the logistic regression (odds ratio = 2.325 and 0.999 with $p = 0.080$ and 0.062, respectively, **Table 2**).

## 5. Discussion

This study represents the first scientific investigation on the association between bone qualities (bone size, vBMD, and bone mechanical properties) and muscle parameters (skeletal muscle mass, lean mass, and handgrip strength) among female patients with AIS. In addition, this research explores the potential application of baseline handgrip strength as a predictive parameter, in addition to existing bone parameters, in predicting curve progression in AIS. The results of this study showed that individuals with progressive AIS exhibited poorer arm lean mass and estimated trunk lean mass, weaker dominant handgrip strength, deranged cortical bone qualities, and lower bone mechanical properties at the baseline when compared with those with stable AIS. This study further showed that a cut-off threshold of 19.75 kg in the dominant handgrip strength, in addition to existing bone parameters, could potentially be used clinically as a predictive parameter in predicting curve progression in AIS.

Patients with AIS are found to have low bone mass (7), deranged bone qualities (5), and low bone mechanical properties (4) when compared with normal age-matched females. Several groups had previously identified some objective bone parameters in predicting curve progression. Hung et al. (7) reported that low bone mass at the femoral neck measured by DXA could predict curve progression in AIS. Yip et al. (8) identified that cortical vBMD at the distal radius measured by HR-pQCT is an important prognostic factor of curve progression to surgical thresholds. Individuals with AIS are known to have low lean mass (11) and muscle imbalance (15). A longitudinal study conducted in the United Kingdom reported that AIS patients who had lower lean mass at 10 years old would have higher risk of scoliosis at the age of 15 (34). Although previous studies have utilized bone parameters such as DXA and HR-pQCT to examine bone qualities, these measurements are often costly, not widely available in clinical settings, and require expertise for interpretation.

Muscle parameter measurements included in this study such as handgrip strength can be measured by a standard dynamometer, which is an easy, quick, and portable clinical assessment tool at a low cost. Handgrip strength is associated with the muscle strength in other areas of the body, including the erector of spine (35), shoulder abductors, and total muscle strength. Consequently, handgrip strength can be used as a rapid indicator of general muscle strength in adolescents (36). A recent large cohort study found that reduced handgrip strength is associated with lower BMD and BMC and concluded that handgrip strength can be a possible indicator of bone health in adolescent students (37). The present findings indicated that progressive AIS patients had both lower handgrip strength and lower bone qualities. The handgrip strength combined with estimated failure load measured by FEA was the best model in predicting curve progression in AIS. We further identified a cut-off threshold of 19.75 kg in this cohort for predicting curve progression. This cut-off threshold of 19.75 kg is close to the normative handgrip strength value of 19.8 kg in Hong Kong girls at 14 years old (38) and 20 kg in Korean girls between the age of 10 and 14 (39). It is slightly higher than the recommended handgrip strength cut-off threshold of 18 kg for sarcopenia diagnosis among older Asian female population (40). We speculated that AIS patients with sarcopenia-like low muscle mass in the trunk and weak muscle strength might have higher risk of curve progression.

With the advancement of genetic analysis, genome-wide association studies (GWAS) have identified several gene loci such as ladybird homeobox 1 (LBX1) (41, 42), basonuclin 2 (BNC2) (43), and fibrillin (FBN1 and FBN2) (44, 45), which are associated with the pathogenesis of AIS. Both LBX1 and BNC2 are functionally related to early muscle development (46), whereas fibrillins are components of connective tissue (47). Some

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TABLE 1 Basic characteristics, lifestyle, and muscle and bone parameters in individuals with progressive AIS and stable AIS.

| | Progressive ($N = 44$) | Stable ($N = 82$) | $p$-value |
|---|---|---|---|
| Age (year)[a] | 12.97 (12.26–13.53) | 13.04 (12.69–13.52) | 0.295 |
| Initial maximum Cobb angle[b] | 22.5 ± 7.5 | 21.3 ± 6.1 | 0.309 |
| Cobb angle at maturity[b] | 32.8 ± 11.5 | 20.9 ± 6.5 | <0.001* |
| Received bracing/ surgery | 75.0% | 36.6% | <0.001* |
| Anthropometric parameters | | | |
| Weight (kg)[a] | 40.2 (36.1–43.3) | 42.4 (38.93–49.2) | 0.010* |
| Maturity | | | |
| TOCI[a] | 7 (5, 8) | 7 (6, 8) | 0.012* |
| Menarche age (year)[a] | 12.24 (11.53–12.8) | 12.02 (11.27–12.7) | 0.486 |
| Onset of menarche[c] | 61.4% | 75.6% | 0.094 |
| Lifestyle parameters | | | |
| Physical activity level[a] | 7.20 (6.53–7.79) | 7.29 (6.63–7.83) | 0.651 |
| Dietary Ca intake (mg/day)[a] | 586.02 (354.76–846.65) | 594.24 (433.13–826.91) | 0.472 |
| **Muscle parameters** | | | |
| Muscle mass by BIA | | | |
| Skeletal muscle mass (kg)[b] | 16.74 ± 2.25 | 17.61 ± 2.45 | 0.053 |
| Trunk lean mass (kg). | 13.08 ± 1.8 | 13.87 ± 1.91 | 0.027* |
| Non-dominant arm lean mass (kg)[b] | 1.17 ± 0.27 | 1.28 ± 0.29 | 0.041* |
| Dominant arm lean mass (kg)[b] | 1.19 ± 0.27 | 1.31 ± 0.3 | 0.035* |
| Non-dominant leg lean mass (kg)[b] | 4.65 ± 0.75 | 4.94 ± 0.8 | 0.052 |
| Dominant leg lean mass (kg)[b] | 4.66 ± 0.74 | 4.94 ± 0.8 | 0.058 |
| Maximum handgrip strength | | | |
| Non-dominant (kg)[b] | 17.14 ± 4.27 | 18.65 ± 4.48 | 0.068 |
| Dominant (kg)[a] | 18.25 (15.25–19.88) | 20 (16.5–23) | 0.027* |
| **Bone parameters (non-dominant)** | | | |
| DXA parameter | | | |
| Femoral neck aBMD ($g/cm^2$)[b] | 0.705 ± 0.082 | 0.752 ± 0.106 | 0.007* |
| Z-score of femoral neck aBMD[b] | −0.511 ± 0.828 | −0.091 ± 1.056 | 0.016* |
| Bone morphometry | | | |
| Total area ($mm^2$)[b] | 182.5 ± 30.2 | 184.4 ± 25.6 | 0.707 |
| Cortical area ($mm^2$)[a] | 19 (11.9–28.2) | 26.8 (18.5–35.1) | 0.003* |
| Trabecular area ($mm^2$)[b] | 150.3 ± 32.6 | 148.58 ± 26.41 | 0.750 |
| vBMD | | | |
| Total vBMD (mg $HA/cm^3$)[a] | 240.7 (203.9–270.3) | 259.8 (221.9–301.3) | 0.088 |
| Cortical vBMD (mg $HA/cm^3$)[b] | 654.5 ± 85 | 699.9 ± 74.7 | 0.002* |
| Trabecular vBMD (mg $HA/cm^3$)[a] | 147.4 (133.1–164) | 147.5 (123.1–164.8) | 0.575 |
| Bone mechanical properties | | | |
| Stiffness (N/mm)[a] | 41,886 (36,226.3–52,529) | 48,240.5 (40,931–57,711.5) | 0.005* |
| Estimated failure load (N)[a] | 1,794.2 (1,504.2–2,123.8) | 2,050 (1,774.3–2,364.2) | 0.004* |

[a]Mann–Whitney $U$ test was used on data which were not normally distributed. Median and range.
[b]Student's $t$-test was used on data with normal distribution. Mean and standard deviation.
[c]Chi-square test was used for the dichotomous data.
*$p \leq 0.05$.

hormones including melatonin, leptin, and calmodulin, which are related to muscle strength and contractility (48–50), are also observed to be connected to muscle deficits in individuals with AIS. Lower free leptin bioavailability was found in female patients with AIS with strong correlation to lower muscle mass and body fat (49). Reduced calmodulin was observed in patients with AIS receiving brace treatment and spinal fusion (51). The paraspinal muscles of AIS patients displayed an asymmetrical distribution of calmodulin and melatonin levels (50, 52). The findings from these studies provided evidence that the onset of scoliosis might be initiated by primary soft tissue and muscle anomalies to be accompanied with subsequent bone–muscle interaction (46) during curve progression, thus supporting the potential prognostic value of muscle parameters for patients with AIS.

The school screening program for AIS in Hong Kong was found to have higher positive predictive value (PPV) when compared with similar programs in other Asian countries (53). The PPV ranged from 35.6%–43.6% for curve angle of ≥20° and 4.3%–6.1% for curve angle of ≥40° (54). However, there is a need for more effective prognostication of significant curve progression during the initial clinical consultation in order to provide timely and necessary treatments. Due to the multifactorial nature of AIS, a recent study had proposed a prognostic composite model consisting of clinical and circulating parameters to predict the risk of curve progression to a severe

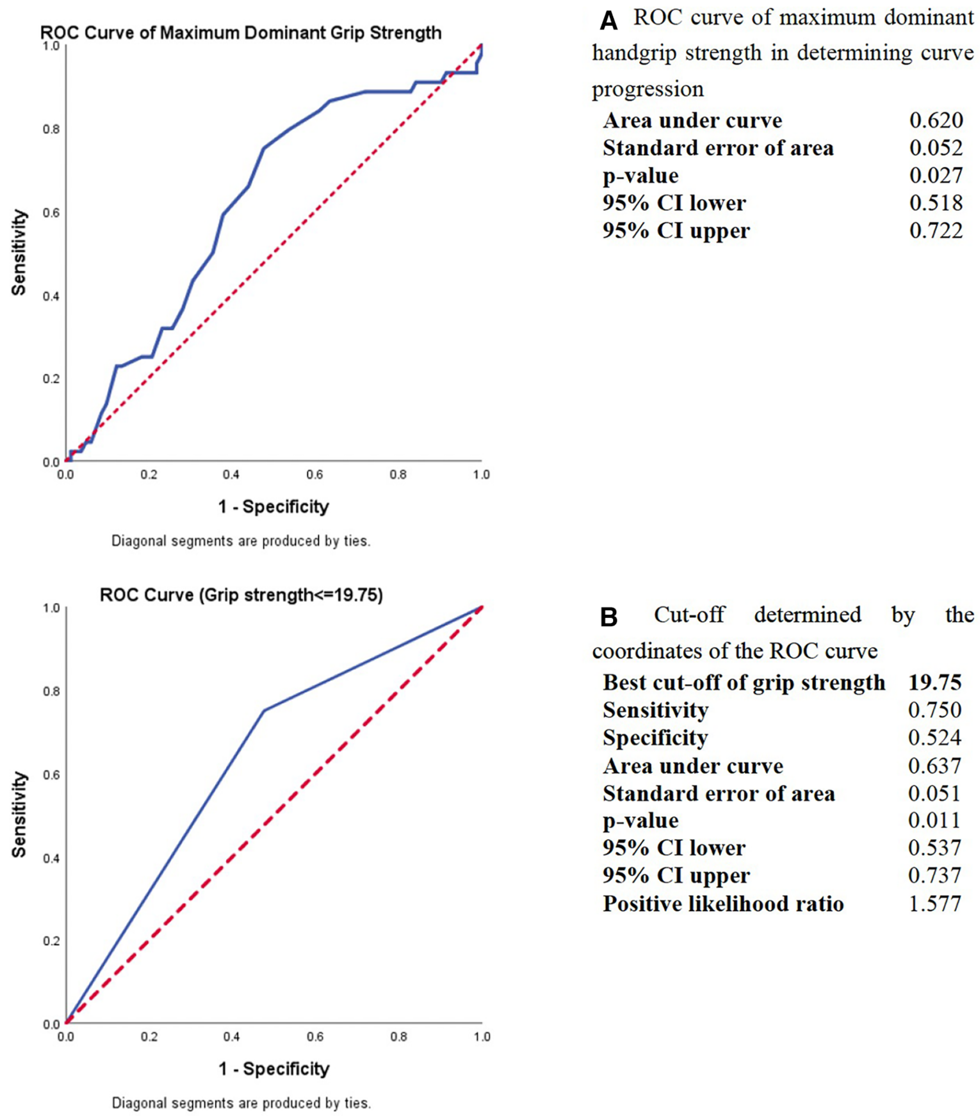


FIGURE 1
ROC curve analysis of maximum dominant handgrip strength in determining the curve progression in AIS. (A) ROC curve of maximum dominant handgrip strength in determining curve progression. (B) Cut-off determined by the coordinates of the ROC curve.

Cobb angle of >40° with a sensitivity of 72.7% and a specificity of 90% (55). While the circulating parameters could only be obtained through invasive blood sampling in a clinical setting, a simple clinical assessment of handgrip strength, along with other clinical measurements including the forward bending test, angle of trunk rotation, and moiré photograph, can be easily performed in school screening program for early screening and identification of individuals with AIS who are at a higher risk of curve progression. In addition to the clinical parameters of anthropometry, maturity, and circulating parameters, the inclusion of handgrip strength assessment could be incorporated into existing prognostication models with curve factors (such as initial Cobb angle, curve type), patient factors (such as gender, age, and maturity), and bone factors (bone health status) to improve the predictive power of curve progression.

The relationship between the muscle and bone in AIS has not been fully investigated. Previous studies revealed the close interaction between the muscle and bone in which sarcopenia and osteoporosis share common mechanisms and risk factors (56, 57). The findings of the present study suggested that handgrip strength plays a more important role in predicting bone qualities and curve progression in AIS. According to the mechanostat hypothesis, muscle contraction provides mechanical stimulation to promote bone formation during growth (58). The bone in AIS might have a unique response to mechanical stimuli, which can be more prominent among progressive AIS. The poorer muscle health in individuals with AIS, particularly in those with progressive AIS, could be reflected by lower handgrip strength. Enhancing overall muscle strength by increasing physical activity could provide beneficial effects on cortical bone growth, including the thickening of the cortical bone and increasing cortical bone density.

There are several limitations in this study. First, the current study only included female subjects with a narrow age range in

TABLE 2 Backward logistic regression to predict the curve progressions based on the significant parameters in univariate comparison shown in Table 1.

| | *B* | SE | *p*-value | exp(*B*) | 95% CI for exp(*B*) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **First step** | | | | | | |
| Weight | −0.065 | 0.073 | 0.374 | 0.937 | 0.813 | 1.081 |
| TOCI | 0.097 | 0.275 | 0.725 | 1.101 | 0.643 | 1.886 |
| Trunk lean mass | −0.638 | 0.774 | 0.409 | 0.528 | 0.116 | 2.406 |
| Non-dominant arm lean mass | −1.620 | 5.704 | 0.776 | 0.198 | 0.000 | $1.42 \times 10^4$ |
| Dominant arm lean mass | 6.766 | 6.980 | 0.332 | 867.990 | 0.001 | $7.59 \times 10^8$ |
| Grip strength ≤19.75 | 0.915 | 0.548 | 0.095 | 2.497 | 0.853 | 7.309 |
| Femoral neck aBMD | 0.724 | 3.920 | 0.853 | 2.062 | 0.001 | 4,477.209 |
| Cortical area | 0.013 | 0.079 | 0.871 | 1.013 | 0.867 | 1.183 |
| Cortical vBMD | −0.006 | 0.011 | 0.559 | 0.994 | 0.973 | 1.015 |
| Stiffness | $1.50 \times 10^{-4}$ | $1.93 \times 10^{-4}$ | 0.435 | 1.000 | 1.000 | 1.001 |
| Estimated Failure Load | −0.004 | 0.005 | 0.422 | 0.996 | 0.985 | 1.006 |
| Constant | 7.844 | 7.414 | 0.290 | 2,549.352 | | |
| Nagelkerke $R^2$ | 0.193 | | | | | |
| **Last step** | | | | | | |
| Grip strength ≤9.75[a] | 0.844 | 0.482 | 0.080 | 2.325 | 0.904 | 5.981 |
| Estimated failure load[a] | −0.001 | 0.001 | 0.062 | 0.999 | 0.998 | 1.000 |
| Constant | 0.933 | 1.305 | 0.475 | 2.542 | | |
| Nagelkerke $R^2$ | 0.146 | | | | | |

B, coefficient; SE, standard error of *B*; exp(*B*), estimated odds ratio; 95% CI for exp(*B*), confidence interval for exp(*B*).
[a]Handgrip muscle strength and estimated failure load were presented in the last step of the logistic regression (odds ratio = 2.325 and 0.999 with $p = 0.080$ and 0.062, respectively).

one single center. The relatively small sample size has limited the predictive ability of this univariate model, and there is undoubtedly room for enhancing performance. However, the current findings are useful to test our hypothesis on using muscle parameters such as handgrip strength to identify patients with higher risk of curve progression which may be indicative to inform timely management of AIS, particularly at the early stages of diagnosis, for better disease control. Second, data of physical activity and dietary calcium intake were self-reported by the subjects with the help from their guardians. Third, only muscle mass and strength were examined whereas other muscle parameters such as muscle size and composition were not included in this study. Fourth, we were unable to account for the changes in lifestyle between the baseline and skeletal maturity stages, as well as the impact of treatments, such as bracing, that were administered to our subjects throughout the duration of the study. The biochemical interaction between the muscle and bone was not studied as blood tests were not performed in the present study. The current findings would provide valuable insights for determining the appropriate sample size for future validation study assessing the translation and adaptation process. Further studies are warranted to include a larger sample size with a wider age range to enhance the predictive power and provide reference values for handgrip strength that are particular to age, ethnicity, and gender. It is also worthwhile to further explore various independent factors, such as handgrip strength assessment identified in this study and formulate these factors into the existing composite model to enhance the predictive sensitivity and specificity of this multifactorial and complex condition. The biochemical cross-talk between the muscle and bone with blood tests can also be investigated in order to unravel the whole picture of muscle and bone interaction in AIS.

In essence, progressive AIS is associated with lower handgrip strength and poorer bone mechanical property, which are important predictors of curve progression in AIS. In addition to existing bone parameters, the implementation of handgrip strength, which is a quick, portable, and low-cost assessment with a cut-off threshold of 19.75 kg in the dominant hand, could be useful for predicting AIS with higher risk of curve progression in order to facilitate timely management at an early stage of diagnosis.

## Data availability statement

The datasets presented in this article are not readily available because of patient privacy and confidentiality. Requests to access the datasets should be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (reference no.: CREC-2009.491 and CREC-2009.020). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

RL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. KC: Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. VH: Writing – review & editing, Data curation, Methodology, Software. FY: Data curation, Methodology, Software, Writing – review & editing. ET: Data curation, Investigation, Methodology, Software, Writing – review & editing. LW: Data curation, Investigation, Software, Writing – review & editing. JZ: Data curation, Investigation, Methodology, Project administration, Software, Writing – review & editing. WL: Supervision, Validation, Visualization, Writing – review & editing. JC: Conceptualization, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – review & editing. TL: Conceptualization, Data curation, Funding acquisition, Resources, Supervision, Validation, Writing – review & editing. AL: Supervision, Validation, Visualization, Writing - review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Advances in genetic factors of adolescent idiopathic scoliosis: a bibliometric analysis

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**Objective:** This study offers a bibliometric analysis of the current situation, hotspots, and cutting-edge domains of genetic factors of adolescent idiopathic scoliosis (AIS).
**Methods:** All publications related to genetic factors of AIS from January 1, 1992, to February 28, 2023, were searched from the Web of Science. CiteSpace software was employed for bibliometric analysis, collecting information about countries, institutions, authors, journals, and keywords of each article.
**Results:** A cumulative number of 308 articles have been ascertained. Since 2006, publications relating to genetic factors of AIS have significantly increased. China leads in both productivity and influence in this area, with the Chinese Academy of Medical Sciences being the most productive institution. The most prolific scholars in this field are Y. Qiu and Z. Z. Zhu. The publications that contributed the most were from *Spine* and *European Spine Journal*. The most prominent keywords in the genetic factors of AIS were "fibrillin gene", "menarche", "calmodulin", "estrogen receptor gene", "linkage analysis", "disc degeneration", "bone mineral density", "melatonin signaling dysfunction", "collagen gene", "mesenchymal stem cell", "*LBX1*", "promoter polymorphism", "Bone formation", "cerebrospinal fluid flow" and "extracellular matrix".
**Conclusion:** This analysis provides the frontiers and trends of genetic factors in AIS, including relevant research, partners, institutions and countries.

KEYWORDS

advances, genetic factors, adolescent idiopathic scoliosis, bibliometric analysis, CiteSpace

## Introduction

Adolescent idiopathic scoliosis (AIS) is a tridimensional structural abnormality of the spine; that impacts adolescents from 10 years old to maturity (1, 2). The main diagnosis is based on the coronal curved Cobb angle, which must be >10° on standard anterior and posterior radiographs (3). AIS affects 1%–4% of teenagers (2), and is more common in girls (3). It can lead to high and low shoulders, trunk displacement, and other appearance deformities (2, 4). The development of AIS involves a variety of factors such as genetics, tissues, spinal biomechanics, and hormones (5). Of these, genetics is the major factor. Early identification of relevant genetic variants can help in the diagnosis and prevention of the disease.

Bibliometrics evaluates published research and predicts research trends (6). It can analyze scientific movements, including relationships among countries, institutions, authors, journals, and keywords (7), and has been widely used in various fields. The knowledge map examines the progress and boundaries of the discipline, facilitating researchers to understand the research hotspots and guiding them in their research directions.

Although various studies have focused on the genetic factors of AIS, bibliometric analysis remains scarce. The purpose of this study is to organize relevant studies of AIS genetic factors from January 1, 1992, to February 28, 2023. It summarizes genetic factors and provides researchers with a macro perspective in this area of research. The study includes analysis of the quantity of published articles, associations and symbioses between authors or countries, co-citation of references, and hot areas associated with keywords in the global research and analysis of genetic factors of AIS.

# Method

## Data sources

All data are obtained from the core collection of the Internet database Web of Science (WoS). The literature on genetic factors of AIS published from January 1, 1992, to February 28, 2023, was searched on WoS. Retrieval strategy: TS = ("adolescent idiopathic scoliosis") and TS = (gene or DNA or "base sequence" or "nucleic acid" or "copy number variants" or "single nucleotide polymorphism" or "SNP"). The database is updated daily and data are collected in a 24-hour period to prevent potential bias. Primary researches and literature reviews were included. Letters, corrections, meeting abstracts, editorial materials, proceeding papers and book chapters were excluded.

## Data analysis

Two separate evaluators (X.W.J. and M.X.Z.) conducted a comprehensive review of the study based on the title and abstract. The compilation and export of references and citations were done in a simple text format. Every bibliographic entry includes a title, author, keywords, abstract and references.

CiteSpace (a Java-based software) was used to perform a bibliometric analysis of the WoS Core Collection. It visualizes information and is frequently employed for evaluating patterns in research (7). It is capable of recognizing leading authors, institutions, and nations, and forming collaborative research connections among these entities. To examine research collaborative connections, a network analysis of references, scholars, and articles using co-citation was proceeded. Extend the co-word network analysis of keywords to provide up-to-the-minute viewpoints and research trends. Co-citation relationships show the recurrence with which a terminology or citation is mentioned over a given period. Co-occurrence surges manifest the recurrence with which a keyword or citation appears over a period of time.

The dimensions of the nodes in the visual network graph represent the extent of co-occurrence or recurrence. The line between nodes is the relationship of cooperation, co-occurrence and co-citation. The width and the extent of the lines indicate the proximity of cooperation between nations, organizations, and scholars. The lines depict the relationship among the nodes. Their color shows the publication year.

This study is primarily descriptive. Absence of statistics analysis, the quantity and proportion (%) of every index demonstrates the dispersion and change trends of different years, countries, organizations, publications, and scholars.

# Results

## Publication outputs

Between January 1, 1992, and February 28, 2023, we retrieved a total of 330 records, of which 308 articles were eligible based on inclusion and exclusion criteria. With this group, there were 270 articles classified as original research and 38 articles categorized as reviews. English publications overwhelmingly dominated, accounting for more than 99% (306), while French and German publications were represented by only 1 paper each. From 1992 to 2022, research on AIS genetic factors exhibited a consistent upward trend, with an annual growth rate of 5.93%. The year 2019 stood out as the peak, with the highest number of papers at 40 (**Figure 1**). Initially, a limited number of publications were observed from 1992 to 2005, but since 2006, there has been a rapid increase. In total, 308 publications garnered 5,771 citations.

## Country/region distribution

40 countries have published articles on AIS genetic factors. China was involved in the publication of most articles (50.3%), followed by the United States (25%), Canada (9.4%), Japan (8.8%) and the United Kingdom (4.2%). **Figure 2** shows the geographic distribution of publications. **Figure 3** shows the cooperation between different regions. **Table 1** shows that the H-index (a common indicator of academic influence) (8) of China, the United States, Canada, Japan and the United Kingdom is 28, 27, 14, 18 and 7 respectively.

## Institution analysis

**Table 2** shows the ranking of institutions involved in publishing articles on genetic factors in AIS. Chinese Academy of Medical Sciences was involved in the largest number of published papers (69; 22.4%), followed by Nanjing University (61; 19.8%), University of Hong Kong (30; 9.7%), RIKEN (21; 6.8%), University of Texas System (21; 6.8%). **Figure 4** presents the cooperation among institutions in this field.

## Journal analysis

**Table 3** shows the ranking of journals that published articles on AIS genetic factors. Most papers were published in *Spine* (62; 20.1%), followed by *European Spine Journal* (17; 5.5%) and *BMC Musculoskeletal Disorders* (11; 3.6%), *Scientific Reports* (11; 3.6%) and *Human Molecular Genetics* (8; 2.6%). They accounted for 35.4% of all publications. **Figure 5** shows the cooperation among these journals.

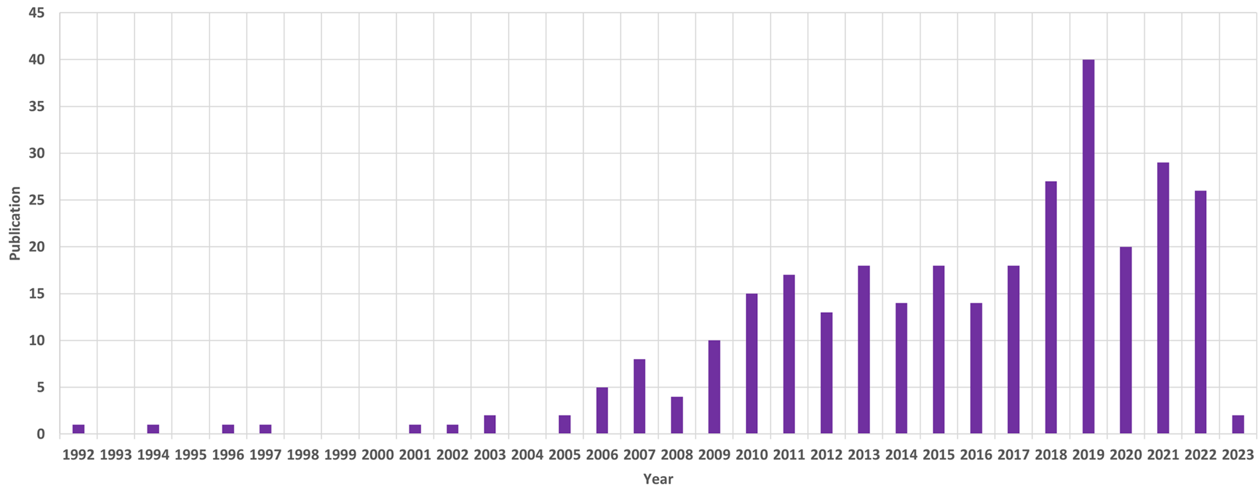


FIGURE 1
The annual patterns of publications.

## Author analysis

One thousand five hundred five scholars participated in the publication of 308 articles. **Table 4** shows the 10 most prolific scholars. **Figure 6** presents the collaboration network of the scholars. Y. Qiu and Z. Z. Zhu contributed to the publication of 59 and 36 papers respectively. The top 3 most cited scholars are Y. Takahashi (113), S. L. Weinstein (111) and N. H. Miller (105). When 2 articles refer to the same article, a common reference link is created. **Figure 7** shows the influential authors associated with the genetic factors of AIS. Authors or co-authors of papers working in identical nations appear in the bibliographic link.

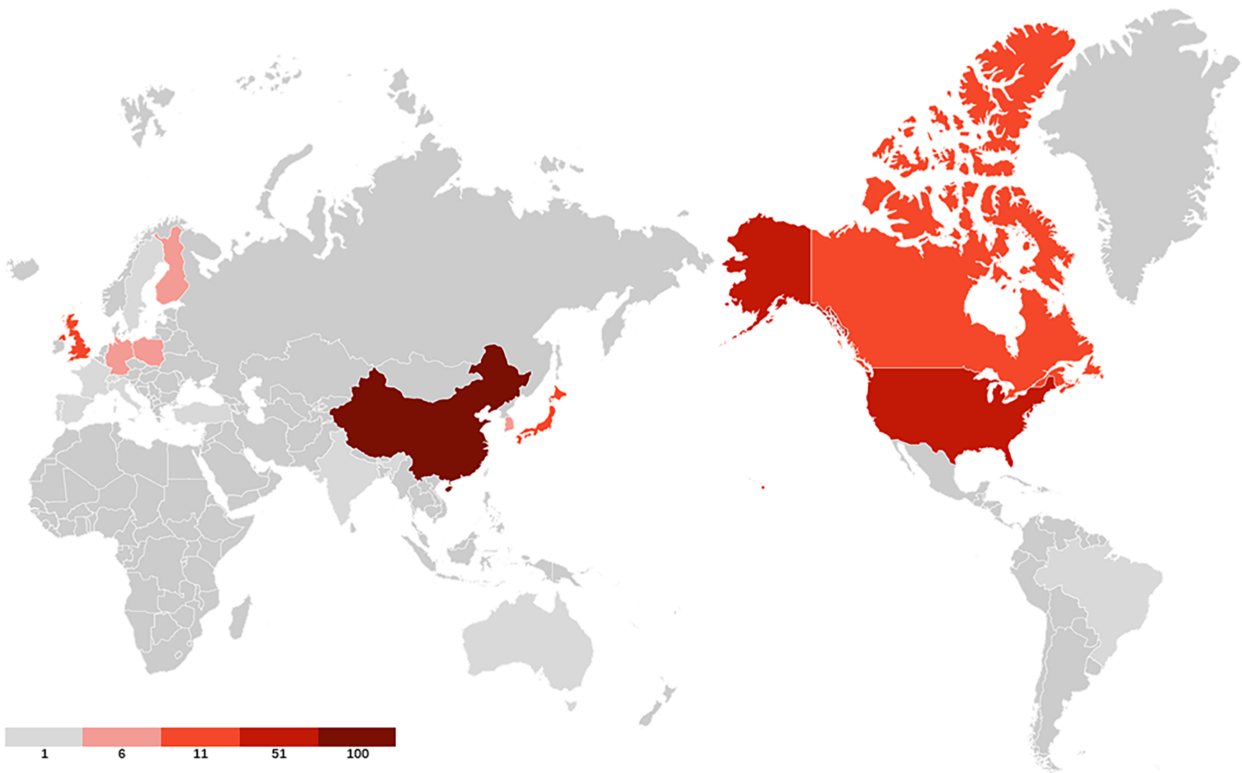


FIGURE 2
The geographic distribution of publications. Darker colors indicate greater number of publications.


FIGURE 3
Collaboration network of productive countries/regions. Nodes represent countries/regions, and lines indicate co-citation relationships. Node colors correspond to different years. Larger nodes indicate higher publication numbers.

## Reference analysis

The spacing of references in co-citation analysis reveals the co-citation relationship. Table 5 enumerates the top 10 cited articles regarding genetic factors in AIS. Among the 10 articles, 4 originate from China, 3 from Japan, 2 from the United States, and 1 from the United Kingdom. Figure 8 displays the network of cited references, depicting the co-citation relationships among them.

## Keyword analysis and research hotspots

Keywords serve as indicators of the study's subject matter. Summarizing frequently occurring and highly prominent keywords proves useful for describing research focal points and trends. The larger the nodes within the keyword co-occurrence map, the more substantial the keyword weight. Enhanced connections are portrayed by reduced distances between nodes. Bolder lines signify an amplified frequency of 2 phrases being referenced simultaneously. Figure 9 presents the network of keywords. Keyword clustering involves grouping words and phrases that exhibit clear domain characteristics. It utilizes feature extraction algorithms to classify text and perform domain-based clustering of words. By managing word frequency, it identifies both general and specific domain-related terms. Figure 10 shows the 12 clusters in this study: "rare variant" #0, "novel locus" #1, "developmental theory" #2, "estrogen receptor gene polymorphism" #3, "GWAS-associated loci" #4, "BMP4 IL6 leptin MMP3" #5, "culture system" #6, "human melatonin" #7, "physiological aging" #8, "potential role" #9, "genetic susceptibility" #10 and "diagnostic biomarker" #11.

Figure 11 presents the top 71 cited keywords. The red and blue bars indicate common and uncommon keywords correspondingly. The most popular keywords in AIS genetic factors were "fibrillin

TABLE 1 Top 5 countries contributed to research publications on the genetic factors of AIS.

| Rank | Country | Number | Percentage | H-index |
|---|---|---|---|---|
| 1 | China | 155 | 50.3 | 28 |
| 2 | United States | 78 | 25.0 | 27 |
| 3 | Canada | 29 | 9.4 | 14 |
| 4 | Japan | 27 | 8.8 | 18 |
| 5 | England | 13 | 4.2 | 7 |

TABLE 2 Top 10 productive institutions in the genetic factors of AIS.

| Rank | Institution | Number | Percentage |
|---|---|---|---|
| 1 | Chinese Academy of Medical Sciences | 69 | 22.4 |
| 2 | Nanjing University | 61 | 19.8 |
| 3 | University of Hong Kong | 30 | 9.7 |
| 4 | RIKEN | 21 | 6.8 |
| 5 | University of Texas System | 21 | 6.8 |
| 6 | Keio University | 20 | 6.5 |
| 7 | Washington University | 20 | 6.5 |
| 8 | University of Montreal | 19 | 6.2 |
| 9 | Central South University | 17 | 5.5 |
| 10 | Naval Medical University | 15 | 4.9 |

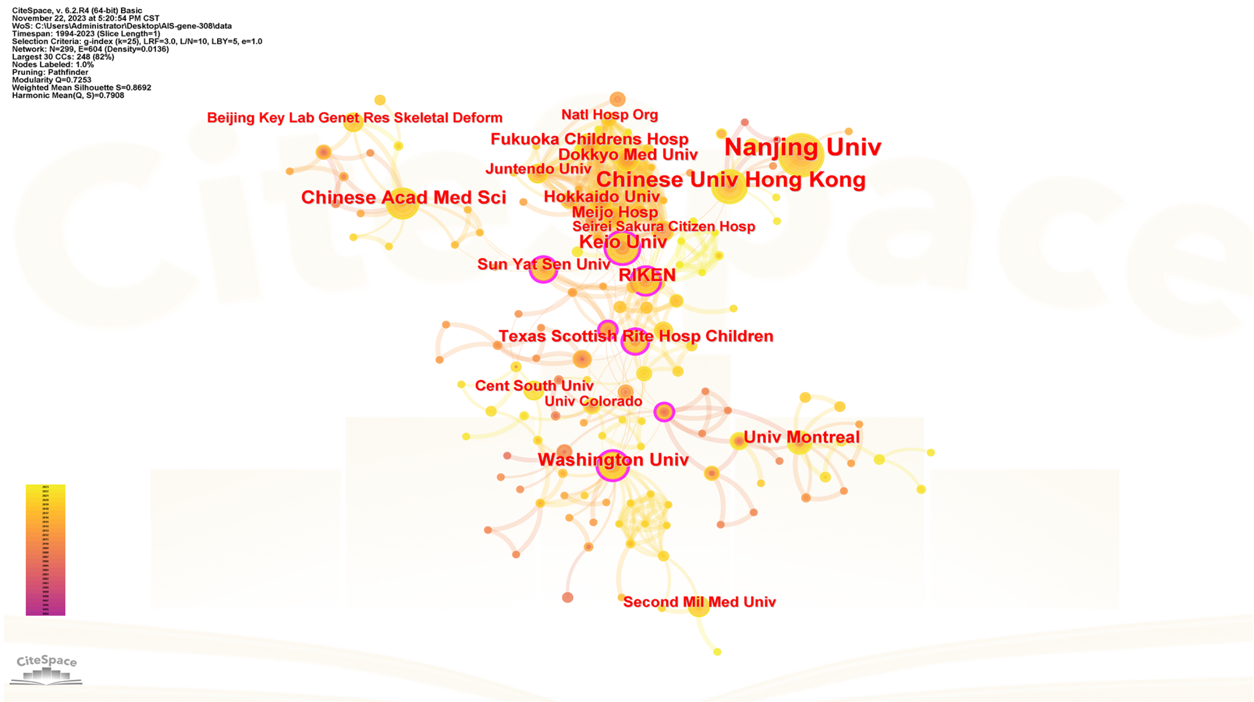


FIGURE 4
Collaboration network of productive institutions. Nodes represent institutions, lines represent co-citation relationships. Node colors indicate different years. Node size reflects publication numbers.

gene", "menarche", "calmodulin", "estrogen receptor gene", "linkage analysis", "disc degeneration", "bone mineral density", "melatonin signaling dysfunction", "collagen gene", "mesenchymal stem cell", "*LBX1*", "promoter polymorphism", "Bone formation", "cerebrospinal fluid flow" and "extracellular matrix".

# Discussion

The research showcases the results of a bibliometric analysis of 308 articles on AIS genetic factors published from January, 1, 1992, to February, 28, 2023 utilizing the WoS database and CiteSpace software. The evolution from 1992 to 2023 is described by 2 phases: 1992–2005, a period of slow growth, and 2006–2023, a phase of swift progress. The number of papers published in 2019 is the largest, but this does not mean that the field has reached its peak. Scholars persist in their field with ongoing research, promising more influential publications ahead.

Analysis of the distribution of countries, institutions and scholars shows international collaboration in this field. According to the article count and the H-index, China stood out as the foremost nation in terms of productivity and impact in AIS genetic factor research. Leveraging its sizable population and proficiency in sample collection from AIS patients, China has witnessed accelerated development in studying AIS genetic factors, propelled by economic, technological, and intellectual advancements. The advancement of the economy has stimulated investment in the healthcare sector, leading to a surge in research productivity (6, 9). In addition, young Chinese spine surgeons excel in basic research and article publication. The USA, a powerhouse of economy, science, and technology, assumes a vital role in studying the AIS genetic factors. When analyzing the dispersion of academic papers by nation, organization, and author, Japan was also a noteworthy participant in research efforts.

Qiu Yong and Zhu Zezhang, affiliated with Drum Tower Hospital, Nanjing University, China, have published extensively on this topic. They have maintained a close collaboration. The quantity of co-authors serves as a significant metric for the status of the research. The visual map of this study indicates inadequate connections among countries, institutions, and authors. Enhancing academic collaboration is imperative.

TABLE 3 Top 10 productive journals in the genetic factors of AIS.

| Rank | Journal | Number | Percentage |
|---|---|---|---|
| 1 | Spine | 62 | 20.1 |
| 2 | European Spine Journal | 17 | 5.5 |
| 3 | BMC Musculoskeletal Disorders | 11 | 3.6 |
| 4 | Scientific Reports | 11 | 3.6 |
| 5 | Human Molecular Genetics | 8 | 2.6 |
| 6 | Journal of Orthopaedic Research | 8 | 2.6 |
| 7 | PLOS ONE | 7 | 2.3 |
| 8 | Spine Journal | 7 | 2.3 |
| 9 | American Journal of Medical Genetics Part A | 5 | 1.6 |
| 10 | Biomed Research International | 5 | 1.6 |

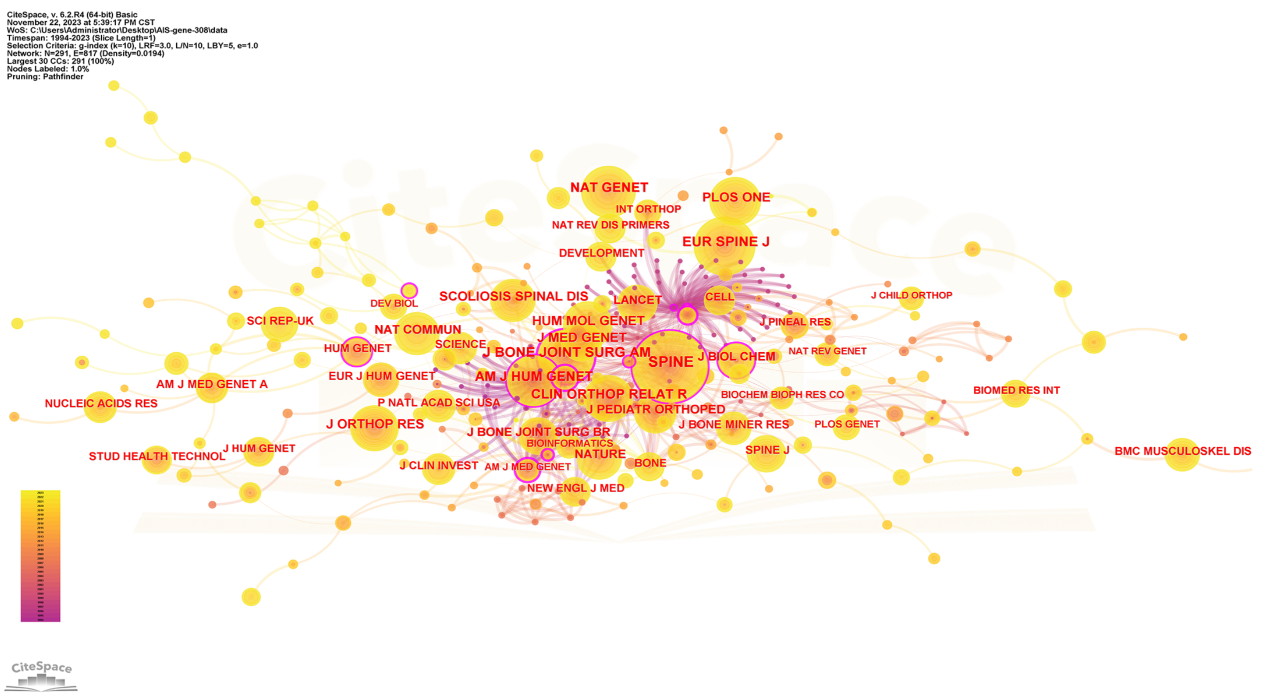


FIGURE 5
Collaboration network of cited journals. Nodes represent journals, lines represent co-citation relationships. Node colors indicate different years. Node size reflects the number of co-citations.

Journal analysis assists researchers in selecting appropriate publications. Spine and European Spine Journal are the mainstream journals on the topic. These journals might exhibit greater openness to researching genetic factors in AIS, and manuscripts featured in these journals have higher chances of gaining attention and citations.

Keywords reflect the focus and trajectory of the research. Keyword evolution analysis provides a crucial basis for exploring the research of AIS genetic factors. After removing keywords related to the topic, the most prominent burst keywords of AIS genetic factors are "fibrillin gene", "menarche", "calmodulin", "estrogen receptor gene", "linkage analysis", "disc degeneration", "bone mineral density", "melatonin signaling dysfunction", "collagen gene", "mesenchymal stem cell", "*LBX1*", "promoter polymorphism", "Bone formation", "cerebrospinal fluid flow" and "extracellular matrix". The results of the burst keywords and clustering revealed that the prominent theme in this field over the last 30 years has been the expression and verification of genes related to the spine and its accessory structures.

Most of the 10 most cited papers investigated the genetic factors of AIS through genome-wide association studies. In 2007, Xu et al. found that the *MTNR1B* gene is lowly expressed in osteoblasts from AIS patients but is not involved in disease progression (10). Subsequently, AIS-related susceptibility genes continue to emerge, including *MATN1* (11), *LBX1* (12), *PAX1* (13), *BNC2* (14) and *GPR126* (15, 16). Except for the *BNC2* gene, all genes were lowly expressed in the tissue cells of AIS patients. AIS-related signaling pathways have also shown remarkable results. Sharma et al. found a possible association between the clinical phenotype of horizontal gaze palsy with progressive scoliosis in patients with compound heterozygous mutations in *ROBO3* and the involvement of the *ROBO3* gene in the regulation of the axon guidance pathway (17). Zhu et al. found that the proportion of type I fibers was higher on the convex side than on the concave side in patients with AIS, which may be related to the asymmetric expression of the Wnt/$\beta$-catenin pathway in the paraspinal muscles on both sides of the spine (18). These studies suggest that AIS may be the result of the combined effects of multiple gene expression and different signaling pathways.

Combining keyword burst analysis and keyword clustering analysis, we summarized the new perspectives of AIS genetic factors research papers published in the last 5 years as: urotensin and its related receptors, cilia, chondrocytes and osteogenesis, muscle tissue, neural crest cells, and connective tissue.

## Urotensin and its related receptors

Zebrafish, genetically similar to humans, are ideal subjects for studying scoliosis due to their inherent susceptibility to the condition (19, 20). The circulation of cerebrospinal fluid (CSF) is associated with spinal development and can result in zebrafish developing spinal deformities (21–23). When CSF flows through neurons in contact with CSF(CSF-cNs) in the central canal, these neurons produce the urotensin-related peptides Urp1 and Urp2 (24–26). These peptides can bind to Uts2r receptors on the membrane of dorsal slow-twitch myocytes in zebrafish embryos,

TABLE 4 The most productive authors in the genetic factors of AIS.

| Rank | Author | Number | Percentage | Affiliation |
|---|---|---|---|---|
| 1 | Y. Qiu | 59 | 19.2 | The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China. |
| 2 | Z. Z. Zhu | 36 | 11.7 | The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China. |
| 3 | L. L. Xu | 32 | 10.4 | The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China. |
| 4 | J. Cheng | 27 | 8.8 | Joint Scoliosis Research Center of The University of Hong Kong, China. |
| 5 | S. Ikegawa | 21 | 6.8 | Laboratory of Bone and Joint Diseases, Center for Genomic Medicine, RIKEN, Tokyo, Japan. |
| 6 | Z. Liu | 20 | 6.5 | The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China. |
| 7 | K. Ikuyo | 17 | 5.5 | Laboratory of Bone and Joint Diseases, Center for Integrative Medical Sciences, RIKEN, Tokyo, Japan. |
| 8 | G. Christina | 15 | 4.9 | Department of Orthopaedic Surgery, Washington University School of Medicine, St. Louis, MO, USA |
| 9 | N. L. Tang | 14 | 4.5 | Departments of Chemical Pathology, University of Hong Kong, China. |
| 10 | Y. Ogura | 14 | 4.5 | Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo, Japan. |

causing the myocytes to contract dorsally and straighten the body axis. Reducing these peptides during zebrafish growth causes spinal deformities similar to human spinal dysplasia (27, 28). Bearce et al. found that zebrafish lacking Uts2r3 have scoliosis in adulthood; and that Uts2r3, as a receptor of the urotensin family, may regulate spinal morphology (21). Research on Chinese Han patients with AIS has additionally verified a substantial correlation between *UTS2R* gene mutation and AIS (29). It can be concluded that mutations in the genes that control the production of urotensin and its receptor may lead to the development of AIS.

## Cilia

Cilia are hairy organelles positioned outside the cell membrane (30). Active cilia produce cellular motility, drive fluid flow or generate signal gradients (22, 31). Cilia assembly and CSF flow are closely associated with AIS (22). Elizabeth et al. suggest that motile cilia in the zebrafish vertebral canal promote the synthesis of Reissner's fibers, which transport epinephrine to the central canal. Epinephrine acts on CSF-cNs to induce Urp peptides secretion. These urotensins signal the zebrafish dorsal slow-twitch muscles to elicit contractions that resolve the ventral curve and promote spinal straightening (28). The mutation rate of the *POC5* gene in French-Canadian and British AIS patients was significantly higher than in normal controls (32). Its aberrant expression affects Urp peptides secretion, which limits the contraction of slow-twitch muscles and imbalances muscle strength on both sides of the spine, causing scoliosis (33). Similarly, variants in the *TTLL11* gene were present in the majority of UK families with concomitant scoliosis; a zebrafish model with the gene knocked out replicated this condition (34). Abnormal ciliary movement may also lead to scoliosis. Zebrafish cilia contribute to Reissner fiber aggregation and straightening of the body axis; and knockout of the ciliary polarity and movement-related gene *cfap298* (35) and ciliary dynamic protein axonal heavy chain 10 genes may affect Reissner fiber aggregation and lead to zebrafish spinal deformity (21, 36). Variants in genes *dnaaf1* and *zmynd10* related to cilia structure and function were also found in AIS patients in southern China by whole exome sequencing (37). Knockout of these genes in viable adult zebrafish recapitulated scoliosis (37). It can be concluded that mutations in cilia-related genes cause AIS by impeding CSF flow, Reissner fiber synthesis, and urotensin release allowing an imbalance of paraspinal musculature.

## Chondrocytes and osteogenic process

Meta-analyses have summarized and confirmed that AIS-related gene mutations affect chondrocyte development and osteogenesis (such as *CDH13*, *ABO* and *COMP*) (38, 39). Among them, *COMP* gene expression is down-regulated in osteoblasts of AIS patients, which synthesize abnormal proteins with cytotoxicity, triggering chondrocyte underdevelopment or even death, resulting in impaired bone growth (39). A number of studies on signaling pathways involved in the process. The *ERK1/2* signaling pathway activates the *AKAP2* gene, promoting the proliferation and specialization of chondrocytes in the human growth plate, while *AKAP2* gene expression was reduced in AIS patients (40). Upregulation of the *RHOA* gene in AIS patients inhibits the differentiation of MSCs to cartilage through the RHOA/ROCK signaling pathway and hinders bone growth (41). *SPRY4* gene is the key to promoting osteogenic differentiation and melatonin response in mesenchymal stem cells. Its overexpression, along with melatonin, enhances osteogenesis, whereas knockout of *SPRY4* hampers osteogenesis in AIS patients (42, 43). Low expression of *ADGRG7*, *GREM1* and *GPR126* genes affects osteogenesis in AIS patients (44–47). *CHD7* and *BOC* gene expression even positively correlated with bone mineral content in AIS patients (48, 49).

## Muscle tissue

AIS is often accompanied by differential expression of genes in paraspinal muscle cells. The abnormal expression of the *LBX1* gene has been replicated in a large sample of multi-ethnic AIS patients

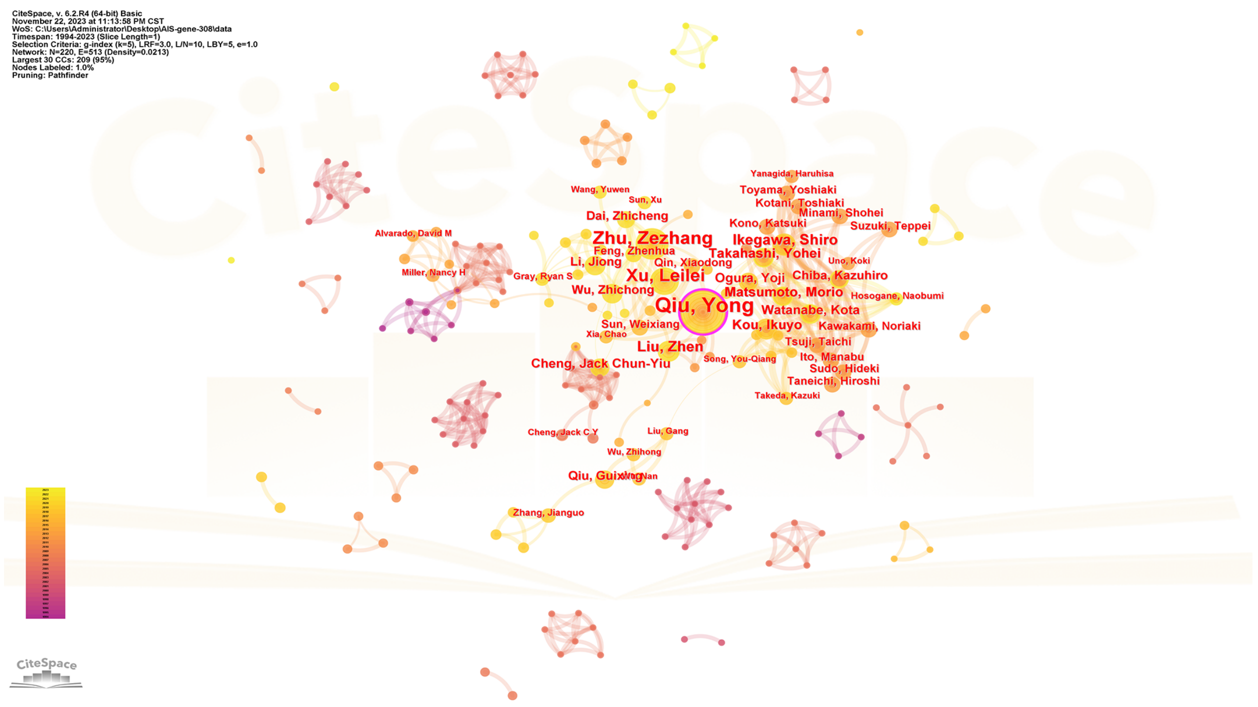

FIGURE 6
Collaboration network of productive authors. Nodes represent authors, lines represent collaborations. Node colors indicate different years. Node size reflects publication count.

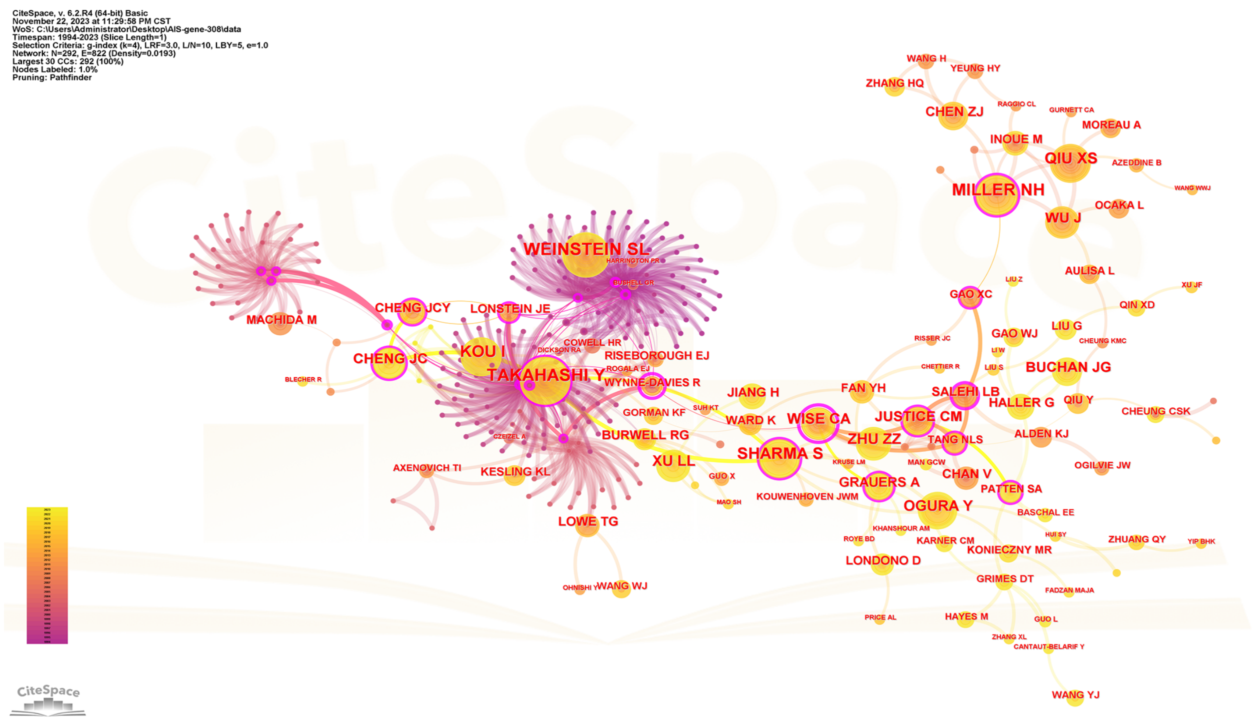

FIGURE 7
Collaboration network of cited authors. Nodes represent co-cited authors. Lines represent co-citation relationships. Node colors indicate different years. Node size reflects the number of co-citations.

TABLE 5 Top 10 cited articles in the genetic factors of AIS.

| Rank | Title | Authors | Corresponding author's country | Journal | Year | Citation |
|---|---|---|---|---|---|---|
| 1 | A *PAX1* enhancer locus is associated with susceptibility to idiopathic scoliosis in females | S. Sharma et al | United States | Nature Communication | 2015 | 36 |
| 2 | Genetic variants in *GPR126* are associated with adolescent idiopathic scoliosis | K. Ikuyo et al | Japan | Nature Genetics | 2013 | 34 |
| 3 | Genome-wide association study identifies new susceptibility loci for adolescent idiopathic scoliosis in Chinese girls | Z. Z. Zhu et al | China | Nature Communication | 2015 | 33 |
| 4 | A genome-wide association study identifies common variants near *LBX1* associated with adolescent idiopathic scoliosis | Y. Takahashi et al | Japan | Nature Genetics | 2011 | 30 |
| 5 | Genome-wide association studies of adolescent idiopathic scoliosis suggest candidate susceptibility gene | S. Sharma et al | United States | Human Molecular Genetics | 2011 | 30 |
| 6 | Melatonin Receptor 1B (*MTNR1B*) Gene Polymorphism Is Associated With the Occurrence of Adolescent Idiopathic Scoliosis | X. S. Qiu et al | China | Spine | 2007 | 29 |
| 7 | A Functional SNP in *BNC2* Is Associated with Adolescent Idiopathic Scoliosis | Y. Ogura et al | Japan | The American Journal of Human Genetics | 2015 | 28 |
| 8 | Promoter polymorphism of matrilin-1 gene predisposes to adolescent idiopathic scoliosis in a Chinese population | Z. J. Chen et al | China | European Journal of Human Genetics | 2009 | 24 |
| 9 | Genome-wide association study identifies novel susceptible loci and highlights *Wnt/β-catenin* pathway in the development of adolescent idiopathic scoliosis | Z. Z. Zhu et al | China | Human Molecular Genetics | 2017 | 24 |
| 10 | Assignment of two loci for autosomal dominant adolescent idiopathic scoliosis to chromosomes 9q31.2-q34.2 and 17q25.3-qtel | L. Ocaka et al | United Kingdom | Journal of Medical Genetics | 2008 | 21 |

(50, 51) and successfully verified in mouse experiments (52). Low expression of the *LBX1* gene may reduce energy supply to skeletal muscle cells and accelerate disease progression by affecting galactose metabolism and glycolytic pathways (53). Genes also regulate the development of paraspinal muscles. High expression of the *TENT5A* gene facilitates myofiber maturation by promoting the proliferative migration of myofibroblasts and maintaining the stability of myogenin; whereas, the *TENT5A* gene is lowly expressed in the paraspinal muscles of patients with AIS (54). In addition to the genes mentioned above, numerous

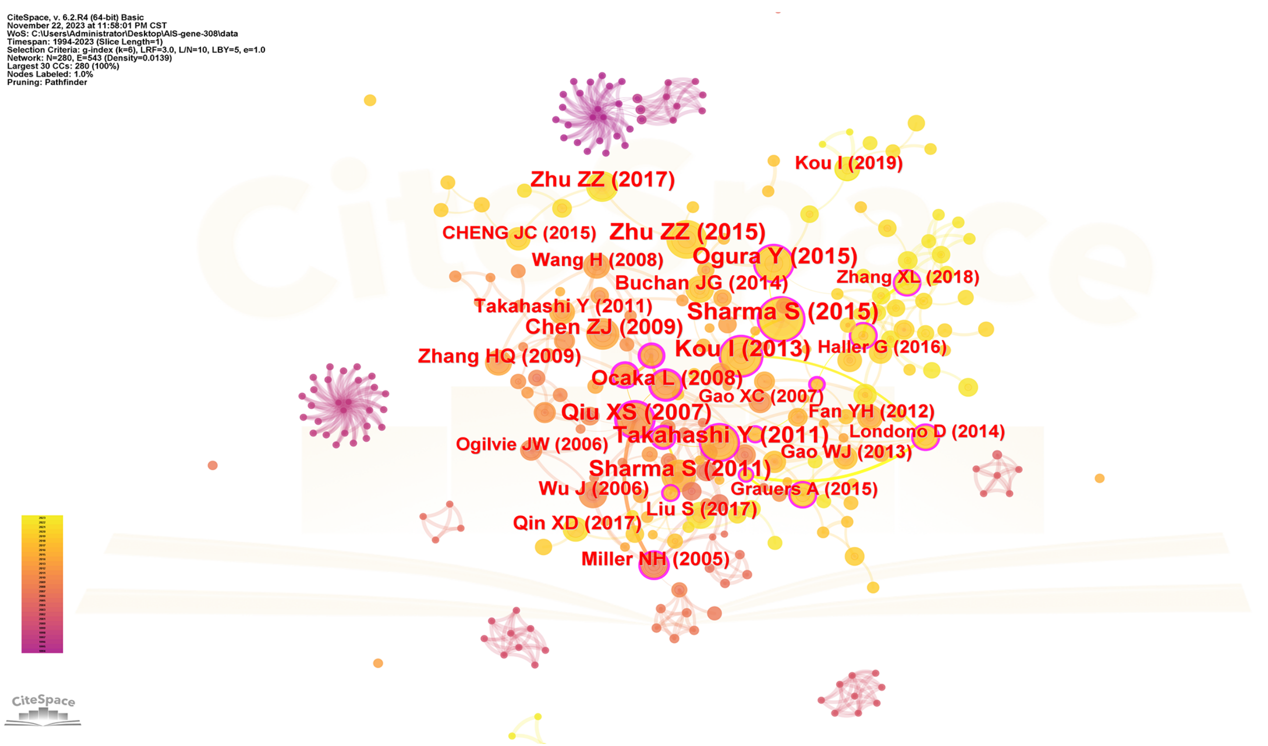


FIGURE 8
The network of cited references. Nodes represent references, lines represent co-citation relationships. Node colors indicate different years. Node size reflects the number of co-citations.

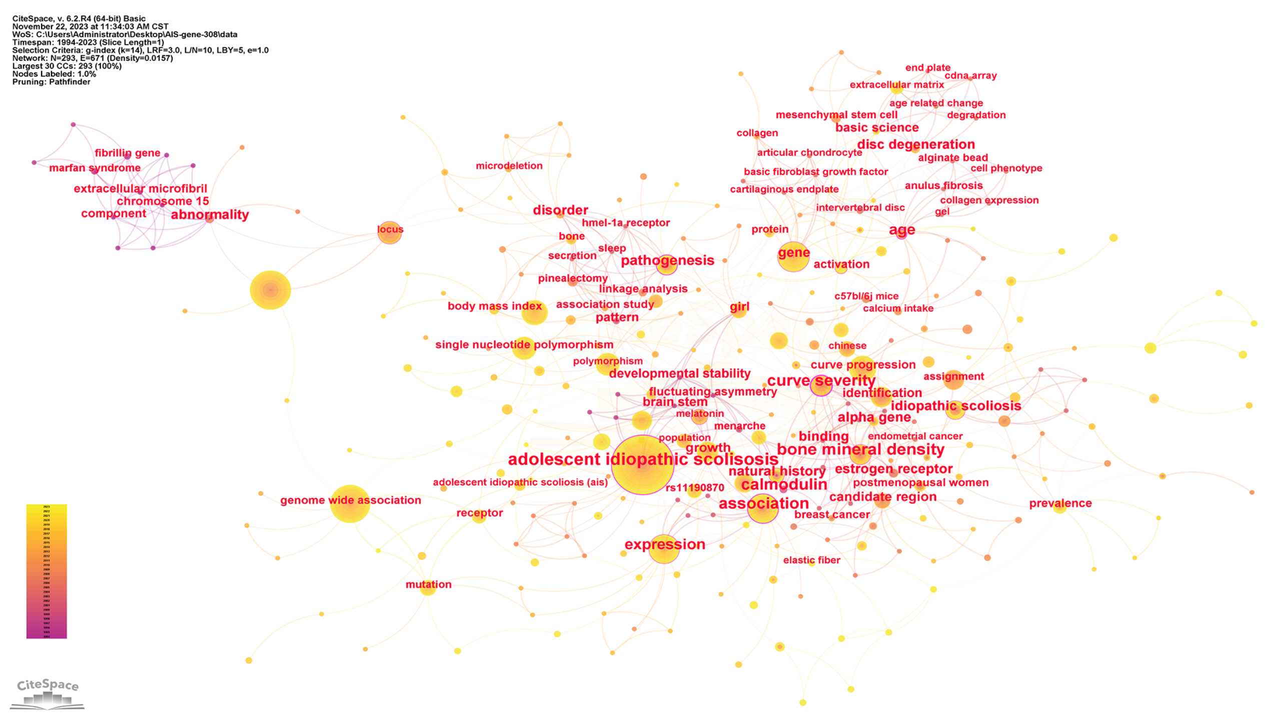


FIGURE 9
The network of keywords. Nodes represent keywords, lines represent co-occurrence relationships. Colors in the nodes indicate different years. Node size reflects its frequency.

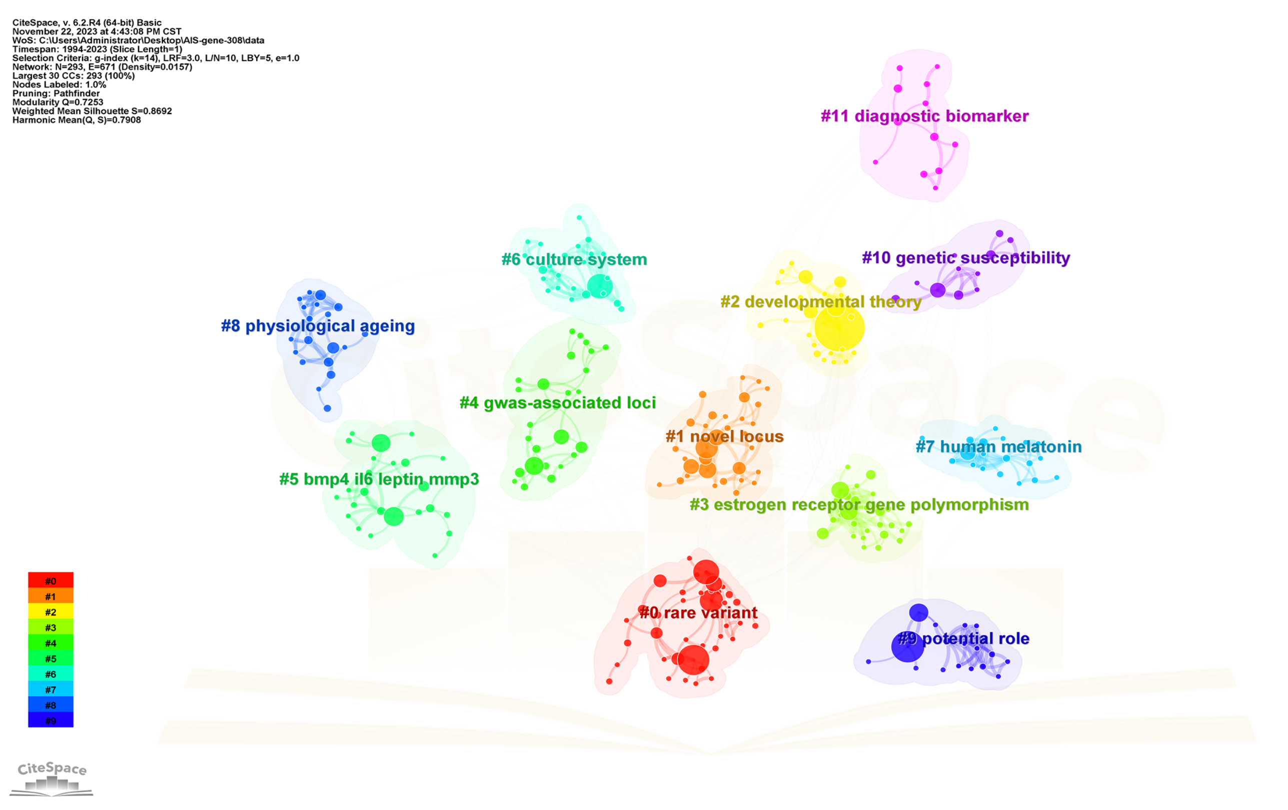


FIGURE 10
The cluster view map. Each grid contains a cluster of locations. The lower the number, the higher the number of keywords included in the clusters.

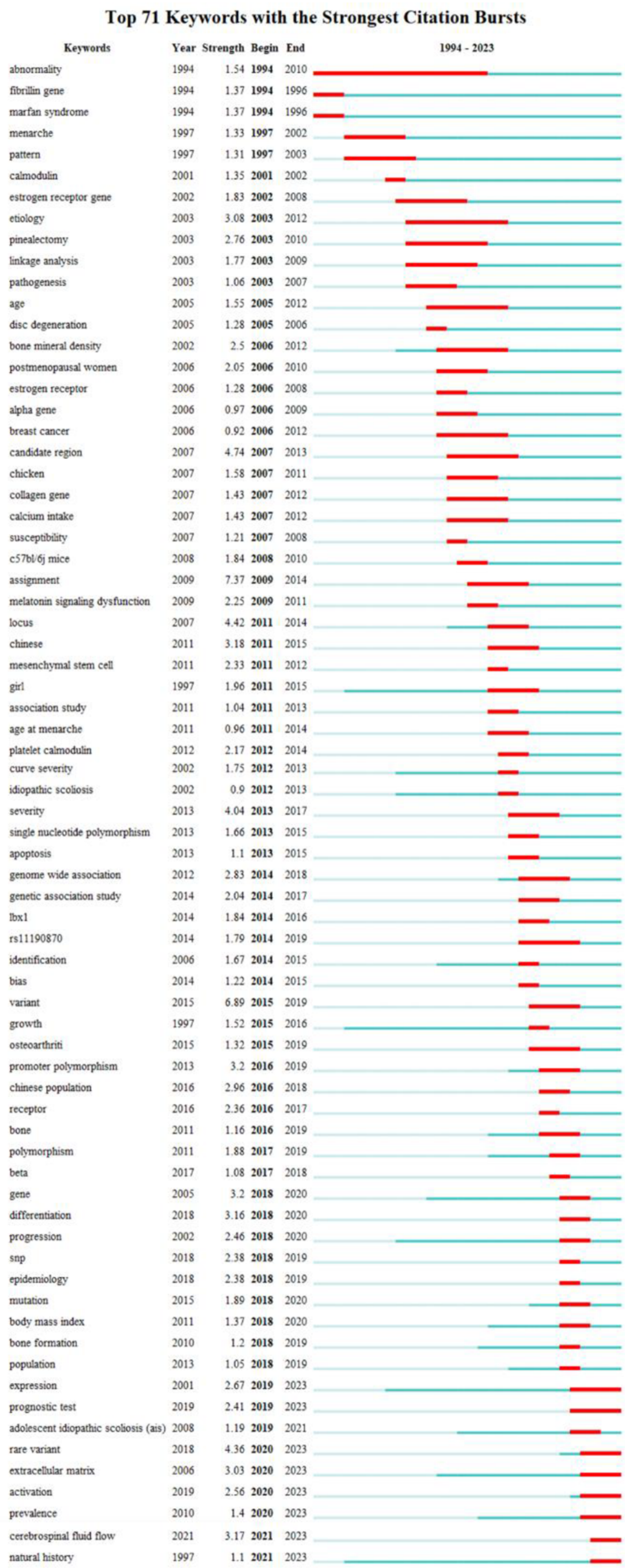


FIGURE 11
Top 71 keywords with the strongest citation bursts. The red bar is the burst phase.

other genes are lowly expressed in the paraspinal muscles of AIS patients, and their functions have yet to be investigated, including *PIEZO2* (55), *CDH13* (56), *ABO* (57), *SLC39A8* (58), *ROBO3* (59), *IRX1* (60), *H19* (61) and *SOCS3* (62).

## Neural crest cell

AIS patients displayed chondroblasts in the curved convex growth plate, while the concave side had neuroblasts and glial blasts (63). Bilateral growth imbalance results in scoliosis. Neural crest cells migrate along a specific pathway during embryonic development to form neuroblasts and glial blasts (63, 64). During migration, neural crest cells experience epithelial-mesenchymal transition (65), facilitating their migration into the mesenchymal extracellular matrix (66). *PAX3* gene is linked to the formation of mesenchymal extracellular matrix, including the expression of two multifunctional proteoglycan subtypes (V1 and V0) (67). Multifunctional proteoglycan can guide the migration of neural crest cells (68, 69). Cartilage differentiation of mesenchymal cells may influence the migration of neural crest cells (70). Therefore, the *PAX3* gene may cause non-synchronous migration of neural crest cells and different phenotypes of cells on both sides of the spine, resulting in idiopathic scoliosis.

## Connective tissue

Connective tissue plays a role in maintaining normal spine morphology, including intervertebral discs, ligaments, and tendons (71, 72). The *ADGRG6* gene regulates the biomechanical structure of intervertebral discs and dense connective tissues to maintain normal spinal morphology through the cAMP/CREB signaling pathway; whereas AIS patients have defective expression of the *ADGRG6* gene (73). The expression of the *PAX-1* gene in the disc is involved in the formation of the spinal structure (74). In addition, upregulation of *ERC2* and *MAFB* gene expression in AIS patients may promote hypertrophy of the ligamentum flavum to adapt to mechanical stresses generated by scoliosis via the TGF-β pathway (75). The *FBN1* gene is crucial for connective tissue function (76), and its low expression reduces the synthesis of extracellular matrix proteins, which is detrimental to maintaining the stability of the biomechanical structure of connective tissues such as ligaments and intervertebral discs, leading to the progression of AIS (77). ADAMTSL2 and LTBPs can bind to FBN1 *in vitro* and upregulate the TGF-β signaling pathway in fibroblasts (78–81). Ryzhkov et al. found that the TGF-β signaling pathway, which is involved in the formation and degradation of extracellular matrix proteins, is more highly expressed on the concave side of the curve than on the convex side in patients with AIS, and may be involved in the process of disc tissue degeneration (82). Therefore, The interaction between ADAMTSL2 and LTBP4 is involved in the development of AIS through the TGF-β pathway (83). The above results show that connective tissue-related genes are involved in the onset and development of AIS.

Although research on genetic factors associated with AIS is recent and extensive, most studies are not in-depth and have some limitations.

1. Most studies have small sample sizes and selection bias, and the samples can not represent the patient group (33, 84).
2. Many studies only examine whether there is a correlation, but do not explain the causality and mechanism of action (14, 16).
3. Some studies are unable to obtain muscle, bone, and other tissues that may be directly related to AIS (85, 86).
4. Integrating the existing research results and establishing the mathematical model of AIS is beneficial for the diagnosis and prevention of the disease (87).

In the process of studying the etiology of AIS, researchers have gradually recognized that AIS is a disease caused by the combined effects of multiple factors. Over the past few decades, the study of AIS etiology has shifted from a macroscopic to a microscopic level, particularly with the rise of GWAS, which allows for comprehensive screening of genes associated with the occurrence and development of AIS. As a result, various tissues related to AIS have been included in the research. While these studies have provided abundant results, they have been scattered, making it difficult to identify the primary effect genes. Additionally, there is a lack of AIS samples from diverse ethnic backgrounds, preventing integration into a unified system.

Artificial intelligence (AI) is well known for its ability to analyze and process large amounts of data, and discover hidden relationships between variables. By consolidating clinical and GWAS data from previous AIS patients and constructing a database that is continuously updated, we can combine the vast clinical information and GWAS data of AIS patients with AI. This integration allows for the training of a dynamic AIS simulation system, which can uncover associations between potential genetic variations and specific clinical phenotypes, predict AIS risk and progression, simulate gene-targeted therapies for AIS, and even customize personalized disease risk assessment models based on individual AIS patients' genomic information and relevant clinical parameters. This approach provides targeted medical advice and treatment plans, contributing to the development of precision medicine and improving treatment outcomes and health management for each patient.

## Advantages and constraints of this research

This is an inaugural bibliometric analysis of the genetic factors of AIS. This study discusses the current situation, progress and trend of the role of genetic factors in AIS, so that scholars can focus on the latest and most important hotspots. This study has several limitations. First, there is a temporal delay as this study did not incorporate recent publications. Second, it is not comprehensive. We only looked at articles from the WoS core collection. Finally, subjective bias exists in the interpretation of the results.

# Conclusion

Research into the genetic factors of AIS indicates a worldwide pattern over time. Beginning in 2006, there has been a significant surge in the quantity of published research. China and the Chinese Academy of Medical Sciences emerge as the most productive countries and institutions in this regard. A large number of articles have been published in *Spine* and *European Spine Journal*. Y. Qiu and Z. Z. Zhu are both prolific authors. The strongest burst keywords among the genetic factors of AIS were "fibrillin gene", "menarche", "calmodulin", "estrogen receptor gene", "linkage analysis", "disc degeneration", "bone mineral density", "melatonin signaling dysfunction", "collagen gene", "mesenchymal stem cell", "*LBX1*", "promoter polymorphism", "Bone formation", "cerebrospinal fluid flow" and "extracellular matrix". In addition, scholars would find valuable insights from the prominent clusters, highly cited publications and references.

# Author contributions

XJ: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. FL: Conceptualization, Writing – review & editing. MZ: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. WH: Formal Analysis, Supervision, Writing – review & editing. YZ: Formal Analysis, Writing – review & editing. BX: Writing – review & editing. KX: Writing – review & editing.


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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Exercise therapy for adolescent idiopathic scoliosis rehabilitation: a bibliometric analysis (1999–2023)

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**Background:** Among the conservative treatments for rehabilitation of adolescent idiopathic scoliosis (AIS), exercise therapy has attracted a large number of studies as its advantages of good clinical effect, high operability, high compliance, few side effects and low cost. We conduct a bibliometric analysis of previous research to identify prevalent areas of study and inform research for the future directions in this paper.
**Methods:** Relevant publications and reviews were collected using the Science Citation Index Expanded from the Web of Science Core Collection. Information from the included studies was analyzed systematically using VOSviewer and Citespace software to identify patterns regarding publications, keywords, authors, citations, countries, institutions and journals.
**Results:** A total of 172 articles published from 1999 to 2023 were identified. Over the last decade, the number of publications has gradually increased, reaching a peak of 21 publications in 2021. China, North America and Western European countries and institutions are leading the way as far as the quantity of publications and the total number of citations are concerned. The current areas of focus are the efficacy of exercise therapy in relation to enhancing the quality of life of adolescents during rehabilitation.
**Conclusions:** This is the first bibliometric analysis that provides a comprehensive review of the research trends and advances in exercise therapy for the rehabilitation of AIS. The study identifies latest research frontiers and hot directions, providing a valuable reference for scholars in the field of exercise therapy.

KEYWORDS
adolescent idiopathic scoliosis, exercise therapy, rehabilitation, bibliometric, hotspots, research trends

## 1 Introduction

Scoliosis refers to a three-dimensional spinal deformity (1). Adolescent idiopathic scoliosis (AIS) presents the most common manifestation of scoliosis. It typically presents between the ages of 10 and 16 (2). The initial manifestation of vertebral rotation is commonly reported by most patients. This is followed by asymmetry of the thoracic cage and unequal shoulder height, as well as other deformities including unequal length of lower limbs, razor back, pelvic tilt, lowering height, and in severe cases, movement imbalance and cardiopulmonary dysfunction can also occur (3, 4).

Furthermore, individuals with AIS may experience psychological issues, including feelings of inferiority and potential development of psychological disorders, due to alterations in their physical appearance caused by the condition (5). Today, AIS has emerged as a prominent disorder that impedes the growth and development of young individuals. Research indicates that AIS has affected 0.47%–5.20% of adolescents globally (6).

According to the growing body of research, individuals with scoliosis and their families report that wearing a brace is a source of stress and hinders physical and social activities. Moreover, it is widely believed that using a brace can hinder the development of independence (7). Thus, it is imperative to explore other conservative treatment options.

Exercise therapy is widely acknowledged by researchers and the medical communities due to its specific curative effect, high operability, strong patient adherence, minimal side effects, and cost-effectiveness (8). Exercise therapy can decelerate scoliosis progression in AIS patients, improve the motor control of spine and enhance cardiopulmonary function. Furthermore, it helps regulate psychological problems such as depression and anxiety (9, 10). Studies have demonstrated that it is an essential treatment option for patients with mild AIS to progress to surgical criteria, and a supplementary technique for patients with severe scoliosis (11).

Exercise therapy has attracted a great deal of research on the conservative treatment of AIS (12). Common examples of exercise therapy in AIS are listed below: (1) The Schroth methodology, originating from Germany, is widely used and studied. The proprietary Schroth Rotational Angular Breathing (RAB) technique is credited with its success. The method is a three-dimensional scoliosis treatment that emphasises patterned postural correction following the Schroth classification (13). (2) Core stabilization exercises improves the stability of the vertebral column by working out core muscles and enhancing the strength of the deep and superficial muscles on either side of the spine. This ensures that patients with scoliosis can maintain spinal stability and balance of the torso, whether at rest or in motion, with the strength of the peripheral muscles of the spine (14). (3) The Lyon therapy, originating in France, is centered around maintaining proper spinal alignment during exercise. This approach involves lordosis of the lumbar spine and prioritising kyphosis of the thoracic region, alongside frontal segmental mobilisation, plane correction, proprioception, core stabilisation, stabilisation, and balance (15). (3) The Scientific Exercise Approach to Scoliosis (SEAS), developed in Italy, is focused on autocorrection and stabilization. Its exercises are designed to alleviate any identified impairments during the initial evaluation, such as weakness, muscle tightness, and poor motor coordination (16). (4) The technique of the Side Shift method in the UK is centered on intensive training in trunk flexion. This is an active self-correcting method, which involves instructing the patient to shift their trunk laterally over the pelvis in the direction contrary to the convexity of the principal curvature (17). (5) The DoboMed technique, which originated in Poland, concentrates on enhancing the thoracic kyphosis. This is achieved through closed kinematic chains, utilizing a pelvis and shoulder girdle placed symmetrically. Moreover, the corrected position is actively stabilized to establish it as habitual (18).

Physiotherapeutic Scoliosis-Specific Exercises (PSSE) and core stabilization exercises have been developed and utilised in multiple countries worldwide. Various other methodologies are also employed across several continents, but principles are akin to those of PSSE. Conservative treatment utilising exercise therapy has demonstrated the capacity to ameliorate quality of life and is deemed a crucial constituent of successful scoliosis rehabilitation with a view to favourable outcomes (19).

In the current situation of increasing demand for AIS rehabilitation, the increasing application of exercise therapy makes it a meaningful research field and show good prospects in the treatment of AIS. The focus of current research is primarily to address the clinical question of whether PSSE can effectively delay the progression or slow down the advancement of the curve. Preventing disease progression is essential to avoid the need for bracing, surgery or both (11). Numerous scholars have conducted bibliometric investigations on various aspects of AIS. Nevertheless, there has been no scientific research that has presented a comprehensive analysis of exercise therapy for rehabilitation of AIS through bibliometrics. A study presents an updated bibliometric analysis of scientific articles on AIS from 1985 to 2020. The analysis focuses on publication trends and the most influential articles in the field of AIS. It should be noted that the study did not examine the growing research on exercise therapy for scoliosis during this period (20). To address the lack of quantitative analysis in the research area, this bibliometric study seeks to gather worldwide scientific research on exercise therapy for scoliosis rehabilitation from inception to 2023. We conducted a comprehensive analysis of publications from the Web of Science Core Collection (WoSCC) database using Citespace and VOSviewer. The purpose of this article is to aid researchers and clinicians in understanding the prominent areas and emerging patterns within this field, which may enable high quality in clinical practice and future research.

## 2 Materials and methods

### 2.1 Source of bibliometric data and search strategy

To ensure the coverage and authority of the data analyzed, Publications with related themes were searched from the Science Citation Index Expanded (SCIE) within the WoSCC,with a time span starting from the inception to 2023, a search time cutoff of 1st August 2023. Two authors searched independently, and **Supplementary Material S1** showed the search strategy of the study. Only English language articles or reviews were selected. All documents included had to be peer-reviewed. Data must be pre-processed prior to analysis to avoid the results of the analysis being influenced by the quality of the data itself. Data from all articles relevant to the bibliometrics were imported into Zotero, and titles, abstracts, and entire texts of the included papers were then independently screened by two researchers to identify usable studies based on predetermined exclusion criteria. Exclusion criterias were including: (1) the intervention modality is not exercise therapy;

(2) the target conditions are not associated with AIS; (3) the implementation of exercise therapy for AIS is not the subject of the paper. In the end, 172 valid documents were obtained. Figure 1 shows the process of searching and analysing bibliometric data.

## 2.2 Data extraction and analysis

Available documents were manually selected from the WOS database after screening and review using Zotero. Then, VOSviewer 1.6.19.0 and Citespace 6.2 R4 were used to analyse the plain text downloaded from the Web of Science database containing information from these files in order to map and visualise the bibliometric network of scientific publications (Supplementary Material S2). Basic data were gathered and co-occurrence and co-citation maps by country, institution, author and journal were created employing VOSviewer and Microsoft Excel. The number of published articles is represented by the size of the nodes in the VOSviewer co-occurrence graph, and the level of collaboration is indicated by the connecting lines between the nodes. The node cluster is depicted by the circle colour. Additionally, this study utilised Citespace to analyse the keyword co-occurrence network, burst keyword and cluster network analysis, revealing current innovative research tendencies. Furthermore, GraphPad Prism 8 was utilised to display the quantity of publications and the extent of collaboration amongst diverse nations.

# 3 Results

## 3.1 Publication outputs and study trend

The initial search of the WoSCC database revealed 4,059 publications. After screening out non-relevant documents,

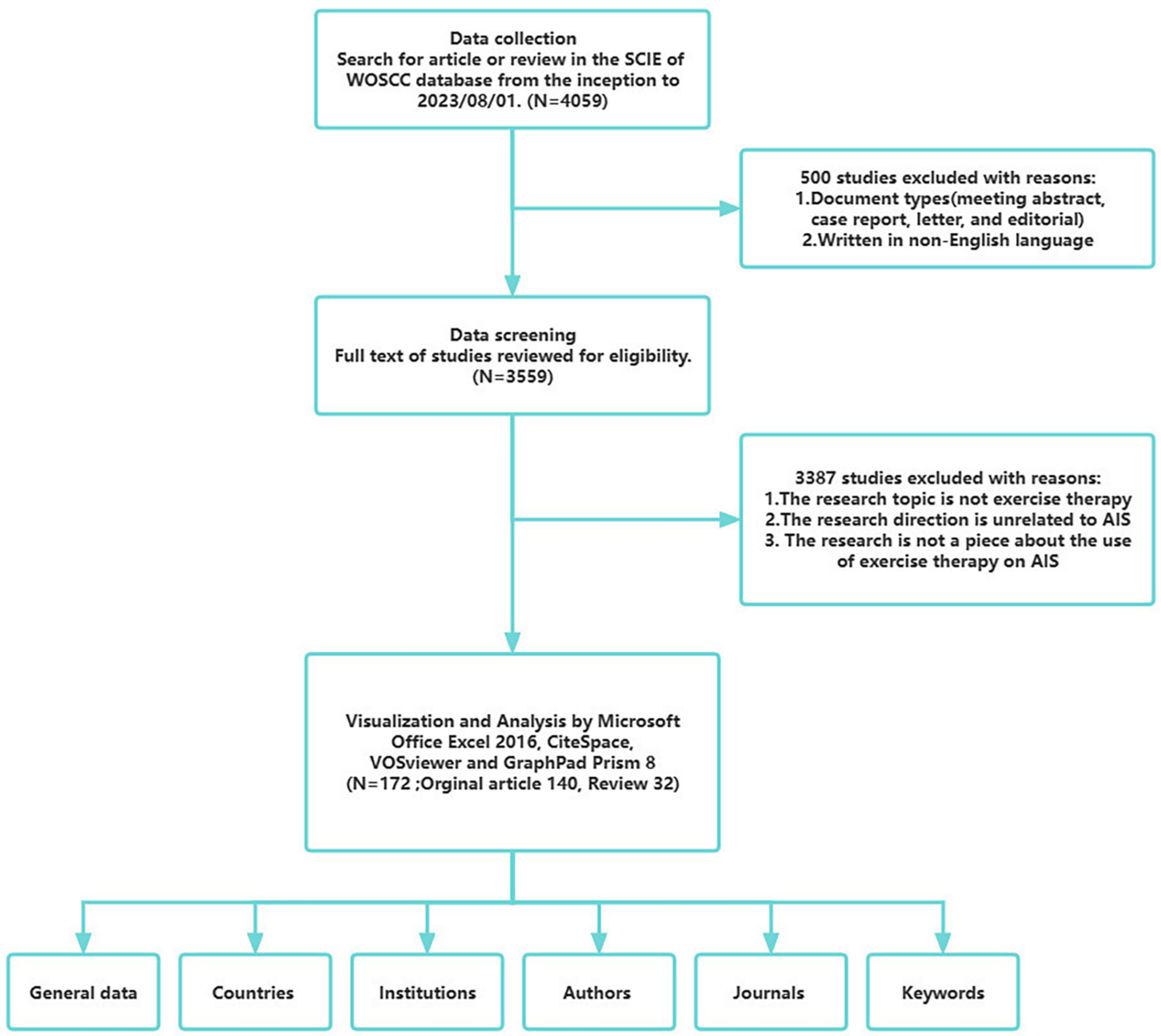



FIGURE 1
Flow chart of the bibliometric search and analysis process.

those in languages other than English, and research topics that were unrelated, a total of 172 papers were selected for the analysis. These papers comprised of 140 articles, consisting of 29 randomized controlled trials (RCTs) and 111 non-RCTs, in addition to 32 reviews. These papers were published between 1999 and 2023. In 1999, Boer et al. published the initial study concerning exercise therapy for rehabilitation of AIS (17), which yielded clinical evidence that supports the employment of Side Shift method on patients with AIS. Figure 2 presents an analysis of the bibliometric trends and the annual numbers of the 172 publications, which can be classified into three phases: the infancy phase (1999–2007), the ups and downs phase (2008–2013), and the rapid growth phase (2014–2023). In its infancy, annual publication remained below 4 except 1999. Over the ups and downs phase, there were small peaks in 2008 and 2012, respectively, and declines the following year. During the rapid growth phase, the number of publications increased significantly, with over 13 papers being released every year. Almost 50% of the publications were published in the final phase, with a maximum in 2021 ($n = 21$). Moreover, according to the linear regression analysis, there was a positive correlation observed between the volume of publications and the year of publication ($R^2 = 0.9933$, $p < 0.001$). It is anticipated that research in this field will persist in growing in the future.

## 3.2 Active countries

Thirty-three countries participated in publications on exercise therapy for AIS rehabilitation. Figure 3A displays the top 10 countries that produced nine or more papers. The five most engaged nations were China (25, 14.5%), USA (22, 12.8%), Germany (18, 10.5%), Italy (17, 10%), and Turkey (16, 9%). Of the 10 nations with the highest publication output, China and Turkey are the only classified as developing, while the remaining eight are classified as developed. The most cited research came from the USA, with 1,261 citations, followed by China (977) and Italy (576). Regarding citations per paper, the USA ranked first with 57.32 citations, followed by China (39.08) and England (37.08). Geographical information from the papers analyzed was extracted with the use of VOSviewer and imported into Scimago Graphica. This process resulted in the creation of a collaborative network between all countries depicted in Figure 3B. The results show that there are three main clusters of countries, namely Western Europe, Eastern Asia and North America. The closest collaboration was observed to be between China and the USA.

## 3.3 Institution distributions

According to the author's address, 313 institutions made contributions to the 172 publications. Figure 4A shows the 8 institutions that were the most productive in publishing over 4 papers. Hacettepe University (Turkey) and the Italian Scientific Spine Institute (Italy) were the most prolific, both publishing 7 papers. The University of Hong Kong (China) followed with 5 papers. The research papers from the Italian Scientific Spine Institute garnered the greatest number of citations (287) and citations per paper (48). Figure 4B displays the collaborative network between prominent institutions engaged in research on exercise therapy for AIS rehabilitation. The top organisations had significant links with remaining organisations, with the yellow block representing the density of collaboration between

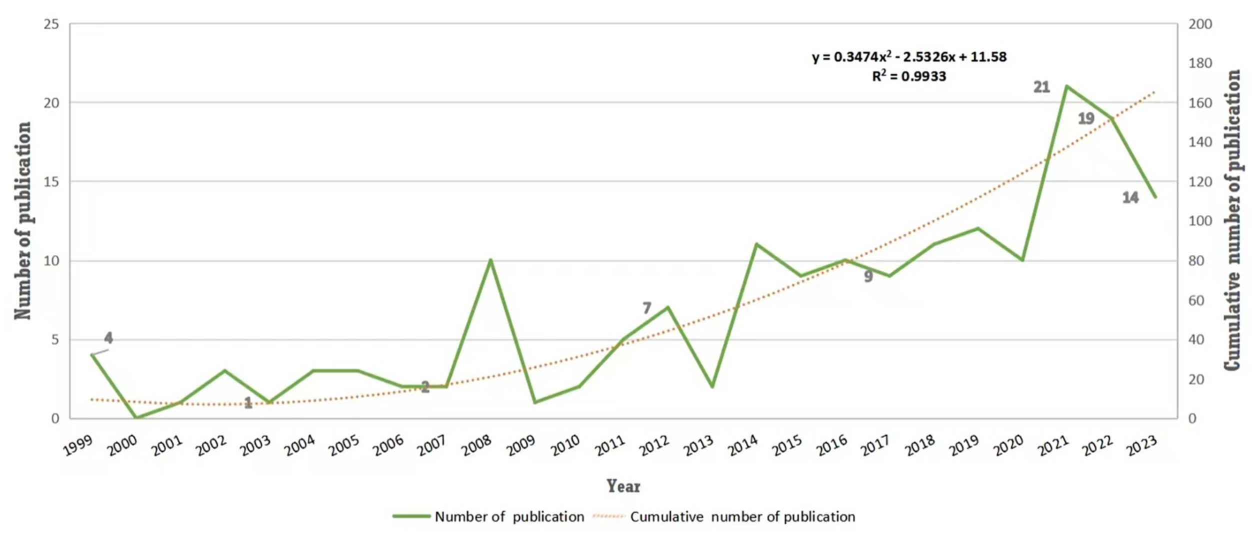
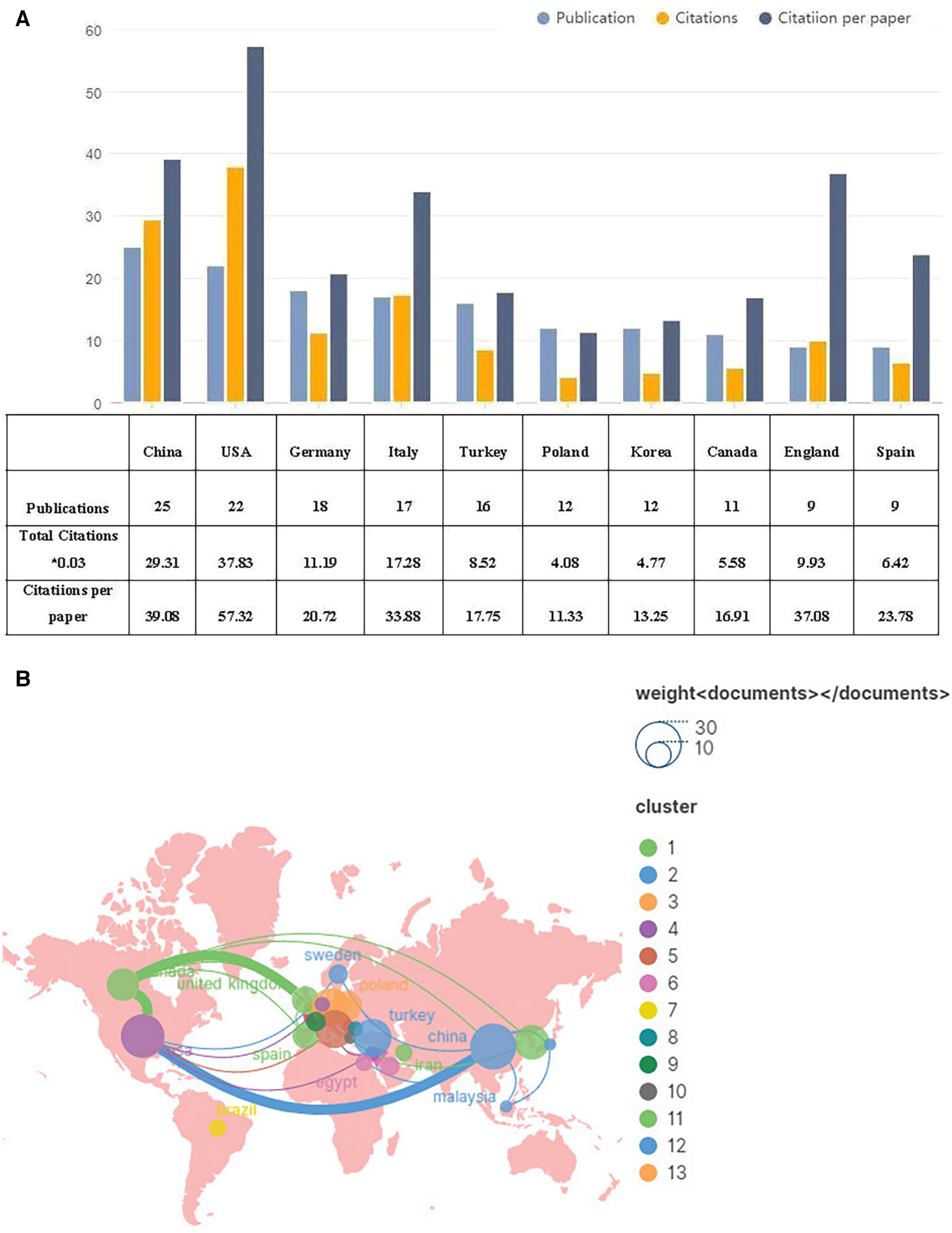



FIGURE 2
Trend of publication outputs from 1999 to 2023 on exercise therapy for AIS rehabilitation topic.




| | China | USA | Germany | Italy | Turkey | Poland | Korea | Canada | England | Spain |
|---|---|---|---|---|---|---|---|---|---|---|
| Publications | 25 | 22 | 18 | 17 | 16 | 12 | 12 | 11 | 9 | 9 |
| Total Citations *0.03 | 29.31 | 37.83 | 11.19 | 17.28 | 8.52 | 4.08 | 4.77 | 5.58 | 9.93 | 6.42 |
| Citatiions per paper | 39.08 | 57.32 | 20.72 | 33.88 | 17.75 | 11.33 | 13.25 | 16.91 | 37.08 | 23.78 |

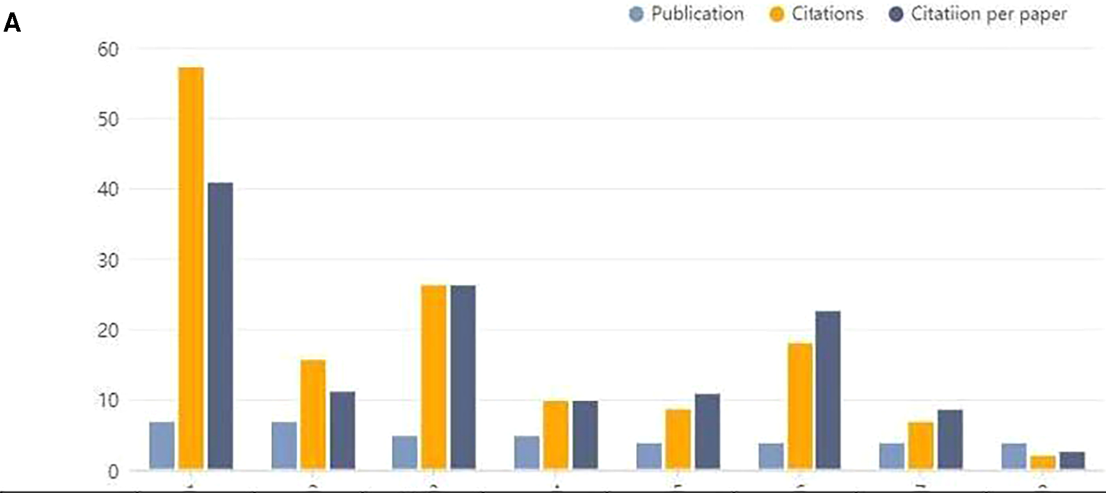
FIGURE 3
The top 10 prolific countries and international collaboration network on exercise therapy for AIS rehabilitation research. (A) The number of publications, total citations, and citations per paper in the top 10 countries. (B) The co-operative network visualization map of countries.

institutions. Closer collaboration was observed between various institutions, specifically the Italian Scientific Spine Institute, University of Alberta, University of Hong Kong, and Karolinska Institutet.

## 3.4 Author analysis

Overall, 735 authors contributed to the literature on rehabilitation exercise for AIS. Table 1 presents the details of

**A**




| | isico italian sci spine inst | hacettepe univ | univ hong kong | univ alberta | hasan kalyoncu univ | hong kong polytech univ | karolinska inst | shanghai jiao tong univ |
|---|---|---|---|---|---|---|---|---|
| Country | Italy | Turkey | China | Canada | Turkey | China | Sweden | China |
| Publications | 7 | 7 | 5 | 5 | 4 | 4 | 4 | 4 |
| Total Citations*0.2 | 57.40 | 15.80 | 26.40 | 10.00 | 8.80 | 18.20 | 7.00 | 2.20 |
| Citatiions per paper | 41.00 | 11.20 | 26.40 | 10.00 | 11.00 | 22.75 | 8.75 | 2.75 |

**B**


FIGURE 4
The top 8 active institutions and the inter-institutional collaboration network on exercise therapy for AIS rehabilitation research. (A) The number of publications, total citations, and citations per paper in the top 8 institutions. (B) The density visualization map of institutions.

TABLE 1 The top 10 active authors who published literature on exercise therapy for AIS rehabilitation.

| Rank | Author | Institution | Country | Publications | Citations | Citations per paper | H-index |
|---|---|---|---|---|---|---|---|
| 1 | Negrini, Stefano | Italian Scientific Spine Institute | Italy | 11 | 421 | 38.27 | 43 |
| 2 | Romano, Michele | Italian Scientific Spine Institute | Italy | 9 | 370 | 41,11 | 25 |
| 3 | Yakut, Yavuz | Hasan Kalyoncu University | Turkey | 5 | 76 | 15.20 | 19 |
| 4 | Zaina, Fabio | Italian Scientific Spine Institute | Italy | 4 | 185 | 46.25 | 33 |
| 5 | Negrini, Alessandra | Italian Scientific Spine Institute | Italy | 4 | 89 | 22.25 | 11 |
| 6 | Diarbakerli, Elias | Karolinska University Hospital | Sweden | 4 | 15 | 3.75 | 9 |
| 7 | Gerdhem, Paul | Uppsala University Hospita | Sweden | 4 | 15 | 3.75 | 33 |
| 8 | Kotwicki, Tomasz | Poznan University of Medical Sciences | Poland | 4 | 88 | 22.00 | 26 |
| 9 | Yagci, Gozde | Hacettepe University | Turkey | 4 | 50 | 12.50 | 8 |
| 10 | Donzelli, Sabrina | Italian Scientific Spine Institute | Italy | 3 | 40 | 13.33 | 15 |

the 10 most prolific authors. The top 3 authors with the highest number of publications were Negrini (11 papers), Romano (9 papers), and Yakut (5 papers). Five of the top ten authors were associated with the Italian Scientific Spine Institute, whereas the remaining authors worked in different research units. Table 1 demonstrates that the Italian Scientific Spine Institute ranked first in terms of the total number of citations and citations per paper, with 287 citations and an average of 47 citations per paper. Furthermore, the author's academic achievement could be accurately reflected by the H-index. Negrini Stefano is ranked first on the H-Index and has the most significant influence in this field (21). An overlay visualization map is exhibited in Figure 5, created by VOSviewer, which analyses author co-occurrence. The graph depicts a prominent cluster centered on Negrini Stefano with a strong collaboration between him and other authors. The remaining authors are situated in smaller groups.

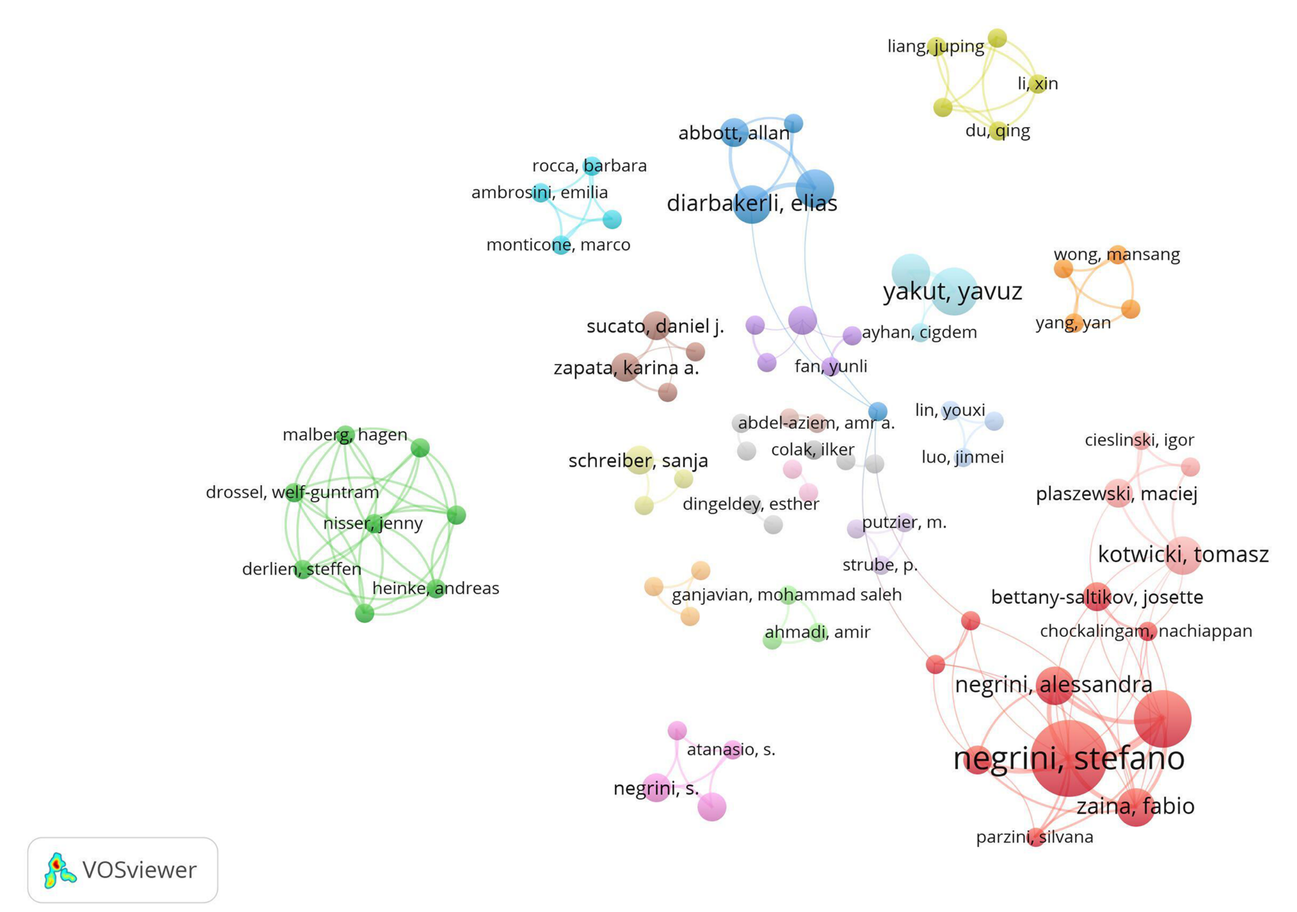



FIGURE 5
Network map of active authors contributed to exercise therapy for AIS rehabilitation research.

TABLE 2 The top 10 most productive journals in the exercise therapy for AIS rehabilitation field.

| Rank | Journal | Publications | Citations | Citations per paper | IF | JCR | OA |
|---|---|---|---|---|---|---|---|
| 1 | Spine | 18 | 408 | 22.67 | 3.50 | Q1 | No |
| 2 | European Spine Journal | 9 | 252 | 28.00 | 3.20 | Q1 | No |
| 3 | Journal of Back and Musculoskeletal Rehabilitation | 9 | 84 | 9.33 | 1.70 | Q2 | No |
| 4 | Journal of Physical Therapy Science | 8 | 91 | 11.38 | / | / | No |
| 5 | PLoS One | 7 | 86 | 12.29 | 3.80 | Q1 | Yes |
| 6 | European Journal of Physical and Rehabilitation Medicine | 6 | 179 | 29.83 | 4.50 | Q1 | No |
| 7 | Prosthetics and Orthotics International | 5 | 79 | 15.80 | 2.10 | Q2 | No |
| 8 | Physiotherapy Theory and Practice | 5 | 23 | 4.60 | 2.00 | Q2 | No |
| 9 | Children-basel | 5 | 4 | 0.80 | 2.60 | Q3 | Yes |
| 10 | Orthopade | 5 | 26 | 5.20 | 1.00 | Q3 | No |

## 3.5 Journal characteristic

The publications included in this study were published in a total of 79 academic journals. Following Bradford's law, those journals that produced over a third of all related papers were identified as core journals, revealing a total of 73 non-core journals and 6 core journals of this field of research. As can be seen in Table 2, the top ten journals with the highest productivity comprised 44.77% (77 articles) of the entire number of research papers. Spine published the most papers (18 papers), followed by European Spine Journal (9 papers) and Journal Of Back And Musculoskeletal Rehabilitation (9 papers). As far as the impact factor (IF) of the journals is concerned, none of the top 10 journals had an IF > 5,000. Seven journals had an IF between 2,000 and 5,000, two journals had an IF < 2,000, and one journal had no current IF. VOSviewer generated a co-citation map of 21 journals that received a minimum of 50 citations. Among these, the most frequently co-cited publications were Spine (3.50), Scoliosis and Spinal Disorders (N/A), and Journal of Bone and Joint Surgery-American Volume (5.30). These journals are notable and respected in the field, as depicted in Figure 6.

## 3.6 Analysis of keywords

Keywords provide a concise summary of a paper by reflecting current themes and predicting future research frontiers through high frequency or burst keywords. As demonstrated in Figure 7A, the three keywords with the highest frequency were adolescent idiopathic scoliosis, idiopathic scoliosis, and curve progression. The keywords could be classified into eleven distinct clusters based on their type, as demonstrated in Figure 7B. Clusters #0, #7 mainly described the target patients. Clusters #2 and #5 indicated the different types of exercise therapy, including Schroth method. Clusters #4 shows another conservative treatment. Clusters #1, #3, #4, #8 and #9 primarily investigated the potential correlations between idiopathic scoliosis and various influencing factors, while other groups of factors were examined in relation to different stages of the disease's development. Furthermore, Citespace has generated the top 25 most significant keywords with the strongest burst, as illustrated in Figure 7C. In terms of burst time, the keywords have been segmented into three periods: 1999–2007, 2008–2013, and 2014–2023. Schroth exercises and reliability indicate the highest burst strength among these keywords. Spinal deformity, physical activity, Schroth exercises, and Schroth have been identified as emerging keywords, indicating potential research focuses in the coming future.

# 4 Discussion

## 4.1 General overview of the results

In this bibliometric analysis, we analysed 172 papers examining exercise therapy as a means of rehabilitating AIS, using Citespace and VOSviewer software to identify research priorities and trends in this area. The literature pertaining to this subject could exhibit fluctuations in research activity and output, divided into three discrete stages. Before 2007, a total papers obtained slightly changed. Exercise therapy has not been extensively utilized in the medical field because of research limitations. Previous studies have shown that surgeons have conducted the majority of research on scoliosis, with a primary focus on the effects of surgical treatments. As a result, there is not enough evidence for non-surgical interventions, and the limited number of available trials have a low level of quality (22). Throughout the 2010 s, numerous studies have highlighted limitations within brace therapy when compared with exercise therapy. As a result, the number of papers examining this issue has gradually gained momentum, drawing the interest of medical practitioners and researchers alike. Since 2020, there has been a significant increase in the number of annual publications, reaching 21 in 2021. This increase can be attributed to the intricate nature of scoliosis surgical treatment, which incurs a rather high expense, along with a complications risk. Therefore, the pursuit of viable alternatives remains active. Over the last decade (Phase III), the number of publications on exercise therapy for AIS has steadily increased, with a significant rise in total papers compared to the previous two phases. This suggests that the popularity of this area of research will continue to grow in the coming future.

In terms of researchers, more than one-fifth of countries globally have published on exercise therapy for AIS rehabilitation. China, the

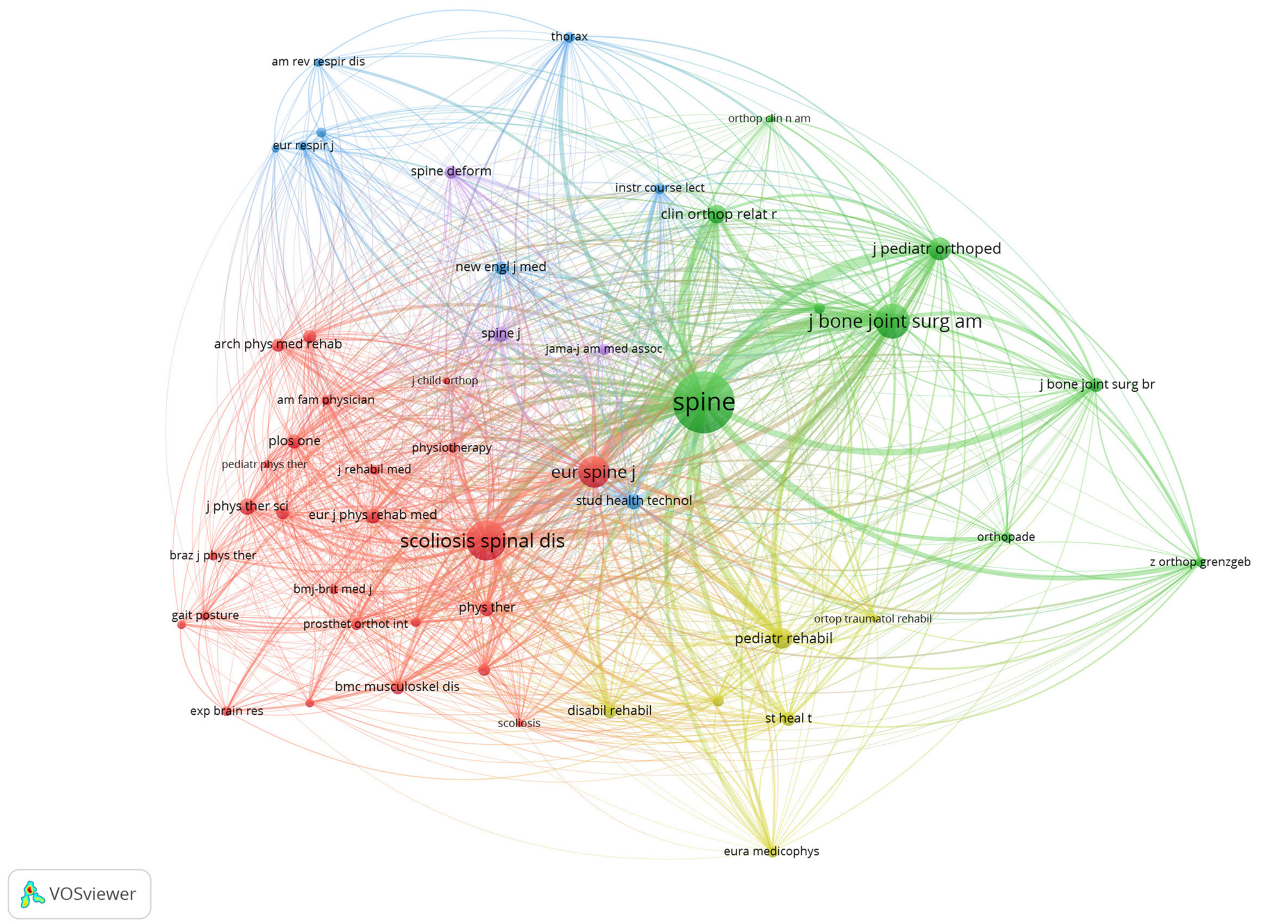



FIGURE 6
Co-citation network map of journals.

USA, Italy, Germany, and Turkey have dominated this field and have also been driving factors in other areas of scoliosis researches (23). It is likely due to the substantial national gross domestic product (GDP) that can offer ample resources on clinical study, and the parents of teenage patients prioritise a holistic treatment strategy aimed at conservative management (24). Around 30% of the top 10 research institutions are situated in China, with Italy ($n = 2$, 20%), Turkey ($n = 2$, 20%), Canada ($n = 1$, 10%), and Sweden ($n = 1$, 10%) following behind. We observed a close collaboration between five nations: the USA, China, Italy, Germany, and Canada. Additionally, Canada engages in active collaborations with Spain, China, Germany, and the USA. When it comes to research institutions, several of them maintain a productive and collaborative relationship, such as Italian Scientific Spine Institute, Karolinsika Institute, Alberta University, Hong Kong University, University of Lowa. However, we found that despite publishing the highest number of papers, Hacettepe University had limited collaboration with other institutions, which could hinder the long-term expansion of scholarly investigation. Although there are some cooperative relationships between specific nations, collaboration between institutions is lacking in extent and scope. Merely minimal cooperation has been observed between institutions located in China and Turkey, which may impede the advancement of the research field in the long term. As a result, we highly recommend that research institutions across different nations collaborate and communicate extensively to promote the growth of exercise therapy for the rehabilitation of AIS.

From the perspective of the author, Negrini stefano, Romano Michele, Yakut Yavuz, Zaina Fabio and Negrini Alessandra have been noted for publishing the most articles, with an average of 7 papers per person. Half of the top 10 researchers listed in Table 1 were associated with the Italian Scientific Spine Institute, Italy. However, their number of citations was lower than those affiliated with North American institutions. One possible explanation for this may be the fact that Italian researchers predominantly produced research papers in the post-2015 period, with limited citations. In addition to these findings, further insights into a particular field could be obtained by analyzing core journals that have a high publication rate. Over one-third of the total quantities of papers were published in the leading 10 journals, which implies that research articles on exercise therapy for AIS rehabilitation were concentrated in these selected journals. Moreover, the active journals in this study did not achieve a high impact factor, indicating that no journal reached a

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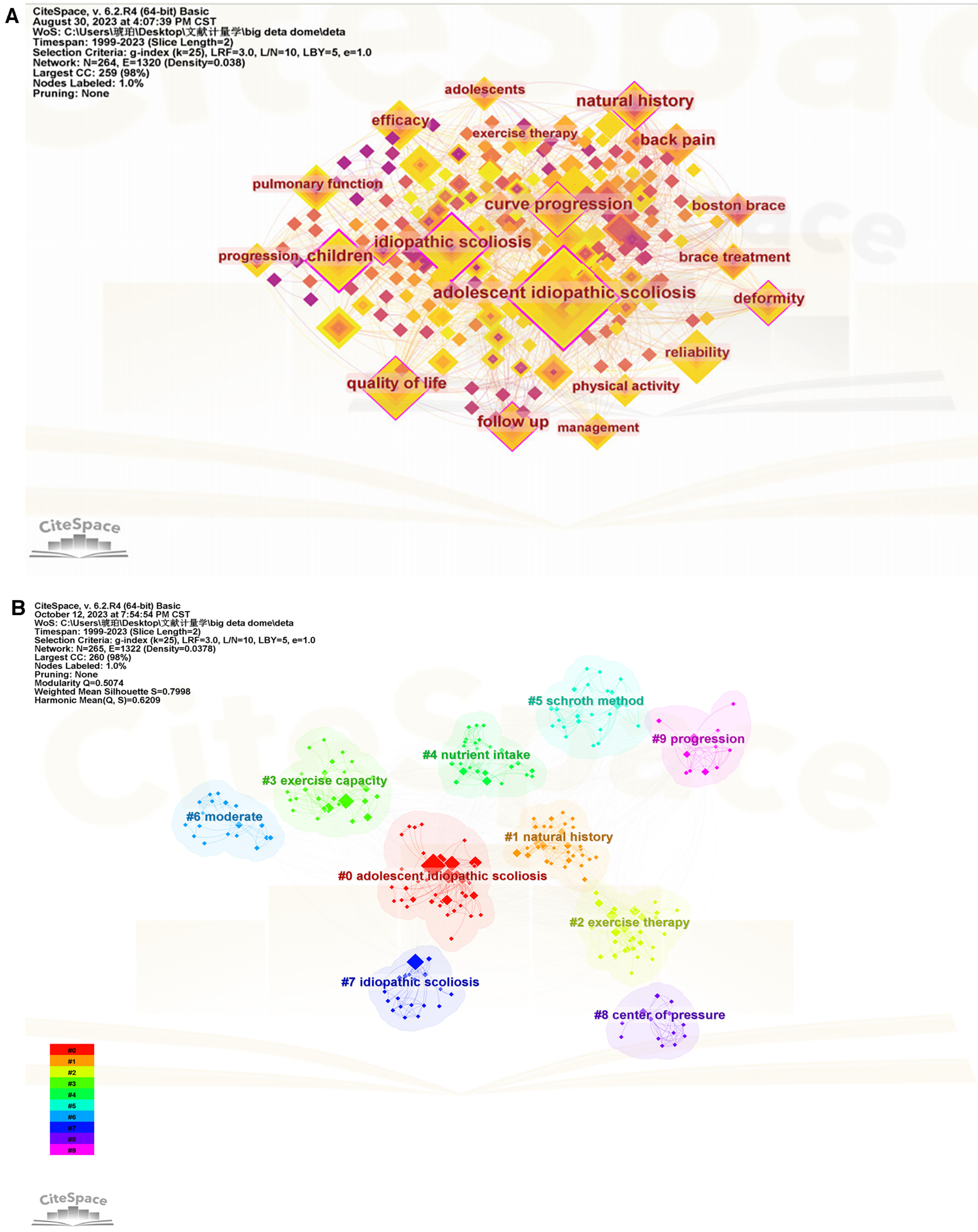


FIGURE 7
(Continued)

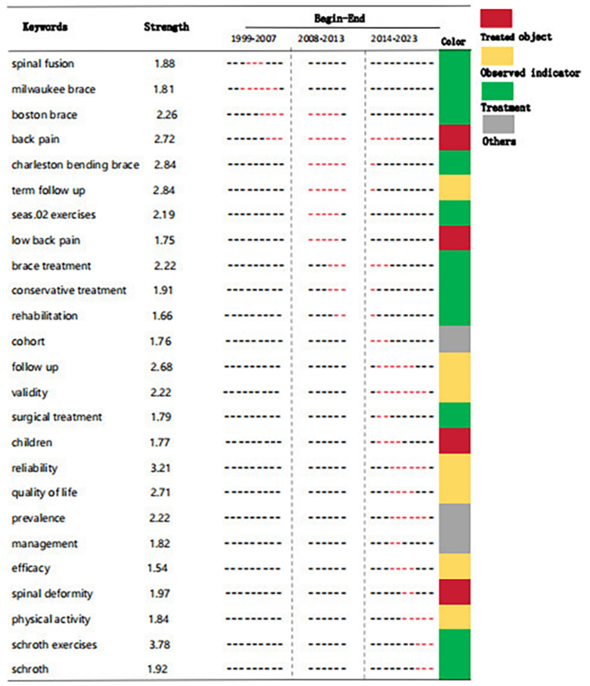


FIGURE 7
Analysis of keywords related to publications on exercise therapy for AIS rehabilitation field. (A) The keyword co-occurrence network map. (B) The keyword cluster map. (C) The top 25 keywords with the strongest citation bursts.

score of 5. Therefore, there is a need for enhancing the standard and quality of research in exercise therapy for AIS rehabilitation. This necessitates international collaboration among authors to conduct clinical studies of high quality.

## 4.2. Hotspots analysis

The author clusters could help to identify historical, current, and future focal points within a particular field. As illustrated in **Figure 5**, a cohort of authors have contributed to the publication of 172 papers, with Negrini Stefano assuming the primary leadership role. The team of Negrini Stefano is concentrated on rehabilitation treatment of idiopathic scoliosis during growth, especially exerise therapy (25, 26). According to previous research, although AIS is diagnosed and treated globally, there are international variations in conservative treatment approaches. The typical approach in North America is to initially monitor their condition before considering bracing if the curvature worsens beyond 25°, for patients with remaining growth (27). Exercise therapy, comprising of both outpatient and inpatient rehabilitation, is recognized as the foremost treatment approach for minor spinal curves and individuals with a low risk of progression, a recommendation consistently emphasized by a plethora of clinicians, primarily based in Europe (28). Exerise therapy has shown to be effective in the rehabilitation of AIS in that exercise can reduce scoliosis progression in AIS patients, enhance the control of spinal nerve movement, play a positive role in cardiopulmonary function, and regulate psychological problems such as depression and anxiety (9). Bettany-Saltikov (15) has reported on the controversial use of exercises as a means of treating AIS. While there is a shortage of high-quality research that supports the efficacy of PSSE in the treatment of AIS, current evidence suggests that PSSE aids in stabilising spinal deformities, enhancing patients' life quality, functionality, disability, and pain, aesthetically improving deformities, and delaying progression. Nevertheless, there is inadequate proof to confirm the superiority of one physiotherapy technique over another. Further robust research is required before advocating the use of PSSE in clinical settings.

References displaying citation bursts indicate emerging subjects in a specific research area, due to the fact that these references have been frequently cited by researchers over the last few years (29). It is apparent that the prevailing areas of interest in the field of exercise therapy for AIS rehabilitation include investigating the therapeutic effects of exercise therapy and the application of PSSE for treating AIS, based on the primary research outlined in highly cited references (**Table 3**). These PSSE physiotherapy contain Schroth, Side Shift, Barcelona Scoliosis Physical Therapy School (BSPTS), SEAS, Functional Individual Therapy of Scoliosis (FITS) and Lyon, Dobomed, respectively.

## 4.3 Keywords and trend analysis

The analysis of keyword co-occurrence and burst clusters could aid in swiftly capturing the distribution and progression of hotspots within the domain of exercise therapy for AIS rehabilitation. Based on the results of the clustering analysis, it can be inferred that exercise therapy primarily targeted children who suffer from spinal deformities and low back pain. Furthermore, apart from the reliability and validity of stabilizing spinal deformity short-term and in long-term follow-up, further investigations have been carried out to examine the advantages of exercise therapy on the quality of life and children's performance in physical activities, and Schroth has been extensively researched and shown to be a successful treatment (15). As depicted by **Figure 7C**, the theme explored in the studies included in this research underwent three distinct stages of variation: Phase I (1999–2007), Phase II (2008–2013), and Phase III (2014–2023).

The literature from 2007 and before focussed primarily on brace rehabilitation for AIS, with less content directed toward exercise therapy. Since 2008, there has been a growing interest among researchers worldwide in adapting exercise therapy to enhance the condition of patients with AIS who are experiencing low back pain. In less severe cases, exercise can be the primary form of treatment while in more severe cases, it can be used as a supplementary treatment (30).

Following the emergence of exercise therapy in the 2014 s, various forms of exercise therapy (PSSE) and exercise-related proper nouns (Schroth exercises) have become available with an enhanced and more uniform research layout. In last 3 years, studies have predominantly confirmed the effectiveness of

TABLE 3 The main research contents of the 15 references with strong citations bursts.

| Rank | Strength | Main research content |
|---|---|---|
| 1 | 3.57 | The status quo of physical exercises as a treatment for adolescent idiopathic scoliosis. |
| 2 | 4.6 | Orthopaedic and Rehabilitation treatment of idiopathic scoliosis during growth guidelines. |
| 3 | 4.4 | The advances of physical exercises in the treatment of adolescent idiopathic scoliosis. |
| 4 | 6.15 | Discuss in detail seven major scoliosis schools and their approaches to Physiotherapy Scoliosis Specific Exercises to improve the conservative management of patients with idiopathic scoliosis. |
| 5 | 5.36 | A double-bilnded randomized controlled clinical trial study active self-correction and task-oriented exercises reduce spinal deformity and improve quality of life in subjects with mild adolescent idiopathic scoliosis. |
| 6 | 4.57 | The status quo of exercises for adolescent idiopathic scoliosis. |
| 7 | 4.15 | SEAS (Scientific Exercises Approach to Scoliosis): a modern and effective evidence based approach to physiotherapic specific scoliosis exercises |
| 8 | 4.08 | A single-bilnded randomized controlled clinical trial study the efficacy of three-dimensional Schroth exercises in adolescent idiopathic scoliosis. |
| 9 | 4.06 | A double-bilnded randomized controlled clinical trial study the effect of Schroth exercises improve the quality of life and muscle endurance in adolescents with idiopathic scoliosis. |
| 10 | 3.64 | A double-bilnded randomized controlled clinical trial study Schroth Physiotherapeutic Scoliosis-Specific Exercises lead to better cobb angle outcomes in adolescents with idiopathic scoliosis. |
| 11 | 3.49 | The current state of exercise protocols for adolescent idiopathic scoliosis. |
| 12 | 2.9 | Introduces the different "Schools" and approaches of physiotherapeutic scoliosis-specific exercises currently practiced and discusses their commonalities and differences. |
| 13 | 5.68 | Guidelines for the management of idiopathic scoliosis during growth in orthopaedic and rehabilitation settings. |
| 14 | 4.22 | A meta-analysis study effects of the Schroth exercise on idiopathic scoliosis |
| 15 | 3.11 | A single-bilnded randomized controlled clinical trial study core stabilization exercises versus scoliosis-specific exercises in moderate idiopathic scoliosis treatment. |

exercise therapy in treating patients with AIS through high-quality RCTs, exemplifying the current cutting-edge approach to AIS rehabilitation through exercise therapy.

## 4.4 Summary of exercise therapy intervention

The agreement that physical therapy can steady or decrease the magnitude of a spinal malformation or ameliorate functional levels in AIS has been established in recent decades (31, 32). Still, some barriers remain for exercise therapy to be successfully applied: (1) There remain several cognitive limitations to be addressed in order to comply with clinical standards and personalized treatment, particularly as many healthcare professionals lack expertise in distinguishing between generalized physiotherapy exercises and PSSE (33, 34). (2) Few studies on exercise therapy have prospectively registered their study protocols. This is expected to be replenished in future research in order to improve methodological standardization and rigor. Exercise therapy research should conform to standard reporting guidelines. This includes the prospective registration of detailed protocols and the use of suitable labelling for exercises, Schroth classification and therapists who are accredited. In addition, exercise names and descriptions should be provided according to their classification, along with details of therapy dosages, prescription methods and adherence (35, 36). (3) In the clinical practice of exercise therapy for the treatment of AIS, research has found that core stabilization exercises has a beneficial impact on the Cobb angle, trunk rotation, and quality of life for individuals with idiopathic scoliosis. The Schroth method has a bigger impact size than do core stabilization exercises. Additionally, these two approaches are compatible and can be combined to achieve better treatment outcomes for AIS patients in the future. While there appears to be clinically significant changes resulting from studies examining the effectiveness of certain PSSE exercise therapies and core stabilization exercises, the scientific validity of the present evidence remains inadequate. Studies of the DoboMed, FITS and Lyon methods have found similar limitations. The examined therapies were discovered to possess a poor overall standard of evidence for the Cobb angle, and an extremely low standard of proof for spine rotation angle and quality of life. To determine the real efficacy of PSSE physiotherapy as a treatment for mild to moderate AIS patients compared to no treatment, further randomised controlled trials are necessary. Furthermore, additional research is required to establish the optimum types of PSSE for varying curve types, as well as the most efficient methods (frequency and intensity) available (37–39). (4) Exercise compliance and follow-up investigation variables should also be considered when designing the subsequent study. Furthermore, future research should comprises methods for objectively monitoring exercise adherence and motor learning, such as group supervised exercise sessions, which is combined with telerehabilitation. A study has demonstrated that patients significantly favoured the weekly digital REDCap survey is preferred to the paper log (40, 41). Exercise therapy has been considered helpful in reducing scoliosis progression in AIS patients, enhancing the control of spinal nerve movement, and playing a positive role in cardiopulmonary function, even regulating psychological problems such as depression and anxiety (42). The results outlined in our paper offer valuable insights and encourage further investigation into the field of interest in order to facilitate more studies and clinical applications.

## 4.5 Strengths and limitations

Bibliometric studies of various aspects of AIS have been carried out by numerous scholars. One study summarised information published in scoliosis-related literature over a 10-year period from 2009 to 2018. A study summarized the publication information of scoliosis-related literature in the 10 years from 2009 to 2018. It analyzed former research hotspots in the field of scoliosis and predicted future areas of interest. Exercise therapy was not mentioned in the study, reflecting the fact that exercise therapy was not a hot topic in the overall scoliosis research field during this decade. Another bibliometric analysis includes the 100 most cited articles on idiopathic scoliosis (43). The results indicate that the evolution of the knowledge on idiopathic scoliosis has been through case reports and case series. The study did not address exercise therapy for scoliosis because of the relatively weak impact of exercise therapy-related articles in the overall field of scoliosis research (44, 45). Our study is the first review to summarise, from a bibliometric point of view, the ongoing publications and the forthcoming patterns of progression of exercise therapy for AIS, which can effectively guide researchers who express an interest in related research. To conduct a thorough and comprehensive evaluation, from the WoSCC database, this study gathered 172 relevant papers published in the last 24 years. Additionally, we utilised widely accepted bibliometric software, VOSviewer and Citespace, to conduct a quantitative assessment of exercise therapy in the area of AIS incorporating country, institution, author, journal, citation and keyword specific data.

Nevertheless, we need to acknowledge that we have failed to deliver. Firstly, the study's data was restricted solely to the WOS database. Thus, incorporating other databases such as PubMed and Scopus could yield a higher number of published documents and more comprehensive results. Secondly, we only included studies published in English. This may have resulted in an underestimation of papers published in non-English languages. Thirdly, the formulation of our study's strategy in this study was primarily based on a broad topic (TS), which may have resulted in the inclusion of irrelevant papers, ultimately causing some bias in the final results. It is possible that we have overlooked several studies on exercise therapy research if the authors did not explicitly state our inclusion criteria in the article topic. Finally, this study aims to provide an accurate representation of the current state of research in this field. Further systematic reviews or high-quality trials with a focused scope are warranted to refine both the specific therapeutic effects and applied techniques of exercise therapy that are necessary for rehabilitation following AIS, and to assist in the formation of clinical guidelines.

## 5 Conclusion

This bibliometric study offers a comprehensive examination of research pertaining to exercise therapy for AIS rehabilitation. Exercise therapy have important application prospects and research value in AIS rehabilitation. Over the last 24 years, there has been a notable increase in the quantity of research conducted in this field. China, Western Europe and North America have proved to be major contributors in terms of publications and overall citations received. However, there is still a need to improve the co-operation and communication between the different countries and institutions. Many journals possess a low Impact Factor, which calls for further consideration in the future. The co-occurrence analysis conducted by Negrini Stefano identified a predominant cluster focusing on the rehabilitation treatment of idiopathic scoliosis during the growing phase. Notably, in addition to expand study design, containing bigger numbers, multi-site institution studies, we should also pay attention to the restrict to factors that contribute to different risks of progression, that is, the inclusion of similar curves. These findings may enable future researchers to gain a deeper understanding of the current key areas and developments.

## Author contributions

RM: Writing – original draft, Writing – review & editing. QW: Writing – original draft, Writing – review & editing. ZX: Writing – original draft. LZ: Writing – review & editing. YW: Writing – review & editing. QG: Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1342327/full#supplementary-material

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# Global research hotspots and trends in non-surgical treatment of adolescent idiopathic scoliosis over the past three decades: a bibliometric and visualization study

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**Background:** In recent years, research on the non-surgical treatment of AIS has been increasingly conducted. To the best of our knowledge, this field doesn't yet have a comprehensive and structured pulse combing analysis. In order to provide inspiration and resources for subsequent researchers, we thus reviewed the literature studies on the non-surgical treatment of AIS from the previous thirty years and highlighted the hotspots and frontiers of research in this field.
**Methods:** Main using Citespace 6.1 software, the data from the core dataset of the WOS database pertaining to the non-surgical management of AIS from 1990 to 2022 was gathered, displayed, and analyzed.
**Results:** 839 papers in all were included in the literature. With 215 papers, the USA came in first place. Chinese Univ Hong Kong ranked first with 32 papers. Research hotspots are adolescent idiopathic spondylitis, Schroth-based physiotherapy-specific exercise efficacy, curve development, Cobb angle, TLSO brace-based clinical efficacy, quality of life, reliability, health-related quality of life questionnaires, finite element biomechanical models, follow-up, and clinical guidelines.
**Conclusion:** There aren't many studies that compare the clinical effectiveness of various non-surgical treatments, and because of variations in inclusion eligibility standards and outcome measures, these studies cannot be directly compared. In addition, the inconsistency of existing growth potential and progression risk assessment systems further affects comparative studies of clinical efficacy; it is recommended to establish primary assessment indicators centered on patient treatment outcomes (including appearance, disability, pain, and quality of life), as well as standardized scoliosis progression risk assessment criteria.

KEYWORDS

adolescent idiopathic scoliosis, bibliometric analysis, brace, physiotherapy scoliosis-specific exercise, rehabilitation studies published in Psychology/Education/Social, Sports/Rehabilitation/Sport

# Introduction

Adolescent idiopathic scoliosis (AIS) is a three-dimensional spinal deformity that develops in teenagers for unexplained causes, including serial abnormalities in the coronal, sagittal, and axial positions (1). The main diagnostic criterion is a Cobb angle of ≥10° in the coronal plane. It occurs in adolescents aged 10–17 years, with an overall prevalence of 1%–3% (2). When the Cobb angle was between 10° and 20°, the proportion of impacted girls to boys was roughly the same (1.3:1), increasing to 5.4:1 between 20° and 30° for the Cobb angle and to 7:1 for angular values above 30° (3, 4). Since adolescents are at the pinnacle of human development and growth, they are also the period when scoliosis progresses most rapidly. In addition to the effects on the spinal structure, there is also damage to the development and function of the adjacent organs of the spine, particularly the thorax and lungs. Treatment options are currently based on the treatment guidelines of the International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment (SOSORT) (5). Bracing is the preferred treatment option for children with Cobb's angle of 26°–45°AIS, and surgery is recommended for patients with Cobb's angles greater than 40°–45°. However, some children with AIS and their parents refuse surgery altogether and insist on wearing a brace. Recently published meta-analyses have shown that bracing can also stop the natural history of scoliosis curves from 40° to 60° (6). In recent years, a growing number of high-quality randomized controlled trials have demonstrated the positive short-term effects of Physiotherapeutic Scoliosis-specific Exercises (PSSE) in the treatment of AIS (7, 8), whereas the effectiveness of the long-term effects is unclear, and usually, PSSE is used as a support for the treatment of AIS. Adjunct to therapy. Currently, there is only one study that lists the top 100 citations for AIS in tabular form (9). In recent decades, despite the significant progress in treatment modalities and outcomes, there have been many debates, and the emergence of new theories and technologies has brought new opportunities and challenges to treatment. The use of coronal-deformity angular ratio (C-DAR), for example, eliminates the need for supine or supine lateral bending radiographs for determining the flexibility of scoliosis curves and is instrumental in planning appropriate treatment (10); FED therapy is statistically more effective than FITS therapy in improving outcomes for girls aged 11–15 years with AIS (11); automatic pressure-adjustable orthotics can improve wear quality and thus provide better biomechanical correction during the study period (12). Examining the hotspots and trends in research on non-surgical AIS treatment is crucial. As a result, this work is the first to map the scientific knowledge of research on this topic using visual research techniques by examining its hotspots, frontiers, and evolutionary trajectories, aiming to give an in-depth overview of the research status and developments in this subject, serving as a reference for researchers.

# Methods

## Search strategy and data retrieval

The Web of Science database's core data set search revealed that the initial research on this topic was first published in 1980, but the number of articles from 1980 to 1990 was very small. Only ten articles were retrieved, and the research literature gradually increased from 1990, so the search time started in 1990. The search time was In the advanced search section, the search formula "TS = (Idiopathic scoliosis) AND (Youth OR Teenager OR Teen OR Adolescent) AND (Therapy OR Ttreatment) NOT (Surgery OR Spinal fusio OR Spondylodesis OR Tether OR Anterior tethering OR Anterior spinal growth tethering)" retrieved a total of 862. Inclusion criteria were: (1) the topic of the study was the non-surgical treatment of AIS; (2) the publication time of the literature was from 1990 to 01-01 to 2022-12-31; (3) the type of the literature was Article and Review, and (4) the language of the literature was English. The exclusion criteria were: (1) the topic of the study was about surgery; (2) the type of the literature was conference abstracts, news, proofreading notices, conference papers, and retraction notices; and (3) the language of the literature was not English. Twenty-three articles were excluded based on inclusion-exclusion criteria. The study encompassed 839 articles, and Figure 1 displays the process flowchart in question.

## Literature selection

The literature was read separately by two evaluators. The article's title and abstract served as the basis for the first screening, which was followed by a second screening based on the criterion for inclusion and exclusion. If there is any dispute, a third assessor reads it and decides on the final go.

## Statistical analysis methods

For the bibliometric analysis in this study, five scientometric programs—CiteSpace (6.1R6, 2023), VOSviewer (1.6.18, 2022), R-Studio based R-bibliometrix (4.6.1, 2023), Pajek (5.16, 2022), and Scimago Graphica (1.0.26, 2022)—as well as Microsoft Excel were employed. The software programs CiteSpace, created by Professor Chen C, and VOSviewer, created by Professors Van Eck and Waltman. With the use of the progressive knowledge domain visualization technique, patterns and trends in the body of scientific publication may be identified and visualized by visualizing the most referenced and important literature, areas of knowledge domain competence, and the creation of research themes (13). According to the pertinent information in the article, the data pertaining to the literature is determined using the CiteSpace visualization program (14). The counting method of VOSviewer is full count. In order to perform the function of

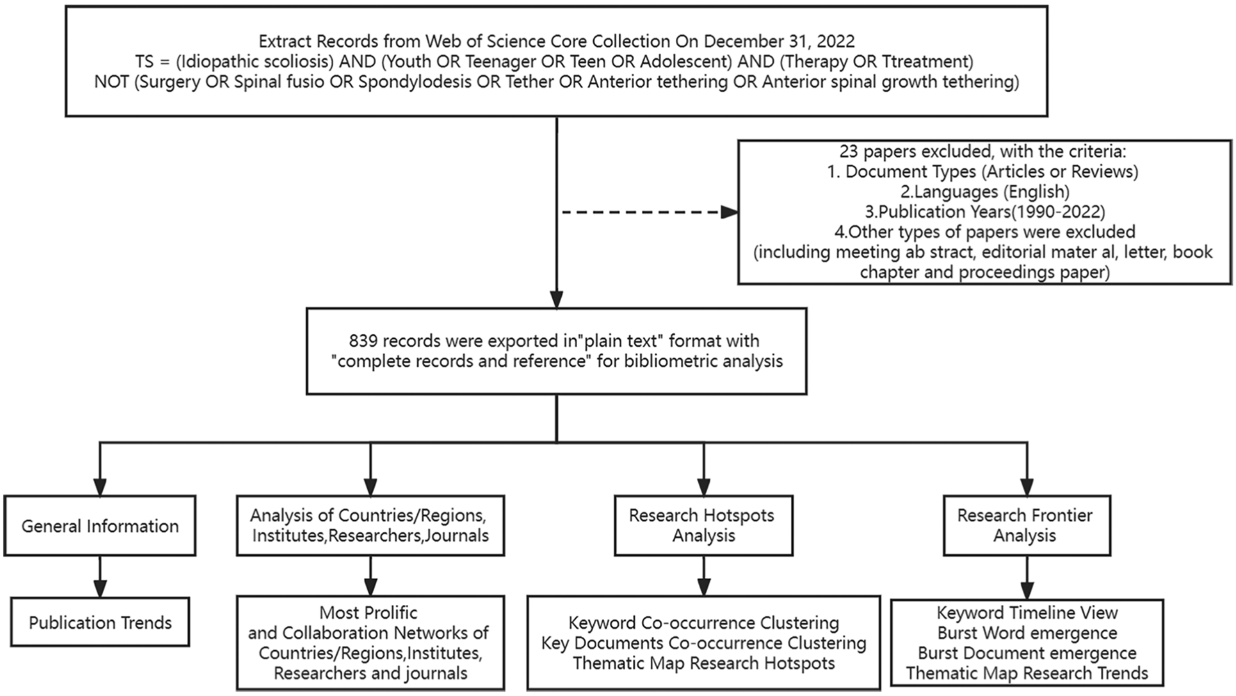


FIGURE 1
Workflow diagram.

assessing the present situation and forecasting the future, the CiteSpace emergent word detection function is utilized to investigate the keyword surge change rate and produce the table of keywords with a high rate of mutation (15). Tools like Citespace and VOSviewer are primarily employed to visualize and study the knowledge structure and development patterns of scientific research on a particular topic (16). Additionally, sub-clusters may be formed from the basic structure of the literature network by employing cluster analysis to find research sub-domains or academic hotspots (17). By using overlap analysis with the software programs R-bibliometrix, VOSviewer, and CiteSpace, it is possible to identify research frontiers that might lead to important discoveries in the next years.

Citespace visual analysis software parameters and data analysis were selected as follows to complete the collection of data through the inclusion and exclusion criteria of the literature records, and then use Web of Science to export the collected data in "plain text" format, including "complete records and references," every 500 records to generate a file, the file is renamed in the form of "download," and then loaded into the input folder of the Citespace program, and finally started the visualization and analysis. In the parameter settings of CiteSpace visualization software, firstly, convert the input file to the output file through the Data tab, and then select the corresponding project and data file in the project execution operation area. In the time selection area, the time span is set to 1990–2022, the time scale is set to 1 year, the filtering criterion is set to "Top N," and the threshold is set to 50. In the Pruning option area, "Pathfinder" and "Pruning sliced networks" were selected as the clipping method to simplify the network structure and highlight important features. For node types, select country, journal, author, institution, cited author, keyword, and cited literature for co-occurrence or cluster analysis, click the "GO" option after selecting nodes, then draw a visual map, and finally fine-tuning the color scheme and font size according to the content of the map, etc. The counting method of VOSviewer is full count.

# Results

## Bibliometrics of publication output

Ultimately, 839 pertinent articles were located, and Figure 2A displays the yearly publishing output in various nations. From 1990 to 2022, the number of research articles on non-surgical management of AIS typically increased with time, with explosive growth in 2007 and 2008, when the number of publications was nearly twice that of 2006, and a trough in 2016, when the number of publications was only 60%. Overall, the US has the highest annual publication volume and is the country with the earliest start and longest duration of research in this field; China has the second highest annual publication volume, with a late start but rapid development in this field. Especially in recent years, it has increased significantly year by year and is already the country with the highest percentage of annual publications. With the help of a polynomial fit analysis, the year of publishing and the total number of articles were shown to be significantly correlated [the coefficients of determination (R2) for all papers, articles, reviews, and randomized controlled trials were 0.9283, 0.9152, 0.8032, and 0.7281, respectively]. We predict that in

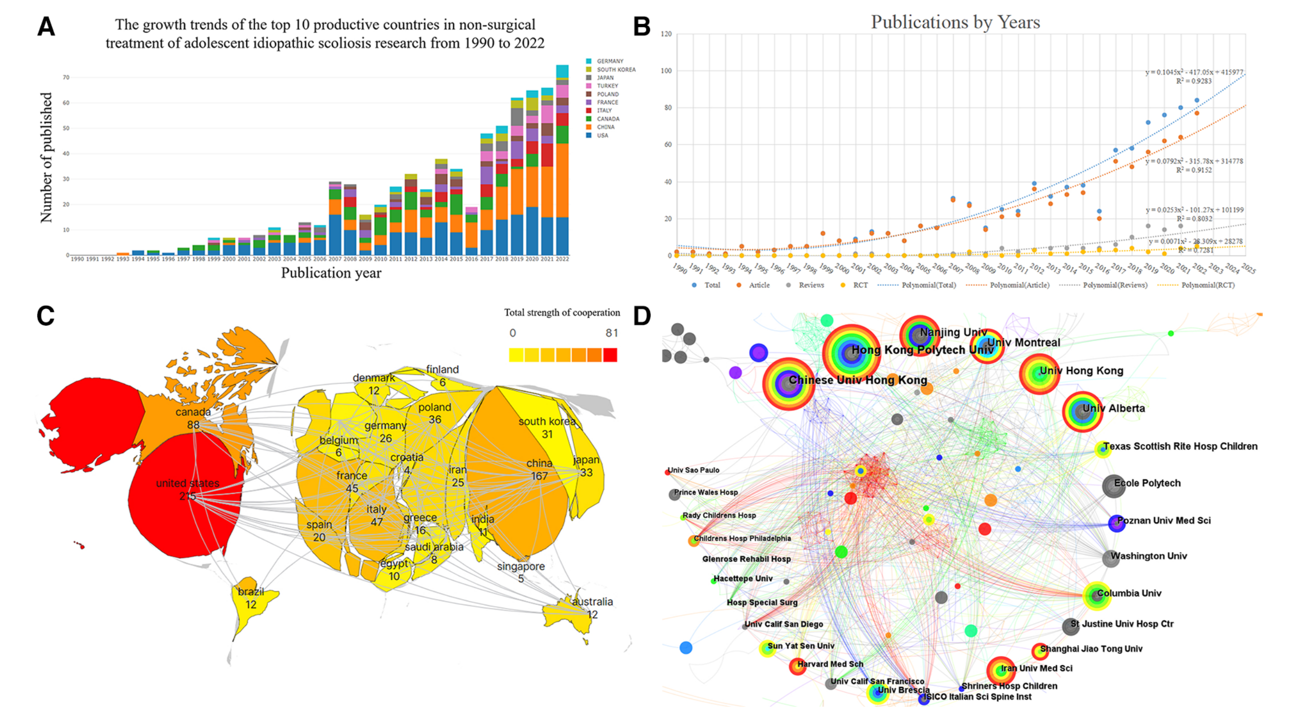


FIGURE 2
(A) Bibliometric analysis of the WoS core database output. The number of publications on non-surgical treatment of AIS studies published in different countries has changed year by year from 1990 to 2022. (B) Trends in publications in the field of non-surgical AIS research and corresponding polynomial fit curves. (C) Filled plot of the collaborative bibliometric analysis of countries in the field of non-surgical AIS research, with darker colors representing more publications and connecting lines representing collaborative relationships. (D) Institutional co-occurrence network diagram for non-surgical treatment of AIS. The circle in the chart indicates the volume of articles issued, the larger the circle indicates the more articles issued by the institution, the thickness of the purple outer circle represents the centrality of the institution, and the connecting line represents the existence of cooperation or co-occurrence.

TABLE 1 Top 10 high-impact countries and institutions for non-surgical AIS research.

| Country | Number of articles issued (articles) | Centrality | Institution | Number of articles issued | Centrality |
|---|---|---|---|---|---|
| USA | 215 | 0.25 | Chinese Univ Hong Kong | 32 | 0.05 |
| Peoples R China | 167 | 0.27 | Hong Kong Polytech Univ | 31 | 0.01 |
| Canada | 88 | 0.15 | Univ Montreal | 26 | 0.05 |
| Italy | 47 | 0.05 | Nanjing Univ | 26 | 0 |
| France | 45 | 0.09 | Univ Alberta | 23 | 0.02 |
| Turkey | 38 | 0.01 | Univ Hong Kong | 23 | 0.01 |
| Poland | 36 | 0.08 | Texas Scottish Rite Hosp Children | 17 | 0.05 |
| Japan | 33 | 0 | Ecole Polytech | 17 | 0.01 |
| South korea | 31 | 0 | Washington Univ | 16 | 0.06 |
| Germany | 26 | 0.1 | Poznan Univ Med Sci | 16 | 0.03 |

2025, there will be around 98 papers published, comprising about 81 articles, 17 reviews, and 5 RCTs, as illustrated in Figure 2B, based on the polynomial fit analysis. In general, the growth of the orthopedics and rehabilitation medicine fields has prompted more study. Despite the annual increase in publications, it is evident that there are still not enough highly qualified RCT trials.

## Countries or regions and cooperation networks

The generated visualization includes a total of 53 nations or regions, of which 13 had ≥20 articles. Information about the top 10 nations in regard to the number of papers is indicated in Table 1. It is known from the figure that all three of these nations have developed strong scientific partnerships with other nations, see Figure 2C.

## Research institutions and cooperation networks

1,165 institutes in all have published studies in this field, among which 11 institutions published ≥15 articles. Information on the top ten organizations in regard to the quantity of articles published is shown in Table 1. With other universities, these three institutions have developed strong research partnerships, see Figure 2D.

## High-impact authors and collaborative networks

Of the 3,472 authors included in the visualization atlas, 15 have published more than 10 articles. Information on the top ten scholars regarding the number of articles and the top ten scholars regarding citation frequency is displayed in Table 2. Figures 3A–C show that there is some collaboration amongst author teams, with this collaboration being more pronounced among the high-yielding writers and lacking among authors with a high centrality in the literature.

## Literature research hotspot disciplines

The distribution of research hotspots in the collected 839 documents was analyzed, and the literature was then categorized into 25 groups. From the data, it can be seen that the field has been widely researched and developed in the fields of orthopedics, clinical neurology, and rehabilitation medicine, Figure 3D.

## High-impact publications and citation patterns

All 839 of the papers found in the search came from 262 publications. The top ten rankings of the number of publications and the ranking of the H-index are shown in Table 3, Figure 3E. According to the VOSviewer journal co-citation study, the top three citation frequencies were Spine (793 times), Journal of Bone and Joint Surgery-American Volume (587 times), and European Spine Journal (561 times), see Figure 4A. Journals that publish in this field of study currently have a significant impact. The biplot overlay's colored trails connecting journal groupings highlight the link between citing and cited journals in terms of citations, illuminating the citation trajectory and information flow (18). The colored paths indicate that studies published in Neurology/Sports/Ophthalmology journals usually cite studies published in Psychology/Education/Social, Sports/Rehabilitation/Sport, Health/Nursing/Medicine, and Molecular/Biology/Genetics. In each cluster, Figure 5 provides more details on the typical cited and cited journals. For example, the most representative journals in the Psychology/Education/Social cluster are the Spine, Arthroscopy, European Spine Journal, and Spine Journal. The most representative journals in the Sports/Rehabilitation/Sport group are the Journal of Bone and Joint Surgery-American Volume, Journal of Pediatric Orthopaedics, Clinical Orthopaedics and Related Research, and Journal of Bone and Joint Surgery-Beitish Volume.

# Keyword visualization analysis

## Hotspot analysis of keyword co-occurrence clustering

The summary of research hotspots and the investigation of research trends depend heavily on keyword analysis (16). Figures 4C,D, Table 4 show the keywords with the highest co-occurrence. Research hotspots over the time period are indicated by terms with high centrality and frequency. According to an examination of common keywords, the primary topics of this field's research were adolescent idiopathic scoliosis, idiopathic scoliosis, quality of life, reliability, curve progression, children, girl Cobb angle, Boston brace, natural history, brace, brace treatment, deformity, spine, Milwaukee brace, follow up, etc. Figure 5A exhibits the keyword co-occurrence clustering graph in this domain. A total of 17 groups were constructed using the typical LLR algorithm, and the keyword clustering analysis indicated that the more aggregation there was, the more homogeneous the relationships between studies were (19). The cluster number and the cluster size are inversely connected, with cluster number 0 representing the largest cluster and so on. The keyword clusters from #0 to #16 were Boston brace, thoracic scoliosis, reliability, health-related quality of life, brace treatment, conservative treatment, severe scoliosis, melatonin, back pain, osteopenia, muscular stabilization, proliferation, curve flexibility, chronic pain, thoracolumbar junction Except for cluster #16, and all clusters were intertwined and closely related to each other.

TABLE 2 Top 10 high-impact authors for non-surgical AIS studies.

| Author | Country | Institution | Number of articles issued | Author | Frequency of citations | Country |
|---|---|---|---|---|---|---|
| Labelle, Hubert | Canada | Univ Montreal | 27 | Negrini S | 54 | Italy |
| Qiu, Yong | China | Gulou Hospital | 24 | Weinstein SL | 49 | USA |
| Aubin, Carl-Eric | Canada | Montreal Polytech Univ | 16 | Kuru T | 22 | Turkey |
| Lou, Edmond | Canada | Glenrose Rehabilitation Hospital | 14 | Berdishevsky H | 20 | USA |
| Negrini, Stefano | Italy | Scientific Spine Institute | 14 | Thompson RM | 17 | USA |
| Newton, Peter O | USA | San Diego Children's Hospital | 14 | Dunn J | 17 | USA |
| Parent, Stefan | Canada | Santo Justin Hospital | 13 | Negrini S | 17 | Italy |
| Zhu, Zezhang | China | Gulou Hospital | 13 | Nachemson AL | 15 | Sweden |
| Li, Ming | China | Changhai Hospital | 12 | Schreiber S | 15 | Canada |
| Zaina, Fabio | Italy | Scientific Spine Institute | 12 | Park JH | 15 | Korea |

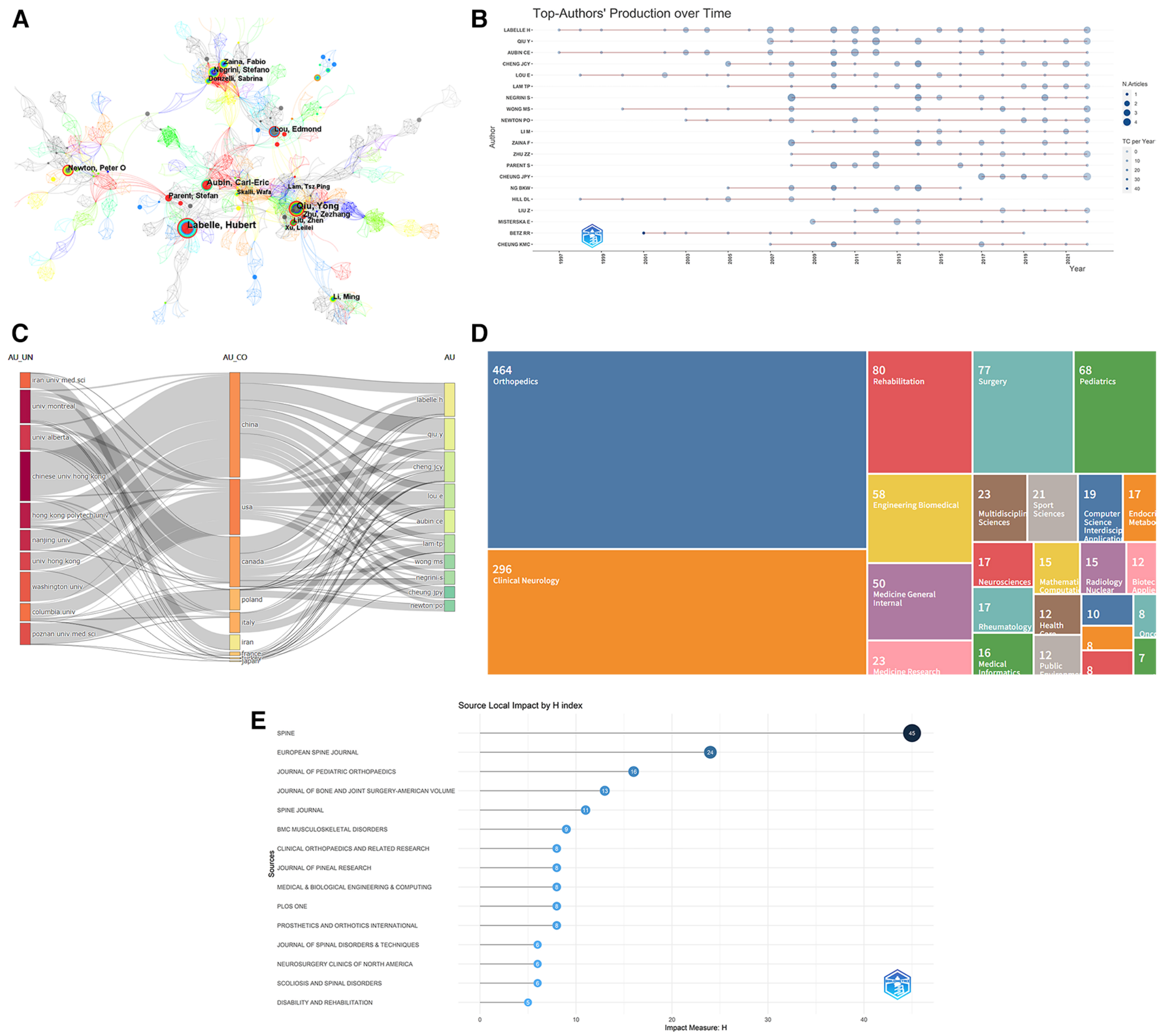


FIGURE 3
(A) Author co-occurrence network diagram for non-surgical treatment of AIS. The circles in the chart indicate the volume of posts, the larger the circle the more the author posts, the thickness of the purple outer circle represents the author's centrality, and the connecting line represents the existence of cooperation or co-occurrence. (B) Plot of high-yield authors of non-surgical treatment of AIS over time. The top twenty most prolific researchers in the field and their publications. The larger the node, the more literature is published. The darker the color, the more citations. The color represents the number of publications, and the color represents the number of citations per year. (C) The three-field plot showing the knowledge flow for non-surgical treatment of AIS. (D) Distribution of hot research disciplines in the literature of non-surgical treatment of AIS. (E) H-index of high-impact journals for non-surgical AIS research, 1990–2022.

Keyword co-occurrence and cluster analysis yielded adolescent idiopathic spondylitis, quality of life, reliability, curve development, girls, Cobb angle, Boston brace, and brace treatment as current research hotspots in the field.

## Analysis of research trends in keyword timeline views

A timeline representation of the literature that the WOS database has filtered allows users to see the temporal dynamics of the clustered keywords, Figures 5B,C. A strong clustering structure is shown by the clustering Modularity ($Q$ value) = 0.65 > 0.5; a persuasive clustering structure is also indicated by the average cluster Silhouette ($S$ value) = 0.8707 > 0.5 (20). From 1990 to 1995, the keywords nonoperative treatment, fusion, term follow up, idiopathic scoliosis, back pain, and pulmonary function received extensive attention; from 1995 to 2000, milwaukee brace, girl, follow up, boston brace, curve progression, adolescent idiopathic scoliosis, brace treatment, natural history, spine, quality of life lumbar spine, rib cage, cotrel dubousset instrumentation, growth, and adolescent

TABLE 3 Status of high-impact journals for non-surgical AIS research, 1990–2022.

| Journal name | Total number of articles | Total number of applications | Average number of citations | IF (2022) | JCR (2022) | H-index |
|---|---|---|---|---|---|---|
| Spine | 122 | 816 | 6.69 | 3.241 | Q1 | 45 |
| European Spine Journal | 77 | 305 | 3.96 | 2.721 | Q2 | 24 |
| Journal of Bone and Joint Surgery-American Volume | 16 | 236 | 14.75 | 6.558 | Q1 | 13 |
| Journal of Pediatric Orthopaedics | 25 | 124 | 4.96 | 2.537 | Q2 | 16 |
| Prosthetics and Orthotice International | 10 | 88 | 8.8 | 1.672 | Q3 | 8 |
| Medical & Biological Engineering & Computing | 10 | 66 | 6.6 | 3.079 | Q2 | 8 |
| Disability and Rehabilitation | 9 | 51 | 5.67 | 2.439 | Q1 | 5 |
| Clinical Orthopaedics and Related Research | 10 | 49 | 4.9 | 4.755 | Q1 | 8 |
| Plos One | 11 | 45 | 4.09 | 3.752 | Q2 | 8 |
| Spine Journal | 20 | 42 | 2.1 | 4.297 | Q1 | 11 |

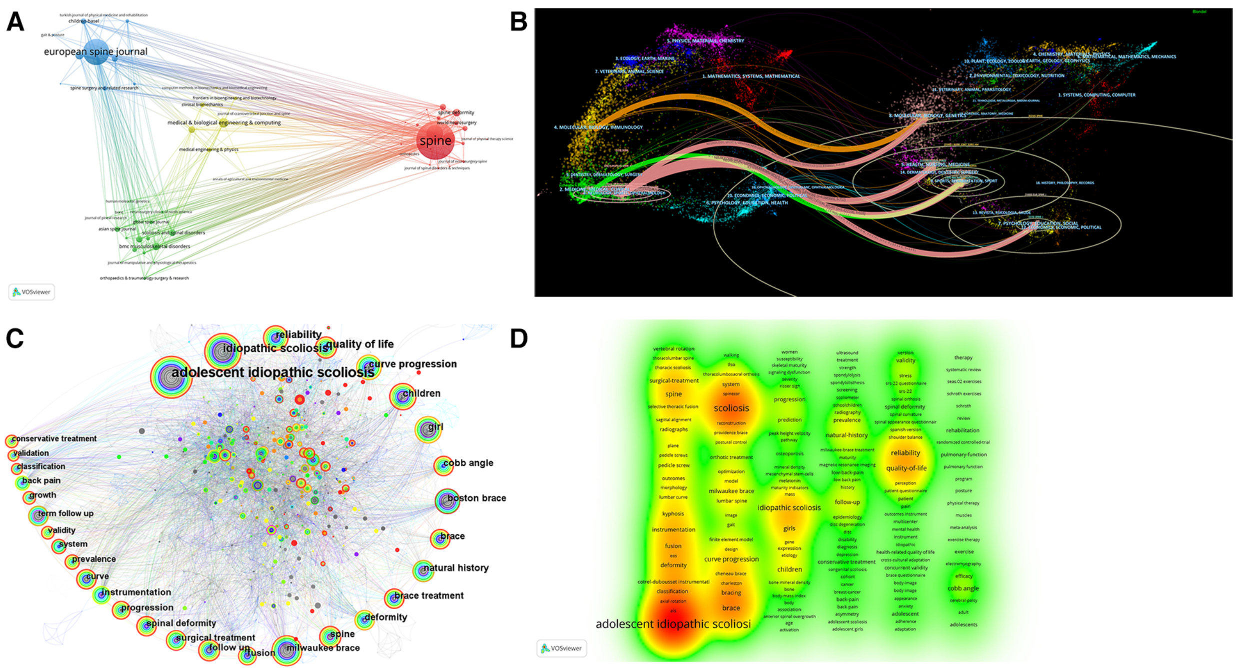


FIGURE 4
(A) Cluster visualization of journal co-citation analysis generated based on VOSviewer software. Each node represents a journal, and the size of each circle is determined by the journal's co-citation. (B) Biplot overlay of cited and cited journals in the field of non-surgical AIS research. Cited journals are on the left, cited journals are on the right, and the line represents the citation status. (C) Keyword co-occurrence map for non-surgical treatment of AIS. The circles in the figure represent keywords, and the larger the circle indicates the higher the frequency of the keyword. The dark to light colors represent the years from far to near, the connecting lines represent the links between the keywords, and the thickness of the purple outer circle represents the centrality of the keywords. (D) VOSviewer-based clustering view of non-surgical treatment AIS keywords.

keywords get attention; from 2000 to 2005 management, system, Instrumentation, spinal deformity, fixation, Cobb angle, classification, radiograph, reliability, progression, children, conservative treatment, curve, and selection keywords get attention; 2005–2010 deformity, exercise, efficiency, validation, validity, peak height velocity, prevalence, and questionnaire keywords get attention; 2010–2015 criteria, construct, interobserver reliability, health-related quality of life, spinal curvature, randomized controlled trial, risk, association, mesenchymal stem cell, school screening program, predictor, gene become new terms; 2015–2020 providence brace, succe, impact, brace questionnaire, magnetic resonance imaging, coronal balance, and expression become new terms; 2020–2022 schroth exercise, skeletally immature patient, 3D printing, mri migratio, postural balance, chondrocyte become new terms. The field is predicted to continue to delve into research around the Schroth exercise, Providence brace, skeletally immature patients, brace questionnaires, and magnetic resonance imaging.

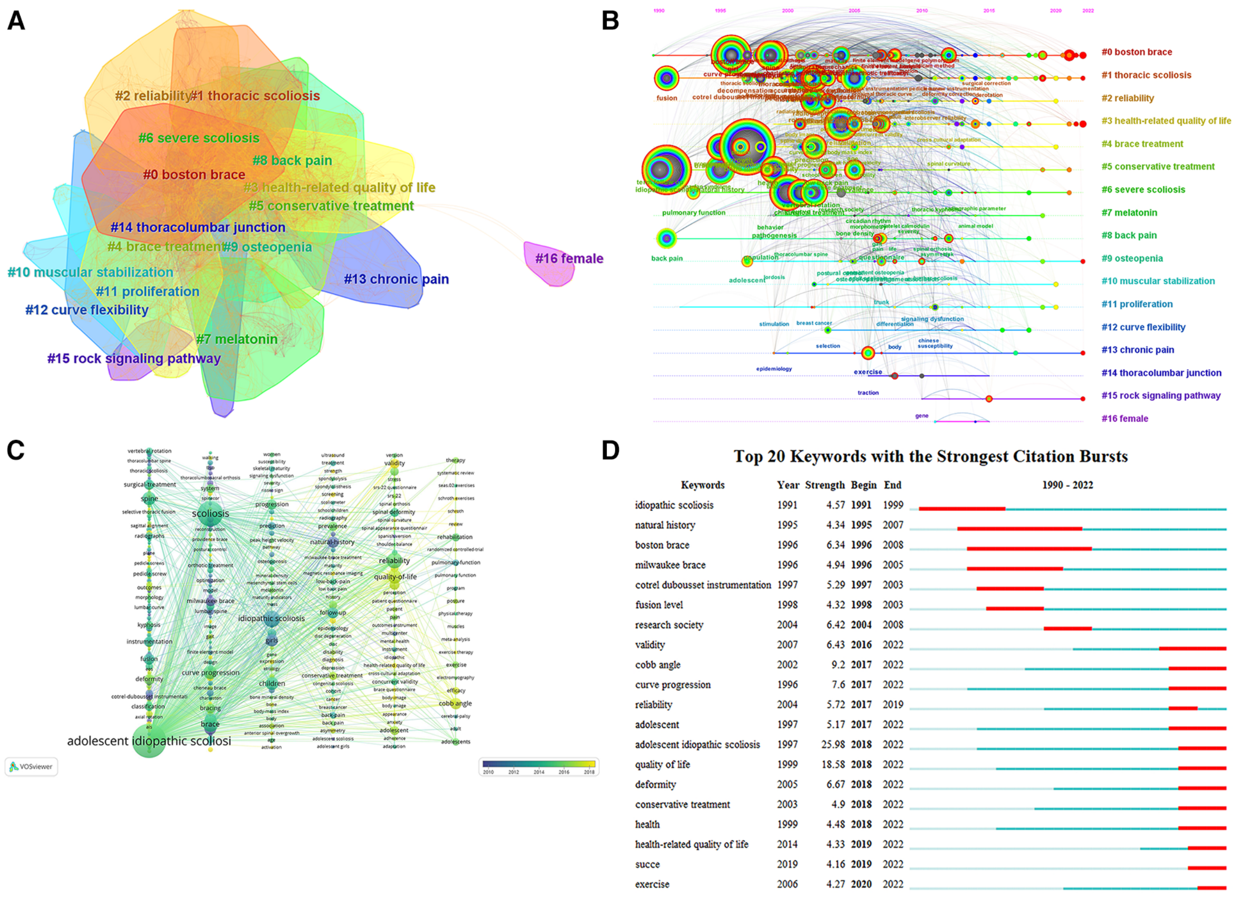


FIGURE 5
(A) Keyword co-occurrence clustering map for non-surgical treatment of AIS. The dark to light colors represent the years from far to near, and the connecting lines represent the links between keywords. (B) Keyword timeline view of non-surgical treatment of AIS. The circles in the figure represent keywords, and the larger the circle indicates the higher the frequency of keywords. The dark to light colors represent the years from far to near, the connecting lines represent the links between the keywords, and the thickness of the purple outer circle represents the centrality of the keywords. (C) VOSviewer-based keyword time view of non-surgical treatment AIS. (D) Keyword emergence map for non-surgical treatment of AIS. The figure of "▬" is a 1-year keyword mark, and "▬" is the emergence of the year of the word.

## Analysis of research trends in emergent word emergence

The emerging words are words that are often used throughout time, showing hotspots and patterns, as seen in Figure 5D. The strongest mutation is "adolescent idiopathic scoliosis" (25.98), followed by "quality of life" (18.58), and in third place is "Cobb angle" (9.2). The keywords with the highest level of mutation during the previous three years include "health-related quality of life" (2019–2022), "succe" (2019–2022), and "exercise" (2020–2022). With the help of Burst emergence analysis and the dynamic temporal evolution of keywords, we may gain a comprehensive understanding of current and upcoming research trends in the field, where the emergent words are validity, Cobb angle, curve progression, deformity, conservative treatment, health, health-related quality of life, succe, and exercise have persisted to date and are likely to remain research hotspots.

# Visual analysis of key documents

## Analysis of research hotspots in key literature

In this field, 839 documents were found, having a total citation frequency of 5,837, and the top 10 rankings of highly cited and highly centralized literature are shown in Figure 6A and Tables 5, 6. In order to identify the research hotspots and evolutionary trajectories in the field of non-surgical treatment of AIS, it is necessary to analyze the literature with the highest citation frequency and co-cite important nodes. They can be divided into three groups depending on the type of study: clinical pilot studies, clinical observational studies, and reviews. Citation frequency 2nd, 3rd, and 9th are clinical experimental studies, centrality 1st, 2nd, 4th, 5th, 6th, 9th, 10th and citation frequency 5th and 8th are clinical observational studies, and

TABLE 4 Non-surgical treatment of AIS high-frequency keywords and centrality TOP10.

| Keywords | Frequency | Keywords | Centrality |
|---|---|---|---|
| Adolescent idiopathic scoliosis | 495 | Bone mineral density | 0.13 |
| Idiopathic scoliosis | 120 | Children | 0.08 |
| Quality of life | 108 | Classification | 0.08 |
| Reliability | 83 | Girl | 0.07 |
| Curve progression | 75 | Follow up | 0.07 |
| Children | 69 | Prevalence | 0.07 |
| Girl | 62 | Prediction | 0.07 |
| Cobb angle | 59 | Cobb angle | 0.06 |
| Boston brace | 57 | Boston brace | 0.06 |
| Natural history | 56 | Milwaukee brace | 0.06 |

centrality 3rd, 7th, 8th and citation frequency 1st, 4th, 6th, 7th, 10th are review studies. The highly cited literature in clinical pilot studies mainly involved clinical efficacy studies with Boston (TLSO) brace as the main study (citation frequency 2nd studies) and physical therapy-specific exercise efficacy studies with Schroth as the main study (citation frequency 3rd and 9th studies). The highly cited literature in clinical observational studies is mainly about the positive effects of brace therapy (citation frequency 5th and 8th studies) and the questionnaire reliability and validity of HRQOL, mainly SRS-22, SRS-7, BSSQbrace and SAQ scales (centrality 1st, 2nd, 4th, 5th, 6th, and 10th studies). The highly cited literature in the review category was mainly research guidelines published by SOSORT (citation frequency 1st and 7th studies), clinical practice (centrality 7th study), Meta-analysis (citation frequency 10th study), and finite element analysis (centrality 8th study). For the assessment of treatment outcomes, most of the questionnaire scores of Cobb angle, angle of trunk rotation (ATR), and HRQOL were mainly used as tests. Changes in questionnaire score values for Cobb's angle, ART, and HRQOL were compared through a certain period of follow-up to illustrate the therapeutic effects of bracing and exercise interventions for AIS. By using bracing and exercise therapy for AIS patients with different curve amplitudes and skeletal maturity, the findings of every clinical study demonstrated that the use of bracing and exercise therapy had an interrupting or slowing effect on the progression of AIS, and the questionnaire score values for Cobb angle, ART, and HRQOL were significantly different from those of the observation-only control group. There are few comparative studies on the clinical

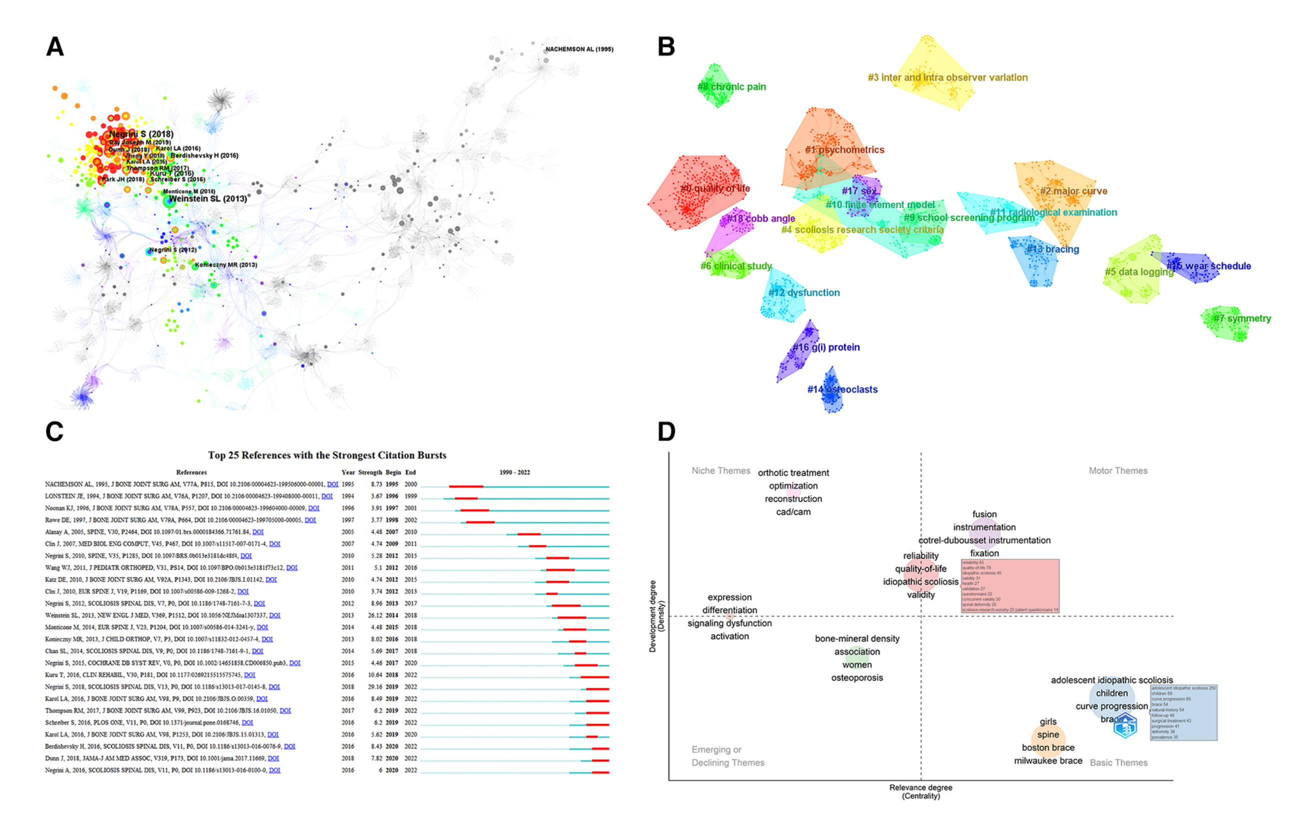


FIGURE 6
(A) Co-cited literature network for non-surgical treatment of AIS. The circles in the figure represent cited literature (showing the first author's name), and the larger the circle, the more citations the literature has received. The thicker the circle is, the more citations the literature has received. The line represents co-citations among the literature, and the thickness of the purple outer circle represents the centrality of the literature. (B) Clustering of co-cited literature for non-surgical treatment of AIS. The dark to light colors represent the years from far to near, and the connecting lines represent the links between keywords. (C) Emergence of key literature on non-surgical treatment of AIS. Note: The "▬" in the figure are the years in which the unexpected citations appeared, and the "▬" in the figure are the nodes in which the number of citations for the unexpected citations suddenly rose, arranged in chronological order from top to bottom. (D) Thematic map of non-surgical treatment AIS.

TABLE 5 Top 10 ranking of cited literature centrality for non-surgical treatment AIS.

| Author | Centrality | Year | Title | Periodicals |
|---|---|---|---|---|
| Danielsson AJ (21) | 0.16 | 2001 | Health-related quality of life in patients with adolescent idiopathic scoliosis: a matched follow-up at least 20 years after treatment with brace or surgery | Eur Spine J |
| Bago J (22) | 0.14 | 2004 | The Spanish version of the SRS-22 patient questionnaire for idiopathic scoliosis: transcultural adaptation and reliability analysis | Spine |
| Altaf F (23) | 0.14 | 2013 | Adolescent idiopathic scoliosis | Bmj-Brit Med J |
| Caronni A (24) | 0.13 | 2014 | Improving the measurement of health-related quality of life in adolescent with idiopathic scoliosis: the SRS-7, a Rasch-developed short form of the SRS-22 questionnaire | Res Dev Disabil |
| Verma K (25) | 0.12 | 2010 | Demographic factors affect Scoliosis Research Society-22 performance in healthy adolescents: a comparative baseline for adolescents with idiopathic scoliosis | Spine |
| Botens-Helmus C (26) | 0.12 | 2006 | The reliability of the Bad Sobernheim Stress Questionnaire (BSSQbrace) in adolescents with scoliosis during brace treatment | Scoliosis Spinal Dis |
| Hresko MT (27) | 0.09 | 2013 | Clinical practice. Idiopathic scoliosis in adolescents | New Engl J Med |
| Clin J (28) | 0.09 | 2010 | Correlation between immediate in-brace correction and biomechanical effectiveness of brace treatment in adolescent idiopathic scoliosis | Spine |
| Bunge EM (29) | 0.09 | 2007 | Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment | Eur Spine J |
| Carreon LY (30) | 0.09 | 2011 | Spinal appearance questionnaire: factor analysis, scoring, reliability, and validity testing | Spine |

TABLE 6 Top 10 ranked frequency of cited literature for non-surgical treatment AIS.

| Author | Frequency of citations | Year | Title | Periodicals |
|---|---|---|---|---|
| Negrini S (5) | 54 | 2018 | 2016 SOSORT guidelines: orthopaedic and rehabilitation treatment of idiopathic scoliosis during growth | Scoliosis Spinal Dis |
| Weinstein SL (31) | 49 | 2013 | Effects of bracing in adolescents with idiopathic scoliosis | New Engl J Med |
| Kuru T (7) | 22 | 2016 | The efficacy of three-dimensional Schroth exercises in adolescent idiopathic scoliosis: a randomised controlled clinical trial | Clin Rehabil |
| Berdishevsky H (32) | 20 | 2016 | Physiotherapy scoliosis-specific exercises—a comprehensive review of seven major schools | Scoliosis Spinal Dis |
| Thompson RM (33) | 17 | 2017 | Brace Success Is Related to Curve Type in Patients with Adolescent Idiopathic Scoliosis | J Bone Joint Surg Am |
| Dunn J (34) | 17 | 2018 | Screening for Adolescent Idiopathic Scoliosis: Evidence Report and Systematic Review for the US Preventive Services Task Force | Jama-J Am Med Assoc |
| Negrini S (35) | 17 | 2012 | 2011 SOSORT guidelines: Orthopaedic and Rehabilitation treatment of idiopathic scoliosis during growth | Scoliosis Spinal Dis |
| Nachemson AL (36) | 15 | 1995 | Effectiveness of treatment with a brace in girls who have adolescent idiopathic scoliosis. A prospective, controlled study based on data from the Brace Study of the Scoliosis Research Society | J Bone Joint Surg Am |
| Schreiber S (37) | 15 | 2016 | Schroth Physiotherapeutic Scoliosis-Specific Exercises Added to the Standard of Care Lead to Better Cobb Angle Outcomes in Adolescents with Idiopathic Scoliosis—an Assessor and Statistician Blinded Randomized Controlled Trial | Plos One |
| Park JH (38) | 15 | 2018 | Effects of the Schroth exercise on idiopathic scoliosis: a meta-analysis | Eur J Phys Rehab Med |

efficacy of bracing and exercise therapy on AIS. The choice of treatment according to the patient's curve amplitude, skeletal maturity, and curve type, including different types of bracing, different exercise therapies, or reasonable use in conjunction with each other, should be complementary and mutually reinforcing treatments.

Of note is a large multicenter randomized controlled trial (BrAIST) in cited frequency study 2th, which demonstrated that brace treatment was successful in stopping Cobb's angle from increasing to the surgical threshold (usually defined as ≥50°). This study has high confidence that bracing is the only strategy proven to be effective for the non-surgical treatment of AIS. In addition, in the cited frequency 5th study, the investigators compared for the first time different curve patterns between the main thoracic and main lumbar spine for the Boston thoracolumbosacral brace (TLSO) brace for AIS to investigate the efficacy of different curve patterns for the brace for AIS. Prior to the publication of this study, curve amplitude and skeletal maturity were considered to be key factors in determining the efficacy of the brace in treating AIS. However, as the study continued, it was found that even with strict adherence to the bracing protocol, between 10% and 24% of the curves still developed (39), and in patients with untreated scoliosis, the shape of the curve was linked to the risk of progression (40, 41). Therefore, this study confirms that TLSO treatment of AIS in the lumbar curve interrupts or slows the progression of scoliosis better than in the thoracic curve. Furthermore, the positive effect of Schroth physiotherapy scoliosis-specific exercise (PSSE) on slowing or interrupting the progression of AIS has been supported by randomized controlled trials (cited frequency 3rd, 9th studies), and several studies have selected different types of exercise protocols for Schroth. The Schroth best practice program is the most effective therapy for treating PSSE, according to Borysov and Mogiliantseva (42). However, in the Cited Frequency 10th study, which compared multiple Schroth exercise protocol types and exercise duration as a treatment modality for patients with Cobb's angle 10°–88° AIS, it was shown that exercise duration is a more important factor, no matter how fancy and well-designed the PSSE program. Patients should exercise for at least one month to have satisfactory clinical outcomes. Also, the Schroth exercise was more beneficial for AIS patients with Cobb angles of 10°–30° compared to AIS patients with Cobb angles greater than 30°.

Among the questionnaire studies of HRQOL, five papers selected the Scoliosis Research Society 22-item questionnaire SRS-22 (centrality 2nd, 4th, and 5th studies), the Bad Sobernheim Stress Questionnaire (BSSQbrace) (centrality 6th study), and the Spinal Appearance Questionnaire. The SRS-22 patient questionnaire has been shown to be an effective tool for the clinical assessment of patients with AIS, especially for patients who may undergo surgical interventions (43), and the widespread use of the SRS-22 in non-English-speaking countries requires its cross-cultural adaptation. The 2nd study of centrality translated and culturally adapted the SRS-22 questionnaire into Spanish, and testing demonstrated adequate internal consistency and excellent reproducibility of the Spanish version of the SRS-22 patient questionnaire. The SRS-22 questionnaire has been widely used to assess patients with scoliosis, but no studies have assessed how demographic differences in normal, unaffected adolescents affect SRS-22 scores to determine a comparative baseline for AIS. The Centrality 5th study derived baseline values for each item of the SRS-22 by assessing 450 normal adolescents. The Centrality 4th study concluded by Rasch analysis that the SRS-22 did not meet the basic measurement requirements and that the SRS-22 was affected by a severe ceiling effect when used for the first assessment of the AIS. Therefore, the SRS-7 questionnaire was modified and optimized on the basis of the SRS-22, with the advantage that it is an interval scale. BSSQbrace is a new tool to assess the stress experienced by scoliosis patients while wearing a brace, and the reliability of the BSSQbrace questionnaire was tested and validated in the centrality 6th. The Centrality 10th study described the factor analysis and scoring of the SAQ and assessed its psychometric properties.

## Analysis of research hotspots for co-occurrence clustering of key literature

On the basis of co-cited literature, cluster analysis can identify subfields that stand in for important areas of research (44). The average cluster Silhouette ($S$ value) = 0.8733 > 0.5, suggesting a compelling cluster, while the clustering Modularity ($Q$ value) = 0.94 > 0.5, showing a strong cluster structure (20). A total of 16 groups were constructed using the typical LLR algorithm, and the keyword clustering analysis indicated that the more aggregation there was, the more homogeneous the relationships between studies were (19). The cluster number and the cluster size are inversely connected, with cluster number 0 representing the largest cluster and so on, Figure 6B. observer variation, scoliosis research society criteria, data logging, clinical study, symmetry, chronic pain, school screening program, finite element model, radiological, examination, dysfunction, bracing, osteoclasts, wear schedule, g(i) protein, sex, Cobb angle. The field's research hotspots in terms of clustering order were exercise therapy, meta-analysis, PSSE and biomechanical models, psychometrics, major curves, interobserver differences, and Scoliosis Research Association standards; the field's research trends in terms of lighter colored clusters were quality of life, exercise therapy, meta-analysis, PSSE, biomechanical models, Cobb's angle, clinical studies, psychometrics, wear time, gender, etc.

## Analysis of research trends emerging from key literature

Burst citations are important works of literature that have been repeatedly mentioned over time, highlighting hotspots and trends, Figure 6C. The Web of Science database evaluated the 25 burst citations with the most co-cited literature, the one with the highest burst intensity was the new SOSORT 2016 guideline published by Negrini S in 2018, which focuses on idiopathic scoliosis background, descriptions of conservative treatments for different populations and flow charts for clinical practice, as well as a literature review and recommendations on assessment, bracing, PSSE and other conservative treatments (29.16); followed by Weinstein SL's 2013 randomized controlled trial and intention-to-treat trial study finding that Boston-type TLSO significantly reduced the high-risk curve progression in patients with AIS to surgical threshold, with hours of brace wear being significantly and positively associated with treatment success (26.12); in third place, Kuru T's randomized controlled trial study in 2016 found that the 3D Schroth exercise program was superior to the home exercise group and control group in the outpatient treatment group with physiotherapist supervision, particularly in terms of scoliosis angle, rotation angle, lumbar asymmetry (lumbar-elbow distance) and maximum hump height. In addition, a progression of scoliosis was observed in the control group that did not receive any treatment (10.64). According to the order in which the literature emerged, it can be broadly split into four categories: the first part focuses on studies exploring the clinical efficacy of Milwaukee braces for the treatment of AIS (1994–2002) (45–47); the second part focuses on popular theoretical studies on the pathogenesis of AIS (48) and a comparison using finite element models of the biomechanical three-dimensional effectiveness of various brace designs for the treatment of AIS (2003–2012) (49, 50); the third part of the guidelines in this field mainly describes the background, epidemiology, clinical practice process, assessment, bracing, literature review of conservative therapies such as PSSE, and recommendations (5, 35, 51) and investigate the effect of patient compliance on the clinical efficacy and HRQOL of AIS treated with braces (2013–2017) (39, 52); the fourth section is focuses on clinical efficacy studies of Schroth-based PSSE for AIS (7, 32, 37) and exploring the importance of early screening for AIS and how to efficiently detect and monitor scoliosis development during growth (2018-present) (34, 53), of which the third and fourth parts of the literature burst intensity has continued to date, and on the basis of a careful reading of the high burst citations, future research trends can be foreseen as standardization of research methods to standardize the effects of conservative treatment, the impact of patient compliance on clinical outcomes, clinical efficacy studies of PSSE, comparative efficacy studies of different Schroth types, the importance of early screening, effective modalities of early screening, the study on the success of different braces and the type of scoliosis curve, optimal use of PSSE with different braces, optimal Cobb angle for various PSSE.

### Research hotspots and trend analysis of thematic maps

The thematic maps generated based on the R-Bibliometrix package are displayed as a two-dimensional matrix. Thus, the first quadrant refers to motor topics, which are both crucial and quite well established; the second refers to niche topics, which are developed but not crucial for the domain at hand; the third refers to marginal topics, which have not been adequately established and may have just emerged and may be about to fade away; and the fourth refers to basic topics, which are crucial for the domain yet not well established, Figure 6D. Depending on which quadrant the critical bubbles are in, it can be hypothesized that fusion, orthopedic treatment, reliability, quality of life, questionnaires, effectiveness, and CAD/CAM are the hot spots for research in this area, while the themes of bone mineral density, women, osteoporosis, expression, differentiation, and signaling dysfunction may develop or vanish in the future, while in children, progression of curves, braces, girls, natural history, Boston brace, and Milwaukee brace thematic directions will require more in-depth study in the future.

## Discussion

### Bibliometric characteristics of non-surgical treatment of AIS

Bibliometrics is a scientific method first used by Alan Pritchard in 1969 (54). It helps to track data relevance and predict future boundaries. Bibliometric analysis and its visualization can effectively support the integration of information and enable researchers to understand the scope of relevant studies. In this study, a thorough bibliometric analysis of international publications on non-surgical AIS research from 1990 to 2022 was carried out. A total of 839 papers with 5,837 citations were published worldwide in the last 30 years, maintaining an overall trend of gradual increase. These results demonstrate the continued interest of researchers in the field. The two leading nations in terms of the quantity and centrality of publications on the topic are America and China, indicating that they have the greatest impact on the field. The institution with the highest number of publications is Chinese Univ Hong Kong (32), followed by Hong Kong Polytechn Univ (31). The most published scholar was Labelle, Hubert, University of Montreal, Canada (27 articles), followed by Qiu, Yong, Gulou Hospital, Nanjing University, China (24 articles). According to yearly publishing volume and trends, the US and China will keep holding the top two spots. The journal with the highest number of publications, H-index, and citations is SPINE (122 articles, 45 points, 793 citations). Data on key authors can help investigators find potential collaborators. The team represented by Labelle H, Clin J, and Phan, P, scholars from the University of Montreal, Canada, whose research areas are finite element biomechanical analysis studies of TLSO brace for AIS and studies related to the evaluation of computer-aided tools to improve brace design; the team centered on Qiu Y, Xu, L, and Cheng JC from Gulou Hospital, Nanjing University, China, whose research areas are susceptibility polymorphisms on the severity of the curve and the effectiveness of bracing in AIS patients, and the comparative study of gender differences in curve patterns, radiological characteristics, and susceptibility genes in patients with AIS; the team centered on Negrini S, Donzelli, S and Zaina, F from the Italian Scientific Spine Institute, whose areas of research were the study of the effectiveness study of the Scientific Exercise Approach to Scoliosis (SEAS) in patients with AIS at high risk of progression and the Rasch consistency study of HRQOL-related questionnaires. The team centered on Lou E, Hill DL, and Raso, James V, University of Alberta, Canada, whose members are working on the impact of patient compliance and quality of brace treatment on AIS outcomes based on a TLSO brace equipped with a wireless data collection system.

### Diversity of options and controversial efficacy of non-surgical treatment of AIS

Currently, there are two main methods of non-surgical treatment for AIS, namely, bracing and physiotherapy scoliosis-specific exercises. SOSORT recommends a non-surgical treatment schedule that selects both modalities based on Cobb angle and skeletal maturity, as shown in Table 7. A total of 14 common braces were summarized according to the characteristics of various braces for AIS, including origin, fabrication method, wearing time, curve type, mechanism of action, opening direction, symmetry, stiffness, and optimal angle, Lyon, ART (55), Boston, Rigo-Chêneau, Gensingen Brace, Milwaukee, Charleston, Providence, Wilmington, SpineCor (56), OMC (Osaka Medical College) (57), Sforzesco (58), PASB (Progressive Action Short Brace) (59), Pressure-adjustable (12), as shown in Table 8. Eight main modalities were summarized based on the main subtypes of physiotherapeutic scoliosis-specific exercises, motor intervention characteristics, classification systems, breathing techniques, and recommended

TABLE 7 Recommended plan for non-surgical treatment of AIS.

| Adolescent | Very Low | | Low | | Moderate | | Severe | |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Min | Max | Min | Max | Min | Max |
| Risser 0 | Obs6 | Obs3 | Obs3 | SSB | HTRB | FTRB | TTRB | Su |
| Risser 1 | Obs6 | Obs3 | Obs3 | SSB | PSSE | FTRB | FTRB | Su |
| Risser 2 | Obs8 | Obs6 | Obs6 | SSB | PSSE | FTRB | FTRB | Su |
| Risser 3 | Obs12 | Obs6 | Obs6 | SSB | PSSE | FTRB | FTRB | Su |
| Risser 4 | NO | Obs12 | Obs12 | SIR | PSSE | FTRB | FTRB | Su |
| Risser 4–5 | NO | Obs12 | Obs12 | SIR | PSSE | FTRB | FTRB | Su |

Cobb degrees (Very Low: Cobb angle <10° +hump; Low: 10–20; Moderate: 21–35; Moderate to severe: 36–40; Severe: 41–50).
Obs 12/8/6/3, Observation every 12/8/6/3 months; SSB, Scoliosis soft braces; PSSE, Physiotherapeutic scoliosis-specific exercises; HTRB, Halftime rigid brace; NTRB, Night-time Rigid Bracing (8–12 h); SIR, Inpatient rehabilitation; FTRB, Full-time Rigid bracing (20–24 h) or cast; Su, Surgery.

brace use, Lyon (60), Schroth (61), Scientific Exercise Approach to Scoliosis (SEAS) (62), Barcelona Scoliosis Physical Therapy School (63), Dobomed (64), Side-Shift (65), Functional Individual Therapy of Scoliosis (66), FED-Method (67), as shown in Table 9. However, based on characteristics such as the volume of publications in this field of research, some trends can already be seen: In an effort to replace the most invasive braces, innovative alternative concepts have been created, with TLSO replacing Milwaukee a few years ago (68). Recently, casting has also been replaced by Sforzesco and ART braces (55). Not all of these new concepts have proven their efficacy. Efforts to gradually improve and develop some of the more established concepts continue, such as the Cheneau, Boston, or Lyon braces. However, there are also recently developed concepts, such as the OMC (57), Sforzesco (58), PASB (59), Pressure-adjustable (12), ART (55), and SpineCor (56) braces.

Bracing treatment affects sagittal spine pelvic parameters in adolescent AIS patients, particularly in thoracic kyphosis and lumbar lordosis (69, 70). A recent comparative study noted approximately equal rates of surgery and success between SpineCor and TLSO, with the main difference being the presence of significant advantages in health-related quality of life for the SpineCor brace, primarily in pain, self-image and functional activity subgroups of the SRS-22 questionnaire (56). A prospective randomized controlled trial with standardized follow-up according to the SRS noted a significantly higher rate of curve progression with the SpineCor brace compared to the rigid brace. Switching to a rigid brace controlled further curve progression in most patients who had previously failed with a SpineCor brace (71). The effectiveness of the SpineCor brace has not been confirmed in the literature. A systematic review found a final acceptance rate of 18% with TLSO braces, 31% with Charleston braces, and 23% with Milwaukee braces (72). Another systematic review found final acceptance rates of 12%–17% for Boston braces, 27%–41% for various braces (Boston-Charleston-TLSO), 17%–25% for nocturnal braces (Providence or Charleston braces); and 25%–33% for TLSO or Rosenberger braces; Wilmington brace 19%–30% (73). Nocturnal bracing is most effective for single lumbar/thoracolumbar curves of less than 35 degrees (74). Regardless of starting curve size and skeletal maturity, the Boston brace was found to be more effective than the Milwaukee brace by Montgomery's research (75). However, the Climent JM study concluded that Milwaukee brace-treated patients outperformed Boston braces, TLSO braces, and Charleston braces in overall Quality of Life Profile for Spine Deformities (QLPSD) scores, back flexibility, and psychosocial functioning (76). The Babaee T study found comparable differences between Milwaukee braces and thoracolumbosacral orthoses in negatively affecting the quality of life in adolescents (77). A curvilinear regression occurs with the wearing of a thoracolumbosacral orthosis and correlates with patient-reported good outcome scores (78). The traditional Lyon brace and the recently developed Sforzesco brace were contrasted in the Negrini study (58). The Sforzesco brace had better radiographic, sagittal, aesthetic, and patient recovery results than the Lyon brace. In a prospective case study, De Mauroy discovered that the ART brace produced better imaging findings than the Lyon brace, and this pattern continued after 6 months and 1 year (79). Although the ART brace demonstrated greater in-branch correction of the lumbar curve, Zaina's comparison of the short-term imaging outcomes of two superrigid braces (the Sforzesco brace and ART brace) revealed equal results (55). A two-center randomized controlled trial noted that the Pressure-adjustable brace provided better biomechanical correction over the study period by improving the quality of wear compared to the conventional brace (12). The Aulisa AG study showed that PASB-based treatment was associated with a better quality of life compared to Lyon braces (59). PASB is very effective in correcting thoracolumbar curves due to its specific biomechanical effect on vertebral body modeling (80).

However, none of these studies are directly comparable cross-sectionally due to differences in inclusion-exclusion criteria and primary endpoints used to define outcomes. It is currently unable to definitively say which brace is superior to the other, and the Scoliosis Research Society (SRS) and SOSORT are actively working to standardize AIS brace studies to address the existing controversy over the efficacy of different types of braces. Therefore, it is recommended that "patient-centered outcomes (including appearance, disability, pain, and quality of life)" be used as the primary indicator for assessing effectiveness and that uniform criteria be established for studies related to the non-surgical treatment of patients with AIS. Aiming to ensure comparability of clinical efficacy studies of different non-surgical treatments for AIS, to resolve the controversial issue of clinical efficacy of the support, and to create good conditions for later analysis of secondary reviews based on the literature base.

TABLE 8 Commonly used braces for non-surgical treatment of AIS and their characteristics.

| Brace | Origin (Developer) | Build method | Indicated/ preferred hours of wear | Curve type | Mechanism of action | Opening | Construction envelope | Brace rigidity | Optimal indications |
|---|---|---|---|---|---|---|---|---|---|
| Lyon | France (Stagnara) | Customized | Full time | Single and double | Three point | Anterior | Symmetric | Rigid | Cobb angle ≥20° for fast growth period and ≥30° for slow growth period,11–13 years. |
| ART | France (de Mauroy) | Customized | Full time | Single and double | Coupled motion | Anterior | Asymmetric | Very Rigid | Cobb angle ≥ 20° |
| Boston | USA (Miller, Hall) | Prefabricated/ Customized | Full time | Single and double | Three point | Posterior | Symmetric | Rigid | The parietal vertebra is located at T8 ~ L2 |
| Rigo-Chêneau | Germany (Chêneau, Rigo) | Customized | Full time | Single and double | Three point | Anterior | Asymmetric | Rigid | Cobb angle 25°–45°, Upper terminal vertebrae below T5. |
| Gensingen Brace | Germany (Weiss) | Customized | Full time | Single and double | Three point | Anterior | Asymmetric | Rigid | Cobb angle ≥ 40° |
| Milwaukee | USA (Blount) | Prefabricated/ Customized | Full time | Upper thoracic, single and double | Elongation. Induced initiative | Posterior | Symmetric | Rigid | Top vertebrae at T7 and above |
| Charleston | USA (Reed, Cooper) | Customized | Nighttime | Single and double | Three point | Anterior | Asymmetric | Rigid | Unspecified |
| Providence | USA (D'Amato, McCoy) | Customized | Nighttime | Single and double | Three point | Anterior | Asymmetric | Rigid | Cobb angle ≤ 35° |
| Wilmington | USA (McEwen) | Customized | Full time | Single and double | Three point | Anterior | Symmetric | Rigid | Unspecified |
| SpineCor | Canada (Colliard, Rivard) | Prefabricated/ custom fit | Full time | Single and double | Movement | dynamic strapping | Symmetric | Soft braces | Unspecified |
| OMC (Osaka Medical College) | Japan (Onomura) | Customized | Full time | Single and double | Three point | Posterior | Asymmetric | Rigid | Cobb angle 25–50°, and an apex of caudad to T7. |
| Sforzesco | Italy (Negrini, Marchini) | Customized | Full time | Single and double | three-dimensional elongation | Anterior | Symmetric | Very Rigid | From T3 to the lumbosacral region. |
| PASB (Progressive Action Short Brace) | Italy (Aulisa) | Customized | Full time | Only for Thoracolumbar and lumbar | Elastic deformation principle | Posterior | Symmetric | Rigid | Unspecified |
| Pressure-adjustable | Canada (Lou) | Customized | Full time | Single and double | Three point | Posterior | Symmetric | Rigid (Pressure adjustable) | Unspecified |

TABLE 9 Main characteristics of the eight main physiotherapeutic scoliosis-specific exercises.

| System Name | Main fractions | Description of the exercise intervention | Classification system | Breathing technique | Brace used |
|---|---|---|---|---|---|
| Lyon (France) (60) | 1. Chaotic<br>2. linear | Physical therapy includes 3D activities of the spine, iliopsoas angle activities (lumbar scoliosis), patient education and activities of daily living, including sitting posture correction. | Ponseti<br>Lenke | RAB | 3D ARTbrace |
| Schroth (Germany) (61) | 1. Thoracic scoliosis<br>a. Thoracic spine only.<br>b. Thorax opposite the lumbar region.<br>c. Lumbar and hip protrusion to the other side.<br>2. Lumbar scoliosis<br>a. Lumbar only with hip protrusion to the other side.<br>b. Thoracic and hip protrusion to the other side.<br>c. Lumbar and thoracic curve with hip in the middle.<br>3. Sagittal plane deformity including increased or decreased thoracic lordosis and increased lumbar lordosis or loss of anterior lordosis. | The principles followed are auto-extension (detorsion), deflection, rotation, rotary breathing and stabilization. Mirror monitoring allows the patient to synchronize corrected motion and postural perception with immediate visual feedback. | Katharina Schroth's Body Blocks | RAB | 3D Chêneau brace |
| Scientific Exercise Approach to Scoliosis (SEAS) (Italy) (62) | 1. Single curve<br>2. Hyperbola<br>3. These curve patterns are described according to the location of the top of the curve—cervicothoracic, thoracic (top above T12-L1), thoracolumbar (top at T12-L1) and lumbar (top below T12-L1), and combined double origin. | SEAS exercises are based on auto-correction and stabilization. The two main goals of the exercises are: to improve the main spinal function, i.e. spinal stability. Improvement of eventual impairments that may be emphasized by the initial assessment | Ponseti | RAB | 3D Sibilla brace (Cobb <30°)<br>Sforzesco brace (Cobb 30°–50°) |
| Barcelona Scoliosis Physical Therapy School(BSPTS) (Spain) (63) | 1. sagittal plane deformities, such as high cervical spondylosis, inverted back and flat back.<br>2. structural scoliosis in the main thoracic region, which can be subdivided into: three-curve scoliosis pattern (3C), four-curve scoliosis pattern (4C), and non-3-non-4 scoliosis pattern (N3N4).<br>3. group 1–2 is defined as lumbar or thoracolumbar curves with a straight thoracic spine. | The correction principles follow overall postural alignment and the application of high intensity forces generated in the body, including isometric tension, dilation and specific breathing. | Katharina Schroth's Body Blocks and Manuel Rigo's radiological classification | RAB | 3D Rigo Chêneau brace |
| Dobomed (Poland) (64) | No traditional classification system, individualized treatment plan according to the patient's condition. | The DoboMed method focuses on deepening the thoracic kyphosis, performed in a closed kinetic chain and developed on the symmetrically positioned pelvic and scapular girdle, followed by active stabilization of the corrected position and endured as a postural habit. | Dobomed | Specific Rotational angular breathing in a "phased-lock" respiration technique | 3D Cheneau brace |
| Side-Shift (United Kingdom) (65) | Type I is any curve pattern that can be corrected by moving the trunk beyond the coronal midline to the opposite side of the scoliosis curve (a very flexible curve). 2. Type II is any curve pattern that can be corrected to the coronal midline. 3. III is any curve pattern that cannot be corrected to the midline. | The technique of the lateral shift approach is based on intensive trunk flexion training. This is an active form of auto-correction in which the patient is taught to move the trunk laterally towards the pelvis in the opposite direction to the convexity of the principal curvature | King | RAB | Milwaukee |
| Functional Individual Therapy of Scoliosis(FITS) (Poland) (66) | No traditional classification system, individualized treatment plan according to the patient's condition. | The FITS approach represents a functionally independent treatment for scoliosis. It mainly includes the detection and elimination of myofascial | NOTCS | 3D corrective breathing into the concavities | 3D Cheneau brace |

(*Continued*)

TABLE 9 Continued

| System Name | Main fractions | Description of the exercise intervention | Classification system | Breathing technique | Brace used |
|---|---|---|---|---|---|
| | | restrictions and the construction of a new series of corrective postural patterns in daily activities | | | |
| FED-Method (Fixation, Elongation, Derotation) (Spain) (67) | There is no traditional classification system, and the focus is on young patients whose motor sensory skills have not yet fully developed and on patients with high curvature resulting in motor sensory impairment. | The FED method is described as three-dimensional stabilization of the spine with simultaneous extension and de-rotation. It is performed using a complex mechanical treatment device that allows corrective forces to act at the level of the scoliosis curve | NOTCS | RAB | FED device (passive-assisting/active-assisting) |

Classification system: physical therapy with braces classification system.
NOTCS, No traditional classification system; RAB, Rotational angular breathing.

## Major factors affecting the efficacy of non-surgical treatment of AIS

At the time of brace initiation, the magnitude of the curve and skeletal maturity play a considerable role in predicting the success of the brace. However, as research continued, it was found that even with strict adherence to the bracing protocol, between 10% and 24% of the curves still developed (39). The risk of curve development is even greater in some patients, so the effectiveness of bracing is influenced by a variety of factors. Among the main factors are immediate correction rate, coronal deformity angular ratio, patient compliance, quality of brace treatment, initial Cobb angle, type of scoliosis, skeletal maturity, and body mass index. The factors that have a greater impact on the non-surgical treatment of AIS are the quality of brace treatment (the amount of pressure exerted by the brace) and patient compliance (the duration of brace wear).

Without controlled pressure and wear time, no meaningful conclusions about the effectiveness of the support can be drawn. Several techniques have been applied to address these issues. For example, temperature sensors (81), pressure switches (82), and force sensors (83) have been used to monitor brace pressure and/or wear time. Methods such as these have shown that the actual brace wear time is often lower than the wear time reported by the patients themselves (84). Studies with BrAIST Level I evidence suggest that brace therapy has a dose-effect relationship, i.e., as brace wear time increases, the treatment effect increases. The treatment success rate in the brace group was 90%–93%, with a mean brace duration of 12.9 h/d. The treatment success rate was 41% when the wearing time of the brace was 0–6 h per day, which was lower than the treatment success rate of the observation group (48%) (31). In addition, another prospective study also found a 100% success rate for patients wearing the brace for at least 14 h per day and a 66.7% success rate for patients wearing the brace for 2 to 10 h per day (85). Worryingly, it has been shown that brace pressure varies considerably with patient activity and posture (86). Even with increased wear time, brace pressure decreases over time (87). The pressure of the brace decreases over time, even with increased wear time (78). Therefore, even honest and compliant patients may not receive optimal results from brace therapy. The immediate rate of correction (IBC) is the most important predictor of brace efficacy, and the Xu study concluded that brace treatment is likely to fail when the IBC is below 10% (88). In contrast, a systematic review by Van de Bogaart concluded that IBC was the strongest predictor of brace success (89). The disparity between the findings of the research mentioned above may be explained by the use of various methodological standards to gauge the strength of the evidence. Coronal deformity angular ratio (C-DAR) is obtained by dividing the largest Cobb angle by the number of vertebrae involved in the same curve in the frontal plane. Lang et al. (10) used C-DAR for the first time to assess the effectiveness of wearing a 6-week short-term Gensingen brace in treating patients with AIS and found that with an initial C-DAR value of <5 and an IBC rate of >50%, the brace therapy may be successful. However, if the value is >6 and the IBC rate is <50%, the effectiveness of the brace will be reduced. Babaee T et al. (90) used C-DAR to assess the outcome of patients with AIS who wore a 2-year long-term Milwaukee brace and found that 63.9%, 29.2%, and 16.9% of patients had an IBC ≥ 50% at C-DAR <5, 5–6, and >6, respectively, and that the success rate of the brace was 89.2% for patients with an IBC ≥ 50%. That is, C-DAR can be used as a predictor of short- and long-term outcomes of AIS brace therapy. Although the initial Cobb angle and growth stage play a major role in the advancement of scoliosis in the natural disease history, it's not apparent if the initial Cobb angle is associated with the success of brace treatment. One of the three main risk factors for brace treatment failure, according to some academics, is an initial Cobb angle greater than 30° (91). The initial Cobb angle, however, has been linked to treatment success rather than failure, according to a systematic study (89). A systematic review has shown that the type of scoliosis can be a predictor of the success of brace therapy (88). The Thompson study showed that a higher proportion of patients with primary thoracic curvature progressed to a Cobb angle of ≥50° with similar initial Cobb angles and daily brace wear times (92). In contrast, some studies have also not identified the type of scoliosis as a significant factor affecting prognosis (93). The most commonly used skeletal maturity parameter is the Risser rating, and studies have found lower Risser scores in patients who failed brace therapy (88). The Karol study's findings revealed that patients with a Cobb angle

>30° had a 63.0% and 32.4% risk of surgery for Risser grade 0 and open and closed acetabular "Y" cartilage, respectively (94). The Hawary study identified low skeletal maturity as a risk factor for failure of brace treatment (91). Body mass index (BMI) is an important indicator to evaluate the nutritional status of the body. A review of studies suggests that there is limited evidence supporting the association of low BMI with orthotic failure, while the evidence supporting the association of high BMI with orthotic failure is controversial (89). The Karol study found that low-weight patients wore the brace for the longest time per day (up to 15.7 h/d) and had better compliance, but they had the highest risk of surgery (60% surgery rate); overweight and obese patients wore the brace for less time per day (11.7 h/d and 9.0 h/d, respectively), while their surgery rates were 28.6% and 55.6%, respectively (95). The efficacy of bracing in the treatment of AIS is definite and has been widely used in the clinic, but the limitations of bracing treatment need to be recognized. Clinical treatment should focus on improving patient compliance, reducing complications, and providing psychological support to patients.

## Diversity of AIS progress risk assessment methods

With strict nonoperative treatment, some patients still end up having to undergo surgery for scoliosis progression, partly due to inaccurate assessment of the risk of progression in AIS patients during the development of nonoperative treatment plans (96). Therefore, the prognosis of AIS patients should be improved by developing different treatment strategies based on an accurate assessment of the risk of scoliosis progression in clinical care. There are numerous methods for assessing growth potential, each with its own strengths and weaknesses. In children who have been diagnosed, assessment of growth potential is essential to determine the stage and approach to treatment. The assessment of growth potential and risk of scoliosis progression in AIS patients reported in the literature is multidimensional and includes mainly skeletal system assessment and anthropometric assessment.

Skeletal system assessment indexes are clinically important in predicting growth potential and scoliosis progression in AIS patients. The commonly used skeletal system assessment indexes in clinical practice include Y-triangle cartilage, Risser's sign, Tanner-Whitehouse III scoring system, digital skeletal age (DSA) scoring system, distal radius and ulnar (DRU) scoring system, The degree of ossification of the Y-triangle cartilage is an important parameter for early prediction of the risk of scoliosis progression in AIS patients. The ossification of the Y-triangle cartilage mostly begins at Risser's sign level 0 and is, therefore, more closely related to the peak height velocity (PHV). It was found that the Y-triangle cartilage was open or incompletely closed in most patients with AIS at the time of PHV, suggesting that open Y-triangle cartilage predicts that the patient is still located before PHV and has a higher risk of scoliosis progression (97). The Risser's sign assesses the degree of ossification of the iliac crest epiphysis and is the most commonly used indicator of bony maturity in the assessment of the risk of scoliosis progression in AIS patients. The lower the Risser's sign, the higher the growth potential and the higher the risk of scoliosis progression. Nault proposed a modified Risser's sign classification, dividing Risser's sign grade 0 into two groups according to the closure of Y cartilage or not, and found a good correlation between Risser's sign grade 0 with Y triangle cartilage closure and Risser's sign grade 1 and DSA score 400–425 (98). This stage is when the iliac crest is just starting to ossify and is, therefore, closely related to the period of rapid scoliosis progression. However, it has been reported in the literature that approximately 40% of patients with AIS have varying degrees of abnormal iliac crest ossification, which, together with the lack of a uniform international standard for grading abnormal ossification, seriously affects the determination of Risser's sign grade. More importantly, there are currently two scoring standards for Risser's sign in this field, American and European, both of which use a 6-point scale and thus are highly confusing in the literature. Among the assessment indexes of the skeletal system, except for the Y-triangle cartilage and Risser's sign, which are simple and convenient to apply, all other assessment indexes are more complex and difficult to master in a short time. For a brief introduction to other assessment metrics, the Tanner-Whitehouse III scoring system was proposed by Tanner and Whitehouse in 1976, and its scoring criteria are based on the different morphologies of the ulnar, radial, metacarpal, and terminal phalangeal epiphyses (99). In 2007, Sanders found that the ulnar and radial bone age scores in the Tanner-Whitehouse III scoring system had the lowest correlation with growth potential, so the bone age scores of the ulna and radius in this scoring system were removed. Removed and only metaphyseal and phalangeal morphologic scores were calculated and redefined as the DSA scoring system (100). More recently, Verma further refined the DSA grading into 8 levels and defined it as the SSMS (simplified skeletal maturity scoring) scoring system (101). Hung proposed the thumb ossification composite index (TOCI) in 2017 based on the DSA scoring, which is simpler and faster and can greatly improve clinical efficiency (102). Among them, the TOCI5 level suggests that most adolescents are at the peak of height growth rate (70.1%–71.8%) (103). In contrast to the DSA score, Luk redefined and reclassified the morphology of the distal radial and ulnar epiphyses in 2014 and developed a new DRU scoring system (104). They found that the growth spurt in patients with AIS occurred at distal radial epiphysis score R7 and distal ulnar epiphysis score U5 and stopped at R10 and U9, respectively. The Greulich-Pyle mapping method is a standardized mapping of bone age based primarily on the appearance and disappearance of wrist ossification centers with age and the appearance and disappearance of the diaphysis (100). The Sauvegrain bone age score is based on morphological changes in the epiphysis of the elbow at four sites: the epicondyle, the humeral glide, the ulnar eminence, and the proximal radius on frontal and lateral radiographs of the elbow (105). The Olecranon method is a morphologic grading method based on the degree of ossification of the ulnar eminence epiphysis (106).

Anthropometric indicators commonly used to assess the risk of scoliosis progression in AIS patients include age at live birth, age at menarche, longitudinal growth rate, response to initial brace treatment, and secondary sex characteristics. Anthropometric indicators are easy to obtain, easy to visualize, and do not require additional radiation exposure, making them indispensable for assessing the risk of scoliosis progression in AIS patients. The most commonly used and simplest indicator for assessing the risk of scoliosis progression in AIS patients is the age at which Abbassi concluded that the onset of rapid height growth occurs at the age of 9 and 11 years for females and males, respectively, and that PHV occurs around 11.5 and 13.5 years for females and males, respectively. Solid footage between 11 and 13 years predicts a high risk for the development of PHV and the progression of scoliosis (107). Mao found that a significantly higher proportion of AIS patients had menarche later than 14 years of age, that menarche occurred on average 7 months (6 months to 2 years) after PHV, and that the onset of menarche represents a deceleration of longitudinal height growth (108). The risk of scoliosis progression was highest in AIS patients between 2 years before and at menarche. The longitudinal growth rate is divided into the longitudinal growth rate of height and the longitudinal growth rate of sitting height. The average PHV reported in the literature is about 8–9 cm/year, and the duration of PHV is about 3–4 years, so AIS patients about 2 years before PHV and 1.5 years after PHV have a higher risk of scoliosis progression (109). Secondary sexual characteristics are most commonly used as a visual indicator to assess the developmental maturity of AIS patients in clinical practice and are most commonly graded by the Tanner sign. When PHV occurs, male patients have a Tanner sign of approximately grade 3–5, whereas female patients tend to have a Tanner grading of grade 2–3 (99). In summary, the risk of scoliosis progression in AIS patients is closely related to their growth potential, and it is important to develop new models that include multiple dimensions with higher predictive sensitivity in the assessment.

## Limitations of the study

Only the English language literature study from the WOS database's core dataset was used in this investigation. As a result, it might have overlooked excellent literature on this topic in other databases or other languages. In the process of developing visualization atlases, there is currently no standard setup procedure for time splitting, thresholds, and cropping approaches, which could result in bias.

## Conclusion

This study offers fresh views for a rapid understanding of the area of non-surgical treatment of AIS by providing the first bibliometric and visual analysis of non-surgical treatment of AIS research during the previous 20 years from several viewpoints. Keywords of research Hotspots were adolescent idiopathic spondylitis, Schroth-based physiotherapy-specific exercise efficacy, curve development, Cobb angle, TLSO brace-based clinical efficacy, quality of life, reliability, questionnaires for HRQOL, finite element biomechanical models, follow-up and clinical guidelines. Keywords of research trends were Schroth exercise, PSSE comparative clinical efficacy studies, standardization of research methods for conservative treatment outcomes, psychometrics, the impact of patient compliance on clinical outcomes, the importance of early screening, wear time, gender, biomechanical modeling, and meta-analysis. Currently, there are fewer studies comparing the clinical efficacy of different non-surgical therapies, and the vast majority of them are not directly comparable due to differences in eligibility criteria and primary endpoints used to define outcomes, and it is recommended that "patient-centered outcomes (including appearance, disability, pain, and quality of life)" be used as the primary indicator to assess effectiveness, and that uniform criteria be established for studies related to the non-surgical treatment of AIS. Early intervention at the peak of growth is important for the prevention and treatment of AIS, but the inconsistency of existing growth potential and progression risk assessment systems may also affect comparative studies of clinical outcomes and even miss the optimal stage of intervention as a result. Therefore, it is necessary to standardize the criteria for assessing the risk of scoliosis progression. The efficacy of non-surgical treatment of AIS is influenced by multiple factors, so the clinical efficacy of different treatments cannot be generalized, and the causes should be analyzed from multiple perspectives.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

JX: Conceptualization, Investigation, Software, Writing – original draft. MC: Data curation, Investigation, Project administration, Writing – original draft. XW: Investigation, Project administration, Resources, Supervision, Writing – original draft. LX: Investigation, Validation, Visualization, Writing – review & editing. XL: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Abdominal pseudohernia in a child after surgical correction of congenital scoliosis: case report

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Abdominal wall relaxation is a rare complication of various surgical procedures or diseases, when the intercostal or upper lumbar nerves are affected, and the innervation of the muscles of the abdominal wall is damaged. The result is a mass that can visually mimic a ventral hernia. We present a clinical case and the results of a literature review on this topic.

**Clinical case:** The 2 years 5 months patient diagnosed with a congenital deformity of the spine (posterolateral hemivertebra) underwent extraction of the hemivertebra from the retroperitoneal approach. In the postoperative period, a pseudohernial protrusion of the anterior abdominal wall was observed. 4.5 months later the protrusion resolved spontaneously.

**Discussion:** Abdominal wall relaxation is studied worldwide and is presented primarily as clinical case reports, mainly in older patients with neurological diseases. Single cases of this pathology are described among children. The Th10-Th12 roots are most often affected. Possible manifestations include: bloating and abdominal pain, pseudo-obstruction of the small and/or large intestine, and constipation. In the described case, only unilateral bloating at rest was observed, which increased with crying and strain. The natural course and prognosis of this diagnosis are usually favorable—the recovery period, according to the literature, takes an average of 4–5 months, which also coincided with our case.

**Conclusion:** Pseudohernias are a rare complication and may can occur during correction of spinal deformities in children. This condition is a transient disorder of the anterior abdominal wall muscles, the cause of which may be neuropathy caused by infection, metabolic disorders, or mechanical damage. The main principles of treatment of this condition include active observation and symptomatic therapy. The prognosis is usually favorable.

KEYWORDS

pseudohernia, congenital scoliosis, children, complications, hernia of the abdominal wall, case report

## 1 Introduction

A hernia of the anterior abdominal wall occurs when an organ or a part of it protrudes through a natural opening (such as the umbilical ring, the inguinal or femoral canal) or a defect in the abdominal wall caused by injury or previous surgery (1). Damage to the intercostal or upper lumbar nerves, which innervate the muscles of the abdominal wall, can externally mimic a ventral hernia. However, this type of hernia differs from a true hernia in that there is no weakening of the abdominal wall due to a defect in the muscles and fascial layers. This type of hernia is rare due to the cross-innervation of the abdominal wall developed.

Information on abdominal wall relaxation is presented primarily in the form of case reports and is presented primarily in adult patients with neurological diseases or complications. The literature contains 84 publications for the keyword "pseudohernia," with more than half of the articles being case reports or case series with small patient samples of pseudohernias caused by herpes zoster infection.

Based on the literature review, it is evident that pseudohernia is a rare complication that occurs due to various surgical interventions or diseases associated with neuropathy or denervation. These complications include infectious and endocrinological diseases [such as herpes zoster (2–4), poliomyelitis (5, 6), and diabetic neuropathy (7)], surgical interventions on the spine (1, 8), and various surgical approaches performed during chest and abdominal surgeries (9–11).

Loewe first described pseudohernia of the anterior abdominal wall in 1936 after injecting a local anesthetic into the abdominal muscles of guinea pigs (12). He noted that the induced relaxation of the abdominal wall occurred without any damage to the musculature of the abdominal wall and called the resulting phenomenon "pseudohernia." Loewe suggested that the occurrence of pseudohernia is associated with a defect in sensory neurons rather than motor neurons, leading to local relaxation as a result of the interruption of the reflex arc that provides muscle tone to the abdominal wall. Later, damage to motor neurons was described in the pathogenesis of pseudohernias in patients with herpes infection (9–11).

In addition to being a rare complication, there is no consensus among the authors on the optimal treatment of this condition. The literature highlights two fundamentally different approaches to the treatment of pseudohernias: active surveillance with or without symptomatic therapy (13, 14) and surgical repair of pseudohernia (15–17).

Few reports are available about the appearance of pseudohernias of the anterior abdominal wall in children. Therefore, we present a clinical case and the results of a literature review on this topic.

## 2 Case report

At the National Research Center for Pediatric Traumatology and Orthopedics, a 2-year old girl with a diagnosis of "Multiple congenital malformations of the spine" was admitted for planned surgical treatment. The diagnosis was made when she was 3 months old and the main complaint of her mother was the presence of spinal deformity. The conventional therapy, however, could not achieve stability or slowing of progression. Upon admission, the child was able to walk independently without any lameness, but an imbalance of the trunk was observed. Specifically, her right shoulder girdle and shoulder blade were located higher than those of her left shoulder, and the chest was not deformed. Asymmetric waist triangles ($D < S$) and a curved spine axis to the right were also observed in the thoracic region. However, the range of motion in the cervical, thoracic, and lumbar spines was not limited and the movements were painless. Additionally, there were no orthopedic pathologies in the upper and lower extremities and no neurological or pelvic organ disorders were detected.

The child underwent clinical, laboratory, functional, neurological, and radiological examinations, including multislice computer tomography (MSCT) of the cervical, thoracic, and lumbar spine. The results of the examinations showed multiple congenital spine malformations resulting from impaired formation, fusion, and segmentation of the thoracic vertebrae. Spondylograms and MSCT of the spine revealed a deviation of the thoracic spine to the right due to anomalies in the shape and structure of the thoracic vertebrae. Additionally, an indistinctly differentiated block of the bodies and arches of the vertebrae of the upper and middle thoracic spine was observed. The degree of the right-sided scoliotic curve Th1-Th8 was 35 degrees by Cobb. At the level of the thoracolumbar junction, a right-sided posterolateral hemivertebra Th13 was visualized, forming a local kyphoscoliotic deformity with a scoliotic component of 23 degrees by Cobb and a local kyphosis of the thoracolumbar junction of 33 degrees by Cobb (Figure 1).

Given the results of the examinations and the presence of multiple spine malformations, a multistage surgical treatment was recommended. In this case, risk of developing permanent mobility disability, impaired trunk posture and sitting ability, and restrictive ventilatory impairment due to unstable chest or severe thoracic deformities were also considered. The first step was the extirpation of the posterolateral hemivertebra Th13 (D) using a combined approach. The patient was placed on her left side and anterolateral and extrapleural access was performed on the right side with resection of the 12th rib. The body of the Th13 hemivertebra was extirpated along with the adjacent intervertebral discs. Then, the hemiarch of the Th13 (D) hemivertebra was removed from the dorsal approach and transpedicular supporting elements were installed in the vertebral bodies Th12, Th14 and L1 on both sides to correct the deformity. Posterior and ventral fusion with autologous bone was performed, and a peridural catheter was placed intraoperatively from the dorsal access for anesthesia in the early postoperative period. The wounds were closed. One of the main goals was to allow further growth of the spine, especially the thoracic spine, leading to increased lung volume.

After completion of surgery and extubation of the child on the operating table, doctors noticed a protrusion on the right side of the anterior abdominal wall. Initially, it was interpreted as relaxation of the abdominal muscles due to the introduction of anesthesia into the peridural space. In the first three days after the operation, the child was kept in the intensive care unit, where a unilateral abdominal protrusion was observed at rest and an increase was observed when the patient cried or strained. The peridural catheter was removed when the child was transferred from the ICU. On the fourth day after surgery, the

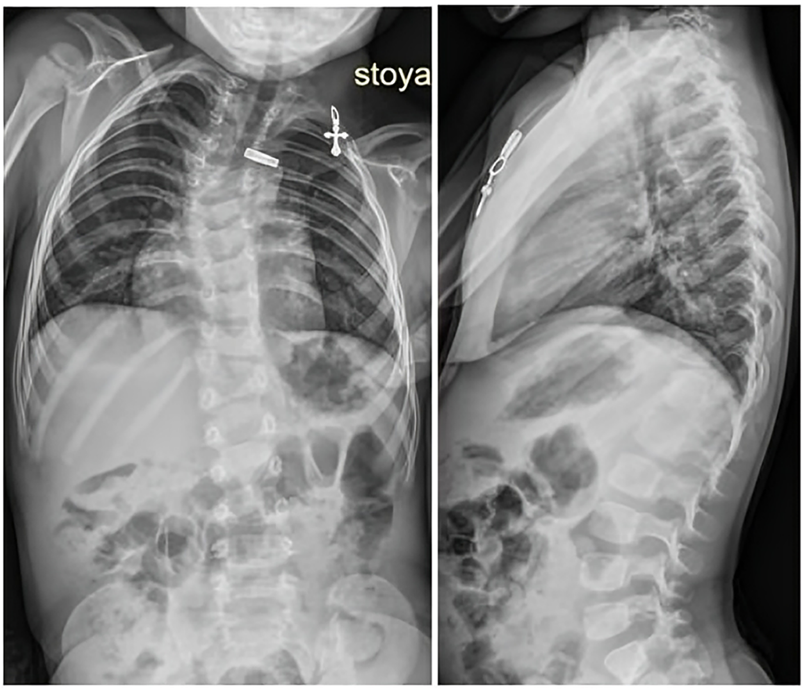


FIGURE 1
Patient spondylograms, frontal and lateral planes.

girl was made to stand, and on the fifth day spondylograms were performed to monitor the correction of the local congenital deformity and the position of the metal structure. The results showed complete correction of the deformity, with the metal structure correctly and stably placed (Figure 2). The muscles of the anterior abdominal wall were found to be intact and there

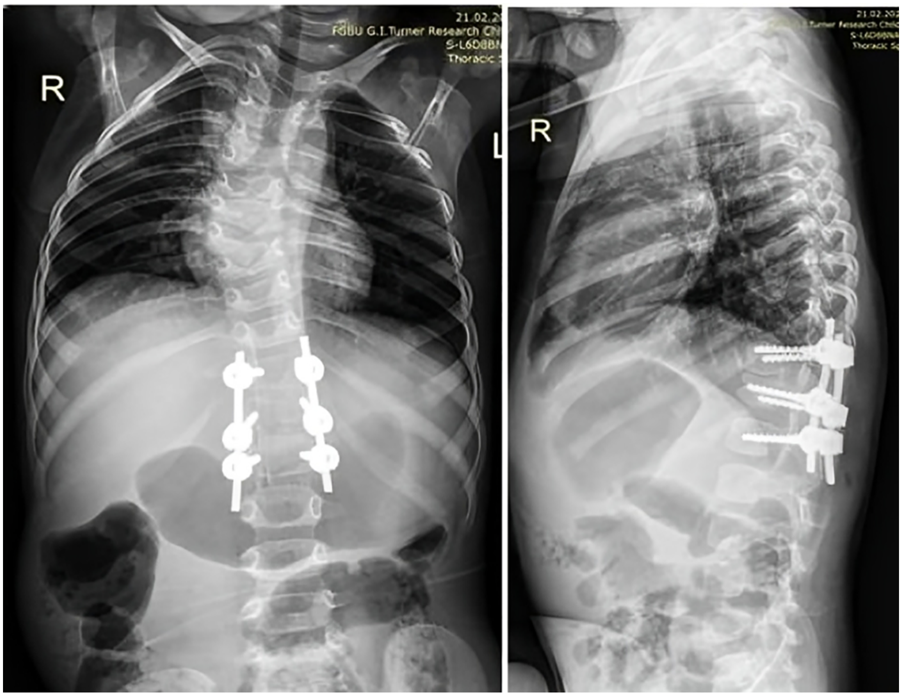


FIGURE 2
Patient spondylograms, frontal and lateral planes, 5th day post-op.

FIGURE 3
Pseudohernia in a patient in a postoperative period.

was no presence of free fluid or air in the abdominal cavity, according to MSCT.

The child received perioperative antibiotic prophylaxis, symptomatic therapy, and physical therapy. Surgical wound dressings were changed every three days and wounds healed through primary closure. On the seventh day after surgery, the child was provided with a rigid corrective corset and discharged from the hospital on the 14th day after surgical treatment. Although the pseudohernia of the anterior abdominal wall persisted throughout the hospital stay, it did not cause any complaints from the child (Figure 3).

At the 3-month follow-up examination, the pseudohernial protrusion remained the same size. However, six-month later, the child did not have a pseudohernial protrusion, and according to mother, the spontaneous restoration of the tone of the abdominal wall occurred 4.5 months after surgical intervention.

The protrusion was believed to be a consequence of intraoperative denervation during the lateral transthoracic approach, including resection of the 12th rib and damage to the intercostal nerve due to prolonged use of the wound retractor, or ligation of the neurovascular bundle during wound closure. Neuropathy symptoms included weakness of the abdominal muscles, which manifested as pseudohernia of the anterior abdominal wall.

## 3 Discussion

As mentioned above, pseudohernias are most commonly observed in adult patients as a complication of herpes zoster infection, specifically segmental herpes zoster abdominal paresis. These hernias are the result of damage to the branches of the Th8-L2 spinal nerve. Two extensive reviews have analyzed the incidence, causes, age range of patients, and clinical symptoms of pseudohernias (2, 18). In 88.9% of patients, a herpes zoster skin rash precedes the onset of pseudohernia, typically at the level of the Th11 segment. The complication affects the elderly and immunocompromised patients, mainly men. The average recovery period is 4–5 months, with spontaneous restoration of the tone of the abdominal wall occurring in our patient after 4.5 months following surgery. Pseudohernias can manifest along with other clinical symptoms, including bloating and abdominal pain, pseudo-obstruction of the small or large intestine, and constipation. In our patient, we observed unilateral bloating at rest, which increased with crying and straining. No other clinical signs were observed, and no other neurological deficits were observed, in addition to weakness in the anterior abdominal wall muscles and impaired surface sensitivity locally in the denervated area, which corresponded to intercostal nerve damage.

In addition to herpes zoster, pseudohernias can also result from trauma. Examples include "cough-induced hernias" and pseudohernias that occur after rib fractures with intercostal muscle damage (19–21). Other reported cases of pseudohernias include those associated with diabetic neuropathy (6) and poliomyelitis in children (5).

Surgical denervation of the anterior abdominal wall during a surgical approach is another widely discussed cause of pseudohernias. This occurs often in the lateral transabdominal or lateral thoracoabdominal approaches. In their study, Chatterjee et al. noted a weakness of abdominal wall denervation in 34 patients (49%) during lateral nephrectomy (8). Gardner observed similar symptoms in 20% of patients after an abdominal aortic plasty performed by lateral retroperitoneal approach (22). Other authors described the clinical picture of pseudohernia after thoracoscopic removal of a Th9-Th10 meningioma (10).

The etiology of pseudohernias may be associated with infectious diseases, metabolic disorders complicated by neurological symptoms, iatrogenic (intraoperative denervation), or traumatic causes. Imaging methods such as ultrasound, MSCT, and magnetic resonance imaging (MRI) can be used for diagnostic purposes to confirm the neuropathic genesis of pseudohernias. Unlike true hernias, the muscle-fascial layers of the abdominal wall remain intact in pseudohernias (15, 23, 24).

In most cases, surgical treatment is not necessary for pseudohernias. Active surveillance and/or conservative therapies such as bandage, physical therapy, and symptomatic and analgesic therapy are generally sufficient. The choice of conservative treatment depends on the underlying cause of pseudohernia. For example, patients with herpes zoster may require anti-herpetic drug therapy and adequate analgesia to relieve neuropathic pain (7).

Surgical treatment of pseudohernias is generally considered ineffective, as there is no physical defect of the abdominal wall that can be corrected by plastic surgery (5, 6). However, not all authors agree with this statement. Some recommend surgical treatment through anterior abdominal wall plasty with the installation of a mesh prosthesis by an open or endoscopic method. They suggest this method for pseudohernias resulting from surgical or traumatic denervation, as well as in cases of irreversible neuropathic hypotrophy of the muscles of the denervated area (16, 25).

# 4 Conclusion

Pseudohernias are protrusions of the anterior abdominal wall that resemble true hernias but do not involve a muscular or fascial defect. These bulges are caused by neuropathy or neurological deficits resulting from infection, metabolic disorders, or mechanical damage. The primary approach to the management of pseudohernias involves active observation and symptomatic therapy. In most cases, surgical treatment is considered unnecessary.

# Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

# Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

# Author contributions

NN designed the study, collected clinical data, and wrote the manuscript. SV contributed to the literature search, data collection, and manuscript writing. AF and NK contributed to the data collection. VS contributed to the writing of the draft and critically revised the manuscript. All authors reviewed the draft, modified it accordingly, and approved the final version. All authors contributed to the article and approved the submitted version.

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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Publisher's note



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# Elasticity and cross-sectional thickness of paraspinal muscles in progressive adolescent idiopathic scoliosis

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**Objectives:** (1) Compare the cross-sectional thickness (CST) and shear wave speed (SWS) of paraspinal muscles (PSM) in adolescent idiopathic scoliosis (AIS) with and without curve progression; (2) investigate the relationship between CST/SWS and radiographic characteristics in AIS with curve progression; (3) compare the CST/SWS between AIS and non-scoliosis controls.
**Methods:** This cross-sectional study analyzed the CST and SWS of PSM in 48 AIS with mild to moderate curvature and 24 non-scoliosis participants. Participants with scoliosis greater than 45° of Cobb angles were excluded. The Change of Cobb angles within the last 6-months was retrieved to allocate AIS into progression and non-progression groups. The SWS and CST of multifidus; longissimus and iliocostalis of the major curve were measured using B-mode ultrasound image with an elastography mode. Discrepancies of the SWS (SWS-ratio: SWS on the convex side divided by SWS on the concave side) and CST (CST-ratio: CST on the convex side divided by CST on the concave side) at the upper/lower end and apical vertebrae were studied.
**Results:** A higher SWS at the apical vertebrae on the concave side of the major curve (multifidus: 3.9 ± 1.0 m/s vs. 3.1 ± 0.6 m/s; $p < 0.01$, longissimus: 3.3 ± 1.0 m/s vs. 3.0 ± 0.9 m/s; $p < 0.01$, iliocostalis: 2.8 ± 1.0 m/s vs. 2.5 ± 0.8 m/s; $p < 0.01$) was observed in AIS with curve progression. A lower SWS-ratio at apical vertebrae was detected with a greater vertebral rotation in participants with curve progression (multifidus [grade II]: 0.7 ± 0.1 vs. grade I: 0.9 ± 0.2; $p = 0.03$, longissimus [grade II]: 0.8 ± 0.2 vs. grade I: 1.1 ± 0.2; $p < 0.01$). CST was not different among the progressive, non-progressive AIS and non-scoliosis controls.
**Conclusions:** Increased SWS of PSM without change of CST was observed on the concave side of the major curve in participants with progressive AIS.

KEYWORDS
adolescent idiopathic scoliosis, elasticity, cross-sectional thickness, shear wave speed, curve progression

## Introduction

Adolescent idiopathic scoliosis (AIS), the most common spine deformity afflicting up to 4% of children globally, refers to a lateral spinal curvature with a Cobb angle larger than 10° coupled with vertebral deformation and sagittal hypokyphosis (1). A recent population-based screening program in China showed 14% incidence of scoliosis in females aged 13–14 years (2). The rapid increase in scoliosis incidence may be due to lifestyle changes, as children spend less time exercising but more time using electronic devices and social media. Without early detection of curve progression, scoliosis can be easily under-diagnosed, as clinically 15%–30% of scoliotic patients will experience curve progression during pubertal growth, leading to Cobb angles larger than 45° for surgical intervention (1). Biomechanical studies of AIS with operative curve magnitude have identified three alterations in muscle architecture in addition to vertebral deformity: increased fat infiltration (3), asymmetrical muscle volume (4), and paraspinal muscle (PSM) stiffness (5). The mechanisms underlying these characteristic changes remain unclear, but evidence suggests that increased muscle stiffness and atrophy are weakening muscle contraction, and change leads to asymmetrical muscle activities, potentially contributing to scoliosis progression (6).

Electromyography (EMG) and magnetic resonance imaging (MRI) have been used to assess motor control (7, 8), in terms of static and dynamic muscle contraction in different postures, and the morphology of PSM in AIS (4). Specifically, higher fat infiltration and muscle atrophy have been observed in the paraspinal muscles at the apical vertebrae (AV) of the major curve with Cobb angle of 50° or more (3, 4). Studies have also revealed higher EMG activity at curve convexity, which was correlated with a greater side deviation (SD) of AV (8, 9). Those findings suggest that the biomechanical properties of PSM and vertebral deformity are interrelated. However, MRI and EMG are not standard clinical methods for patients with AIS. Shear wave elastography, as an alternative technique, stimulates tissue vibration and generates shear wave through the emission of acoustic radiation force (10). The shear wave speed (SWS) is then calculated and used to evaluate the biomechanical property of musculoskeletal tissues (10). The harder tissue is, the faster SWS will be (11, 12). Ultrasonography has been preferred in studies to evaluate the biomechanical features of PSM, uncovering an asymmetry in stiffness and thickness of PSM in AIS with operative curve magnitude (13–15). In cases of mild to moderate scoliosis, this relationship remains inconclusive. No study has examined how various paraspinal muscle characteristics are correlated with temporal changes in the scoliotic curvature during curve progression in patients with mild to moderate AIS. Accordingly, evaluating paraspinal muscle properties, along with known prognostic factors such as spinal growth velocity, may enhance the prediction of subsequent curve progression (6). Identifying muscle property changes of PSM in mild to moderate AIS during the progressive period can offer clinical value by aiding early treatment decisions, and by aiming to prevent curve progression into the operative threshold.

This study used real-time ultrasonography to assess the cross-sectional thickness (CST) and muscle elasticity, interpreted using the SWS, of multifidus, longissimus, and iliocostalis muscles at AV and upper end vertebrae (UEV) and lower end vertebrae (LEV) of the major curve. Our findings elucidate the characteristics of biomechanical properties of PSM in mild to moderate AIS during curve progression. In this study, we posed three specific research questions:

(1) How do the CST and elasticity of PSM in AIS differ in cases with and without curve progression?
(2) How are the biomechanical features of PSM and vertebral deformities (Cobb angle, apical wedging [AW]/rotation [AR]/SD, thoracic kyphosis [TK] and lumbar lordosis [LL]) correlated with curve progression?
(3) How do CST and the elasticity of PSM differ between AIS and non-scoliosis controls?

## Materials and methods

This was a cross sectional study conducted in accordance with the Declaration of Helsinki principles. Ethics approval [(2022)123] was obtained from the local institutional review board, and informed consent was obtained from the participants and their parents/legal custodians before study.

## Participants

Participants with AIS and non-scoliosis controls were consecutively enrolled into this study from June 2022 and July 2023 in our spine clinic. The inclusion criteria were as follows:

(1) Diagnosis of AIS, with Cobb angle ranging from 10° to 45°
(2) Latest radiography taken no more than one month before this study
(3) Prior radiography was within the last 6 months showing changes in Cobb angles
(4) Non-scoliosis controls with Cobb angle less than 10°
(5) Age ranging from 10 to 17 years
(6) Skeletal immaturity characterized by Risser stage of less than 5.

The exclusion criteria were as follows:

(1) Diagnoses other than AIS
(2) Cobb angle greater than 45°
(3) Presence of back pain [this criteria was set to minimize the effects of pain in altering the architecture of the multifidus (16)]
(4) A history of spinal orthosis [this criteria was set to minimize the effects of bracing on muscle weakness (9), which affects the biomechanical properties of back muscles].

### Radiographic measurement

Two spine surgeons retrieved and measured the latest and preceding 6-months radiographic parameters of the participants. These included the curve pattern, Cobb angle of the major curve, AW, SD, AR, TK (T5-12), LL (L1-5), and Risser stage. AR was measured at the major curve AV using the Nash and Moe system, graded from I to V (17). SD was defined as the distance between the center of AV and the central sacral vertical line (18). AW was calculated as the ratio of the major curve AV between sides $\left(AW = \frac{\text{vertebral height on convex side}}{\text{vertebral height on concave side}}\right)$ reflecting the reformation of the AV in the coronal plane (19). Skeletal immaturity was assessed in terms of Risser staging, with 0 referring to Risser sign 0 with open triradiate cartilage, 0 + referring to Risser sign 0 with closed triradiate cartilage and 4 + indicating a stage where the iliac apophysis is capped but not yet fused (20). Additionally, Lonstein-Carlson risk of scoliosis progression $\left(LCR = \frac{\text{Cobb angle} - 3 * \text{Risser sign}}{\text{Chonological age}}\right)$ was adopted to evaluate participants' risk of prospective curve progression (21). Using the LCR equation in addition to the changes of Cobb angles, which helped in discriminating progressive and non-progressive cases before group allocation (22). Curves were classified as either major thoracic curves (major T: single right thoracic or a major right thoracic with a minor left lumbar) or major lumbar curves (major L: single left lumbar or a major left lumbar with a minor right thoracic or left thoracolumbar curve). Participants were allocated into groups based on the increase of curve magnitude:

(1) Those with a change greater than 5° to the progression group
(2) Those with a change of Cobb angle between −5° and 5° were allocated to the non-progression group
(3) Those with a Cobb angle less than 10° were allocated to the non-scoliosis group.

## Ultrasonographic measurement

The elasticity and CST of the multifidus, longissimus, and iliocostalis muscles was assessed using B-mode ultrasound imaging with elastography. The elasticity index was quantified by measuring the SWS in this study. European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) recommended using SWS to evaluate biomechanics in musculoskeletal system (23). SWS was chosen for its superior reliability and repeatability in assessing the elasticity of skeletal muscles, which have anisotropic and inhomogeneous tensile properties (24). Thus, SWS was determined using force-deformation data between the superficial muscle layer and bottom muscle layer (longissimus and iliocostalis)/the bone surface of vertebral laminae (multifidus) at the UEV, AV, and LEV for participants with scoliosis, and at the eighth thoracic (T8) and the third lumbar vertebrae (L3) for non-scoliosis participants, using ultrasound elastography (5).

Ultrasonographic measurement was performed with participants in a prone lying posture on a physiotherapy plinth, with a small pillow situated beneath the abdomen to minimize lumbar spine movement. A spinal surgeon located the spinal process of AV, UEV, LEV, T8, and L3 by palpation according to their radiographs and marked the skin before ultrasonographic measurement. The location of each targeted vertebra and the adjacent multifidus, longissimus, and iliocostalis muscles were identified with a longitudinal sonographic scan before data collection. To acquire the CST and SWS of paraspinal muscles, a real-time diagnostic high-definition ultrasound unit (HDI-5000, Resona 7OB, Mindrary, Shenzhen, China) with a shear wave elastography mode, was used, along with a 3–9 MHz transducer (L9-3). With a posterior approach, the transducer was held perpendicular to the skin surface on the back of the patient. Cross-sectional images of the paraspinal muscles, 3 cm horizontally away from the spinal process, on both sides of the spine were acquired, with the echogenic tip of the spinous process in the middle and the vertebral laminae at the anterior margin of the multifidus muscles serving as consistent landmarks. The maximum anteroposterior diameter of the multifidus, longissimus, and iliocostalis muscles were collected at AV, UEV, and LEV levels in scoliotic participants and at T8 and L3 in non-scoliosis controls. A loading force of 4–5 N was then applied to the paraspinal muscles through the elastography transducer and subsequently released. Loading–unloading cycles were performed at least three times to derive the effective elastography (image with reliability ≥0.9). The load-indentation response data were based on the applied load and the deformation ratio. The ultrasound scanning was repeated five times, yielding five images for determining the average values of the CST and SWS. Both SWS ratio $\left(\text{SWS-ratio} = \frac{\text{sws on the convex side}}{\text{sws on the concave side}}\right)$ and the ratio of cross-sectional thickness $\left(\text{CST-ratio} = \frac{\text{CST on the convex side}}{\text{CST on the concave side}}\right)$ were calculated to interpret the discrepancies in muscle elasticity and thickness of the PSM in AIS. The SWS-ratio and CST-ratio were determined by the SWS and CST on the right (left) side at T8 (L3) divided by the SWS and CST on the left (right) side at T8 (L3) for non-scoliosis controls. This was to match the calculations regarding the curve pattern of participants with AIS.

## Reliability tests and power analysis

The reliability tests involved four AIS and two non-scoliosis participants, with two operators participating. The SWS and CST were measured by each operator five times at 3 cm horizontally away from spinal process of AV on the convex and concave sides of the major curve in participants with AIS, and at the T8 and L3 vertebrae in non-scoliosis controls. These repeated measurements demonstrated strong interoperator reliability for both SWS (multifidus intraclass coefficient [$ICC_{3,2}$]: 0.90, longissimus [$ICC_{3,2}$]: 0.92, iliocostalis [$ICC_{3,2}$]: 0.90) and CST (multifidus [$ICC_{3,2}$]: 0.89, longissimus [$ICC_{3,2}$]: 0.93, iliocostalis [$ICC_{3,2}$]: 0.88) and consistent intraoperator repeatability across consecutive trials for SWS (multifidus: coefficient of variation [CV] 1.4%–2.3%, longissimus: [CV] 1.1%–2.0%, iliocostalis: [CV] 1.8%–2.1%) and CST (multifidus: [CV] 3.1%–4.0%, longissimus: [CV] 2.9%–3.6%, iliocostalis: [CV] 2.4%–4.1%).

A power analysis was conducted to compare AIS and non-scoliosis groups. Our pilot SWS data set on four AIS and two non-scoliosis participants revealed a mean difference of 0.22 of SWS-ratio at the AV, with the largest standard deviation being 0.37. Power calculations indicated that 60 participants were required to achieve a power of 80% at $p = 0.05$, assuming a null hypothesis of no difference.

## Statistical analysis

Quantitative variables, namely age, body mass index (BMI), sport intensity, asymmetrical trunk rotation (ATR), Cobb angles, SWS, CST, AW, SD, TK, and LL, were compared using one-way analysis of variance (ANOVA). Categorical variables, namely sex, handedness, AR, Risser stage, and curve patterns, were tested using Pearson's Chi-squared tests. The *t* test was used to study the difference in SWS and CST between the curve convexity and concavity in participants with AIS. Post hoc intra-/inter-group comparison and multivariate general linear model analysis were performed to investigate the relationship between SWS/CST and radiographic parameters in participants with curve progression if a significant difference in either SWS-ratio or CST-ratio was detected between groups. All statistical analyses were performed using SPSS 27.0 for Windows (SPSS, Chicago, IL, USA).

# Results

## Patient characteristics

After curve magnitudes in 144 spinal radiographs from 58 adolescents with scoliosis and 24 peers without scoliosis were measured, 48 participants with AIS (progression [$n = 24$]: increase of Cobb angle by 6.2 ± 1.8°; LCR = 2 ± 0.8 [80%], non-progression [$n = 24$]: change of Cobb angle ≤0.0 ± 2.3°; LCR = 1 ± 0.8 [<20%]) and 24 non-scoliosis controls [Cobb angle: 8.0 ± 1.0° with LCR = 0.2 ± 0.4 (<5%)] were enrolled in this study (Figure 1). The groups did not significantly differ in age, sex, BMI, handedness, Risser stage, curve pattern or sport intensity (Table 1). The greater ATR, AR, SD and curve magnitude and the lower TK were observed in participants with progressive AIS (Table 1). Upon comparison between latest radiographs and those 6 months prior, increases in AR (latest radiograph: grade II [$n = 10$]; grade I [$n = 14$], preceding radiograph: grade II [$n = 5$]; grade I [$n = 19$], $\chi^2$ test: $p < 0.01$) and SD (38 ± 9.2 mm vs. 42 ± 9.9 mm, paired *t* test: $p < 0.01$) were detected, along with an increase of Cobb angles in the progression group.

## SWS and CST

### Progression vs. non-progression

A higher SWS on the concave side with no change of CST was observed at AV of the major curve in the progressive case (Figure 2). This resulted in a smaller SWS-ratio (repeated measurements: 0.8 ± 0.2, 0.9 ± 0.3, 0.9 ± 0.2) at the AV of the multifidus ($p < 0.01$), longissimus ($p < 0.01$), and iliocostalis ($p = 0.04$) muscles in the progression group (Table 2). However, these findings were not observed at the UEV or LEV in either progression or non-progression groups. The CST and CST-ratio did not differ between the progression and non-progression groups at AV, UEV, or LEV (Table 2). The CST showed no differences between scoliosis and non-scoliosis controls.

A discrepancy in SWS, characterized by a smaller SWS-ratio at AV, was observed in the progression group but not in the non-scoliosis controls (repeated measurements: multifidus [$F = 8$, $p < 0.01$], longissimus [$F = 6.8$, $p < 0.01$], iliocostalis [$F = 3.8$, $p = 0.03$], Table 2). Moreover, CTS was consistent between sides in both AIS and non-scoliosis controls at all tested vertebral levels (Table 2).

### Correlation with clinical features

Significant differences in ATR, AR, SD, and TK were observed between the progression and non-progression groups (Table 1).

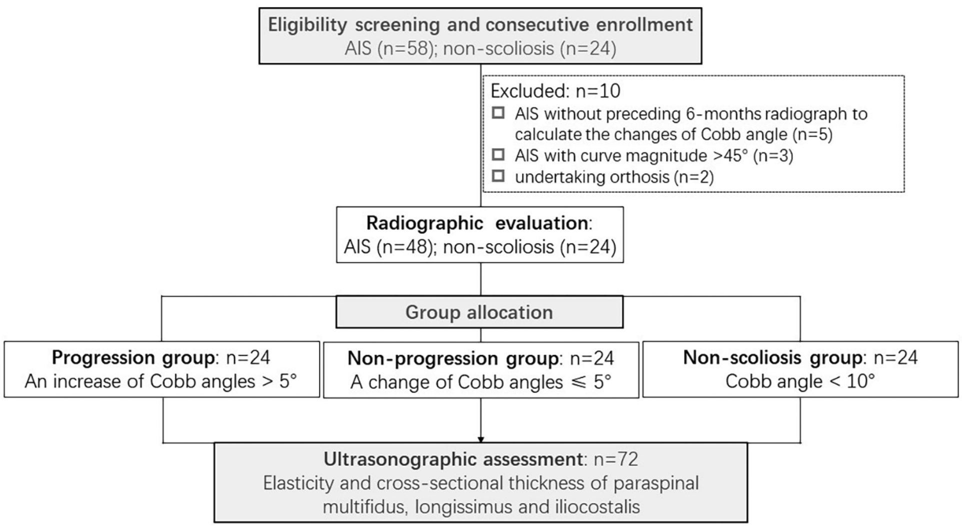


FIGURE 1
Study flow chart. AIS, adolescent idiopathic scoliosis.

TABLE 1 Participants' characteristics.

| | AIS | | Non-scoliosis controls ($n = 24$) | *P* value |
|---|---|---|---|---|
| | Progression ($n = 24$) | Non-progression ($n = 24$) | | |
| Age: years | 12 ± 2.2 | 13 ± 1.9 | 12 ± 2.1 | 0.1 |
| Sex (female/male): *n* | 15/9 | 19/5 | 17/7 | 0.4 |
| BMI | 18 ± 1.9 | 18 ± 3.6 | 19 ± 2.4 | 0.06 |
| Handedness (right/left): *n* | 21/3 | 20/4 | 20/4 | 0.9 |
| Sport intensity: hours/week | 7 ± 1.2 | 7 ± 1.2 | 7 ± 1.4 | 0.3 |
| ATR: ° | 7 ± 1.2 | 6 ± 1.4 | 5 ± 0.7 | <0.01 |
| LCR | 2 ± 0.8 (80%) | 1 ± 0.8 (<20%) | 0.2 ± 0.4 (<5%) | <0.01 |
| Risser staging: *n* | | | | 0.2 |
| 0 | 3 | 0 | 5 | |
| 0+ | 2 | 0 | 2 | |
| 1 | 4 | 4 | 2 | |
| 2 | 6 | 5 | 5 | |
| 3 | 0 | 5 | 3 | |
| 4 | 8 | 8 | 4 | |
| 4+ | 1 | 2 | 3 | |
| Curve pattern: *n* | | | | 0.8 |
| **Major T** (T4–12)/AV at T8/9 | 12 | 11 | – | |
| **Major L** (T10–L5)/AV at L3 | 8 | 10 | – | |
| **Major TL** (T8–L3)/AV at T12/L1 | 4 | 3 | – | |
| Cobb angle: ° | | | | |
| Present | 32 ± 6.8* | 26 ± 9.1 | 8 ± 1.0 | <0.01 |
| Preceding 6-months | 26 ± 6.2 | 26 ± 8.7 | – | 0.95 |
| Changes | 6.2 ± 1.8 | 0.0 ± 2.3 | – | <0.01 |
| Vertebral deformity | | | | |
| AR (AR-prior): *n* | II = 10, I = 14 | II = 4, I = 20 | II = 0, I = 24 | 0.02 |
| | (II = 5, I = 19) | (II = 4, I = 20) | (II = 0, I = 24) | (0.2) |
| SD (SD-prior): mm | 42 ± 9.9* (38 ± 9.2) | 32 ± 11.5 (33 ± 11) | – | <0.01 |
| AW (AW-prior) | 1.1 ± 0.1 (1.1 ± 0.1) | 1.1 ± 0.1 (1.1 ± 0.1) | – | 0.1 |
| TK (TK-prior): ° | 19 ± 2.3° (18 ± 3.3°) | 24 ± 4.8° (23 ± 3.9°) | – | <0.01 |
| LL (LL-prior): ° | 38 ± 3.3° (39 ± 3.5°) | 40 ± 2.9° (40 ± 3.2°) | – | 0.3 |

BMI, body mass index; ATR, asymmetrical trunk rotation; LCR, Lostein-Carlson risk of scoliosis progression; Major T, a major thoracic scoliosis; Major L, a major lumbar scoliosis; Major TL, a major thoracolumbar scoliosis; AV, apical vertebrae; AR, apical rotation; SD, side deviation; AW, apical wedging; TK, thoracic kyphosis; LL, lumbar lordosis.
*Significantly differed to the value at preceding 6-months in the progression group.

The lower SWS-ratio at AV of multifidus (grade II: 0.7 ± 0.1 vs. grade I: 0.9 ± 0.2; $p = 0.03$) and longissimus (grade II: 0.8 ± 0.2 vs. grade I: 1.1 ± 0.2; $p < 0.01$) were detected in progressive cases with higher AR. The lower SWS-ratio was weakly related to the greater curve magnitude and ATR in participants with AIS (linear regression analysis: latest Cobb angles [$r = 0.3$, $p = 0.04$], ATR [$r = 0.4$, $p = 0.03$]). However, no such relationship was detected between the SWS ratio and SD/TK. The smaller SWS-ratio at AV was distinctly found in multifidus of male participants with curve progression (0.8 ± 0.1 vs. 1.0 ± 0.3, $p < 0.01$).

## Discussion

The data acquired in this study addressed our second research question, revealing that curve progression in mild to moderate scoliosis is associated with distinct changes in the elasticity of PSM. This association was observed with greater AR of the major curve, independent of the curve pattern and SD/KT/LL. However, no such relationship was detected in the CST of PSM. Moreover, no difference in CST of PSM was found between the non-scoliosis and AIS groups in this study cohort (Table 2). Overall, the multifidus, longissimus, and iliocostalis muscles on the concave side of the major curve exhibited greater stiffness (a higher SWS) without a change in thickness in participants with mild to moderate progressive AIS (Figure 2). This change may lead to a discrepancy in PSM elasticity, potentially affecting muscle contractile function.

A difference in muscle contractile activity is considered as a risk factor for scoliosis progression, along with skeletal immaturity and vertebral deformity (6). The observed changes in muscle elasticity without muscle thickness alterations suggest that stiffness and thickness of PSM do not occur simultaneously in mild to moderate scoliosis during curve progression. The increased muscle elasticity leads to a stiffer muscle architecture (24). A significant decrease in muscle thickness and an increase in muscle stiffness, predominantly on the concave side, were observed in patients with operative scoliotic magnitude (4, 5, 12, 15, 16). Such a correlation was not

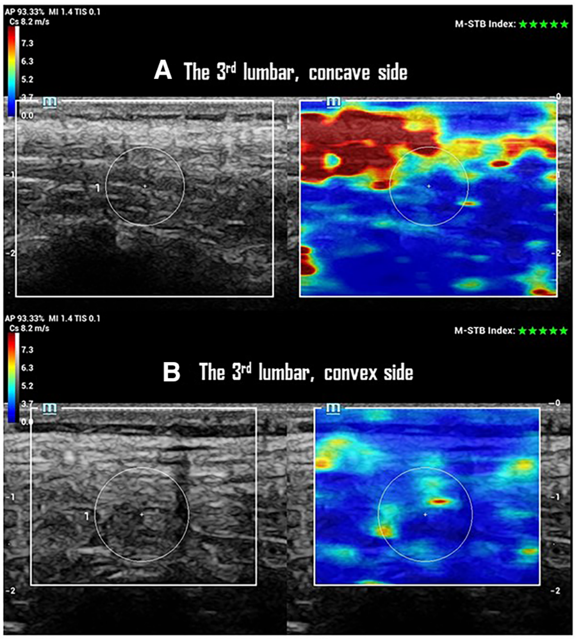


FIGURE 2
SWS and CTS of paraspinal multifidus at the 3rd lumbar vertebrae of one participant with a 25° left lumbar scoliosis in the progression group. (A) Ultrasonographic imaging shows a 10 mm CTS with 4.4 ± 1.4 m/s of SWS in multifidus on the concave side of the curve. (B) Ultrasonographic imaging shows a 10 mm of CTS with 3.9 ± 1.0 m/s of SWS in multifidus on the convex side of the curve.

observed in our study, likely due to the inclusion of participants with only mild to moderate scoliosis. This implies that changes in muscle elasticity precede changes in muscle volume during scoliosis progression. Given that muscle stiffness weakens muscle contractile function and may affect the spinal stability (16), our findings imply that the asymmetrical elasticity of PSM is a potential driving force and being a predictive marker in scoliosis progression. Thus, early intervention such as scoliosis-specific exercise to improve the discrepancy in muscle activity may prevent curve progression and reduce muscle atrophy in patients with AIS (25).

A higher elasticity in multifidus, longissimus, and iliocostalis muscles was observed on the concave side of the major curve at AV but not at UEV/LEV in the progression group. Additionally, this discrepancy in muscle elasticity was distinctive in progressive cases with greater AR and curve progression. These findings confirm that changes in biomechanical properties and vertebral deformity are interrelated. AIS, being the most common structural scoliosis, often results in the AV being most deformed in rotation (17). Our findings are consistent with those of studies indicating increased muscle stiffness predominantly on the concave side at the apical level (3–5, 13, 15), suggesting a relationship between muscle stiffness and vertebral rotation. Alternatively, the lower SWS-ratio was weakly related to greater ATR and curve magnitude in this study cohort. This may be because of the difference of ATR was <1° between the progression and non-progression groups in this study, and curve magnitude was reduced simultaneously with lying position when doing ultrasound measurement. The 1° of difference was statistically different but within the measurement error. Other researchers have identified a stiffer muscle architecture associated with greater SD in AIS (5). However, such a relationship was not observed in our study, possibly due to the smaller curve magnitude and lesser SD in our study cohort. The decrease in SD is associated with a decrease in Cobb angles when the spine is not bearing weight (26), a condition referred to as gravity unloaded, such as in the prone lying posture used for elastography in our study. In addition, a smaller SWS-ratio, indicative of higher muscle elasticity on the concave side, was found in male participants with curve progression. Possible explanations include differences between the sexes in the muscle architecture of back muscles (27) and a higher likelihood of progression in male AIS (1). Our previous study found that weaker EMG activity on the concave side of the major curve was related to curve progression in untreated AIS (8). This study expands on that work, suggesting that the muscle is stiffer on the concave side of the major curve in progressive mild to moderate AIS. Thus, interventions targeting the reduction of PSM stiffness on the concave side of the major curve merit future study.

The CST of PSM did not differ between the AIS group and the non-scoliosis controls in this study cohort. This finding contrasts with another study that detected a smaller CST on the concave side of the major curve in patients with AIS with operative curve magnitude (15). The smaller CST was attributed to muscle atrophy, which was caused by the inhibition of muscle activity due to muscle stiffness and the inability of a muscle or ligament to return to its original resting length, owing to increased fat infiltration in PSM (3). This smaller cross-sectional area, in conjunction with a larger fat area in PSM in AIS with big curve magnitude, implies increased infiltration of noncontractile materials and a reduction in muscle contractile function (3). However, patients in other studies who exhibited these characteristics presented with large scoliotic magnitudes and had undergone bracing treatment (3–5). Prolonged bracing can reduce muscle strength and lead to atrophy (28). Thus, the smaller CTS and higher fat area may result from severe scoliotic deformation and prior bracing treatment. The relationship between these factors and mild to moderate scoliosis remains unclear. Our findings fill this knowledge gap, suggesting that CST is comparable between adolescents with mild to moderate scoliosis and age-matched peers without scoliosis.

We acknowledge that the small sample size of 72 participants, including 48 AIS and 24 non-scoliosis controls, limits our interpretation of the muscle elasticity findings. However, sample size estimation and pilot study were conducted before data collection, our results satisfied statistical power to illustrate our findings. Moreover, lacking severe scoliosis with operative curve magnitude was another limitation in this study. Understanding biomechanical features of PSM in severe scoliosis helps clinicians to determine patients' spinal flexibility preoperatively (29). Additionally, the allocation of more male participants, although without significant intergroup difference, to the progression group may cause sex to be a potential confounding factor, because men and women differ in myofascial tone and their elastography findings (27).

TABLE 2 SWS and CTS of PSM.

| | AIS | | | | | | Non-scoliosis controls (*n* = 24) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Progression (*n* = 24) | | | Non-progression (*n* = 24) | | | | | |
| | Multifidus | Longissimus | Iliocostalis | Multifidus | Longissimus | Iliocostalis | Multifidus | Longissimus | Iliocostalis |
| **SWS (convex; concave)** | | | | | | | | | |
| UEV: m/s | 3.5 ± 1.0; | 3.1 ± 1.3; | 2.7 ± 0.7; | 3.4 ± 1.2; | 3.1 ± 1.0 | 2.6 ± 0.6; | | | |
| | 3.5 ± 1.0 | 3.1 ± 0.9 | 2.7 ± 0.8 | 3.4 ± 1.0 | 2.9 ± 0.8 | 2.6 ± 0.7 | | | |
| AV: m/s | 3.1 ± 0.6**,*; | 3.0 ± 0.9**,*; | 2.5 ± 0.8**; | 3.6 ± 1.2; | 3.3 ± 1.2; | 2.6 ± 0.8; | 3.1 ± 0.8; | 2.8 ± 0.6; | 2.6 ± 0.6; |
| | 3.9 ± 1.0* | 3.3 ± 1.0* | 2.8 ± 1.0 | 3.4 ± 1.1 | 2.8 ± 0.6 | 2.5 ± 0.7 | 3.1 ± 0.8 | 2.8 ± 0.7 | 2.5 ± 0.5 |
| LEV: m/s | 3.2 ± 0.9; | 3.2 ± 0.8; | 2.7 ± 0.7; | 3.3 ± 0.9; | 3.2 ± 1.4; | 2.7 ± 0.9; | | | |
| | 3.2 ± 0.8 | 3.0 ± 0.8 | 2.8 ± 0.7 | 3.2 ± 1.0 | 2.7 ± 0.5 | 2.5 ± 0.5 | | | |
| **SWS-ratio** | | | | | | | | | |
| UEV | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.3 | 1.0 ± 0.3 | 1.0 ± 0.3 | 1.1 ± 0.2 | | | |
| AV | 0.8 ± 0.2* | 0.9 ± 0.3* | 0.9 ± 0.2* | 1.1 ± 0.3 | 1.2 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 |
| LEV | 1.1 ± 0.2 | 1.1 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.2 ± 0.4 | 1.1 ± 0.5 | | | |
| **CST (convex; concave)** | | | | | | | | | |
| UEV: mm | 9.9 ± 2.2; | 9.8 ± 2.6; | 8.5 ± 2.8; | 9.3 ± 2.2; | 10.8 ± 3.5; | 9.2 ± 2.6; | | | |
| | 9.0 ± 1.9 | 10.0 ± 3.4 | 8.1 ± 2.5 | 8.9 ± 2.4 | 10.5 ± 3.0 | 8.7 ± 2.5 | | | |
| AV: mm | 8.4 ± 1.9; | 13.1 ± 2.9; | 10.1 ± 3.3; | 8.7 ± 1.8; | 12.7 ± 4.3; | 11.4 ± 3.9; | 8.4 ± 1.9; | 13.7 ± 4.9; | 12.0 ± 6.2; |
| | 8.3 ± 1.7 | 12.7 ± 3.0 | 11.1 ± 2.8 | 8.6 ± 2.4 | 12.5 ± 4.1 | 11.1 ± 3.1 | 8.2 ± 2.2 | 13.1 ± 4.4 | 11.9 ± 5.5 |
| LEV: mm | 8.2 ± 2.0; | 14.6 ± 3.6 | 13.3 ± 4.1; | 8.0 ± 2.5; | 14.1 ± 4.8 | 13.4 ± 4.1; | | | |
| | 7.8 ± 2.0 | 14.3 ± 3.6 | 14.5 ± 4.0 | 7.8 ± 1.9 | 13.8 ± 4.8 | 12.8 ± 4.3 | | | |
| **CST-ratio** | | | | | | | | | |
| UEV | 1.0 ± 0.1 | 1.0 ± 0.2 | 1.1 ± 0.2 | 1.3 ± 0.2 | 1.0 ± 0.2 | 1.1 ± 0.2 | | | |
| AV | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.1 ± 0.2 | 1.0 ± 0.1 | 1.0 ± 0.1 | 1.0 ± 0.2 |
| LEV | 1.1 ± 0.2 | 1.0 ± 0.1 | 0.9 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.2 | | | |

AIS, adolescent idiopathic scoliosis; SWS, shear weave speed (m/s). CST, cross-sectional thickness. UEV, upper end vertebrae. AV, apical vertebrae (measured at the 8th thoracic and the 3rd lumbar vertebral levels in the non-scoliosis group). LEV, lower end vertebrae.

*significantly differ to the non-progression group and non-scoliosis controls

**Significantly differ to the concave side in the progression group.

However, considering the established effects of sex on curve progression (30), we valued the opportunity to study the biomechanical characteristics of male patients with progressive AIS. Thus, we did not perform sex matching before group allocation. Moreover, this is the first study to quantify the curve progression of patients and focus specifically on the biomechanical characteristics of PSM in progressive cases. Our findings encourage diagnostic study to investigate the predictive value of PSM in scoliosis progression. Another limitation can be our use of CST to interpret muscle volume in PSM, because muscle volume can be precisely quantified using MRI. However, MRI is not a routine clinical assessment for mild to moderate AIS, and most MRI facilities are not equipped with an elastography mode for biomechanical assessment. Ultrasound elastography, as a reliable tool for characterizing the biomechanical properties of back muscles in healthy individuals and those with disease-related conditions (14), may offer an accessible and user-friendly mechanical parameter to encourage quantitative tissue assessments.

## Conclusion

Discrepancies in muscle elasticity were observed in the PSM of participants with progressive AIS who had mild to moderate curve magnitudes. Greater muscle elasticity on the concave side of the major curve was correlated with AR and more prevalent in the progressive AIS. This relationship was not detected in the CST, which did not differ between AIS and non-scoliosis controls. Our findings imply that changes in muscle elasticity occur in the early stages of scoliosis progression without changing the CST with mild to moderate AIS.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by the study was approved by the ethic committee of the Hong Kong University—Shenzhen Hospital [Ethic approval: 2022(123)]. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

YF: Funding acquisition, Writing – original draft, Writing – review & editing. HZ: Investigation, Writing – original draft. LF: Formal Analysis, Writing – review & editing. MT: Funding acquisition, Visualization, Writing – review & editing. G-MK: Formal Analysis, Writing – review & editing. EY: Data curation, Investigation, Writing – review & editing. KC: Resources, Validation, Visualization, Writing – review & editing. LL: Conceptualization, Methodology, Project administration, Validation, Writing – review & editing. JC: Conceptualization, Funding acquisition, Project administration, Visualization, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1323756/full#supplementary-material

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# Comparison of the efficacy of thoracolumbosacral and lumbosacral orthosis for adolescent idiopathic scoliosis in patients with major thoracolumbar or lumbar curves: a prospective controlled study

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**Introduction:** Thoracolumbosacral orthosis (TLSO) is the most commonly used type of brace for the conservative treatment of adolescent idiopathic scoliosis (AIS). Although lumbosacral orthosis (LSO) is designed to correct single thoracolumbar or lumbar (TL/L) curves, its effectiveness remains underexplored. This novel article aims to compare the effectiveness of LSO with TLSO in treating AIS with main TL/L curves.
**Methods:** This prospective controlled cohort study enrolled patients with AIS with main TL/L curves and minor thoracic curves who were treated with either TLSO or LSO. Demographic and radiographic data were compared between the two groups. Treatment outcomes were also assessed. Risk factors for minor curve progression were identified, and a cut-off value was determined within the LSO group.
**Results:** Overall, 82 patients were recruited, including 44 in the TLSO group and 38 in the LSO group. The initial TL/L curves showed no difference between both groups. However, the baseline thoracic curves were significantly larger in the TLSO group compared to the LSO group (25.98° ± 7.47° vs. 18.71° ± 5.95°, $P < 0.001$). At the last follow-up, LSO demonstrated similar effectiveness to TLSO in treating TL/L curves but was less effective for thoracic curves. The initial magnitude of thoracic curves was identified as a risk factor for minor curve outcomes in the LSO group. The ROC curve analysis determined a cut-off value of 21° for thoracic curves to predict treatment outcomes.
**Discussion:** In contrast to TLSO, LSO exhibits comparable effectiveness in treating main TL/L curves, making it a viable clinical option; however, it is less effective for thoracic minor curves. The initial magnitude of the minor thoracic curves may guide the selection of the appropriate brace type for patients with AIS with main TL/L curves.

KEYWORDS
adolescent idiopathic scoliosis, lumbosacral orthosis (LSO), brace treatment, lumbar curves, thoracolumbosacral orthosis (TLSO)

# 1 Introduction

Adolescent idiopathic scoliosis (AIS) is one of the most common spinal deformities in school-age children and teenagers (1). Numerous studies have validated the effectiveness of bracing for moderate curves, specifically those ranging from approximately 20° to 40°. This approach has been shown to reduce the rate of curve progression when compared to observation alone (2–4). However, many factors affect the outcomes of bracing treatment, including brace design, curve magnitude, curve type, maturity, in-brace correction (IBC), and compliance (5). Different brace designs exert varying correction forces, which influence wearing compliance and potentially affect patients' outcomes (6, 7). A more significant IBC rate and adherence to a full-time brace usually indicate a better prognosis (8, 9).

Currently, there are three types of braces according to the different anatomical regions, namely cervicothoracolumbosacral orthosis (CTLSO), thoracolumbosacral orthosis (TLSO), and lumbosacral orthosis (LSO) (10). The Milwaukee brace was a widely used CTLSO that controls upper thoracic curves in a way that traditional under-arm braces cannot (11). However, this came at the cost of impaired aesthetics and discomfort; hence, the brace was associated with poor compliance (12). The Milwaukee brace has been gradually replaced by low-profile underarm TLSO, such as Boston or Chêneau braces (13). While TLSO designs are generally more tolerated and aesthetically pleasing, compliance with these braces is not always satisfactory for some patients (14). Karol et al. reported that patients who were counselled about compliance data wore their braces for an average of 13.8 h daily, compared to 10.8 h for those who were not counselled, which were both significantly less than the recommended minimum of 20 h daily (15). Therefore, improving bracing compliance remains a significant challenge in clinical practice (16).

The LSO is primarily designed to correct single thoracolumbar or lumbar (TL/L) curves. It lacks the underarm corrective force, making it more compact, portable, and easier to wear than the TLSO (10). Theoretically, patients who wear LSO are more comfortable and have more compliance. However, only a few studies in the literature have discussed its effectiveness. According to the latest scoliosis classification of braces by the International Society On Scoliosis Orthopedic and Rehabilitation Treatment (SOSORT), the Progressive Action Short Brace (PASB) is categorized as a type of LSO, intended solely for treating thoracolumbar or lumbar (TL/L) curves. However, some earlier studies have described its original design as that of a TLSO (10, 17). Aulisa et al. reported that most patients with TL/L curves obtained curve correction after PASB treatment (18, 19). Nevertheless, they only used it for single TL/L curves, and patients with minor thoracic curves were omitted. Therefore, this novel prospective controlled study aimed to compare the effectiveness of LSO with TLSO in treating AIS with both main TL/L curves and minor thoracic curves.

# 2 Materials and methods

## 2.1 Cohorts

This prospective controlled cohort investigation was approved by the Institutional Review Board of our hospital (XHEC-C-2023-040-1) and conducted according to the principles of the Helsinki Declaration. All patients in this study visited our clinic between January 2017 and December 2021 to consult a senior physician (Prof. J.L. Yang), who has extensive expertise in the conservative treatment of AIS. The inclusion criteria were as follows: (1) AIS patients with main TL/L curves and minor thoracic curves; (2) main curve magnitude between 25° and 45°; (3) age >10 years; (4) a Risser stage of 0–2; (5) receiving TLSO or LSO with a minimum follow-up duration of 2 years; and (6) optimal bracing compliance to eliminate the potential impact of compliance on treatment outcomes. Treatment compliance was considered optimal if the difference between the prescribed bracing hours and the actual duration the brace was worn was less than 2 h (19). Compliance with bracing was assessed using patients' self-reports and confirmed by their parents. If necessary, magnetic resonance imaging (MRI) and electromyography were performed to rule out any potential neuromuscular disorders. To enhance treatment adherence, follow-ups for patients were consistently conducted by the same doctor (Prof. J.L. Yang). Patients who had undergone other prior treatments (4 cases) or had incomplete clinical data (2 cases) were excluded from the study. Eight patients who did not reach the goals of optimal bracing compliance during treatment were also excluded. Informed consent to participate in the study was obtained from the legal guardians of the enrolled patients.

## 2.2 Bracing protocol

According to the latest classification of scoliosis braces developed by SOSORT, it is necessary to delineate the following features of braces: rigidity, primary action for detorsion, primary corrective plane in three dimensions, construction type as monocot, and closure method as ventral (10). In light of the different anatomical regions where curves were controlled, both TLSO and LSO types were used in this study. The selection of the specific brace type was determined by the doctor's recommendation after fully informing the patients about the potential effects of both brace types. For minor curves ≥25°, TLSO was recommended; for minor curves <25°, LSO was used if the minor curve was considered non-structural; otherwise, a TLSO was recommended (Figures 1, 2). After the patients fit their selected braces, in-brace radiographs were taken within 2 weeks. Afterwards, regular follow-up visits were recommended every 4–6 months for all patients. The patients were also required to wear braces for at least 20 h daily. Upon reaching skeletal maturity, the patients underwent the final radiographic assessments and discontinued bracing through a weaning process.

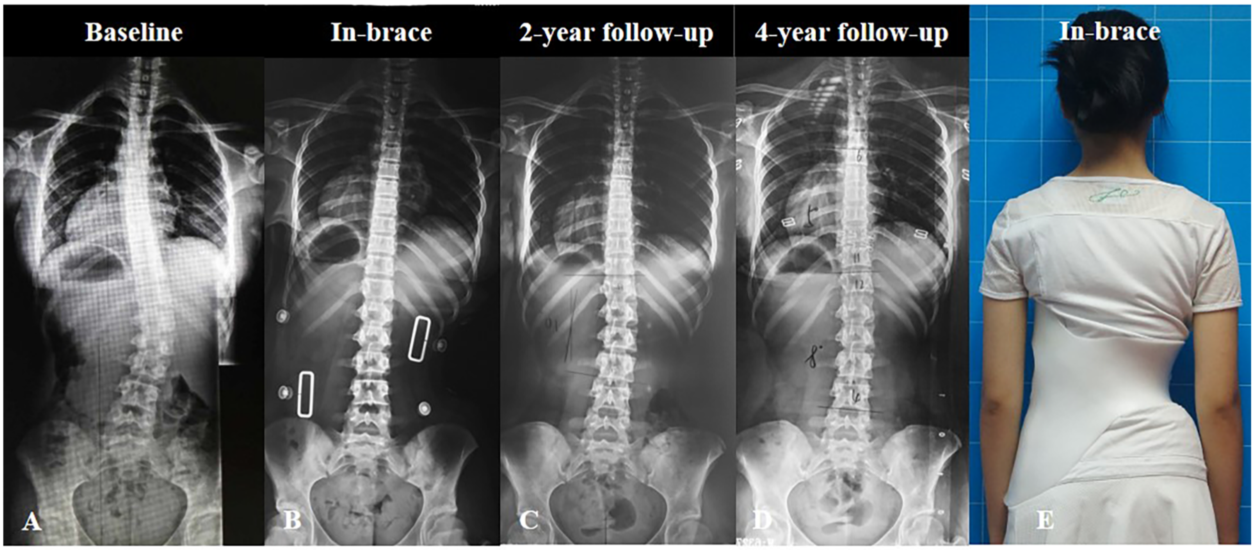


FIGURE 1
A 12-year-old girl diagnosed with adolescent idiopathic scoliosis was treated with lumbosacral orthosis (LSO). The main lumbar curve was 30° and the minor thoracic curve was 18° at baseline (A) The in-brace radiograph showed excellent correction of both curves (B) After 2 years of treatment, the patient had satisfactory curve improvement (C), which was adequately maintained over a 4-year follow-up period (D) Clinical in-brace appearance of the patient (E).

The weaning process typically involved wearing the brace at night only, consistently for 6–12 months (20). Skeletal maturity was defined as having a Risser sign of 4 or 5, or 2 years post-menarche for female patients. The patients also underwent physiotherapeutic scoliosis-specific exercises (PSSE). It mainly comprised daily corrective postures and intensive corrective exercises, including muscle strengthening and curve stretching movements. Patients were required to exercise for at least 1 h daily (21).

## 2.3 Clinical and radiological evaluation

The demographic information collected at the initiation of brace treatment included age, sex, body mass index, and Risser sign. The patients were required to undergo full spinal posteroanterior and lateral radiographic assessments after the braces had been removed for over 24 h at each visit during follow-up. The Risser sign and curve magnitude (using Cobb's

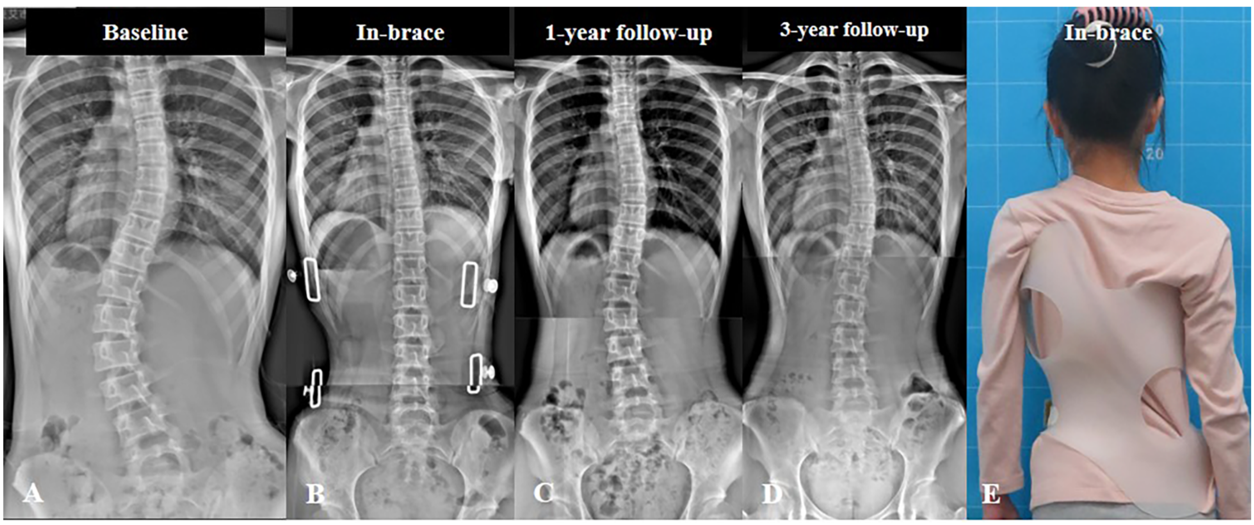


FIGURE 2
A 13-year-old girl diagnosed with adolescent idiopathic scoliosis treated with thoracolumbosacral orthosis (TLSO). The main lumbar curve was 42°, and the minor thoracic curve was 30° at baseline (A) In-brace radiograph shows excellent correction of both curves (B) After 1 year of treatment, the patient had satisfactory curve improvement (C), which was adequately maintained over a 3-year follow-up period (D) Clinical in-brace appearance of the patient (E).

method) were measured on spinal radiographs. The main curve location was divided into TL (apex between T12 and L1) or L (apex below L1 and above L3) according to the location of the apical vertebra. The apical vertebral rotation of the main curve was assessed using the methods developed by Nash and Moe (22). The in-brace correction (IBC) rates were calculated using the following formula:

$$\begin{aligned}&\text{In} - \text{brace correction (IBC) rates}\\&\quad = \text{(Cobb angle at baseline-in-brace Cobb angle)}\\&\quad\ /\text{Cobb angle at baseline} \times 100\%\end{aligned}$$

The ratio of curve magnitude (minor curve/main curve) was also calculated to investigate whether the minor curve was structural or non-structural. A minor curve was considered structural if the Cobb magnitude was ≥80% of the magnitude of the primary curve (23). The Brace Questionnaire (BrQ) that explicitly evaluates the health-related quality of life of patients with AIS undergoing brace treatment was investigated for all patients in this study during follow-up (24, 25). The treatment outcome was defined based on the evolution of the main curve or the minor curve as follows: (1) improve (>5° reduction in the curve magnitude); (2) stabilize (≤5° change in the curve magnitude); and (3) progress (>5° increase in the curve magnitude). Radiographic measurements were completed by two authors (Dr. L. Sha and Dr. T.Y. Zhang), and the mean values were used in the analysis.

## 2.4 Statistical analysis

Statistical analysis was performed using the SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The univariate comparison included the independent *t*-test for comparing continuous variables and the chi-square test for comparing categorical parameters. The parameters between the two groups were compared at baseline, initial in-brace, and during the last follow-up visit. With potentially related variables entered, factors significantly associated with treatment outcome were identified by logistic regression in forward stepwise methods. The receiver operating characteristic (ROC) curve was used to determine the threshold value for treatment outcome. A $P$ value of <0.05 was considered statistically significant.

# 3 Results

The study included 82 patients who met the inclusion criteria. The demographic and clinical data for these patients are presented in Table 1. Based on the type of braces used, 44 patients were fitted with TLSO and 38 with LSO. A comparison of demographic and clinical data between the two groups revealed no significant differences (Table 2, all $P > 0.05$).

In terms of radiographic evaluation, the initial main curve was 34.68° ± 6.40° in the TLSO group and 32.99° ± 6.88° in the LSO group, showing no statistically significant difference ($P = 0.252$). However, the minor curves were significantly larger in the TLSO group than in the LSO group (25.98° ± 7.47° (range, 20°–37°) vs. 18.71° ± 5.95° (range, 10°–24°), $P < 0.001$). Similarly, the minor curve/main curve ratio was also larger in the TLSO group than in the LSO group ($P < 0.001$). The IBC rates for the main curves ($P = 0.170$) were comparable between the two groups; however, the TLSO group demonstrated significantly better IBC rates for minor curves ($P = 0.004$). After an average follow-up of 28.54 ± 4.58 months, both main and minor curves showed no significant difference between the two groups (Table 3, all $P > 0.05$). Regarding health-related quality of life, patients in the LSO group had significantly higher BrQ scores than did those in the TLSO group (81.92 ± 4.19 v.s. 79.36 ± 4.40, $P < 0.001$).

TABLE 1 Demographic and clinical data of patients included in this study.

| | Included patients |
|---|---|
| Numbers | 82 |
| Sex | |
| Female | 74 |
| Male | 8 |
| Age (years) | 12.78 ± 1.31 |
| Risser | |
| 0 | 31 |
| 1 | 21 |
| 2 | 30 |
| BMI (kg/m$^2$) | 17.47 ± 2.38 |
| Initial main curve (°) | 33.90 ± 6.64 |
| Initial minor curve (°) | 22.61 ± 7.68 |
| Main curve location | |
| Thoracolumbar | 38 |
| Lumbar | 44 |
| Apical vertebra rotation | |
| 1 | 27 |
| 2 | 53 |
| 3 | 2 |
| Follow-up (months) | 28.54 ± 4.58 |

TABLE 2 Comparison of demographic and clinical information between both groups.

| | TLSO group | LSO group | *P* value |
|---|---|---|---|
| Numbers | 44 | 38 | – |
| Sex | | | |
| Female | 40 | 34 | 0.827 |
| Male | 4 | 4 | |
| Age (years) | 12.82 ± 1.26 | 12.74 ± 1.37 | 0.780 |
| Risser | | | |
| 0 | 17 | 14 | 0.805 |
| 1 | 10 | 11 | |
| 2 | 17 | 13 | |
| BMI (kg/m$^2$) | 17.42 ± 2.36 | 17.52 ± 2.43 | 0.864 |
| Main curve location | | | |
| Thoracolumbar | 17 | 21 | 0.131 |
| Lumbar | 27 | 17 | |
| Apical vertebra rotation | | | |
| 1 | 16 | 11 | 0.776 |
| 2 | 27 | 26 | |
| 3 | 1 | 1 | |
| Follow-up (months) | 28.41 ± 5.22 | 28.68 ± 3.76 | 0.788 |

TABLE 3 Comparison of radiographic parameters between both groups.

| | TLSO group | LSO group | *P* value |
|---|---|---|---|
| Baseline main curve (°) | 34.68 ± 6.40 | 32.99 ± 6.88 | 0.252 |
| Baseline minor curve (°) | 25.98 ± 7.47 | 18.71 ± 5.95 | <0.001* |
| Minor curve/main curve (%) | 74.50 ± 13.39 | 56.71 ± 13.47 | <0.001* |
| In-brace main curve (°) | 11.95 ± 8.29 | 13.11 ± 7.54 | 0.515 |
| CR of main curve (%) | 67.50 ± 19.94 | 61.39 ± 19.85 | 0.170 |
| In-brace minor curve (°) | 12.48 ± 7.85 | 11.59 ± 6.18 | 0.578 |
| CR of minor curve (%) | 54.32 ± 23.66 | 37.92 ± 26.80 | 0.004* |
| Last main curve (°) | 27.02 ± 10.75 | 26.03 ± 10.21 | 0.669 |
| Last minor curve (°) | 22.64 ± 9.98 | 18.79 ± 8.59 | 0.067 |

CR, correction rate.
*Means significantly different.

There was no significant difference at the last follow-up for the treatment outcomes of the main curves (Table 4, $P = 0.761$). Regarding the minor curves, 21 patients had improved, 15 patients were stabilized, and 8 patients had progressed in the TLSO group. On the other hand, 7 patients had improved, 21 patients were stabilized, and 10 patients had progressed in the LSO group. The LSO group had worse treatment outcomes on minor curves than did the TLSO group ($P = 0.017$). To further investigate the factors that influence the outcomes of minor curves in the LSO group, a binary logistic regression analysis was conducted. The results showed that the initial curve magnitude of minor curves was an independent risk factor ($P = 0.007$). The ROC curve determined that a minor curve of 21° was the best cut-off value to predict the treatment outcome of minor curves. The area under the ROC curve was 0.793, with a sensitivity of 80.0% and a specificity of 82.1%, indicating good predictive capability.

# 4 Discussion

The present study aims to evaluate whether LSO is effective in the conservative treatment of AIS in patients with main TL/L and minor thoracic curves. To the best of our knowledge, this is the first study to compare the treatment outcomes of TL/L and thoracic curves between LSO and TLSO.

We found that for the main TL/L curves, both groups showed significant improvement (both $P < 0.001$), decreasing from 34.68° ± 6.40° to 27.02° ± 10.75° and from 32.99° ± 6.88° to 26.03° ± 10.21°, respectively. The high IBC rate (averaging more than 60%) and good bracing compliance may account for the satisfactory outcomes observed. However, only patients in the TLSO group demonstrated improvement for minor thoracic curves ($P = 0.001$), decreasing from 25.98° ± 7.47° to 22.64° ± 9.98°, while the LSO group showed almost no change from 18.71° ± 5.95° to 18.79° ± 8.59° ($P = 0.918$). Moreover, the evolution of the curve magnitude also showed significantly better results in the TLSO group [47.7% (21/44) improved; 34.1% (15/44) were stabilized; and 18.2% (8/44) progressed] than in the LSO group [18.4 (7/38) improved; 55.3% (21/38) were stabilized; and 26.3% (10/38) progressed]. Therefore, the treatment outcomes of minor thoracic curves in the LSO group were worse than in the TLSO group. These results were consistent with our hypothesis. We also found that the initial thoracic curve magnitude was an independent risk factor for treatment outcomes of minor thoracic curves in the LSO group. Patients with minor thoracic curves of less than 21° may achieve better outcomes after LSO treatment based on the ROC results (Figure 1). Lastly, patients in the LSO group scored significantly higher on the BrQ than those in the TLSO group (81.92 ± 4.19 vs. 79.36 ± 4.40, $P < 0.001$), suggesting that LSO offers advantages in terms of improved quality of life and better compliance in clinical practice.

TABLE 4 Comparison of treatment outcomes between both groups.

| | TLSO group | LSO group | *P* value |
|---|---|---|---|
| Main curve | | | |
| Improve | 30 | 23 | 0.761 |
| Stabilize | 8 | 9 | |
| Progress | 6 | 6 | |
| Minor curve | | | |
| Improve | 21 | 7 | 0.017* |
| Stabilize | 15 | 21 | |
| Progress | 8 | 10 | |

*Means significantly different.

In this study, 60.5% (23/38) of patients showed TL/L curve improvement, and 15.8% (6/38) showed curve progression in the LSO group at the last follow-up. The outcomes of our study did not match the levels of curve correction seen in studies on the PASB (94% for thoracolumbar curves and 82.5% for lumbar curves). This discrepancy is likely because the initial curve magnitudes in our study were larger than in previous studies (18, 19). The mean baseline main curve was 32.99° ± 6.88° in this study, while they were 29.30° ± 5.16° for TL curves and 26.4° ± 2.8° for L curves in previous PASB studies. Furthermore, Aulisa et al. performed a long-term follow-up study of more than 10 years and found that the TL/L curves treated using PASB achieved positive long-term outcomes (26). However, minor thoracic curves were not investigated in their articles. Our study determined that a cut-off value of 21° for thoracic curves could predict the outcomes of the LSO group. Therefore, for AIS with a main TL/L curve, LSO may achieve satisfactory outcomes if the thoracic curve is less than 21°. However, if the thoracic curve is more than 21°, TLSO may achieve better control than LSO. Another potential risk of wearing LSO is the rapid progression of the thoracic curve and the need to switch to a long brace during treatment. Although some patients (10/38) in this study encountered thoracic curve progression, no patient was required to change to TLSO because the curve progressions we observed were minimal and acceptable. Moreover, the inclusion of daily physiotherapeutic exercises in the treatment regimen helped control the progression of minor curves. However, if a minor curve rapidly progresses or even exceeds the magnitude of the main curve, switching to TLSO is strongly recommended.

Besides the curve correction for thoracic curves, another difference between TLSO and LSO is patients' compliance with bracing. Theoretically, patients have better adherence to LSO than to TLSO due to its specific designs. Therefore, to eliminate the influence of bracing compliance, only patients with optimal compliance are enrolled in this study to compare the outcomes of TLSO and LSO (19). Numerous studies have identified bracing compliance as a crucial factor that influences treatment outcomes (27, 28). However, numerous factors could affect patients' adherence to braces.

Rahimi et al. concluded that compliance could be enhanced by focusing on factors related to the design and delivery of the brace. Improvements in the appearance and comfort of the brace can enhance psychological acceptance, thereby increasing compliance (29). This approach aligns with the principles of the LSO. Additionally, Karol et al. found that compliance monitoring and effective counseling could enhance patients' adherence (15). Brigham et al. reported that the most critical factors that promoted compliance with brace wearing were a patient's desire to avoid surgery and to prevent curve progression (30). Considering the above, LSO should be a possible solution for AIS with main TL/L curves in clinical practice due to its natural advantages of good compliance and better quality of life.

The main limitation of this study resides in the study design. First, the assignment of patients to the experimental group (LSO) and the control group (TLSO) was not conducted using a randomized, double-blind method. Therefore, a potential selection bias exists. Second, the total sample size of 82 patients is relatively small, which may limit the generalizability of the study's findings. A larger sample size could increase the statistical power and improve the reliability of the results. In the future, a multicenter prospective randomized controlled study of large cohorts is needed to validate the current results.

## 5 Conclusions

Compared to TLSO, LSO demonstrates similar effectiveness for main TL/L curves but is less effective for thoracic minor curves. For patients who have AIS with main TL/L and minor thoracic curves, LSO is a viable option that is associated with a better quality of life in clinical practices. The initial thoracic curve magnitude is a risk factor that affects the treatment outcomes of minor curves, and the cut-off value of 21° may guide the selection of appropriate braces.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Ethics Committee of Xin Hua Hospital affiliated to Shanghai Jiao Tong University School of Medicine (Approval number: XHEC-C-2023-040-1). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

LS: Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. TZ: Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. WS: Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Supervision, Validation, Writing – review & editing. QF: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing. JiY: Data curation, Project administration, Supervision, Writing – review & editing. YD: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing. ZH: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. JuY: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Radiographic and clinical outcomes of robot-assisted pedicle screw instrumentation for adolescent idiopathic scoliosis

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**Introduction:** Pedicle screw instrumentation (PSI) serves as the widely accepted surgical treatment for adolescent idiopathic scoliosis (AIS). The accuracy of screw positioning has remarkably improved with robotic assistance. Nonetheless, its impact on radiographic and clinical outcomes remains unexplored. This study aimed to investigate the radiographic and clinical outcomes of robot-assisted PSI vs. conventional freehand method in AIS patients.
**Methods:** Data of AIS patients who underwent PSI with all pedicle screws between April 2013 and March 2022 were included and retrospectively analyzed; those with hybrid implants were excluded. Recruited individuals were divided into the Robot-assisted or Freehand group according to the technique used. Radiographic parameters and clinical outcome measures were documented.
**Results:** In total, 50 patients (19, Freehand group; 31, Robot-assisted group) were eligible, with an average age and follow-up period of 17.6 years and 60.2 months, respectively, and female predominance (40/50, 80.0%). The correction rates of Cobb's angles for both groups were significant postoperatively. Compared to freehand, the robot-assisted technique achieved a significantly reduced breech rate and provided better trunk shift and radiographic shoulder height correction with preserved lumbar lordosis, resulting in significantly improved visual analog scale scores for back pain from the third postoperative month.
**Conclusion:** Overall, robot-assisted PSI provides satisfactory radiographic and clinical outcomes in AIS patients.

KEYWORDS

robot-assisted, pedicle screw instrumentation, adolescent idiopathic scoliosis, AIS, radiographic, clinical, outcome

Abbreviations

AIS, Adolescent idiopathic scoliosis; CR, correction rate; CSVL, center sacral vertical line; EBL, estimated blood loss; EQ5D, EuroQol five-dimensions; FH, freehand; IQR, interquartile range; LBP, low back pain; LL, lumbar lordosis; LOS, length of stay; ODI, Oswestry disability index; PCOs, posterior column osteotomies; PI, pelvic incidence; PSI, postoperative shoulder imbalance; PT, pelvic tilt; QALYs, quality-adjusted life years; RSH, radiographic shoulder height; RO, robot-assisted; SS, sacral slope; SVA, sagittal vertical axis; TS, trunk shift; VAS, visual analog scale; VTRL, vertical trunk reference line.

# 1 Introduction

Scoliosis, defined as abnormal spinal rotation with a coronal curve greater than 10°, can be classified into three subtypes: congenital, neuromuscular, or idiopathic. Approximately 85% of cases are idiopathic, further categorized by age of onset: infantile (≤2 years), juvenile (3–9 years), and adolescent (≥10 years) (1). Adolescent idiopathic scoliosis (AIS) is the most common form, affecting 1%–3% of children aged 10–16 years (2). Approximately 10% of affected individuals progress and require surgical intervention (3). Surgery is indicated in individuals with a primary curve greater than a Cobb's angle of 45° (2). Correction of spinal deformity is crucial for improving a patient's health-related quality of life. Pedicle screw-only construct is safe, effective and reliable in correcting spinal deformities (4–6) and is still considered the widely accepted surgical option. However, screw implantation is particularly challenging if the patient presents with a higher degree of deformity or hypoplasia of the spinal pedicle (7). Spinal robotic technology offers a solution to this problem (8, 9). The Mazor Robotics's SpineAssist™ became the first FDA-approved robot to guide the placement of pedicle screws in 2004 (10). The accuracy of pedicle screw implantation has been well studied (8, 11, 12). However, there is a paucity of information on the radiographic and clinical outcomes, especially in patients with AIS. This study aimed to investigate the radiographic and clinical outcomes of robot-assisted (RO) pedicle screw instrumentation for AIS compared to those of the conventional freehand (FH) method.

# 2 Materials and methods

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of our institution (No. CE21251B, date of approval: Jul 28, 2021). The requirement for written informed consent was waived by the institutional review board.

## 2.1 Study design

Considering our study's aim, we hypothesized that surgery using the RO technique approach would outperform that using the FH method regarding radiographic and clinical outcomes. To investigate this hypothesis, we consecutively enrolled 50 AIS patients who underwent all-pedicle-screw posterior instrumentation surgeries between April 2013 and March 2022 and analyzed their data. Medical records and radiographic images were retrospectively reviewed. Individuals were recruited according to the following criteria: (1) minimal follow-up period of one year, (2) availability of pre- and postoperative images, (3) all-pedicle-screw construct only, and (4) primary surgery. The exclusion criteria included: (1) congenital vertebral malformation (e.g., hemivertebra, spina bifida) and neuromuscular abnormalities, (2) spinal anchors other than pedicle screws (e.g., hook, clamp, wire), and (3) revision surgery.

The recruited individuals were divided into two cohorts according to the use of the spinal robotic system. All patients underwent conventional surgery before the robotic system was introduced in our institute in 2018. Patients in the RO group underwent surgery with the assistance of Mazor Robotics Renaissance™ (Medtronic, Denver, CO, USA), whereas those in the FH group underwent conventional FH pedicle screw placement. The process of installation and implementation has been explained in detail in a previous article (13).

All surgeries were performed via an open approach with a midline incision. Three brands of pedicle screws were used: Xia™ (Stryker, Kalamazoo, MI, USA), GZ Spinal Fixation System™ (Yi Hua Medical, Taichung, Taiwan), and Wiltrom Spinal Fixation System™ (Wiltrom Medical, Hsinchu, Taiwan). Screw diameters varied from 4.5–6.5 mm. Fusion bed preparation and bone grafting procedures were identical in both groups. We performed posterior column osteotomies (PCOs) at the apex of the scoliosis curve to achieve better correction of the deformity. Thorough decortication of the bilateral lamina was also performed at every level. Local bone chips, along with Bicera™ bone graft substitute (Wiltrom Medical, Hsinchu, Taiwan), were utilized for bone grafting. Lastly, the derotation technique was adapted for reduction of the spinal deformity.

## 2.2 Radiographic parameters

Radiographic parameters observed in both coronal and sagittal radiographs included the following: Cobb's angle, coronal balance, trunk shift (TS), radiographic shoulder height (RSH), thoracic kyphosis, lumbar lordosis (LL), sagittal vertical axis (SVA), pelvic tilt (PT), pelvic incidence (PI), and sacral slope (SS), which were defined according to the Spinal Deformity Study Group manual (14) and measured using Surgimap™ software (Nemaris, New York, NY, USA). Screw density was defined as the total number of pedicle screws implanted per vertebra (15). The correction rate (CR) was calculated using the following formula: (preoperative Cobb's angle − postoperative Cobb's angle)/(preoperative Cobb's angle) × 100% (15). Normative data of the sagittal alignment parameters were extracted from the studies of Yukawa et al. (16) and Zhou et al. (17) in light of the geographical proximity and ethnic similarity, whereas coronal parameters were extracted from the study by Clement et al. (18). All definitions and normative data of these parameters are shown in Table 1 and illustrated in Figure 1. Additionally, the breech rate of the pedicle screws were evaluated on postoperative computed tomography (CT) by Gertzbein and Robbins' classification (19) and further defined as satisfactory (grade A or B) or unsatisfactory (grade C, D, or E) (20).

## 2.3 Clinical outcome measures

Clinical outcome measures included the visual analog scale (VAS) score for back pain, Oswestry Disability Index (ODI), and quality-adjusted life years (QALYs) obtained at each follow-up appointment, including at 1, 3, 6, and 12 months postoperatively.

TABLE 1 Definitions and normative data of radiographic parameters.

| Parameters | Definitions | Normative data (mean ± SD) |
|---|---|---|
| CB | Alignment of C7PL in relation to CSVL. Positive value if C7PL is on the right side. | −4 ± 12 mm (18) |
| TS | Horizontal distance between VTRL and CSVL. A trunk shift to the right of the CSVL is a positive value. | NA |
| RSH | Vertical distance between SHRL and IHRL. Positive value if the right shoulder is up. | 5 ± 10 mm (18) |
| TK | Angle between T4 superior endplate and T12 inferior endplate. | 41.8° ± 11.1° (17) |
| LL | Angle between L1 superior endplate and S1 superior endplate. | 52.4° ± 13.1° (16) |
| SVA | Alignment of C7PL in relation to the posterior-superior corner of S1. Positive value if C7PL lies anteriorly. | −4.6 ± 13.5 mm (16) |
| PT | Angle between a line originating from center of femoral head to midpoint of sacral endplate and VRL. Positive value if VRL lies anteriorly. | 11.4° ± 6.6° (16) |
| PI | Angle between a line originating from center of femoral head to midpoint of sacral endplate and a line perpendicular to center of sacral endplate. | 51.8° ± 11.7° (16) |
| SS | Angle between S1 superior endplate and HRL. | 40.3° ± 9.1° (16) |

CB, coronal balance; TS, trunk shift; RSH, radiographic shoulder height; TK, thoracic kyphosis; LL, lumbar lordosis; SVA, sagittal vertical axis; PT, pelvic tilt; PI, pelvic incidence; SS, sacral slope; C7PL, C7 plumbline; CSVL, center sacral vertical line; VTRL, vertical trunk reference line; SHRL, superior horizontal reference line; IHRL, inferior horizontal reference line; VRL, vertical reference line; HRL, horizontal reference line; NA, not available; SD, standard deviation.

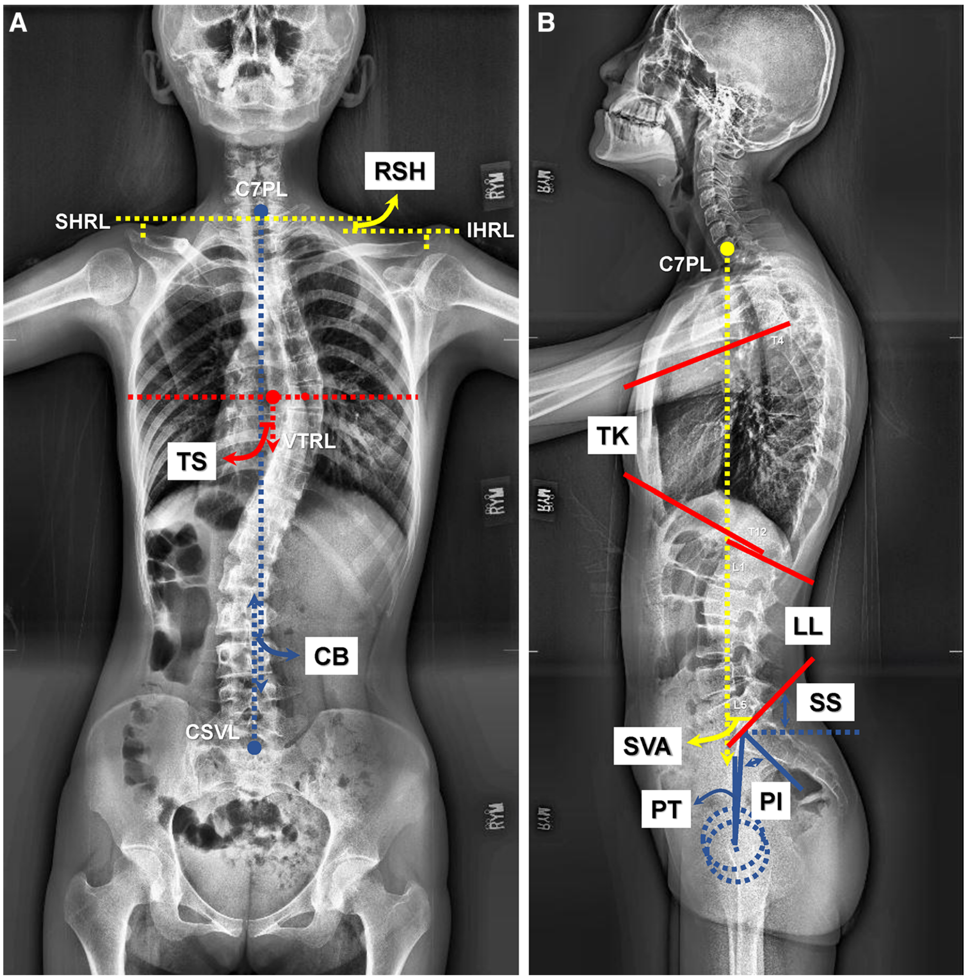


FIGURE 1
Illustration of the coronal and sagittal parameters on plain films. (A) Methods of measurement of the coronal parameters including coronal balance (CB), trunk shift (TS), and radiographic shoulder height (RSH) on plain anteroposterior radiograph. (B) Methods of measurement of the sagittal parameters including thoracic kyphosis (TK), lumbar lordosis (LL), sagittal vertical axis (SVA), pelvic tilt (PT), pelvic incidence (PI), and sacral slope (SS) on plain lateral radiograph.

Initially, the patients completed the EuroQol five-dimensions (EQ5D) questionnaire, which was further converted to QALYs using the Japanese value set published by Tsuchiya (21).

## 2.4 Statistical analysis

The Mann–Whitney *U*-test and chi-squared test were used for continuous variables and categorical variables, respectively. Data in the tables are presented as medians with interquartile ranges (IQRs) enclosed by square brackets for continuous variables, and frequency with percentage enclosed by parentheses for categorical variables. The difference of radiographic parameters between pre- and postoperative values were analyzed using the Wilcoxon signed-rank test. Statistical analysis was conducted by professional statisticians affiliated with our institution using the SPSS 25 software (IBM, Armonk, NY, USA). The significance level was set at $p < 0.05$.

# 3 Results

## 3.1 Patient demographics and perioperative details

In total, 50 patients (19, FH group; 31, RO group) were eligible, with an average age of 17.6 years, an average follow-up period of 60.2 months, and female predominance (40/50, 80.0%). The demographic characteristics and preoperative status of the enrolled patients are outlined in Table 2, and there were no significant differences, except for the follow-up period. The perioperative details are described in Table 3. The Wiltrom Spinal Fixation System™ was utilized for 88.0% of all participants, and the proportion of brands used by the two groups was identical, $p = 0.661$. The RO technique placed significantly more pedicle screws per patient (median: 21.0, IQR: 17.0–24.0) than the FH group (13.0, 8.0–15.0), $p < 0.001$, while vertebrae instrumented per patient were similar. Consequently, the RO group achieved significantly higher pedicle screw density (2.0, 1.8–2.0) than the FH group (1.1, 0.8–1.8), $p < 0.001$. The correction rates were 59.1% for the FH group and 61.5% for the RO group, $p = 0.204$. The operative time was significantly prolonged with the assistance of the robot, at 510.0 (403.0–607.0) min, compared to 375.0 (299.0–450.0) min for FH surgery, $p = 0.005$. Nonetheless, operative time per screw was not different, 25.0 min for the RO group and 23.4 min for the FH group, $p = 0.662$. Additionally, the estimated blood losses (EBL) were not statistically different: 1,200.0 (800.0–2,700.0) ml for the RO group and 800.0 (700.0–1,700.0) ml for the FH group, $p = 0.131$. The EBL per screw were also similar, 70.6 and 72.7 ml for the RO and FH groups, respectively, $p = 0.484$. The average length of stay (LOS) was less for the RO group [7.0 (6.0–8.0) days] than that for the FH group [8.0 (7.0–9.0) days], although this was not statistically significant, $p = 0.123$.

TABLE 2 Overview of the demographic characteristics of the two groups.

| | FH group ($n = 19$) | | RO group ($n = 31$) | | *p*-value |
|---|---|---|---|---|---|
| Age (years) | 17.0 | [15.0–19.0] | 16.0 | [14.0–21.0] | 0.561 |
| Sex | | | | | |
| Female, *n* (%) | 14 | (73.7%) | 26 | (83.9%) | 0.474 |
| BMI (kg/m$^2$) | 18.3 | [15.9–19.1] | 17.6 | [16.8–21.1] | 0.624 |
| Curve type, *n* (%) | | | | | |
| 1 | 4 | (21.1%) | 8 | (25.8%) | 0.106 |
| 2 | 1 | (5.3%) | 10 | (32.3%) | |
| 3 | 4 | (21.1%) | 3 | (9.7%) | |
| 4 | 3 | (15.8%) | 1 | (3.2%) | |
| 5 | 6 | (31.6%) | 9 | (29.0%) | |
| 6 | 1 | (5.3%) | 0 | (0.0%) | |
| Preoperative Cobb's angle (°) | 57.7 | [44.8–76.8] | 61.8 | [47.8–75.3] | 0.920 |
| Preoperative VAS | 1.0 | [0.0–2.0] | 3.0 | [0.0–6.0] | 0.216 |
| Preoperative ODI | 2.2 | [0–15.6] | 11.1 | [0–15.6] | 0.095 |
| Preoperative QALYs | 0.8 | [0.7–1.0] | 0.8 | [0.5–1.0] | 0.214 |
| Follow-up (months) | 98.0 | [63.0–110.0] | 37.0 | [24.0–45.0] | <0.001* |

FH, freehand; RO, robot-assisted; BMI, body mass index; Curve type: the Lenke classification system for AIS. VAS, visual analog scale; ODI, Oswestry disability index; QALYs, quality-adjusted life years. Mann–Whitney *U*-test was applied for continuous variables. Chi-squared test was applied for categorical variables. Data presentation: median [interquartile range]; frequency (percentage).
*Indicates $p < 0.05$.

TABLE 3 Perioperative details of the two groups.

| | FH group | | RO group | | *p*-value |
|---|---|---|---|---|---|
| Implant brands, *n* (%) | | | | | |
| Stryker | 3 | | | | 0.661 |
| Wiltrom | 16 | (15.8%) | 28 | (90.3%) | |
| GZ | | (84.2%) | 3 | (9.7%) | |
| Screws inserted per patient | 13.0 | [8.0–15.0] | 21.0 | [17.0–24.0] | <0.001* |
| Vertebrae instrumented per patient | 12.0 | [8.0–13.0] | 11.0 | [10.0–13.0] | 0.628 |
| Screw density | 1.1 | [0.8–1.8] | 2.0 | [1.8–2.0] | <0.001* |
| Postoperative Cobb's angle (°) | 22.8 | [13.6–43.3] | 21.8 | [16.9–28.3] | 0.332 |
| Correction rate (%) | 59.1 | [48.5–71.6] | 61.5 | [58.9–72.7] | 0.204 |
| Operative time (min) | 375.0 | [299.0–450.0] | 510.0 | [403.0–607.0] | 0.005* |
| Operative time per screw (min) | 23.4 | [17.4–34.0] | 25.0 | [22.3–28.8] | 0.662 |
| EBL (ml) | 800.0 | [700.0–1,700.0] | 1,200.0 | [800.0–2,700.0] | 0.131 |
| EBL per screw (ml) | 72.7 | [50.0–113.3] | 70.6 | [37.5–127.8] | 0.484 |
| LOS (days) | 8.0 | [7.0–9.0] | 7.0 | [6.0–8.0] | 0.123 |

FH, freehand; RO, robot-assisted; EBL, estimated blood losses; LOS, length of stay. Mann–Whitney *U*-test for continuous variables. Chi-squared test for categorical variables. Data presentation: median [interquartile range]; frequency (percentage).
*Indicates $p < 0.05$.

## 3.2 Radiographic parameters

There were no significant differences in preoperative radiographic parameters between the two groups (Table 4). Table 5 further demonstrates the influence of surgical intervention on radiographic parameters, comparing both surgical methods. Patients in both groups had significantly improved Cobb's angles

TABLE 4 Preoperative radiographic parameters of the two groups.

| | FH group | | RO group | | *p*-value |
|---|---|---|---|---|---|
| Cobb's angle (°) | 57.7 | [44.8–76.8] | 61.8 | [47.8–75.3] | 0.920 |
| CB (mm) | −9.9 | [−13.8–11.8] | −1.5 | [−15.5–13.8] | 0.826 |
| TS (mm) | 7.2 | [−20.9–20.1] | 12.4 | [−4.3–27.1] | 0.194 |
| RSH (mm) | 10.4 | [−7.1–22.4] | 11.4 | [2.6–21.9] | 0.569 |
| TK (°) | 24.2 | [8.5–40.9] | 22.0 | [14.7–33.7] | 0.813 |
| LL (°) | 55.5 | [46.4–67.9] | 53.5 | [40.3–59.6] | 0.330 |
| SVA (mm) | −28.0 | [−40.2–10.5] | 9.9 | [−10.3–22.9] | 0.071 |
| PT (°) | 5.1 | [−0.7–15.2] | 9.8 | [1.2–13.9] | 0.646 |
| PI (°) | 43.4 | [36.8–55.5] | 46.4 | [38.4–52.7] | 0.835 |
| SS (°) | 40.4 | [36.1–44.3] | 38.5 | [31.1–46.0] | 0.656 |

FH, freehand; RO, robot-assisted; CB, coronal balance; TS, trunk shift; RSH, radiographic shoulder height; TK, thoracic kyphosis; LL, lumbar lordosis; SVA, sagittal vertical axis; PT, pelvic tilt; PI, pelvic incidence; SS, sacral slope. Mann–Whitney *U*-test was performed. Data presentation: median [interquartile range].

after corrective surgery. The RO technique provided a greater corrective force for TS (from 12.4 to −5.3 mm) and RSH (from 11.4 to −1.2 mm), both $p = 0.001$. The postoperative LL of both groups was within the normal range, while FH surgeries significantly reduced the LL from 56.0° to 47.4°, $p = 0.013$. FH surgery significantly changed the SVA, from negative to positive (−28.0–11.8 mm, $p = 0.017$). In contrast, the SVA in the RO group remained similar postoperatively. None of the three spinopelvic parameters, including PT, PI, and SS, differed postoperatively in either group. The breech rate of the pedicle screws was significantly lower for the RO group (9.5%) compared to the FH group (32.3%), $p < 0.001$ (Table 6).

## 3.3 Clinical outcome measures

All three clinical outcome measures (VAS score for back pain, ODI, and QALYs) were similar preoperatively between the two cohorts as shown in Table 2. Table 7 further compares clinical outcome measures between groups preoperatively and at each follow-up point. Postoperative changes in the ODI and QALYs were not significantly different between the two groups, except for at the third month postoperatively ($\Delta ODI_{3m}$, $p = 0.031$). The

TABLE 6 Breech rates of the pedicle screws of the two groups.

| | FH group (*n* = 127) | RO group (*n* = 497) | *p*-value |
|---|---|---|---|
| Satisfactory, *n* (%) | 86 (67.7%) | 450 (90.5%) | <0.001* |
| Unsatisfactory, *n* (%) | 41 (32.3%) | 47 (9.5%) | |

FH, freehand; RO, robot-assisted; Satisfactory: Gertzbein and Robbins classification grade A or B; Unsatisfactory: Gertzbein and Robbins classification grade C, D, or E. Chi-squared test was performed. Data presentation: frequency (percentage).
*Indicates $p < 0.05$.

patients who underwent RO surgery experienced improved VAS scores from the third month postoperatively ($\Delta VAS_{3m}$), $p = 0.017$, as compared to those in the FH group, until the last follow-up one year after surgery ($\Delta VAS_{12m}$). Figure 2 demonstrates the trend in VAS changes. Postoperative $\Delta VAS_{12m}$ in both groups was significantly improved from preoperative values. To compare the radiographic outcomes of the two surgical techniques, we present one case each for the two cohorts (Figures 3, 4).

# 4 Discussion

The RO technique may outperformed the conventional FH posterior instrumentation surgery for AIS patients in certain aspects. However, the follow-up period was significantly shorter in the RO group, as the Renaissance™ robotic system was not introduced in our institute until 2018. A higher pedicle screw density was attained with RO compared to that with the FH method. The correction rates were similar, at approximately 60%. The operative time per screw and EBL per screw did not differ between the two surgical methods.

Both groups underwent an open approach with a midline incision, with similar LOS in both groups; this correlates with the findings by Schatlo et al. (22) that LOS was not statistically different between RO and conventional FH open-approach techniques (9.8 days vs. 10.3 days), $p = 0.390$. Hyun et al. (23) compared robot-guided minimally invasive surgery and fluoroscopic-guided open surgery, with LOS reported to be 6.8

TABLE 5 Comparison of the preoperative and postoperative radiographic parameters for the FH and RO groups.

| | FH group | | | | | RO group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Preoperative | | Postoperative | | *p*-value | Preoperative | | Postoperative | | *p*-value |
| Cobb's angle (°) | 57.7 | [44.8–76.8] | 22.8 | [13.6–43.3] | <0.001* | 61.8 | [47.8–75.3] | 21.8 | [16.9–28.3] | <0.001* |
| CB (mm) | −9.9 | [−13.8–11.8] | −10.2 | [−18.2 to −5.9] | 0.092 | −1.5 | [−15.5–13.8] | −9.4 | [−17.3–3.8] | 0.210 |
| TS (mm) | 7.2 | [−20.9–20.1] | −7.4 | [−18.6 to −2.8] | 0.103 | 12.4 | [−4.3–27.1] | −5.3 | [−13.1–6.3] | 0.001* |
| RSH (mm) | 10.4 | [−7.1–22.4] | 0.0 | [−6.2–10.3] | 0.198 | 11.4 | [2.6–21.9] | −1.2 | [−8.9–10.6] | 0.001* |
| TK (°) | 24.2 | [12.8–45.9] | 31.3 | [14.1–41.2] | 0.575 | 22.1 | [14.7–33.7] | 20.0 | [13.5–23.8] | 0.118 |
| LL (°) | 56.0 | [49.1–71.9] | 47.4 | [40.8–51.9] | 0.013* | 53.5 | [40.3–59.6] | 48.8 | [37.9–53.1] | 0.104 |
| SVA (mm) | −28.0 | [−40.2–10.5] | 11.8 | [−1.9–29.1] | 0.017* | 3.9 | [−9.3–22.9] | 5.5 | [−16.5–16.1] | 0.447 |
| PT (°) | 4.1 | [−2.4–14.9] | 2.3 | [−1.3–20.7] | 0.333 | 6.8 | [−2.1–11.3] | 7.9 | [−0.6–18.0] | 0.119 |
| PI (°) | 43.3 | [36.3–56.1] | 39.0 | [36.5–53.0] | 0.262 | 43.3 | [34.9–49.5] | 42.3 | [35.9–51.8] | 1.000 |
| SS (°) | 41.4 | [35.2–46.3] | 38.1 | [32.3–39.2] | 0.066 | 38.5 | [25.6–45.5] | 37.4 | [28.4–41.7] | 0.256 |

FH, freehand; RO, robot-assisted; CB, coronal balance; TS, trunk shift; RSH, radiographic shoulder height; TK, thoracic kyphosis; LL, lumbar lordosis; SVA, sagittal vertical axis; PT, pelvic tilt; PI, pelvic incidence; SS, sacral slope. Wilcoxon signed-rank test was performed. Data presentation: median [interquartile range].
*Indicates $p < 0.05$ between preoperative and postoperative values within each group.

TABLE 7 Median changes (Δ) of clinical outcome measures of the two groups.

| VAS | $\Delta VAS_{1m}$ | $\Delta VAS_{3m}$ | $\Delta VAS_{6m}$ | $\Delta VAS_{12m}$ |
|---|---|---|---|---|
| FH group | 0 [−1.0–2.0] | 0 [−2.0–1.0] | 0 [−2.0–1.0] | 0 [−2.0–0] |
| RO group | −1.0 [−4.0–1.0] | −3.0 [−5.5–0] | −3.0 [−6.0–0] | −3.0 [−6.0–0] |
| *p*-value | 0.053 | 0.017* | 0.011* | 0.040* |
| **ODI** | $\Delta ODI_{1m}$ | $\Delta ODI_{3m}$ | $\Delta ODI_{6m}$ | $\Delta ODI_{12m}$ |
| FH group | 22.2 [6.7–26.7] | 8.9 [−2.2–15.6] | 4.4 [−2.2–11.1] | 0 [−6.7–6.7] |
| RO group | 13.3 [4.5–22.2] | −2.2 [−14.5–8.9] | −2.2 [−22.2–8.9] | −12.2 [−25.6–6.1] |
| *p*-value | 0.272 | 0.031* | 0.100 | 0.308 |
| **QALYs** | $\Delta QALYs_{1m}$ | $\Delta QALYs_{3m}$ | $\Delta QALYs_{6m}$ | $\Delta QALYs_{12m}$ |
| FH group | −0.06 [−0.19–0.03] | 0 [0–0.21] | 0.02 [0–0.27] | 0.19 [0–0.27] |
| RO group | −0.07 [−0.28–0.18] | 0.06 [0–0.33] | 0.23 [0–0.51] | 0.17 [0–0.54] |
| *p*-value | 0.775 | 0.181 | 0.167 | 0.371 |

FH, freehand; RO, robot-assisted; VAS, visual analog scale; ODI, Oswestry disability index; QALYs, quality-adjusted life years; $\Delta VAS_{1m}$, the change in VAS for back pain between the first month postoperatively and preoperative value; $\Delta VAS_{3m}$, the 3rd month; $\Delta VAS_{6m}$, the 6th month; $\Delta VAS_{12m}$, the 12th month; $\Delta ODI_{1m}$, the change in ODI between the first month postoperatively and preoperative value; $\Delta ODI_{3m}$, the 3rd month; $\Delta ODI_{6m}$, the 6th month; $\Delta ODI_{12m}$, the 12th month; $\Delta QALYs_{1m}$, the change in QALYs between the first month postoperatively and preoperative value; $\Delta QALYs_{3m}$, the 3rd month; $\Delta QALYs_{6m}$ the 6th month; $\Delta QALYs_{12m}$, the 12th month. Mann–Whitney *U*-test was performed. Data presentation: median [interquartile range].
*Indicates $p < 0.05$ between the two groups.

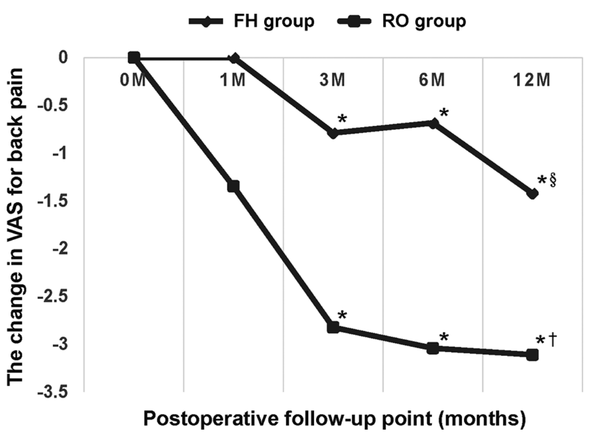


FIGURE 2
This line graph represents the change in visual analog score (VAS) score for back pain of the two groups at each follow-up point compared with preoperative value. The robot-assisted (RO) technique significantly outperformed conventional freehand (FH) surgery from the third postoperative month. * Indicates $p < 0.05$ between the two groups. § Indicates the significant improvement of $\Delta VAS_{12m}$ in the FH group compared with preoperative value ($p < 0.05$). † Indicates the significant improvement of $\Delta VAS_{12m}$ in the RO group compared with preoperative value ($p < 0.05$).

days vs. 9.4 days, $p = 0.020$. It can be concluded that the surgical approach, open or minimally invasive, independently affects LOS, regardless of robotic use (9, 23).

A retrospective multicenter study of postoperative TS in patients with AIS deemed a horizontal deviation greater than 2 cm of the vertical trunk reference line (VTRL) from the center sacral vertical line (CSVL) post-surgically as positive TS. The prevalence of positive TS was found to reduce from 29.3% to 13.6% after surgical intervention (24), similar to the results of our study (from 48.0% to 8.0%). We further conducted the McNemar test to analyze the change in positive TS postoperatively using two different techniques. The TS for the RO group was significantly reduced from 45.1% to 3.2%, $p < 0.001$, a larger reduction than that for the FH group (52.7%–15.8%), $p = 0.065$. Patient without trunk shift preoperatively who developed trunk shift after the surgery was considered iatrogenic. In the FH group, two patients (10.5%) exhibited iatrogenic trunk shift, while in the RO group, there were no instances (0%). The RO technique provides more effective correction for TS, and also reduces the risk of iatrogenic trunk shift compared to the FH method.

The existing literature primarily focuses on using RSH as a parameter to predict postoperative shoulder imbalance (PSI). Unbalanced shoulders are defined as having an RSH of 10 mm or more (25). Studies have identified preoperative RSH as an independent predictor of PSI (26). Our data suggest that shoulder imbalance shows significant improvement after RO surgery, in contrast to the FH group, where RSH remains relatively unchanged. We recommend considering RO surgery for patients with preoperative shoulder imbalance to achieve better RSH correction and thereby reduce the risk of PSI.

Due to the financial limitations imposed by our National Health Insurance system, titanium rod remains the sole option for posterior spinal instrumentation in our healthcare setting. Previous literature suggests that cobalt-chromium rods are generally considered better than titanium rods for effectively reducing the rate of rod fractures, correcting spinal deformities, and ensuring postoperative stability (27, 28). Limited to using titanium rods, we need to increase pedicle screw density to effectively and safely perform the reduction by derotation technique with the rods. Through preoperative planning and the assistance of a robot during surgery, surgeons are able to implant a greater number of pedicle screws, achieving a higher screw density.

Postoperative plain radiographs demonstrated significantly reduced LL values for patients in the FH group, whereas RO surgery maintained the LL. Iatrogenic loss of LL is a disabling complication after corrective scoliosis surgery, resulting in the inability to stand upright and back pain (29). Chun et al. (30) also reported a strong relationship between low back pain (LBP)

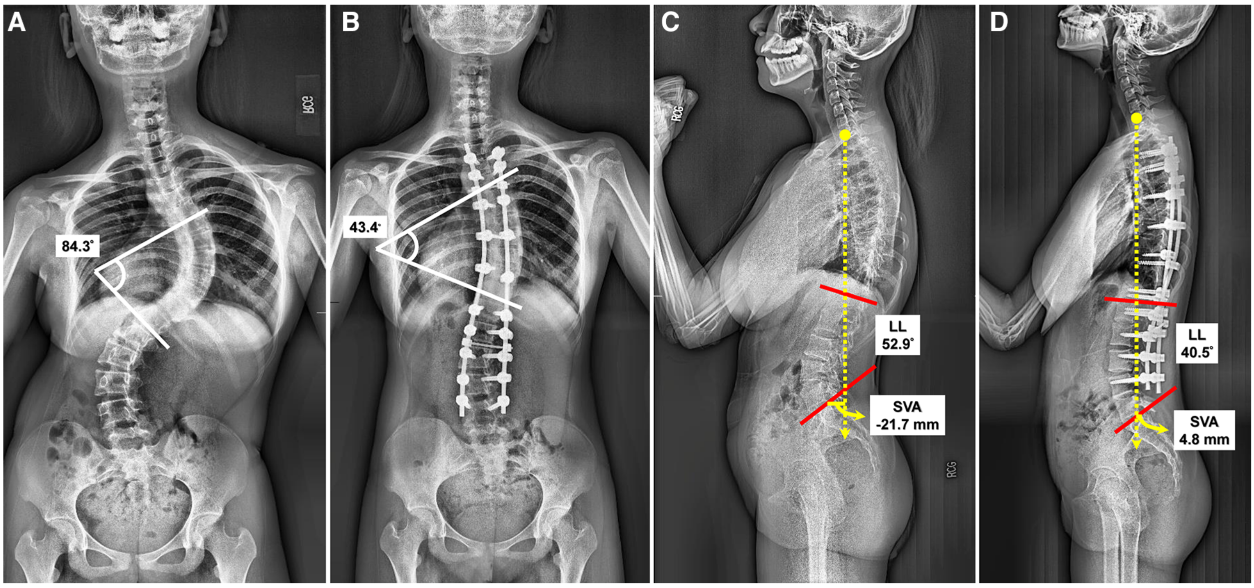


FIGURE 3
A female classified as lenke 3CN received freehand surgery at the age of 14 years. (A) The preoperative anteroposterior (AP) radiograph revealed a Cobb's angle of 84.3°. (B) The postoperative AP radiograph revealed a Cobb's angle of 43.4°, and correction rate (CR): 48.52%. The screw density was 1.43. (C) The preoperative lateral view showed lumbar lordosis (LL): 52.9°, and sagittal vertical axis (SVA): −21.7 mm. (D) The postoperative lateral view showed reduced LL (40.5°), and anteriorly moved SVA (4.8 mm).

and lumbar lordotic angle. Given this evidence, we concluded that the RO technique could provide sustained postoperative LL, resulting in less LBP than the conventional FH method. This corresponded with our finding of significantly improved back pain three months postoperatively ($\Delta VAS_{3m}$) with the use of a robot. We suggest that special attention should be paid while

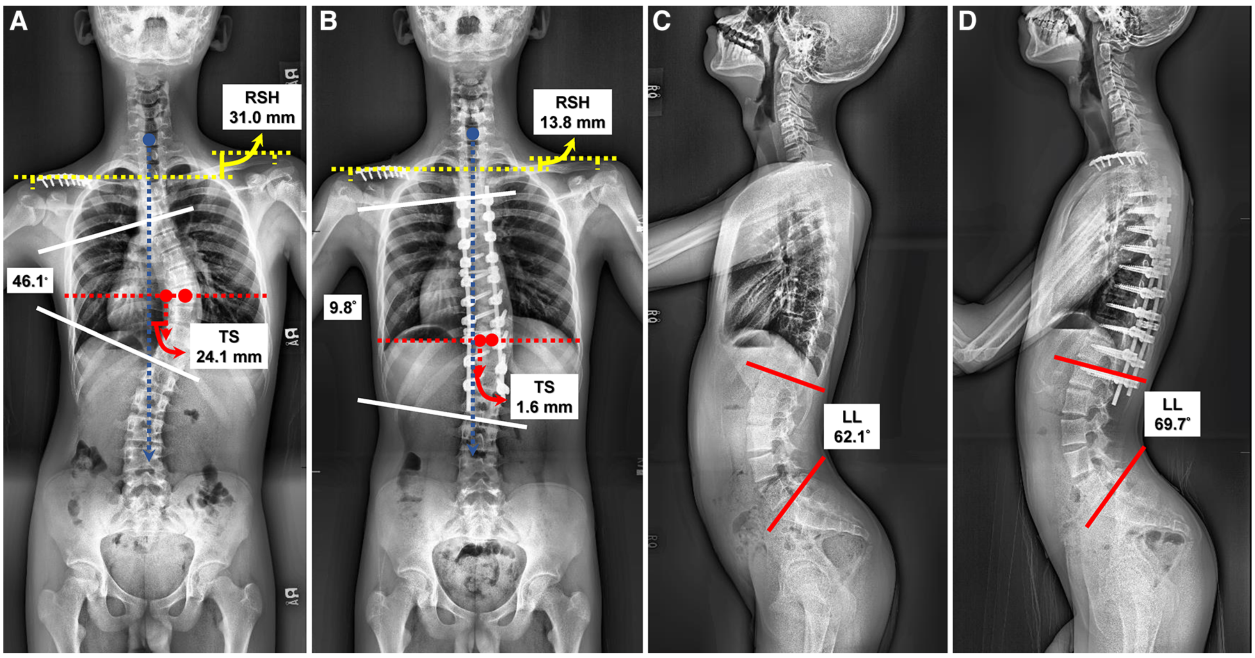


FIGURE 4
Another 14-year-old male with Lenke 1A- scoliosis underwent robot-assisted surgery. (A) The preoperative anteroposterior (AP) radiograph revealed a Cobb's angle of 46.1°, radiographic shoulder height (RSH): 31.0 mm, and trunk shift (TS): 24.1 mm. (B) The postoperative AP radiograph revealed a Cobb's angle of 9.8°, correction rate (CR): 78.74%, improved RSH (13.8 mm) and TS (1.6 mm). The screw density was 2.00. (C) The preoperative lateral view showed lumbar lordosis (LL): 62.1°. (D) The postoperative lateral view showed preserved LL (69.7°).

operating on patients with especially small LL using the traditional FH method.

We observed that SVA was significantly increased, moving anteriorly, after conventional FH surgery, but remained unchanged in the RO group. The postoperative SVAs for both groups were within the physiological range of the child (−31.6–22.4 mm). Notably, postoperative SVA in the FH group was beyond the normal range (9.5 mm) of the adult Schwab Adult Spinal Deformity Classification (31). The RO technique may be better for sustaining patient SVA.

As for the accuracy of RO pedicle screw instrumentation, previous studies have already verified its accuracy, ranging from 90% to 100% (32). In our study, the rate of satisfactory screw position was 90.5%; we believe that this is related to the pedicle hypoplasia commonly present in AIS patients. Additionally, we aimed to achieve a higher screw density when performing surgery. Provided that the screw could reach the vertebral body during preoperative planning, we could specially design an "in-out-in" trajectory for some patients with pedicle hypoplasia. To avoid medial wall violation, it is feasible to increase the total number of pedicle screws in a safe way (only lateral breech), and further achieve better corrective force. Conversely, such a trajectory could not be designed preoperatively if using the conventional FH method, and we would rather not insert screws at the vertebrae of patients with pedicle hypoplasia.

Our data demonstrates that the RO group had a significantly lower breach rate compared to the FH group (9.5% vs. 32.3%, $p < 0.001$). This reduced breach rate allows for the successful placement of a larger number of pedicle screws, significantly increasing screw density. Hwang et al. have reported that high-density pedicle screw constructs lead to better deformity correction in AIS patients (33). The RO technique, by achieving higher screw density, provides stronger spinal fixation, enabling surgeons to safely perform more effective deformity corrections.

The changes in the ODI and QALYs after surgery were not significantly different between the two groups, except for $\Delta ODI_{3m}$. However, all patients reported better function and quality of life 12 months postoperatively compared with that observed preoperatively. The VAS for back pain was the main clinical parameter that verified the superiority of the RO surgery. The RO technique outperformed conventional FH surgery at alleviating LBP from the third postoperative month ($\Delta VAS_{3m}$). This correlated with the radiographic finding that RO surgery could maintain postoperative LL, resulting in reduced LBP compared with that with the conventional FH method.

Costa et al. (34) performed a biomechanical study and found that a misplaced screw in the craniocaudal direction was associated with significantly less primary stability than screws in the centered sagittal position. Açikbaş et al. (35) also found that significant spinal motion on flexion-extension radiographs was observed in patients with screw misplacement, and this significant motion was correlated with more intense back pain. Robotic technology has demonstrated significantly superior accuracy with fewer misplaced pedicle screws compared to that with conventional techniques (8, 11, 12), providing stability to the spinal structures and further alleviating back pain.

To our knowledge, this study is the first to highlight the radiographic and clinical outcomes of RO pedicle screw instrumentation in patients with AIS; this is clinically important in assisting surgeons with adopting RO techniques.

## 5 Limitations

First, the sample size was small, which could be owing to the inclusion of only all-pedicle-screw construct and exclusion of hybrid implants. Second, there is chronological bias. Before the robotic system was first introduced in our institute in 2018, patients could only choose conventional FH surgery, which caused a significant difference in follow-up time between the two groups. Finally, data from only one institute were included.

## 6 Conclusions

Overall, RO pedicle screw instrumentation achieves a significantly reduced breech rate and provides satisfactory radiographic and clinical outcomes in AIS patients. TS and RSH were significantly corrected with preserved LL, resulting in an improved VAS score for back pain.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Institutional Review Board of Taichung Veterans General Hospital (No. CE21251B, date of approval: Jul 28, 2021). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the consent was not necessary according to the official ethics regulation of our institution and considering the retrospective design of this study.

## Author contributions

Y-SC: Conceptualization, Methodology, Writing – original draft. Y-HL: Formal Analysis, Software, Writing – original draft. Y-CW: Investigation, Visualization, Writing – original draft. C-MS: Data curation, Resources, Writing – original draft. K-HC: Validation, Writing – review & editing. C-HL: Project administration, Writing – review & editing. W-HL: Supervision, Writing – review & editing. C-CP: Conceptualization, Methodology, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Prevalence and plasma exosome-derive microRNA diagnostic biomarker screening of adolescent idiopathic scoliosis in Yunnan Province, China

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**Background:** Idiopathic scoliosis significantly affects the physical and mental health of children and adolescents, with varying prevalence rates in different regions. The occurrence of idiopathic scoliosis is associated with genetic regulation and biochemical factors, but the changes in exosome-derived miRNA profiles among idiopathic scoliosis patients remain unclear. This study aimed to determine the prevalence of idiopathic scoliosis in Yunnan Province, China, and identify key exosome-derived miRNAs in idiopathic scoliosis through a cohort study.
**Methods:** From January 2018 to December 2020, a cross-sectional study on idiopathic scoliosis in children and adolescents was conducted in Yunnan Province. A total of 84,460 students from 13 cities and counties in Yunnan Province participated in a scoliosis screening program, with ages ranging from 7 to 19 years. After confirmation through screening and imaging results, patients with severe idiopathic scoliosis and normal control individuals were selected using propensity matching. Subsequently, plasma exosome-derived miRNA sequencing and RT-qPCR validation were performed separately. Based on the validation results, diagnostic performance analysis and target gene prediction were conducted for differential plasma exosome-derived miRNAs.
**Results:** The overall prevalence of idiopathic scoliosis in children and adolescents in Yunnan Province was 1.10%, with a prevalence of 0.87% in males and 1.32% in females. The peak prevalence was observed at age 13. Among patients diagnosed with idiopathic scoliosis, approximately 12.8% had severe cases, and there were more cases of double curvature than of single curvature, with thoracolumbar curvature being the most common in the single-curvature group. Sequencing of plasma exosome-derived miRNAs associated with idiopathic scoliosis revealed 56

Abbreviations
IS, idiopathic scoliosis; AIS, adolescent idiopathic scoliosis; miRNA, microRNAs; RPM, revolutions per minute; RT-Qpcr, real-time fluorescence quantitative PCR; SSS, school screening for scoliosis; ATR, angle of trunk rotation; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; $\chi^2$, Chi-square test; ROC, subject operating characteristics.

upregulated and 153 downregulated miRNAs. Further validation analysis confirmed that hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246 have potential diagnostic value.
**Conclusions:** We gained insights into the epidemiological characteristics of idiopathic scoliosis in Yunnan Province and conducted further analysis of plasma exosome-derived miRNA changes in patients with severe idiopathic scoliosis. This study has provided new insights for the prevention and diagnosis of idiopathic scoliosis, paving the way for exploring clinical biomarkers and molecular regulatory mechanisms. However, further validation and elucidation of the detailed biological mechanisms underlying these findings will be required in the future.

KEYWORDS

idiopathic scoliosis, children and adolescents, Yunnan region, school scoliosis screening, plasma exosome-derived miRNA, biomarkers

# 1 Introduction

Scoliosis is a three-dimensional spinal deformity characterized by a coronal curvature exceeding 10° and accompanied by vertebral rotation. Idiopathic scoliosis (IS) is the most common type of scoliosis, adolescent idiopathic scoliosis (AIS) referring to IS with onset between the ages of 10 and 18, accounting for approximately 90% of IS cases (1). AIS develops faster during adolescence. Without early detection and intervention, as the degree of deformity worsens, low back pain, impaired cardiorespiratory function, and nerve damage or even paraplegia eventually occur, severely affecting the physical and mental health of children and adolescents (2). Therefore, early detection and intervention is the current consensus in the treatment of AIS. The diagnosis and screening of AIS primarily rely on the patient's clinical appearance and x-ray images. However, the United States Preventive Services Task Force and the American Academy of Family Physicians recommend against routine scoliosis screening for asymptomatic adolescents due to its low specificity, potentially subjecting many low-risk adolescents to unnecessary x-rays and referrals (3–5). In clinical practice, when patients present with asymmetry in physical appearance, the best time for conservative treatment has often been missed. So, there is an urgent need to find new diagnostic markers for AIS to facilitate early screening for AIS.

The influence of factors such as region, ethnicity, and lifestyle, as well as differences in research methods and inclusion criteria, has led to significant variations in the prevalence of AIS (6). Globally, the prevalence of AIS ranges from approximately 0.47% to 5.2%. The prevalence is higher in females than in males, with female-to-male ratios ranging from 1.5 to 11 (7, 8). In China, the prevalence of AIS is reported to be between 0.11% and 2.6%, with most data originating from economically developed eastern and southern regions, while there is limited reporting of AIS prevalence in western China (9, 10). Yunnan, located on the southwestern border of China and situated on the Yunnan-Guizhou Plateau, is home to 26 different ethnic groups, making it the province with the most diverse national minority in China. As a result, the prevalence of scoliosis in this region may differ. But the epidemiological characteristics of AIS among primary and secondary school students in this area remain unclear.

AIS arises from complex interactions between genetic and environmental factors, and these interactions are mediated through integrated biological and biomechanical mechanisms (7). Environmental, nutritional, and lifestyle factors can modulate the epigenome, thereby promoting AIS progression (11). Consequently, epigenetics holds the potential to provide new biomarkers for the diagnosis and prognosis of AIS, aiding in the analysis of the molecular factors underlying the disease. RNA serves as a vital epigenetic regulatory entity. Studies have demonstrated that the expression levels of key messenger RNAs, microRNAs (miRNAs), or long noncoding RNAs are associated with the height of AIS patients, and their expression varies among different developmental stages, Cobb angles, and Risser grades (12–15). Exosome-derived miRNAs in peripheral blood are considered significant contributors to osteogenesis and bone metabolism. They are closely associated with intervertebral disc degeneration. This makes them intriguing biological molecules for investigating the causes of AIS (16–19). However, research on exosome-derived miRNAs in AIS is still in its nascent stage.

This study was based on the results of school scoliosis screening (SSS) conducted in 13 regions of Yunnan Province, China, involving children and adolescents aged 7–19 years. The aim was to investigate the characteristics and prevalence of AIS in Yunnan Province and to provide more theoretical basis for the control of AIS in Yunnan Province. Additionally, a portion of AIS patients and age-matched individuals with normal spine conditions were selected from the screened population, and their plasma samples were collected for the sequencing and bioinformatics analysis of AIS-related peripheral blood exosome-derived miRNAs. Real-time quantitative PCR (RT-qPCR) was employed to validate the expression of these exosome-derived miRNAs, laying the foundation for exploring early AIS-specific molecular markers and potential mechanisms.

# 2 Methods

## 2.1 Study design and subjects

This study was divided into two phases. The first phase involved a cross-sectional SSS study in children and adolescents in Yunnan Province. It was conducted in school health clinics from January

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2018 to December 2020. The study covered 13 different regions in Yunnan Province, including Kunming City, Zhaotong City, Shangri-La City, Yuxi City, Chuxiong City, Dali Prefecture, Wenshan Prefecture, Honghe Prefecture, Qujing City, Pu'er City, Lijiang City, Lincang City, and Tengchong City. Primary school students, junior high school students, high school students, and students enrolled in vocational high schools from different schools in the 13 cities and municipalities were randomly selected as the study subjects, and the age range of the participants in the survey was mainly 7–19 years.

The second phase involved radiological assessment and the screening of AIS plasma markers. All subjects identified as potentially having scoliosis through the initial screening were referred to local medical facilities for radiological assessments. Upon completion of the imaging assessment and regular follow-up, peripheral blood was collected for study use if the subject met the inclusion and exclusion criteria for plasma exosomal molecular marker screening. The inclusion criteria for plasma exosomal molecular marker screening comprised the following: individuals diagnosed with AIS, with a Cobb angle greater than 40°, at risk of progressive Cobb angle increase during follow-up, without prior surgical treatment, and aged between 10 and 18 years. Exclusion criteria included bad habits such as smoking, the occurrence of active infections or inflammatory diseases within the last one month, long-term use of drugs affecting bone metabolism, neurological pathologies, congenital developmental anomalies or nutritional deficiencies, and a history of tumours. Students who did not provide consent to participate in the study either themselves or through their guardians were also excluded. Additionally, a subset of adolescents aged 10–18 years who were physically healthy and free of AIS were also recruited as a control group, and their peripheral blood was collected for the study.

The study was approved by the schools in the surveyed area and the Medical Research Ethics Committee of the First Affiliated Hospital of Kunming Medical University (2022-L152). Parents or guardians provided consent for students to participate in this study before the students completed the surveys and underwent imaging assessments. All the subjects in this study provided written consent for their samples and related information to be used in this study. All experimental procedures, protocols and methods were in accordance with relevant clinical guidelines and regulations, following standard operating procedures.

## 2.2 Phase one screening methodology and procedures

Prior to their participation in the SSS, uniform training was provided to all screening inspectors. The screening process primarily consisted of two steps. First, students underwent the Adam Forwards Bend Test to observe whether they exhibited any signs of chest asymmetry, shoulder blade asymmetry, waist asymmetry, pelvic tilt, or deviation of the spinous process line from the midline (20). Students who were positive for one of these were further examined for angle of trunk rotation (ATR) (6). Following the guidelines established by the International Society on Scoliosis Orthopaedic and Rehabilitation Treatment (21) and the Screening Criteria for Scoliosis in China (GB/T 16133–2014) (6), students with an ATR ≥ 5° were considered to have suspected positive results in the scoliosis screening. They were subsequently referred to a hospital for confirmation of the condition through full-length spinal x-ray examinations.

## 2.3 Phase two screening methodology and procedures

For students with suspected positive results, anterior-posterior and lateral x-ray images of the spine were taken, and the Cobb angle was measured using the standard Cobb method. Students with a Cobb angle ≥10° were diagnosed with scoliosis. Information such as age, sex, ethnicity, family history, place of origin, educational stage, and anthropometric measurements (including height, weight, and sitting height) was collected for students who were confirmed through radiological methods. Additionally, information on neurological, muscular, or skeletal conditions was gathered to exclude congenital scoliosis, neuromuscular scoliosis or other related conditions. Students with a Cobb angle ≥10° and <20° were advised to undergo regular observation, while those with a Cobb angle ≥20° and <40° were recommended to undergo rehabilitation exercises or wear orthotic devices under the guidance of healthcare professionals. Students with a Cobb angle ≥40° were advised to undergo surgical treatment (22). Selected AIS subjects and healthy individuals who met the inclusion exclusion criteria for the plasma exosomal molecular marker screening study were recruited at this stage. Peripheral blood was collected for subsequent studies after signing an informed consent form.

## 2.4 Peripheral blood plasma collection and study subgroups

For volunteers providing peripheral blood, 10 ml of fasting peripheral venous blood was collected in EDTA-K2 anticoagulant tubes. After collection, samples were centrifuged at 3,500 rpm for 5 min using a low-speed refrigerated centrifuge (5702R, Eppendorf, Germany) to remove blood cells and platelets, and 3–4 ml of the plasma supernatant was collected. Purified samples were then labelled and stored in liquid nitrogen. For all the collected plasma samples, the AIS group and the normal control group were matched one-to-one based on age, sex, and ethnicity using propensity score matching. After grouping, one group was randomly selected for the isolation and identification of plasma exosomes, while six other groups underwent high-throughput sequencing of exosome-derived miRNAs. The remaining groups were subjected to RT-qPCR validation based on the sequencing results.

## 2.5 Plasma exosome isolation and purification

The 4 ml plasma samples were rapidly thawed at 37°C. Exosome isolation and purification were performed using the

Plasma/Serum Exosome Purification Kit (Qiagen, Norgen Biotek, Canada) following the manufacturer's instructions. Initially, the plasma was diluted by adding 12 ml of nuclease-free water, followed by the addition of 300 µl of ExoC Buffer and 400 µl of Slurry E. After being incubated at room temperature for 5 min, the mixture was centrifuged at 2,000 revolutions per minute (RPM) for 2 min to remove the supernatant. Subsequently, 400 µl of ExoR Buffer was added, and the mixture was incubated for 10 min. Afterwards, it was centrifuged using a spin column at 6,000 RPM for 1 min, resulting in purified exosomes.

## 2.6 Exosome identification

The purified exosomes were subjected to transmission electron microscopy, size analysis, immunofluorescence and nanoflow cytometry detection. For transmission electron microscopy, 10 µl of exosomes was dropped onto a copper grid, allowed to settle for 1 min, and then stained with uranyl acetate (Sigma-Aldrich, USA). After incubation and drying, the exosomes were imaged using a Hitachi HT-7700 transmission electron microscope at 100 kV. A 10 µl aliquot of exosome sample was initially diluted to 30 µl. Subsequently, the exosome size was analysed using an N30E size analyser (NanoFCM, China). A 30 µl aliquot of diluted exosome sample was mixed with 20 µl of fluorescently labelled antibodies, including CD9 (FITC Mouse Anti-Human CD9, BD) and CD81 (FITC Mouse Anti-Human CD81, BD). The mixture was incubated in the dark for 30 min. Subsequently, it was subjected to ultracentrifugation at 110,000 ×g and 4°C for 70 min twice to obtain the supernatant. Afterwards, the exosomes were resuspended in 50 µl of PBS and analysed using a nanoscale flow cytometer (NanoFCM, China).

## 2.7 Plasma exosome-derived miRNA sequencing

After propensity matching, a total of 6 sample groups were selected (AIS patients = 6, healthy individuals = 6) for exosome-derived miRNA sequencing analysis. Following sample thawing, exosomes were purified using the Plasma/Serum Exosome Purification Kit (Qiagen, Norgen Biotek, Canada). Exosome-derived miRNA was extracted using the Exosomal RNA Isolation Kit (Qiagen, Norgen Biotek, Canada) according to the manufacturer's protocol. The extracted exosome-derived miRNA was then amplified. TruSeq Small RNA Sample Prep Kits (Illumina, San Diego, USA) were employed for library preparation. Sequencing was carried out using the Illumina Hiseq2000/2500 platform with a single-end sequencing read length of 1 × 50 bp.

## 2.8 Analysis of sequencing results

After sequencing was completed, the data were analysed using the miRNA data analysis software ACGT101-miR (LC Sciences, Houston, Texas, USA). The analysis process was as follows: the raw data were processed by quality control to obtain clean reads, and the 3' junctions were removed from the clean reads and screened based on length, retaining sequences with base lengths of 18–26 nt. The remaining sequences were filtered against the mRNA database, RFam database and Repbase database, and the non-miRNA components, such as ribosomal RNA, transfer RNA, mini-RNA and minicellular RNA, were excluded, while the remaining were considered valid data. Then, the valid data from the AIS and normal groups were compared, and the exosome-derived miRNAs with $P < 0.05$ and with 2-fold higher or lower expression in each AIS sample than in the matched normal sample were selected as the candidate differential exosome-derived miRNAs.

## 2.9 Validation of candidate exosome-derived miRNAs by RT-qPCR

Candidate exosome-derived miRNAs were subjected to RT-qPCR validation analysis using additional samples from the AIS group ($n = 23$) and the normal group ($n = 23$). Exosome-derived miRNA extraction was performed using the method described above. The NovoScript miRNA First-Strand cDNA Synthesis and SYBR qPCR Kit (Qiagen, Novoprotein, Japan) was utilized following the manufacturer's instructions for first-strand cDNA synthesis and qPCR amplification. A mixture containing 1 µg of miRNA samples, 10 µl of 2× miRNA RT Reaction Mix, 1 µl of NovoScript miRNA RT Enzyme Mix, and 9 µl of nuclease-free water was prepared, with a final volume of 20 µl. The mixture was incubated at 39°C for 60 min, followed by 5 min at 85°C to complete first-strand cDNA synthesis. Two-step amplification was performed using the ABI PRISM 7500 sequence detection system (Applied Biosystems, Bedford, Massachusetts, USA). Each PCR was performed in triplicate. Primer sequences and reference sequences are provided in Supplementary Table S1. The relative expression levels of exosome-derived miRNAs were calculated using the $2^{-\Delta\Delta CT}$ method.

## 2.10 Target gene analysis and statistical analysis of pathway and functional enrichment

The significantly different exosome-derived miRNAs were subjected to target gene prediction using two software programs: TargetScan (v5.0) (23–25) and miRanda (v3.3a) (26–28). Target genes predicted by each software were filtered according to their respective scoring criteria. For the TargetScan algorithm, target genes with context score percentiles below 50 were excluded. For the miRanda algorithm, target genes with a Max Energy greater than −10 were removed. The final target genes of different exosome-derived miRNAs were selected as the intersection of the predictions from these two software programs (i.e., the threshold was set as TargetScan_score ≥ 50 and miranda_Energy < −10). Gene Ontology (GO) enrichment and Kyoto Encyclopedia of

Genes and Genomes (KEGG) enrichment analyses were conducted on the identified target genes.

## 2.11 Statistical analysis

The data from the first stage of the study were entered into a database file using Microsoft Excel 2021, including all questionnaire information, radiological assessment results, and epidemiological survey results. Statistical analysis and result visualization were performed using GraphPad Prism v9.5.0 (GraphPad Software Inc., San Diego, CA). Differences in height, weight, and sitting height between the AIS group and the normal group were compared using independent sample *t* tests or nonparametric tests. Pearson's chi-squared test ($\chi^2$) was used to assess the differences in BMI and educational stage between the AIS and normal groups. $\chi^2$ or Fisher's exact tests were used to compare AIS prevalence among different age groups and sexs, as well as differences in spinal deformity among different AIS subgroups. $P < 0.05$ was considered indicative of statistical significance.

In the second stage of the study, the sequencing results data were first normalized, and the normality of the data was assessed. When biological replicates were present, differences between two sample groups were analysed using the t test, and differences among multiple groups were analysed using ANOVA. When there were no biological replicates, differences between two sample groups were assessed using Fisher's exact test and $\chi^2$, while differences among multiple groups were assessed using $\chi^2$. For RT-qPCR results, differences between two sample groups were calculated using the *t* test or nonparametric tests. The differences between the two sample groups in RT-qPCR results were calculated using either the t test or nonparametric tests. The area under the receiver operating characteristic curve (ROC) was used to evaluate the predictive efficiency of differential exosome-derived miRNAs. All statistical analyses and result visualizations were performed using the OmicStudio tools (at: https://www.omicstudio.cn/tool) or GraphPad Prism v9.5.0 (GraphPad Software Inc., San Diego, CA). $P < 0.05$ was considered indicative of statistical significance.

# 3 Results

## 3.1 Scoliosis screening summary

In this study, a total of 84,460 children and adolescents aged 7–19 years underwent scoliosis screening. These individuals included 41,115 males and 43,345 females, with a male-to-female ratio of 1:1.2. Among the screened individuals, 4,679 (5.54%) were suspected of having scoliosis and underwent radiographic examination and reassessment. Among them, 929 (1.10%) were diagnosed with IS, and 309 (0.37%) were diagnosed with other types of scoliosis. Ultimately, among the confirmed IS patients, 459 (49.41%) were recommended for observation, 338 (36.38%) were advised to undergo rehabilitation via exercise or orthotic wear, and 132 (14.21%) required surgical intervention. Blood plasma samples were collected from patients requiring surgical intervention and from individuals without scoliosis. Subsequently, propensity score matching was performed to obtain 29 sets of AIS samples and normal samples with matched age, sex, and ethnicity. Six groups underwent high-throughput sequencing of exosome-derived miRNAs, while the remaining 23 groups were used for the validation of the diagnostic efficacy of candidate differential exosome-derived miRNAs (Figure 1).

## 3.2 Prevalence of scoliosis stratified by age

The prevalence of IS among the 929 patients was compared by grouping them according to sex and age. The results, as shown in Table 1, illustrate the disease prevalence among different age and sex groups. The overall prevalence rate among males was 0.87%, while among females, it was 1.32%. The overall prevalence rate among females was significantly higher than that among males ($P < 0.05$). The prevalence was higher among females than males at all ages. However, there was no significant difference between the prevalence rates of males and females at ages 7–11 years ($P > 0.05$), and the difference was significant at ages 12–16 years ($P < 0.05$). At age 13, there was a peak in the prevalence of IS among females (2.54%) and males (1.56%). Subsequently, the prevalence rates gradually decreased in both genders, and by the age of 17, there was no statistically significant difference in the prevalence rates between males and females ($P > 0.05$). At the peak of the disease prevalence, females had a prevalence rate 1.62 times higher than that of males.

## 3.3 Participant demographic characteristics and is-related factors

The population characteristics of the participants and the risk factors associated with IS are detailed in Table 2. When comparing the IS group to the normal group, there were no statistically significant differences in height, but there were statistically significant differences in weight and sitting height ($P < 0.05$). In the IS group, 477 individuals (51.35%) had a BMI less than 18.5, while in the normal group, 43,708 individuals (52.52%) had a BMI less than 18.5, with no statistically significant difference between the two groups. Among students attending primary school, junior high school, and high school, there were 262 cases (28.20%), 369 cases (39.72%), and 298 cases (32.08%) of IS, respectively, with the highest prevalence among junior high school students, with a significant difference ($P < 0.0001$).

## 3.4 Characteristics of the spinal deformities in is patients

The prevalence and number of Cobb angles varied by age group. Cobb angles were determined in IS patients of all ages, and it was found that the mean Cobb angle was larger in

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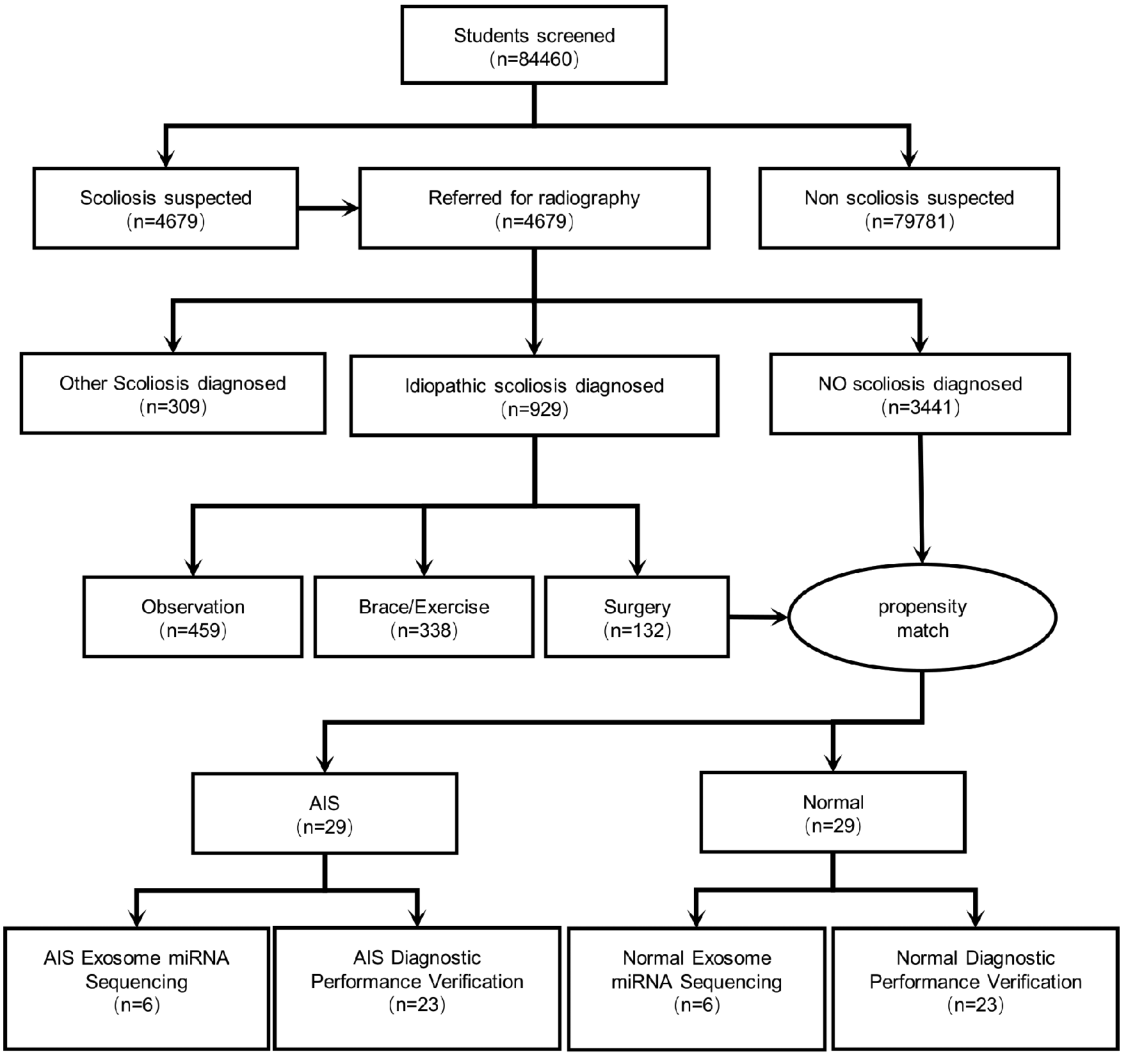


FIGURE 1
Study workflow diagram.

TABLE 1 Prevalence of IS by age and gender.

| Age | Male | | | Female | | | Chi-square | *P* |
|---|---|---|---|---|---|---|---|---|
| | Total number | Scoliosis screening positive | Positive rate % | Total number | Scoliosis screening positive | Positive rate % | | |
| 7 | 3,093 | 6 | 0.19 | 3,128 | 8 | 0.26 | 0.264 | 0.514 |
| 8 | 2,831 | 5 | 0.18 | 2,970 | 5 | 0.17 | 0.005 | 0.939 |
| 9 | 3,025 | 9 | 0.30 | 3,540 | 13 | 0.37 | 0.237 | 0.626 |
| 10 | 3,283 | 20 | 0.61 | 3,432 | 28 | 0.82 | 1.010 | 0.315 |
| 11 | 3,697 | 20 | 0.54 | 3,834 | 34 | 0.89 | 3.162 | 0.0754 |
| 12 | 3,196 | 40 | 1.25 | 3,294 | 74 | 2.25 | 9.305 | 0.002 |
| 13 | 3,077 | 48 | 1.56 | 3,234 | 82 | 2.54 | 7.439 | 0.006 |
| 14 | 3,152 | 47 | 1.49 | 3,352 | 84 | 2.51 | 8.477 | 0.003 |
| 15 | 2,955 | 43 | 1.46 | 3,011 | 65 | 2.16 | 4.154 | 0.041 |
| 16 | 3,178 | 46 | 1.45 | 3,525 | 82 | 2.33 | 6.890 | 0.008 |
| 17 | 3,531 | 40 | 1.13 | 3,570 | 51 | 1.43 | 1.227 | 0.267 |
| 18 | 3,371 | 19 | 0.56 | 3,574 | 28 | 0.78 | 1.247 | 0.264 |
| 19 | 2,726 | 14 | 0.51 | 2,881 | 18 | 0.62 | 0.305 | 0.581 |
| Total | 41,115 | 357 | 0.87 | 43,345 | 572 | 1.32 | 39.51 | 0.0001 |

TABLE 2 Analysis of participants' demographic characteristics and risk factors.

| Variant | IS ($n = 929$) | Normal ($n = 83,222$) | Chi-square/$t$ | $P$ |
|---|---|---|---|---|
| Hight (cm)* | 156.53 ± 14.45 | 156.84 ± 14.95 | 0.650 | 0.5158 |
| Sitting height (cm)* | 82.48 ± 7.78 | 83.23 ± 7.57 | 2.923 | 0.0036 |
| Weight (kg)* | 46.69 ± 10.91 | 47.35 ± 10.33 | 1.835 | 0.0669 |
| BMI ($n$, %) | | | | |
| ≥18.5 | 496 (53.39) | 43,752 (52.57) | 0.2466 | 0.6195 |
| <18.5 | 433 (46.61) | 39,470 (47.43) | | |
| Education level ($n$, %) | | | | |
| Primary School | 262 (28.20) | 38,915 (46.76) | 197.4 | 0.0001 |
| Junior High School | 369 (39.72) | 18,342 (22.04) | | |
| Senior High School | 298 (32.08) | 25,965 (31.20) | | |

IS* data are expressed as the average ± SD.

13- and 15-year-old patients (Figure 2A). Among the 929 scoliosis patients, 121 individuals were classified as having severe scoliosis (Cobb angle ≥ 40°), resulting in a detection rate of 12.80%. The male-to-female ratio was approximately 9:11, and there was no statistically significant difference in the prevalence of severe IS between sexs (Figure 2B). Analysis of the curvature deformities was conducted, and the results indicated that among the 929 IS patients, the most common type of curvature deformity was double major curves. When specifically examining the cases with single-curvature scoliosis, it was observed that the majority of mild cases (10° < Cobb angle < 20°) and moderate cases (20° ≤ Cobb angle < 40°) had left convex thoracolumbar curves. Among the severe cases, the most prevalent type of curvature deformity was right convex thoracolumbar curves (Figure 2C). The number of patients with single- or double-curvature scoliosis differed between the mild group and the moderate and severe groups and did not differ between the moderate and severe groups (Figure 2D). Among patients with single-curvature scoliosis, most had thoracolumbar curvatures, followed by thoracic curvatures, with lumbar curvatures being the least common, and there was no difference in the distribution of curvatures between the groups (Figure 2E). Among mild single-curvature cases, left convex curves were more common than right convex curves. In moderate single-curvature cases, left convex curves were slightly less common than right convex curves, and in severe single-curvature cases, left convex curves were significantly less common than right convex curves. Statistically significant differences were observed among all groups in terms of curve convexity (Figure 2F).

## 3.5 Clinical profile of patients with AIS

In all the collected peripheral blood samples, AIS plasma samples and normal control plasma samples were paired using propensity matching to minimize bias in the results due to age, sex, and ethnicity. This matching process resulted in 29 sets of samples. Six sets were randomly selected for sequencing, while the remaining 23 sets underwent RT-qPCR validation. There were no differences in the corresponding human measurement parameters (BMI, family history, and Risser sign), as shown in Table 3.

## 3.6 Plasma exosome characteristics

This study analysed the characteristics of plasma exosomes in AIS patients. Exosomes were extracted using a centrifugation column method, and the morphology of isolated exosomes was observed using transmission electron microscopy. Both groups of exosomes exhibited a spherical vesicular shape (Figure 3A). The particle size analysis results (Figure 3B) showed that the average particle size of exosomes in the AIS group was 81.83 nm, with a median particle size of 77.25 nm, while in the normal group, the average particle size of exosomes was 81.39 nm, with a median particle size of 77.25 nm. Nanoflow cytometry analysed the surface-tagged proteins CD9 and CD81 on exosomes from both sets of samples and found that both sets of samples expressed both proteins. The results of two randomly selected samples are shown below (Figure 3C).

## 3.7 Sequencing analysis of plasma exosome-derived miRNAs

High-throughput RNA sequencing was employed to analyse the miRNA profiles of plasma exosomes in 6 propensity-matched AIS patients and 6 healthy controls. The obtained sequences were aligned and compared with the mRNA, RFam (which includes rRNA, tRNA, snRNA, and snoRNA sequences), and Repbase databases (Figure 4A). The percentage of identified exosome-derived miRNAs in AIS samples averaged 42.24%, while in the healthy control group, it averaged 44.84%. There was no significant difference between the two groups. The statistical analysis of the identified exosome-derived miRNA lengths (Figure 4B) revealed that the lengths were primarily concentrated between 21 and 23 base pairs, with the highest number of exosome-derived miRNAs having a length of 22 base pairs.

The miRNA expression levels were normalized using ACGT101-miR software, followed by differential expression analysis. A comparison of exosome-derived miRNA expression between the AIS group and the normal group was conducted, and a volcano plot was generated (Figure 4C). Compared to the normal group, there were 209 differentially expressed exosome-derived miRNAs in AIS patients ($P < 0.05$), with 56 upregulated and 153 downregulated miRNAs. Differential exosome-derived miRNAs were also compared between matched samples, and it was observed that the differential exosome-derived miRNAs were different in each group (Supplementary Figure S1).

The biological functions of all differentially expressed exosome-derived miRNAs in AIS patients ($P < 0.05$) were predicted for target genes, followed by GO and KEGG enrichment analyses. The GO enrichment results are shown in the bubble chart (Figure 4D). In the molecular function category, the most significantly enriched and gene-abundant function was related to protein synthesis. In the cellular component category, the most significantly enriched and gene-abundant component was the cytoplasm. In the biological process category, the most significantly enriched and gene-

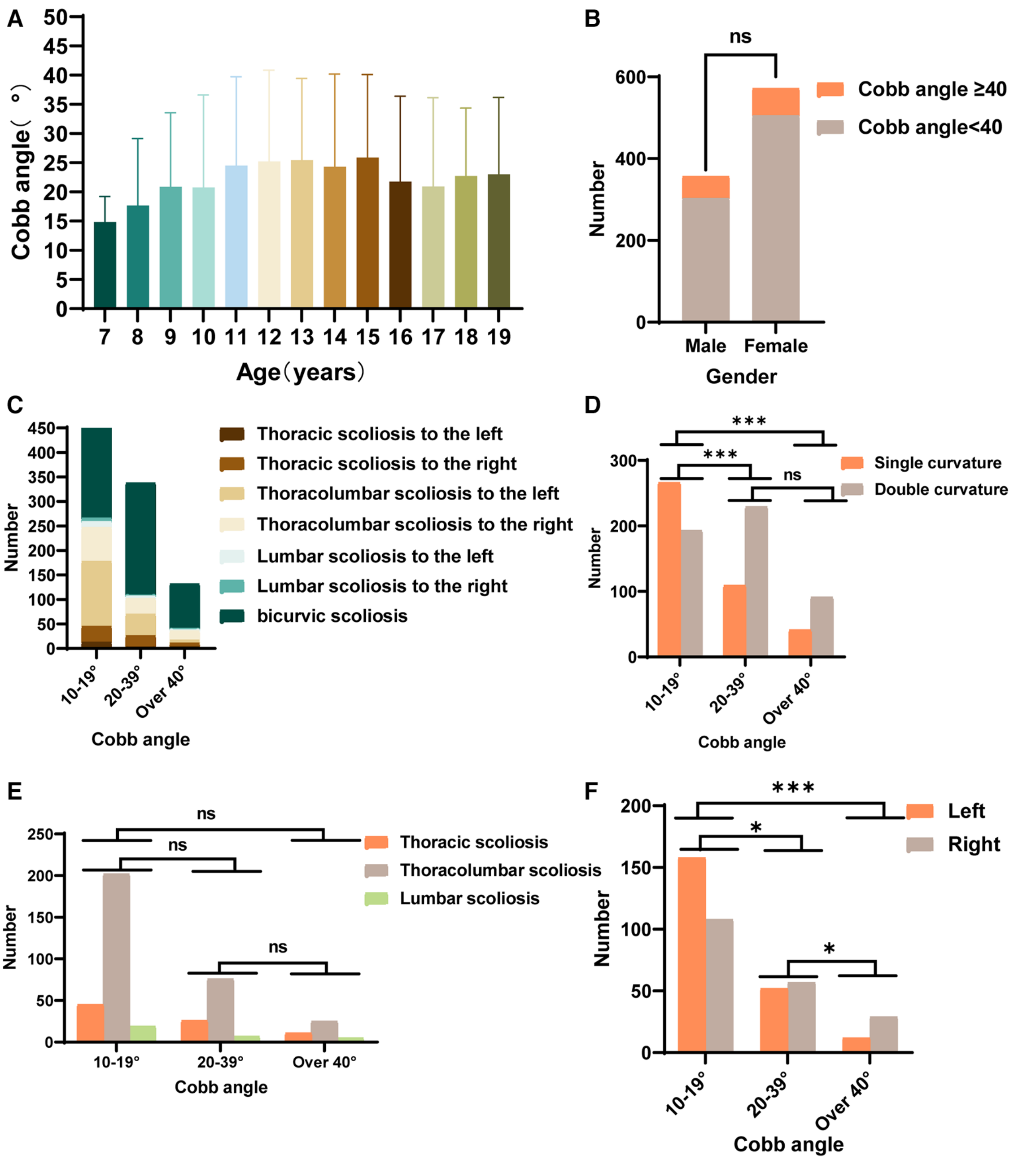


FIGURE 2
Statistics of spinal deformities in IS patients. (A) The distribution of Cobb angles in IS patients across different age groups. (B) The number of males and females with Cobb angles ≥ 40° among IS patients. (C) The distribution of spinal deformity types in IS patients with mild, moderate, and severe curvatures. (D) Statistics for the number of individuals with double curvature and single curvature among IS patients with mild, moderate, and severe curvatures. (E) Statistics for the number of patients with thoracic curvature, thoracolumbar curvature, and lumbar curvature among IS patients with mild, moderate, and severe curvatures. (F) Statistics for the number of IS patients with main spinal curves showing left or right convexity among those with mild, moderate, and severe curvatures. (ns $P > 0.05$, *$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$).

abundant process was positive regulation of transcription by RNA polymerase II. The top 20 KEGG enrichment results are shown in the bubble chart (Figure 4E). The cancer-related signalling pathway had the highest number of enriched genes and was significantly enriched. The enrichment level of the PI3K-Akt signalling pathway was slightly lower than that of the cancer pathway.

## 3.8 Plasma candidate-specific exosome-derived miRNA screening

Comparison of differential exosome-derived miRNAs among the 6 groups and screening for shared differential exosome-derived miRNAs were performed (Figure 5A). A total of 10 miRNAs were screened in the 6 groups, namely, hsa-miR-1246,

TABLE 3 Subject information.

| Variant | Exosome-derived miRNA sequencing groups | | | RT-qPCR validation group | | |
|---|---|---|---|---|---|---|
| | AIS ($n = 6$) | Normal ($n = 6$) | $P$ | AIS ($n = 23$) | Normal ($n = 23$) | $P$ |
| Age[a,b] (year) | 11.83 ± 2.14 | 11.83 ± 2.14 | – | 15.13 ± 2.26 | 15.13 ± 2.26 | – |
| Male/Female[a,b] | 4/2 | 4/2 | – | 6/17 | 6/17 | – |
| BMI (kg/m$^2$) | 18.60 ± 3.37 | 18.87 ± 2.39 | 0.878 | 18.83 ± 3.11 | 18.84 ± 3.19 | 0.9870 |
| Family history | No | No | – | No | No | – |
| Cobb angle (°) | 66.17 ± 15.52 | 0 | – | 52.04 ± 19.93 | 0 | – |
| Risser sign | 0.83 ± 1.33 | 0.67 ± 1.03 | 0.999 | 2.87 ± 1.66 | 2.78 ± 1.62 | 0.7835 |

[a]Represents the information used for propensity matching, which was the same between the two groups.
[b]Values are shown as averages ± SD.

hsa-miR-125b-2-3p, hsa-miR-193b-3p, hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-27a-5p, hsa-miR-454-3p, hsa-miR-490-3p, hsa-miR-539-5p, and hsa-miR-1285-p5. Cluster analysis of the expression levels of these 10 differentially expressed exosome-derived miRNAs in each sample was performed (Figure 5B). Compared to the normal group, hsa-miR-125b-2-3p, hsa-miR-193b-3p, hsa-miR-490-3p, and hsa-miR-1285-p5 in AIS samples exhibited lower expression levels that were inconsistent with other samples. Hsa-miR-1246 and hsa-miR-27a-5p showed decreased expression in all AIS samples, while hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-454-3p, and hsa-miR-539-5p showed increased expression in all AIS samples. Therefore, hsa-miR-1246, hsa-miR-27a-5p, hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-454-3p, and hsa-miR-539-5p were selected as candidate AIS-specific exosome-derived miRNAs in plasma.

## 3.9 RT-qPCR validation of candidate exosome-derived miRNA diagnostic efficacy

Validation of the 6 candidate differentially expressed exosome-derived miRNAs (hsa-miR-1246, hsa-miR-27a-5p, hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-454-3p, hsa-miR-539-5p) in the

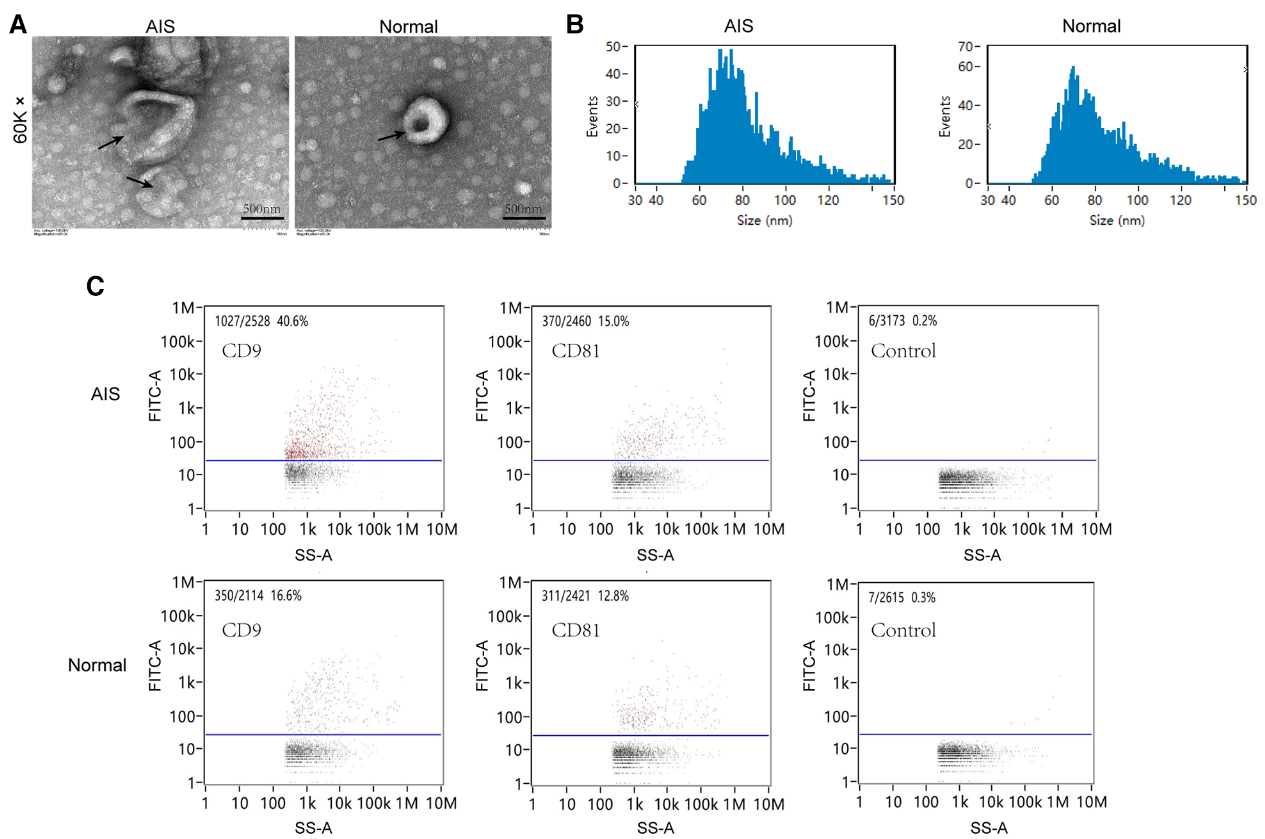


FIGURE 3
Plasma exosome characterization. (A) Transmission electron microscopy scanning of plasma exosomes from AIS and normal samples. (B) Particle size analysis of plasma exosomes in AIS and normal samples. (C) Nano flow cytometry analysis of CD9/CD81 in plasma exosomes from AIS and normal samples.

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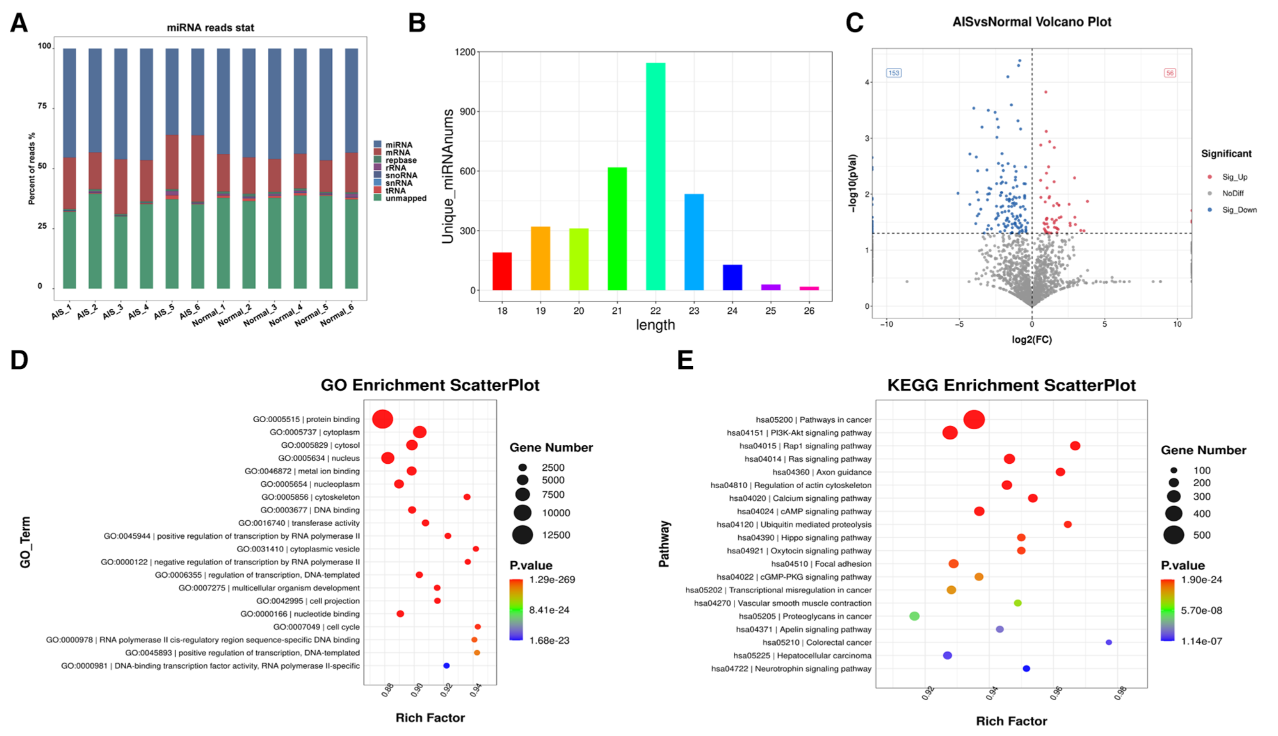


FIGURE 4
Exosome-derived miRNA sequencing. (A) Comparison of sequencing results with various databases. (B) Length distribution of exosome-derived miRNAs. (C) Differentially expressed exosome-derived miRNAs between the AIS group and the normal group ($P < 0.05$). (D) GO-enriched TOP20 bubble plot of differential exosome-derived miRNAs. (E) KEGG-enriched TOP20 bubble plot of differential exosome-derived miRNAs.

plasma samples of 23 AIS patients and 23 normal volunteers was performed using quantitative RT-qPCR technology. Based on the sequencing results, hsa-miR-26a-5p exhibited high expression abundance in all samples and showed minimal differences among the groups. Therefore, it was chosen as an internal reference (29). After normalization using hsa-miR-26a-5p, the expression levels of 6 candidate plasma exosome-derived miRNAs were compared between peripheral blood from AIS patients and that from normal volunteers (Figures 6A–F). The results showed that compared to the normal group, AIS patients had significantly downregulated expression of hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246 in plasma exosomes ($P < 0.05$). However, there was no statistically significant difference in the expression of hsa-miR-20a-5p, hsa-miR-20b-5p, or hsa-miR-454-3p between the two groups ($P > 0.05$). Then, ROC curves were constructed using the normalized $2^{-\Delta\Delta CT}$ values to validate the diagnostic efficacy of these differentially expressed exosome-derived miRNAs for AIS (Figures 6G–L). The results showed that low expression of hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246 was able to successfully differentiate AIS patients from healthy individuals, with AUCs of 0.7722 (95% CI: 0.6360–0.9084, sensitivity = 78.26%, specificity = 69.57%), 0.8422 (95% CI: 0.7314–0.9530, sensitivity = 82.61%, specificity = 69.57%) and 0.7684 (95% CI: 0.6266–0.9102, sensitivity = 78.26%, specificity = 65.22%), respectively.

## 3.10 Differential exosome-derived miRNA target gene prediction and GO and KEGG enrichment analyses

Target gene prediction was conducted for hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246, followed by GO and KEGG enrichment analyses of the predicted target genes. First, the GO enrichment results were categorized and displayed according to biological processes, cellular components, and molecular functions (Figure 7A). The three exosome-derived miRNAs were primarily involved in two biological processes: signal transduction and regulation of RNA polymerase II transcription. They mainly belonged to cellular membrane and cytoplasmic components, and their main molecular function was related to protein synthesis. The top 20 results from GO enrichment and KEGG enrichment are displayed in bubble charts (Figures 7B,C). Among the top 20 enriched KEGG pathways, two pathways of interest were identified: "Endocrine and other factor-regulated calcium reabsorption" and "Signaling pathways regulating pluripotency of stem cells." A miRNA-mRNA-KEGG pathway Sankey diagram (Figure 7D) was created using the genes of interest with significant flow in the two pathways. The majority of the genes shown to be regulated in this diagram were directed towards the "Signaling pathways regulating

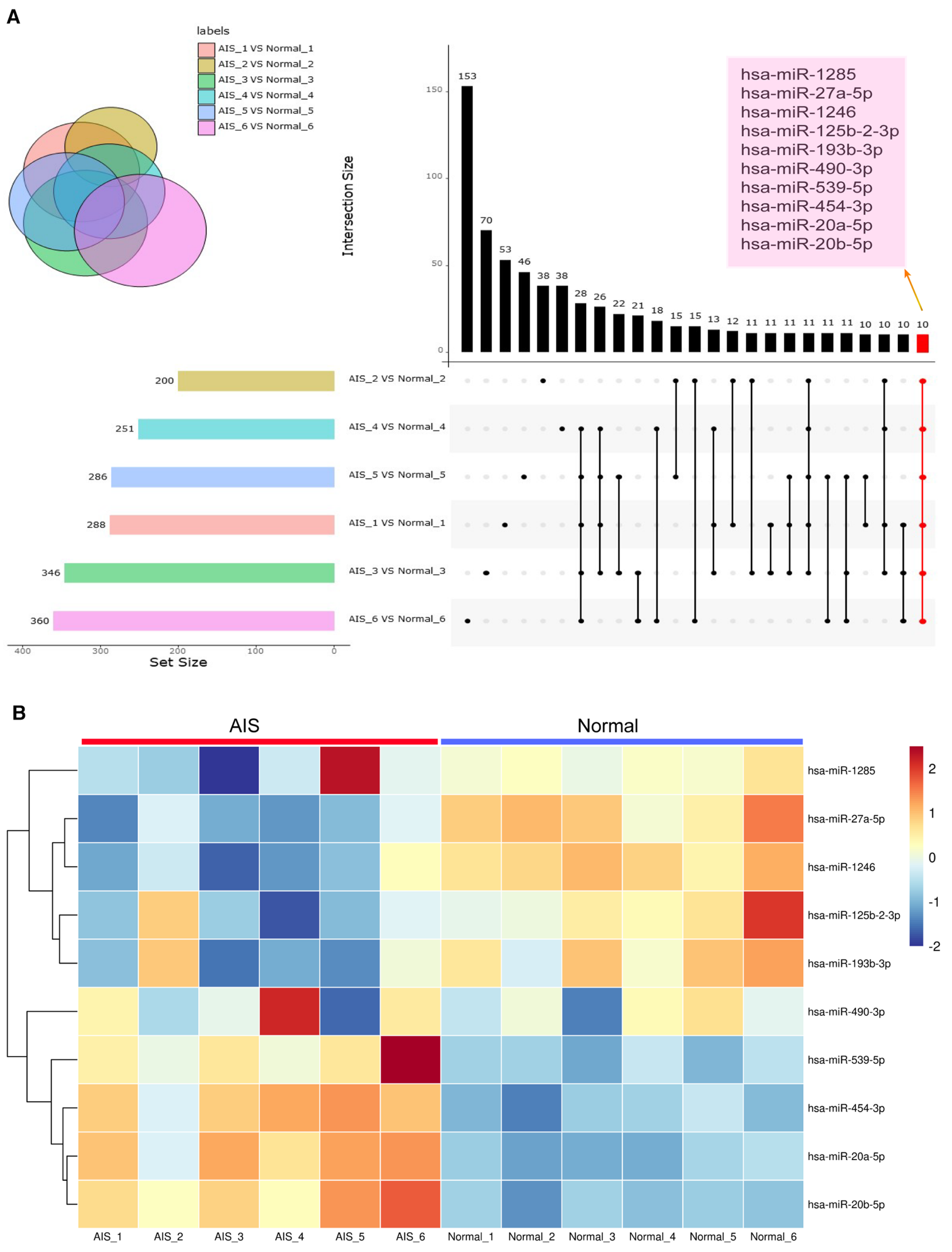


FIGURE 5
Exosome-derived miRNA analysis. (A) The setup figure compares differentially expressed exosome-derived miRNAs in the plasma exosomes of 6 AIS patients and their matched normal controls. The common differentially expressed exosome-derived miRNAs in all 6 groups are highlighted in coloured boxes. (B) The heatmap compares the expression levels of shared differentially expressed exosome-derived miRNAs in 6 AIS patients and 6 normal volunteers.

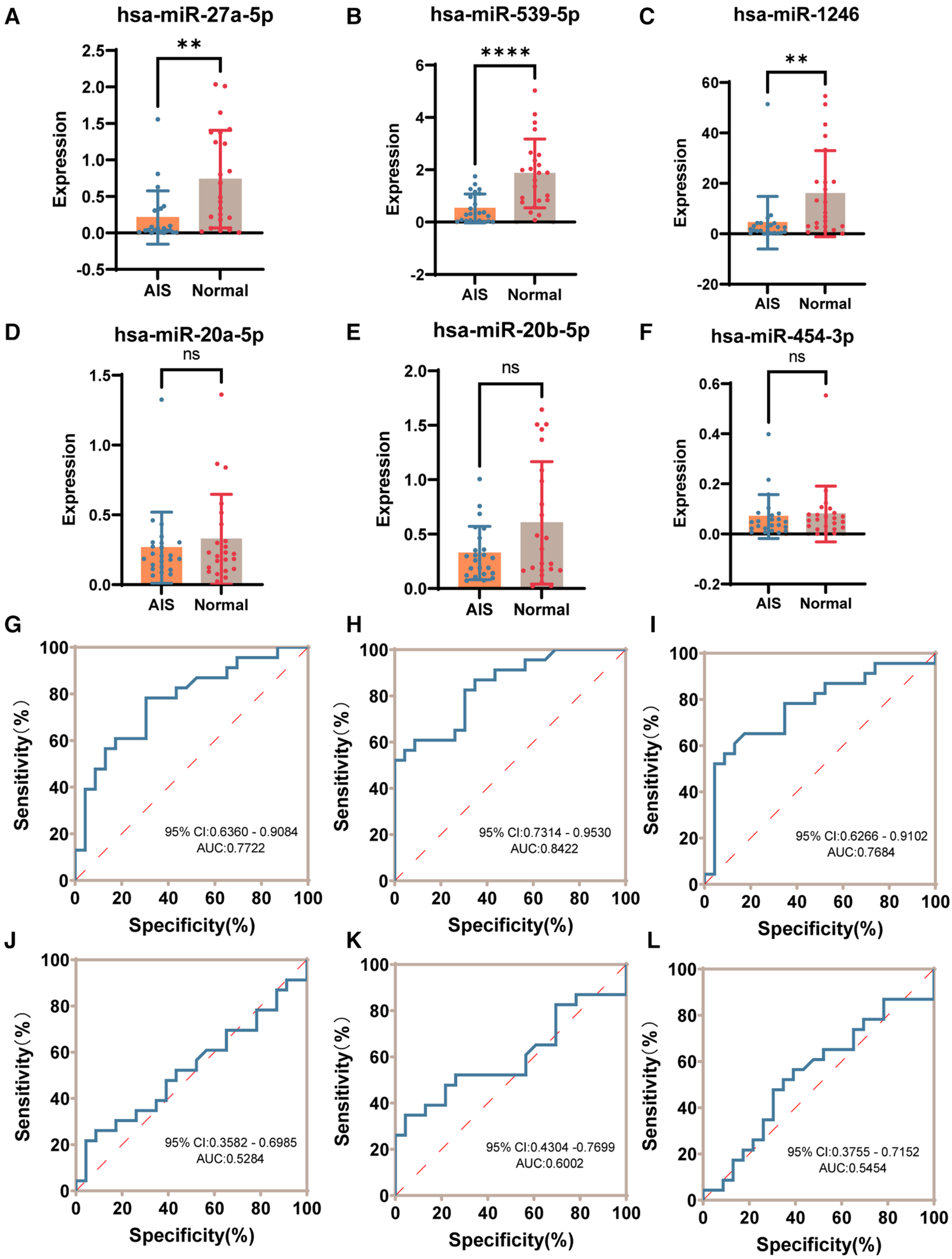


FIGURE 6
RT-qPCR validation of candidate differential exosome-derived miRNAs. (A) Expression of hsa-miR-27a-5p in the AIS and normal groups. (B) Expression of hsa-miR-539-5p in the AIS and normal groups. (C) Expression of hsa-miR-1246 in the AIS and normal groups. (D) Expression of hsa-miR-20a-5p in the AIS and normal groups. (E) Expression of hsa-miR-20b-5p in the AIS and normal groups. (F) Expression of hsa-miR-454-3p in the AIS and normal groups. (G) ROC curve of hsa-miR-27a-5p validating the diagnostic efficacy. (H) ROC curve of hsa-miR-539-5p to validate diagnostic efficacy. (I) ROC curve of hsa-miR-1246 validating the diagnostic efficacy. (J) ROC curve of hsa-miR-20a-5p validating the diagnostic efficacy. (K) ROC curve of hsa-miR-20b-5p validating the diagnostic efficacy. (L) ROC curve of hsa-miR-454-3p validating the diagnostic efficacy. (ns $P > 0.05$, *$P < 0.05$, **$P < 0.005$, ***$P < 0.001$, ****$P < 0.0001$).

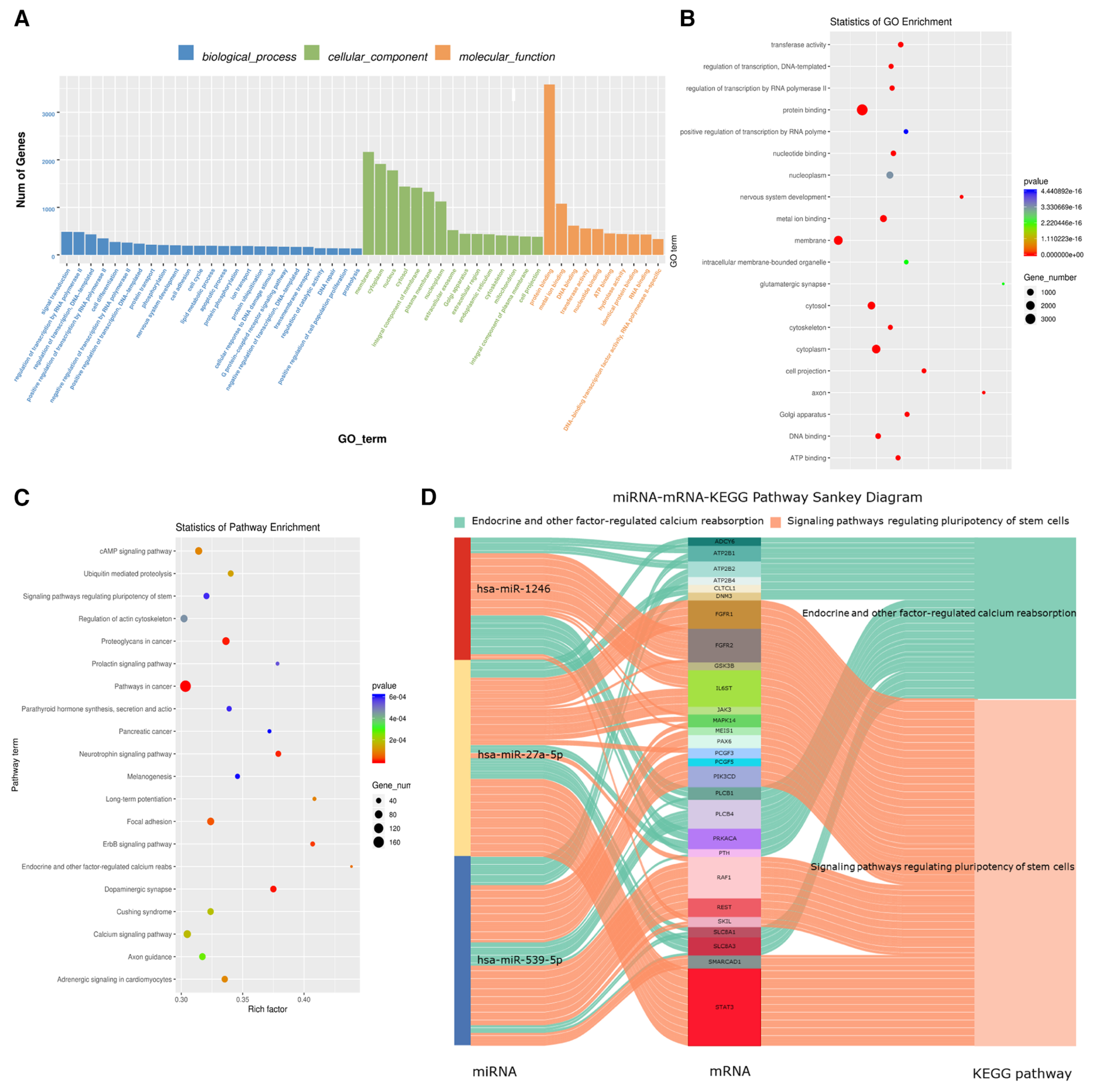


FIGURE 7
AIS plasma-specific exosome-derived miRNA target gene prediction and enrichment analysis. (A) GO enrichment results are categorized according to biological process, cellular component and molecular function. (B) GO enrichment Top 20 bubble chart. (C) KEGG enrichment Top 20 bubble chart. (D) "Endocrine and other factor-regulated calcium reabsorption" and "Signaling pathways regulating pluripotency of stem cells" pathway miRNA-mRNA-KEGG Pathway Sankey diagram.

pluripotency of stem cells" pathway. Specifically, hsa-miR-27a-5p primarily regulated this pathway through STAT3, hsa-miR-539-5p mainly regulated it through RAF1, and hsa-miR-1246 regulated it through FGFR1 and FGFR2. Additionally, both hsa-miR-1246 and hsa-miR-27a-5p jointly regulated IL6ST, which had an impact on this pathway. These results suggest that the dysregulation of the plasma exosome-derived hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246 may be associated with the pathogenesis of AIS.

# 4 Discussion

AIS is the most common type of spinal curvature disorder, and screening for scoliosis in children and adolescents is of significant importance. The Scoliosis Research Society recommends that children undergo scoliosis screening at least 1–2 times at the ages of 10 and 12 to allow for early detection and intervention (30). SSS is considered an effective screening method that helps in the early detection of AIS and in timely intervention, potentially reducing the need for surgical treatment (31–33). This survey conducted through the SSS found that the overall prevalence of IS among 7- to 19-year-olds in Yunnan Province is 1.10%, which is slightly higher than the national prevalence rate (1.02%). However, it falls within the range of prevalence rates observed in different provinces in China (ranging from 0.11% to 2.64%) (9, 10, 34, 35). Research indicates that the prevalence of AIS is associated with various factors, such as ethnicity, altitude of residence, and socioeconomic status (6, 35). The prevalence of AIS varies among countries, including the United States (0.52%) (8), Japan (0.87%) (36), Saudi Arabia (0.78%) (37), India (0.61%) (33), Korea (0.497%) (38), and Iran (0.62%) (39).

This study reveals that in Yunnan Province, the incidence rate of IS stands at approximately 1.10%. Furthermore, a notable sex disparity was observed, with females exhibiting a higher prevalence of IS, being approximately 1.5 times more susceptible than males. Nevertheless, there was no statistically significant difference in the proportion of individuals with a Cobb angle ≥40° between the two sex. The prevalence of IS in Yunnan Province was found to be lower than that in certain regions, such as the Qinghai-Tibet Plateau, which is characterized by a high-altitude environment and a predominantly Tibetan population; However, the prevalence of IS in Yunnan Province showed a similar trend to previous studies in other ethnic groups and regions in China (6, 34, 35). Furthermore, it was observed that the incidence of IS exhibited a gradual rise in correlation with advancing age, peaking in the 13–14 years age range, followed by a subsequent gradual decline. Similarly, the Cobb angle also exhibited a similar trend, with the peak Cobb angle occurring at an age of 15 years. There may be two reasons for this trend: first, adolescents in this age group, especially girls, are in their growth spurt, and the rapid growth in height leads to a higher prevalence and rapid progression of scoliosis; second, adolescents in this age group experience a greater burden of schooling, and habits such as sedentary lifestyle, insufficient sleep and insufficient exercise increase the risk of scoliosis (20) This study also revealed that the IS population in Yunnan Province exhibited lower body weight and sitting height compared to the normal population. Moreover, the prevalence of IS varied across different educational stages, with the highest prevalence observed among middle school students. However, there was no significant difference in underweight prevalence between the two groups, which is consistent with findings from the study conducted by Scaturro and colleagues (40). Middle school students are in their growth spurt phase, and they also face significant academic pressure and reduced physical activity. This combination contributes to the higher prevalence of IS in this age group. In addition, among the 929 identified scoliosis patients, the distributions of severe scoliosis cases in males and females were similar. Among the single-curve scoliosis patients, thoracolumbar curves were the most common, and right-sided curves were more prevalent than left-sided curves. Furthermore, it was observed that there were more cases of double-curve scoliosis than single-curve scoliosis among the screened individuals. The diversity in the direction of IS scoliosis remains unclear but may be associated with asymmetrical activity of the muscles around the spine and compensatory curves (41). Some research suggests that right-handed dominance may be more likely to lead to rightward spinal curvature (42, 43).

The interaction between environmental factors and epigenetics may contribute to the imbalance in spinal growth and development, leading to the occurrence of AIS. While genetic factors play a significant role in AIS, they cannot fully explain the differences observed among patients. For example, identical twins with AIS may have no genetic differences, yet they can exhibit variations in the progression of spinal curvature. This suggests that epigenetics play an important role in the pathogenesis of AIS (44). Exosomes are a type of vesicle secreted by cells that serve as communication vehicles between cells. They contain a significant amount of miRNA. In recent years, increasing research has indicated that exosome-derived miRNAs, as epigenetic factors, are associated with bone metabolism (44–46). Exosome-derived miRNAs play a role in regulating processes related to the development of the musculoskeletal system, including embryonic development, osteoblast differentiation, bone marrow mesenchymal stem cell osteogenesis, paraspinal muscle differentiation, and cartilage formation., and they are directly or indirectly involved in the development of AIS (47–49). Additionally, exosome-derived miRNAs are protected by the outer vesicle, allowing them to remain stable in the RNA enzyme-rich environment of the blood (50, 51). Therefore, plasma exosome-derived miRNAs hold promise as specific molecular markers for the early screening of AIS. However, there is currently a lack of relevant research on the role of exosome-derived miRNAs in AIS.

AIS is a disease with an unpredictable and challenging natural history. Determining which patients require conservative or surgical treatment can be challenging. Early brace treatment can help reduce the progression of the curvature, improve aesthetic appearance, and decrease the need for surgery. Therefore, AIS screening before the Cobb angle exceeds 40° is of significant importance for conservative treatment (52, 53). To date, many experiments have verified the feasibility of exosome-derived miRNAs as markers for the diagnosis or treatment of diseases such as cancer (54), osteoporosis (55), osteoarthritis (56), and ankylosing spondylitis (57); however, studies on exosome-derived miRNAs in AIS patients are currently lacking. This study identified hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246 as key exosome-derived miRNAs associated with AIS, and verified that they have potential diagnostic value for AIS. Furthermore, José et al. (58) identified differentially expressed hsa-miR-27a-5p among AIS plasma miRNAs and validate its potential diagnostic value for AIS. Notably, the expression of plasma exosomal hsa-miR-539-5p was upregulated in sequencing data but downregulated in the RT-qPCR validation results in AIS patients in our study, which may be due to the bias caused by high-throughput sequencing and the small number of sequenced samples. However, due to the small number of high-throughput sequencing samples and relatively low accuracy, the results should be based on RT-qPCR validation results. In the future, more samples are still needed for validation regarding the diagnostic value of hsa-miR-539-5p in AIS.

The occurrence of AIS is associated with factors such as vertebral dysplasia, intervertebral disc development, neuromuscular conditions, and genetic regulation. However, these factors do not fully explain AIS (1). This study, through target gene prediction and pathway enrichment analysis, identified that hsa-miRNA-27a-5p, hsa-miRNA-539-5p, and hsa-miRNA-1246 are associated with two pathways: calcium metabolism and the regulation of stem cell differentiation. Skeletal growth and the maintenance of bone homeostasis are highly dependent on calcium metabolism and the differentiation of bone cells, particularly osteoblasts and osteoclasts (59). Furthermore, studies by Li et al. (60) found that extracellular vesicle-derived miR-27a-5p is related to bone formation. Research by Gautvik et al. (61) also showed that miR-27a-5p is associated with bone density. Pepe et al. (55) discovered that extracellular vesicle-derived miR-1246 is linked to osteoclast differentiation. Tripathi et al. (62) found that miR-539 is related to the regulation of osteoblastogenesis. Based on this evidence, it is inferred that the aberrant expression of hsa-miRNA-27a-5p, hsa-miRNA-539-5p, and hsa-miRNA-1246 in AIS patients may be associated with the progression of AIS. However, further exploration of regulatory mechanisms and functions is needed in the future.

In summary, this study was the first epidemiological survey of scoliosis conducted within all Yunnan Province, and the study cohort constructed by screening was further screened and validated for AIS-related plasma exosome-derived miRNAs, which provided new ideas and methods for the diagnosis and treatment of AIS. However, this study has certain limitations. Due to the economic disparities and uneven population distribution in most areas of Yunnan Province, information related to population distribution, economic conditions, lifestyle habits, etc., was not collected. Future work will focus on improving scoliosis surveys in remote areas and further analysing the regional differences in relevant risk factors. Additionally, the samples collected for exosome-derived miRNA sequencing and validation in this study were all from severe AIS patients. Future research will involve validation and analysis in patients with varying degrees of scoliosis from different regions and explore the functions and mechanisms of differential exosome-derived miRNAs.

## 5 Conclusions

This study was based on the SSS program conducted in Yunnan Province, China, and involved epidemiological screening for scoliosis in children and adolescents aged 7–19 years. The overall prevalence of IS was found to be 1.10%, and approximately 1.5 times higher in females than in males. The peak age for IS was 13 years, and there were more cases of double-curve deformities than single-curve deformities. At the same time, based on the established AIS research cohort, specific plasma-derived exosome-derived miRNAs associated with AIS were identified, including hsa-miR-27a-5p, hsa-miR-539-5p, and hsa-miR-1246. These exosome-derived miRNAs hold the potential to serve as molecular markers for diagnosing AIS and may be associated with the progression of the condition.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.ncbi.nlm.nih.gov/, Series GSE235203.

## Ethics statement

The studies involving humans were approved by The Medical Research Ethics Committee of the First Affiliated Hospital of Kunming Medical University (2022-L152). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

PY: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. Z-HW: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – review & editing. HJ: Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Writing – review & editing. Y-HW: Conceptualization, Data curation, Supervision, Writing – review & editing. J-YY: Data curation, Formal Analysis, Funding acquisition, Investigation, Writing – review & editing. L-ML: Data curation, Funding acquisition, Investigation, Writing – review & editing. W-TW: Data curation, Software, Validation, Writing – review & editing. JC: Project administration, Resources, Supervision, Validation, Writing – review & editing. D-HL: Data curation, Formal Analysis, Software, Validation, Writing – review & editing. S-YL: Formal Analysis, Software, Validation, Visualization, Writing – review & editing. WZ: Data curation, Software, Visualization, Writing – review & editing. FH: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. W-ZW: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1308931/full#supplementary-material

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# Systematic review and meta-analysis for the proximal junctional kyphosis in adolescent idiopathic scoliosis

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**Objective:** The risk factors of PJK (proximal junctional kyphosis) related to AIS (adolescent idiopathic scoliosis) are inconsistent due to heterogeneity in study design, diagnostic criteria, and population. Therefore, the meta-analysis was conducted to investigate the factors affecting PJK after posterior spinal fusion for AIS patients.

**Methods:** We implemented a systematic search to obtain potential literature relevant to PJK in AIS surgery. Then, a meta-analysis was performed to assess the incidence of PJK and its risk factors.

**Results:** We retrieved 542 articles, and 24 articles were included. The PJK incidence was 17.67%. The use of hooks at UIV (upper instrumented vertebrae) ($p = 0.001$) could prevent PJK. Before surgery, the larger TK (thoracic kyphosis) ($p < 0.001$), GTK (global thoracic kyphosis) ($p < 0.001$), and LL (lumbar lordosis) ($p < 0.001$) were presented in the PJK group. Immediately post-operatively, in the PJK group, the following parameters were higher: TK ($p = 0.001$), GTK ($p < 0.001$), LL ($p = 0.04$), PJA (proximal junctional angle) ($p < 0.001$), and PJA-RCA (rod contouring angle) ($p = 0.001$). At the final follow-up, the following parameters were higher in the PJK group: TK ($p < 0.001$), GTK ($p < 0.001$), LL ($P < 0.001$), and PJA ($P < 0.001$). Sub-group analysis detected that before surgery, the following parameters were larger in the PJK group: TK ($p < 0.001$), LL ($p = 0.005$), and PJA ($p = 0.03$) in Lenke type 5 AIS patients. Immediately post-operatively, in the PJK group, the following parameters were higher: TK ($p < 0.001$), LL ($p = 0.005$), and PJA ($p < 0.001$). At the final follow-up, the following parameters were higher in the PJK group: TK ($p < 0.001$), LL ($p < 0.001$), and PJA ($p < 0.001$).

**Conclusion:** The individuals with larger preoperative TK were more susceptible to PJK, and PJA was mainly influenced by the adjacent segments rather than the whole sagittal alignment. Using hooks or claws at UIV should prevent PJK.

KEYWORDS

proximal junctional kyphosis, AIS, adolescent idiopathic scoliosis, meta-analysis, complication

Abbreviations
TK, thoracic kyphosis; GTK, global thoracic kyphosis; LL, lumbar lordosis; PT, pelvic tilt; PI, pelvic incidence; PI-LL, pelvic incidence minus lumbar lordosis; SVA, sagittal vertical axis; PJA, proximal junctional angle; RCA, rod contouring angle; DJK, distal junction kyphosis; PSF, after posterior spinal fusion; UIV, upper instrumented vertebrae; PJF, proximal junction failure; WMD, weight mean difference; OR, odds ratio; CI, confidence interval.

# Introduction

Adolescent idiopathic scoliosis (AIS) is the most common spinal deformity, and females aged 10 to 18 are more susceptible to AIS (1). It is widely recognized that AIS can lead to appearance abnormalities (2), psychological disorders (3), cardiopulmonary dysfunction (4), and so on. Its treatment is a comprehensive process, which requires consideration of Cobb angle, curve shape, growth potential, and other factors. Generally, clinical observation is recommended for patients with a Cobb angle of less than 20 degrees, and for patients with a Cobb angle between 20 and 40 degrees, brace treatment is recommended (5). Even through, it is reported that bracing is also effective for large curves of higher than 40 degrees in this patient population that forcefully reject the surgical treatment and insist on to use a brace (6), correction surgery is commonly recommended (7, 8). With the application of pedicle screws and osteotomy technology, we can reconstruct the spine alignment in coronal, sagittal and transverse planes (9). However, the corresponding complications cannot be ignored such as proximal junctional kyphosis (PJK), rod breakage, and pseudoarthrosis (10–12).

PJK is a common complication after long-segment spinal internal fixation. In 1994, Lowe et al. (13) firstly used the concept of junctional kyphosis to describe the phenomenon of PJK and distal junction kyphosis (DJK) after posterior spinal fusion (PSF) in Scheuermann's disease. However, it did not provide diagnostic criteria for PJK. Referencing the physiological curvature of the spine, Lee et al. (14) proposed the PJK diagnostic criteria in 1999 as follows: the kyphotic angle between the upper endplate of T2 vertebrae and the lower endplate of upper instrumented vertebrae (UIV) was more than 5 degrees higher than the physiological kyphosis. Yang et al. (15) defined PJK as the local kyphosis angle increased by 10° compared with that immediately after surgery. The measurement method is the angle between the UIV upper endplate and the UIV + 2 lower endplate (15). At present, the widely used measurement and diagnostic criteria were put forward by Glattes et al. (16) in 2005: the kyphotic angle between the lower endplate of UIV and the upper endplate of UIV + 2 was greater than 10°, which is more than 10° higher than that before surgery. The recently reported PJK diagnostic criteria include that the angle between UIV and UIV + 1 is greater than 15 degrees (17), and the angle between UIV and UIV + 2 is greater than or equal to 20 degrees (18). Initially, the studies reported that PJK was only an imaging change that had little relationship with clinical outcomes (13). Nowadays, it is accepted that PJK can cause back pain, severe deformity, and nerve compression symptoms (19). In particular, the concept of proximal junction failure (PJF), combined with the high surgical revision rate (20), has got more attention to PJK and PJF.

Given the different definitions of PJK and the heterogeneity of samples, the incidence varied from 3.22% to 46% (21–28) in AIS patients. The Lenke type 5 curve AIS was more susceptible to PJK (29). Correspondingly, a series of literature reported the influencing factors of PJK. The influencing factors of PJK can be roughly divided into three categories: (1) patient factors, such as bone maturity, gender, curve shape, preoperative Cobb angle; (2) factors related to surgical procedures, such as rod material, whether the posterior ligament is resected, whether the UIV uses the lamina hook, fusion segments; (3) postoperative spinal alignment, such as whether there is flat back deformity and whether there is a mismatch of PI-LL. However, the results reported in different studies are inconsistent. For example, Kim et al. (30) reported that the hybrid construct (proximal hooks) was a risk factor for PJK, while Ogura et al. (31) reported that using hooks at UIV might prevent PJK. Several studies reported that the larger preoperative thoracic kyphosis (TK) was related to PJK (27, 32–34), while Kim et al. and Chen et al. reported that the preoperative TK was not associated with PJK. In terms of preoperative lumbar lordosis(LL), Albay et al. (34) and Ferrero et al. (28) detected a larger LL in the PJK group, while other studies reported no difference in LL (22, 23, 35).

Overall, there are many reports about PJK after AIS, and the risk factors reported in different studies are inconsistent due to heterogeneity in study design, diagnostic criteria, and population. Therefore, the meta-analysis was conducted to investigate the rate of PJK and its risk factors in AIS populations after PSF.

# Materials and methods

## Literature retrieval and screening

To ensure the quality of the research, every step of the research strictly followed the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (36). To obtain potential literature relevant to PJK in AIS surgery, we implemented a systematic search based on the following abstract databases including PubMed, Web of Science, and Embase December 12th, 2023. The following were the search terms: (proximal junctional kyphosis) AND (scoliosis) AND (adolescent OR pediatric).

## Inclusion and exclusion criteria

Inclusion criteria: (1) case-control, retrospective, or cohort study designs based on AIS patients; (2) posterior spinal fusion was performed for each case; (3) the study mainly reported the incidence and risk factors of PJK;(4) the diagnostic criteria of PJK was that the kyphotic angle between the lower endplate of UIV and the upper endplate of UIV + 2 was greater than 10°, which is more than 10° higher than that before surgery (16); (5) the literature was written in English. Exclusion criteria: (1) the study focused on other types of scoliosis; (2) anterior spinal fusion was performed; (3) the diagnostic criteria of PJK did not meet that the kyphotic angle between the lower endplate of UIV and the upper endplate of UIV + 2 was greater than 10°, which is more than 10° higher than that before surgery (16); (4) the literature was not written in English. According to the inclusion criteria, the two authors independently judge the inclusion or exclusion of the literature. If there is a dispute about the inclusion of a certain literature, the research group will decide whether to include it in this meta-analysis through discussion and voting. The Newcastle-Ottawa quality assessment scale (NOQA) was used to assess the quality for each paper.

## Data collection

The following items were extracted from papers meeting the inclusion criterion: (1) the author's name, publication year, study design, follow-up period, age, and gender distribution; (3) radiographic parameters: thoracic kyphosis (TK), global thoracic kyphosis (GTK) lumbar lordosis (LL), pelvic tilt (PT), pelvic incidence (PI), pelvic incidence minus lumbar lordosis (PI-LL), sagittal vertical axis (SVA), proximal junctional angle (PJA), RCA (rod contouring angle); (4) Surgery details: the fusion segments, screws at UIV, UIV hooks at UIV.

## Publication bias

The Begg's test was conducted and the funnel plot was employed to evaluate the publication bias.

## Sensitivity analysis

Sensitivity analyses were performed by omitting each included paper in sequence.

## Statistical analysis

The statistics were pooled using the Review Manager Version 5.3. For the enumeration data, the odds ratio (OR) with the 95% confidence interval (95%CI) was calculated, while the weight mean difference (WMD) with the 95%CI was employed to assess the difference of measurement data between groups. That $P < 0.05$ meant the statistical significance between PJK and Non-PJK groups. That $I^2 \geq 50\%$ meant that the random effect model should be used, while the fixed effect model would be used when $I^2 < 50\%$.

# Results

## Paper selection and characteristics

Through systematic retrieval of the databases, 542 articles were retrieved. Among them, 24 articles met the inclusion criteria (21–29, 31–35, 37–46). Four studies groups were based on Lenke 1/2 AIS patients (26–28, 44), and 8 studies were based on Lenke 5 AIS patients (21–25, 34, 35, 46), while the remaining studies did not clearly distinguish different types of AIS when investigate the incidence of PJK and its influencing factors (29, 31–33, 37–43, 45) (Table 1). Figure 1 demonstrates the details of the literature screening procedures. A total of 4,063 AIS cases were included in this meta-analysis, and the incidence of PJK was 17.67% for the whole population (PJK = 718, non-PJK = 3,885). However, the corresponding rate of PJK inclined to 23.88% in Lenke type 5 AIS patients (PJK = 166, non-PJK = 529).

## Meta-analysis results for the whole population

There was no difference in age at surgery ($p = 0.47$), gender distribution ($p = 0.1$), BMI ($p = 0.52$), Risser sign ($p = 0.37$), or follow-up time ($p = 0.89$) between groups. However, the pooled results showed more fusion segments (WMD = 0.49, 95% = 0.29~0.68, $p < 0.001$) in PJK groups. Compared with the use of screws at UIV, the use of hooks (OR = 0.48, 95% = 0.31~0.47, $p = 0.001$) could prevent PJK (Table 2).

Before surgery, the larger TK (WMD = 8.49, 95%CI = 7.69~.30, $p < 0.001$), and GTK (WMD = 10.1, 95%CI = 5.55~14.66, $p < 0.001$) were observed in PJK group, and a lager LL (WMD = 4.11, 95%CI = 3.40~4.82, $p < 0.001$) was also presented in PJK group (Figure 2). For the pelvic parameters, a smaller PT (WMD = −1.02, 95%CI = −1.85~−0.18, $p = 0.02$) was observed in the PJK group. However, there was no difference in PI ($p = 0.16$), SS ($p = 0.38$), PI-LL ($p = 0.14$), SVA ($p = 0.65$), RCA ($p = 0.39$), and PJA ($p = 0.94$).

Immediately postoperatively, the pooled results demonstrated higher values in the PJK group for the following parameters: TK (WMD = 5.09, 95%CI = 2.01~8.17, $p = 0.001$), GTK (WMD = 10.07, 95%CI = 7.05~13.09, $p < 0.001$), LL (WMD = 3.53, 95% CI = 0.21~6.85, $p = 0.04$), PJA (WMD = 5.00, 95%CI = 4.03~5.94, $p < 0.001$), and PJA-RCA (WMD = 3.89, 95%CI = 1.53~6.25, $p = 0.001$) (Figure 3). However, a smaller PI-LL (WMD = −7.52, 95%CI = −14.79~−0.25, $p = 0.04$) was observed in the PJK group, and no difference was demonstrated in PI ($p = 0.34$), PT ($p = 0.15$), SS ($p = 0.80$) and SVA ($p = 0.06$).

At the final follow-up, the following parameters were higher in the PJK group: TK (WMD = 5.13, 95%CI = 4.09~6.16, $p < 0.001$), GTK (WMD = 12.30, 95%CI = 8.16~15.99, $p < 0.001$), LL (WMD = 3.33, 95%CI = 2.09~4.56, $P < 0.001$), and PJA (WMD = 13.20, 95%CI = 11.06~15.34, $P < 0.001$). However, a smaller PI-LL (WMD = −11.65, 95%CI = −17.48~−5.81, $p < 0.001$) was observed in the PJK group, and no difference was demonstrated in PI ($p = 0.19$), PT ($p = 0.05$), SS ($p = 0.77$) and SVA ($p = 0.97$) (Table 3).

## Sub-group analysis in lenke type 5 AIS patients

Before surgery, the following parameters were larger in the PJK group: TK (WMD = 8.39, 95%CI = 6.32~10.46, $p < 0.001$), LL (WMD = 5.14, 95%CI = 2.88~7.39, $p = 0.005$), and PJA (WMD = 0.79, 95%=0.07~1.50, $p = 0.03$). For the pelvic parameters, a smaller PT (WMD = −2.10, 95%CI = −3.47~−0.73, $p = 0.003$) was observed in the PJK group. However, there was no difference in PI ($p = 0.05$), SS ($p = 0.43$), PI-LL ($p = 0.18$), and SVA ($p = 0.58$).

Immediately post-operatively, the pooled results demonstrated higher values in the PJK group for the following parameters: TK (WMD = 7.04, 95%CI = 3.63~10.46, $p = 0.02$), LL (WMD = 3.06,

TABLE 1 The basic information of the included research literatures.

| First author | Publication year | Sample | | Age (years) | Follow-up time (years) | Lenke type (1/2/3/4/5/6) |
|---|---|---|---|---|---|---|
| | | PJK | Non-PJK | | | |
| Wang et al. | 2023 | 33 | 173 | PJK: 14.9 ± 2.3<br>Non-PJK: 14.4 ± 2.3 | PJK: 2.8 ± 1.4<br>Non-PJK: 2.7 ± 1.3 | PJK:20/13/0/0/0/0<br>Non-PJK: 101/72/0/0/0/0 |
| Erkilinc et al. | 2023 | 30 | 307 | 14.2 ± 1.9 | 3.14 ± 1.01 | 215/5/29/0/61/27 |
| Coury et al. | 2023 | 17 | 177 | 14.9 ± 5 | 2~5 | 0/0/0/0/149/28 |
| Luhmann et al. | 2022 | 25 | 75 | 14.6 ± 2.1 | 3.9 ± 1.6 | PJK: 9/2/5/2/4/3<br>Non-PJK: 39/12/10/4/5/5 |
| Boeckenfoerde et al. | 2022 | 30 | 139 | PJK:16.9 ± 8.66<br>Non-PJK:16.1 ± 4.36 | 14.7 ± 6.25 | Unavailable |
| Hu et al. | 2022 | 23 | 75 | PJK: 15.3 ± 2.6<br>Non-PJK: 15.7 ± 2.6 | 3.12 (2-3) | 0/0/0/0/98/0 |
| Albay et al. | 2022 | 41 | 74 | 14.6 ± 2.9 | 4.82 ± 2.29 | 0/0/0/0/115/0 |
| Ogura et al. | 2021 | 15 | 330 | PJK: 14.5 + 2.1<br>Non-PJK: 14.5 + 2.2 | PJK: 2.0 + 0.9<br>Non-PJK: 2.2 + 1.3 | PJK: 5/2/3/1/0/4<br>Non-PJK: 108/92/44/31/27/28 |
| Kim et al. | 2021 | 7 | 62 | PJK: 13.9 ± 0.9<br>Non-PJK: 14.2 ± 2.2 | PJK: 9.4 ± 2.8<br>Non-PJK: 8.3 ± 3.5 | PJK: 2/0/0/0/5/0<br>Non-PJK: 41/21/1/4/6/8 |
| Clément et al. | 2021 | 102 | 468 | PJK: 15.6<br>Non-PJK: 15.1 | PJK: 9.4 ± 2.8<br>Non-PJK: 8.3 ± 3.5 | PJK: 59/24/8/1/0/10<br>Non-PJK: 292/125/19/9/0/23 |
| Langlais et al. | 2021 | 2 | 58 | 16 ± 2 | a minimum of 2 years' follow-up | 40/0/20/0/0/0 |
| Zhou et al. | 2021 | 13 | 57 | 15.3 ± 2.1 | 3,01 ± 1.29 | 0/0/0/0/70/0 |
| Wang et al. | 2021 | 12 | 40 | 14.0 ± 1.8 | 2.9 ± 0.9 | 0/0/0/0/52/0 |
| Chen et al. | 2021 | 15 | 20 | PJK: 15.7 ± 1.9<br>Non-PJK: 15.7 ± 2.1 | 3.58（2 = 7.67） | 0/0/0/0/35/0 |
| Clément et al. | 2020 | 7 | 77 | PJK: 14.7 ± 1.8<br>Non-PJK:15.0 ± 2.6 | 2.9 (2~8.2) | 37/23/3//7/11/3 |
| Wang et al. | 2020 | 20 | 64 | PJK: 14.60 ± 1.43<br>Non-PJK: 14.55 ± 1.28 | 2 | Lenke 1/2 |
| Peng et al. | 2020 | 10 | 34 | 18.27 ± 3.61 | 3.15 ± 2.67 | 0/0/0/0/44/0 |
| Alzakri et al. | 2019 | 13 | 72 | 15.6 ± 1.99 | a minimum of 2 years' follow-up | |
| Ferrero et al. | 2018 | 57 | 308 | 15 ± 2.6 | 2.5 ± 0.4 | 296/69/0/0/0/0 |
| Zhao et al. | 2018 | 35 | 52 | 13.85 ± 1.49 | 4.67 ± 1.17 | 0/0/0/0/87/0 |
| Lonner et al. | 2017 | 60 | 791 | 14.4 | a minimum of 2 years' follow-up | 394/182/58/23/106/88 |
| Ghailane et al. | 2017 | 5 | 45 | 14.8 (11.6–22.4) | 1.5 (0.83–2.17) | 25/2/17/2/0/4 |
| Wang et al. | 2010 | 35 | 88 | PJK: 15.0 (13.0, 16.0)<br>Non-PJK: 15.0 (13.0, 16.0) | 3.5 | Unavailable |
| Kim et al. | 2007 | 111 | 299 | PJK: 14.5 ± 1.83<br>Non-PJK: 14.8 ± 2.03 | 2 years' follow-up | 195/76/51/13//31/44 |

95%CI = 0.90–5.22~−0.90, $p = 0.005$), and PJA (WMD = 5.54, 95% CI = 3.57~7.52, $p < 0.001$). However, a smaller PI-LL (WMD = −9.76, 95%CI = −17.90 ~−1.63, $p = 0.02$) was observed in the PJK group, and no difference was demonstrated in PI ($p = 0.33$), PT($p = 0.09$), SS ($p = 0.80$) and SVA ($p = 0.58$).

At final follow-up, the following parameters were higher in the PJK group: TK (WMD = 9.51, 95%CI = 5.03~13.99, $p < 0.001$), LL (WMD = 4.75, 95%CI = 2.57~6.93, $P < 0.001$), and PJA (WMD = 11.47, 95%CI = 8.21~14.74, $P < 0.001$). However, a smaller PI-LL (WMD = −13.23, 95%CI = −19.70~−6.75, $p < 0.001$) and a smaller PT (WMD = −3.70, 95%CI = −6.75~−0.66, $p = 0.02$) were observed in PJK group, and no difference was demonstrated in PI ($p = 0.12$), SS ($p = 0.90$) and SVA ($p = 0.56$) (Table 4).

## Clinical outcome

There was no significant difference in the preoperative ($p = 0.18$) and postoperative SRS-22 scores ($p = 0.46$) between the PJK group and the non-PJK group.

## Publication bias

Based on the preoperative TK Begg's test was performed, and a symmetrical funnel graph was obtained. So, there was no significant publication bias in this meta-analysis (Figure 4).

## Sensitivity analysis

No single paper resulted in huge fluctuations in the pooled results.

# Discussion

## The rate of PJK in AIS individuals after PSF

The incidence of PJK reported in previous studies fluctuates greatly. Based on the diagnostic criteria of PJK by Glattes (16), the highest PJK rate varied from 3.33% to 42.86% (23, 26).

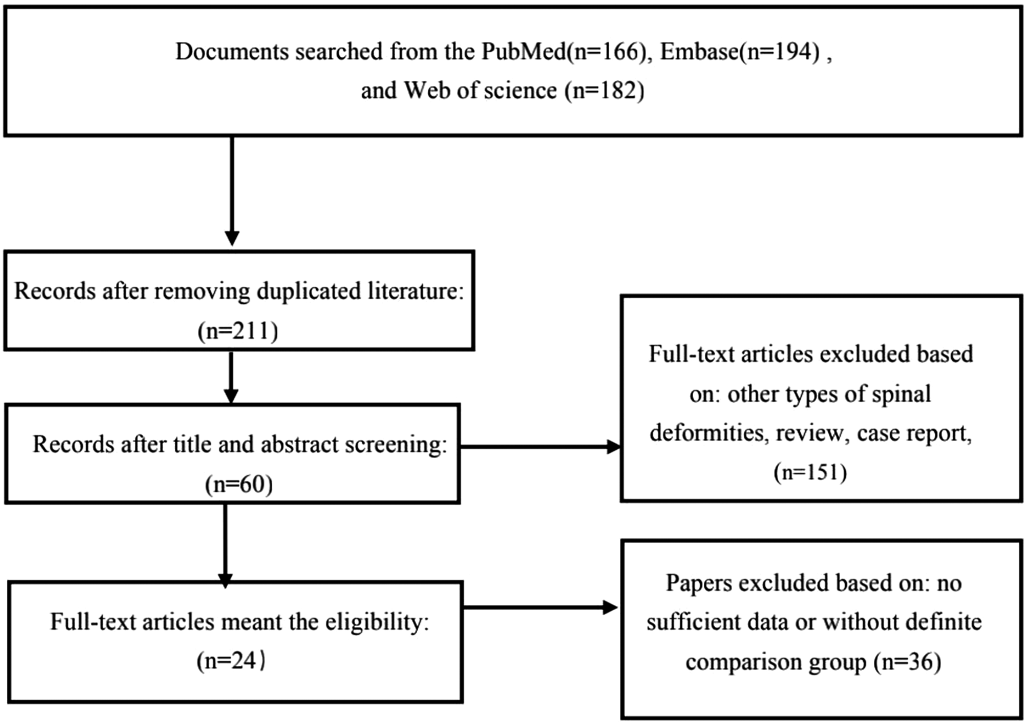


FIGURE 1
The flow chart showed the details process of paper selection.

TABLE 2 The pooled results between the between the PJK and Non-PJK group for the whole population.

| Variables | Test of difference | | | Model | Heterogeneity | |
|---|---|---|---|---|---|---|
| | WMD/OR | 95%CI | *P*-value | | *P*-value | $Chi^2$(%) |
| Preoperative age | −0.12 | −0.33∼0.09 | 0.47 | F | 0.79 | 0 |
| Gender (female vs. male) | 0.83 | 0.64∼1.09 | 0.19 | F | 0.48 | 0 |
| BMI | 0.18 | −0.37∼0.73 | 0.52 | F | 0.52 | 0 |
| Risser sign | −0.10 | −0.32∼0.12 | 0.37 | F | 0.47 | 0 |
| Follow-up time | 0.32 | −4.36∼5.00 | 0.89 | R | 0.07 | 48 |
| Fusion segments | 0.49 | 0.29∼0.68 | <0.001 | F | 0.29 | 18 |
| UIV hooks versus screw | 0.48 | 0.31∼0.74 | 0.001 | F | 0.09 | 47 |

F, fix effect model; R, random effect model.

While the majority of papers reported that the rate of PJK was 15∼30% (32, 33, 40–42). The current meta-analysis detected an incidence of PJK to be 16.50% for the whole population, while the corresponding figure inclined to 23.88% in Lenke type 5 AIS patients. Previously, several studies also reported that Lenke type 5 AIS patients were more susceptible to PJK after PSF with the rates varying from 18.57% to 42.86% (21–25, 34, 35). Therefore, the PJK phenomenon in AIS should be paid enough attention.

## Radiographic factors associated with PJK in AIS individuals after PSF

Previous studies have investigated various influencing factors that might be related to PJK in AIS patients. Among all the factors, the most reported ones are radiographic factors, and the current research mainly investigated the influence of sagittal spinopelvic parameters on PJK. It is commonly accepted that the UIV always locates in the thoracic segments, which means that the TK is always composed of PJA. Before surgery, Boeckenfoerde et al. (38) reported that the PJK group had significantly larger T4–T12 kyphosis (31.1° ± 13.93° vs. 23.3° ± 14.93°, $p = 0.016$). Kim et al. (30) reported that the preoperative TK > 40° was one of the risk factors for PJK. Currently, the pooled results also demonstrated the larger TK (WMD = 8.49, 95%CI = 7.69∼.30, $p < 0.001$), and larger GTK (WMD = 10.1, 95% CI = 5.55∼14.66, $p < 0.001$) in PJK group. Correspondingly, other studies also detected a more kyphotic thoracic spine in the PJK group before surgery (32, 33, 38). The subgroup analysis also detected a larger TK in the PJK group in Lenke type 5 AIS

| Study or Subgroup | PJK Mean | PJK SD | PJK Total | Non-PJK Mean | Non-PJK SD | Non-PJK Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.4.1 Lenke 5** | | | | | | | | |
| Albay et al. 2022 | 31.8 | 12.7 | 41 | 21.4 | 9.7 | 74 | 3.2% | 10.40 [5.93, 14.87] |
| Chen et al. 2021 | 21.4 | 8.7 | 15 | 17.9 | 13 | 20 | 1.3% | 3.50 [−3.70, 10.70] |
| Hu et al. 2022 | 24.7 | 13.7 | 23 | 18.7 | 8.3 | 75 | 1.9% | 6.00 [0.09, 11.91] |
| Peng et al. 2020 | 29.51 | 11.68 | 10 | 21.45 | 19.35 | 34 | 0.7% | 8.06 [−1.67, 17.79] |
| Wang et al. 2021 | 23 | 7.4 | 12 | 13.3 | 12.9 | 40 | 1.9% | 9.70 [3.91, 15.49] |
| Zhao et al. 2018 | 28.31 | 7.8 | 35 | 20.33 | 9.1 | 52 | 5.1% | 7.98 [4.40, 11.56] |
| Zhou et al. 2021 | 30.7 | 13.4 | 13 | 18.9 | 8.7 | 57 | 1.1% | 11.80 [4.17, 19.43] |
| **Subtotal (95% CI)** | | | **149** | | | **352** | **15.1%** | **8.39 [6.32, 10.46]** |
| Heterogeneity: $Chi^2 = 4.20$, df = 6 (P = 0.65); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 7.95 (P < 0.00001) | | | | | | | | |
| **1.4.2 Lenke 1/2** | | | | | | | | |
| Ferrero et al. 2018 | 32 | 16 | 57 | 27 | 18 | 308 | 3.0% | 5.00 [0.39, 9.61] |
| Wang et al. 2020 | 32.44 | 5.6 | 20 | 27.19 | 5.14 | 64 | 8.5% | 5.25 [2.49, 8.01] |
| **Subtotal (95% CI)** | | | **77** | | | **372** | **11.6%** | **5.18 [2.82, 7.55]** |
| Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 4.29 (P < 0.0001) | | | | | | | | |
| **1.4.3 Lenke 1~6** | | | | | | | | |
| Alzakri et al. 2019 | 30.6 | 12.6 | 13 | 22.1 | 11.6 | 72 | 1.2% | 8.50 [1.15, 15.85] |
| Boeckenfoerde et al. 2022 | 31.1 | 13.93 | 30 | 23.3 | 14.93 | 139 | 2.1% | 7.80 [2.23, 13.37] |
| Burton et al. 2020 | 47.8 | 10.8 | 7 | 37.6 | 11 | 77 | 0.9% | 10.20 [1.83, 18.57] |
| Erkilinc et al. 2023 | 35.81 | 3.09 | 30 | 26.52 | 0.77 | 307 | 52.7% | 9.29 [8.18, 10.40] |
| Kim et al. 2007 | 29 | 14 | 111 | 22 | 14.1 | 299 | 6.9% | 7.00 [3.94, 10.06] |
| Kim et al. 2021 | 27.2 | 20.4 | 7 | 16.6 | 10.4 | 62 | 0.3% | 10.60 [−4.73, 25.93] |
| Lonner et al. 2017 | 30.73 | 12.47 | 60 | 21.78 | 13.28 | 791 | 6.0% | 8.95 [5.66, 12.24] |
| Luhmann et al 2022 | 35.6 | 12.5 | 25 | 26.8 | 11.3 | 75 | 2.1% | 8.80 [3.27, 14.33] |
| Ogura et al. 2021 | 37.3 | 14.9 | 15 | 24.8 | 19.7 | 330 | 1.1% | 12.50 [4.67, 20.33] |
| **Subtotal (95% CI)** | | | **298** | | | **2152** | **73.3%** | **9.04 [8.10, 9.98]** |
| Heterogeneity: $Chi^2 = 2.99$, df = 8 (P = 0.93); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 18.84 (P < 0.00001) | | | | | | | | |
| **Total (95% CI)** | | | **524** | | | **2876** | **100.0%** | **8.49 [7.69, 9.30]** |
| Heterogeneity: $Chi^2 = 16.00$, df = 17 (P = 0.52); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 20.68 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: $Chi^2 = 8.80$, df = 2 (P = 0.01), $I^2 = 77.3\%$ | | | | | | | | |

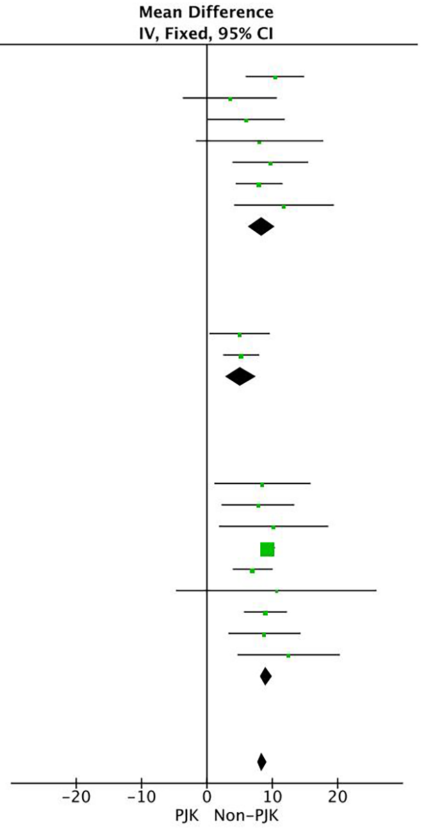


FIGURE 2
The pooled result showed that the PJK had a larger TK before surgery.

| Study or Subgroup | PJK Mean | PJK SD | PJK Total | Non-PJK Mean | Non-PJK SD | Non-PJK Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.5.1 Lenke 5** | | | | | | | | |
| Chen et al. 2021 | 33 | 6.3 | 15 | 22.2 | 9.6 | 20 | 7.7% | 10.80 [5.52, 16.08] |
| Hu et al. 2022 | 26.6 | 7.4 | 23 | 20.6 | 7.5 | 75 | 8.9% | 6.00 [2.53, 9.47] |
| Peng et al. 2020 | 23.5 | 10.07 | 10 | 19.35 | 8.66 | 34 | 6.7% | 4.15 [−2.74, 11.04] |
| Wang et al. 2021 | 19.9 | 12.1 | 12 | 12.1 | 9.8 | 40 | 6.3% | 7.80 [0.31, 15.29] |
| Zhao et al. 2018 | 21.43 | 8.68 | 35 | 19.46 | 8.69 | 52 | 8.7% | 1.97 [−1.75, 5.69] |
| Zhou et al. 2021 | 29.3 | 5.7 | 13 | 17.7 | 8.5 | 57 | 8.7% | 11.60 [7.80, 15.40] |
| **Subtotal (95% CI)** | | | **108** | | | **278** | **46.9%** | **7.04 [3.63, 10.46]** |
| Heterogeneity: $Tau^2 = 11.73$; $Chi^2 = 15.63$, df = 5 (P = 0.008); $I^2 = 68\%$ | | | | | | | | |
| Test for overall effect: Z = 4.04 (P < 0.0001) | | | | | | | | |
| **1.5.2 Lenke 1/2** | | | | | | | | |
| Ferrero et al. 2018 | 33 | 14 | 57 | 34 | 16 | 308 | 8.5% | −1.00 [−5.05, 3.05] |
| Wang et al. 2020 | 21.82 | 3.9 | 20 | 21.63 | 5.02 | 64 | 9.5% | 0.19 [−1.92, 2.30] |
| **Subtotal (95% CI)** | | | **77** | | | **372** | **18.1%** | **−0.06 [−1.93, 1.81]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.95) | | | | | | | | |
| **1.5.3 Lenke 1~6** | | | | | | | | |
| Boeckenfoerde et al. 2022 | 29.6 | 9.73 | 30 | 23.7 | 10.01 | 139 | 8.6% | 5.90 [2.04, 9.76] |
| Erkilinc et al. 2023 | 55.44 | 2.62 | 30 | 45.6 | 0.71 | 307 | 9.9% | 9.84 [8.90, 10.78] |
| Kim et al. 2007 | 20 | 9.4 | 111 | 19 | 9.1 | 299 | 9.6% | 1.00 [−1.03, 3.03] |
| Kim et al. 2021 | 25.3 | 8.4 | 7 | 21.4 | 8.1 | 62 | 6.9% | 3.90 [−2.64, 10.44] |
| **Subtotal (95% CI)** | | | **178** | | | **807** | **35.0%** | **5.27 [−0.29, 10.82]** |
| Heterogeneity: $Tau^2 = 28.55$; $Chi^2 = 62.95$, df = 3 (P < 0.00001); $I^2 = 95\%$ | | | | | | | | |
| Test for overall effect: Z = 1.86 (P = 0.06) | | | | | | | | |
| **Total (95% CI)** | | | **363** | | | **1457** | **100.0%** | **5.09 [2.01, 8.17]** |
| Heterogeneity: $Tau^2 = 24.75$; $Chi^2 = 140.15$, df = 11 (P < 0.00001); $I^2 = 92\%$ | | | | | | | | |
| Test for overall effect: Z = 3.24 (P = 0.001) | | | | | | | | |
| Test for subgroup differences: $Chi^2 = 14.36$, df = 2 (P = 0.0008), $I^2 = 86.1\%$ | | | | | | | | |

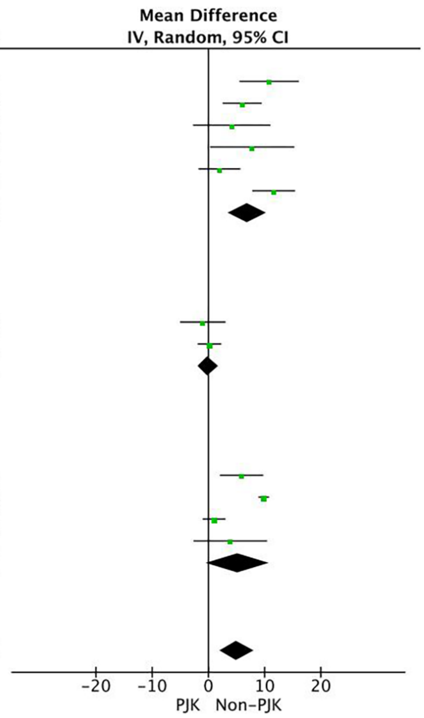


FIGURE 3
The pooled result showed that the PJK had larger TK before and immediately after surgery.

TABLE 3 Comparison of the radiographic parameters between the PJK and Non-PJK group for the whole population.

| Variables | Test of difference | | | Model | Heterogeneity | |
|---|---|---|---|---|---|---|
| | WMD/OR | 95%CI | *P*-value | | *P*-value | $Chi^2$ |
| Preoperative | | | | | | |
| TK | 8.49 | 7.69~9.30 | <0.001 | F | 0.52 | 0 |
| GTK | 10.1 | 5.55~14.66 | <0.001 | F | 0.68 | 0 |
| LL | 4.11 | 3.40~4.82 | <0.001 | F | 0.85 | 0 |
| PI | −1.51 | −3.88~0.85 | 0.21 | R | <0.001 | 80 |
| PT | −1.02 | −1.85~−0.18 | 0.02 | F | 0.09 | 37 |
| SS | −0.77 | −2.47~0.94 | 0.38 | R | 0.04 | 50 |
| PI-LL | −5.08 | −11.85~1.69 | 0.14 | R | <0.001 | 87 |
| SVA | 1.56 | −5.14~8.26 | 0.65 | R | <0.001 | 65 |
| PJA | −0.03 | −0.87~0.81 | 0.94 | R | 0.01 | 58 |
| RCA | 0.78 | −1.01~2.57 | 0.39 | R | <0.001 | 74 |
| Immediate post-operation | | | | | | |
| TK | 5.09 | 2.01~8.17 | 0.001 | R | <0.001 | 92 |
| GTK | 10.07 | 7.05~13.09 | <0.001 | F | 0.29 | 12 |
| LL | 3.53 | 0.21~6.85 | 0.04 | R | <0.001 | 88 |
| PI | −2.06 | −6.31~2.19 | 0.34 | R | <0.001 | 90 |
| PT | −1.93 | −4.55~0.68 | 0.15 | R | <0.001 | 74 |
| SS | −0.21 | −1.87~1.45 | 0.80 | F | 0.54 | 0 |
| PI-LL | −7.52 | −14.79 ~−0.25 | 0.04 | R | <0.001 | 87 |
| SVA | 3.85 | −0.09~7.79 | 0.06 | F | 0.17 | 31 |
| PJA | 5.00 | 4.03~5.94 | <0.001 | R | 0.03 | 53 |
| PJA-RCA | 3.89 | 1.53~6.25 | 0.001 | R | 0.10 | 64 |
| Final follow-up | | | | | | |
| TK | 5.13 | 4.09~6.16 | <0.001 | R | <0.001 | 92 |
| GTK | 12.30 | 8.16~15.99 | <0.001 | F | 0.75 | 0 |
| LL | 3.33 | 2.0~4.56 | <0.001 | F | 0.46 | 0 |
| PI | −2.90 | −7.24~1.43 | 0.19 | R | <0.001 | 86 |
| PT | −2.26 | −4.55~0.03 | 0.05 | R | 0.002 | 68 |
| SS | −0.18 | −1.38~1.03 | 0.77 | F | 0.19 | 31 |
| PI-LL | −11.65 | −17.48~−5.81 | <0.001 | R | <0.001 | 81 |
| SVA | 0.12 | −0.63~6.62 | 0.97 | R | 0.01 | 59 |
| PJA | 13.20 | 11.06~15.34 | <0.001 | R | <0.001 | 89 |

F, fix effect model; R, random effect model.

patients, which was also consistent with several previous reports (21, 22, 25, 34). Generally, the greater the thoracic kyphosis, the greater the lumbar lordosis. Ferrero et al. (28) and Clément et al. (39) reported that the preoperative LL was significantly greater in the PJK group. However, several reports did not detect differences in preoperative LL between groups (22–24, 32, 34, 38). The pooled result detected a larger preoperative LL (WMD = 3.53, 95%CI = 0.21~6.85, $p = 0.04$) in the PJK group, and a similar result was also presented in subgroup analysis LL ($p = 0.005$). So, it is necessary to take appropriate measures to prevent PJK for patients with large TK before surgery, especially for those with TK greater than 40 degrees (30).

The pooled results detected that both TK and LL in the PJK group were greater in the non-PJK group immediately after operation and at the last follow-up. After PSF, the patient's thoracic kyphosis and lumbar lordosis are not completely developed and shaped. It was commonly accepted that the formation of physiological curvature of the thoracic kyphosis and lumbar lordosis involved the whole spinal segments. Correction surgery fixed several segments which were relatively stable after surgery. This was bound to interfere with the formation of thoracic or lumbar curvature. So, the proximal unfused segments may increase kyphosis in compensation for the development of thoracic kyphosis, which may be the potential mechanism of the increasing PJA after surgery. However, it was reported that the increase in PJA might mainly compensate for the SVA increase in adult spinal deformity patients, while the decompensation led to PJK (47). Therefore, there may be some differences in the main mechanism of PJK in different age groups after surgery.

In terms of pelvic parameters, only a smaller preoperative PT was detected in the PJK group, which was consistent with the reports by Wang et al. (22) and Chen et al. (23). At the last follow-up, subgroup analysis also detected a smaller PT in the PJK group. On the contrary, one of the main influencing factors of PJK is the larger preoperative PT in adult spinal deformity, and the follow-up PT was larger in the PJK group. This again showed that there were differences in the main influencing factors and evolution process of PJK between AIS and adult spinal deformity patients. PJK-related theory, which is applicable to explain adult degenerative spinal deformity, cannot

TABLE 4 Comparison of the radiographic parameters between the PJK and Non-PJK group in lenke type 5 AIS patients.

| Variables | Test of difference | | | Model | Heterogeneity | |
|---|---|---|---|---|---|---|
| | WMD/OR | 95%CI | *P*-value | | *P*-value | $Chi^2$ |
| **Preoperative** | | | | | | |
| TK | 8.39 | 6.32∼10.46 | <0.001 | F | 0.65 | 0 |
| LL | 5.14 | 2.88∼7.39 | 0.005 | F | 0.37 | 6 |
| PI | −6.34 | −12.78∼0.10 | 0.05 | F | <0.001 | 79 |
| PT | −2.10 | −3.47∼−0.73 | 0.003 | F | 0.11 | 42 |
| SS | −0.60 | −2.11∼0.90 | 0.43 | F | 0.13 | 40 |
| PI-LL | −6.14 | −15.11∼2.83 | 0.18 | R | <0.001 | 84 |
| SVA | 1.71 | −4.37∼7.78 | 0.58 | F | 0.15 | 38 |
| PJA | 0.79 | 0.07∼1.50 | 0.03 | F | 0.38 | 2 |
| **Immediate post-operation** | | | | | | |
| TK | 7.04 | 3.63∼10.46 | <0.001 | R | <0.001 | 68 |
| LL | 3.06 | 0.90∼5.22 | 0.005 | F | 0.37 | 6 |
| PI | −9.39 | −28.39∼9.62 | 0.33 | R | <0.001 | 94 |
| PT | −3.86 | −8.34∼0.63 | 0.09 | R | <0.001 | 80 |
| SS | −0.21 | −1.87∼1.45 | 0.80 | F | 0.54 | 0 |
| PI-LL | −9.76 | −17.90 ∼−1.63 | 0.02 | R | <0.001 | 82 |
| SVA | 1.71 | −4.37∼7.78 | 0.58 | F | 0.15 | 38 |
| PJA | 5.54 | 3.57∼7.52 | <0.001 | R | 0.005 | 73 |
| **Final follow-up** | | | | | | |
| TK | 9.51 | 5.03∼13.99 | <0.001 | R | <0.001 | 77 |
| LL | 4.75 | 2.57∼6.93 | <0.001 | F | 0.36 | 8 |
| PT | −3.70 | −6.75∼−0.66 | 0.02 | R | 0.03 | 63 |
| PI | −7.07 | −16.04∼1.90 | 0.12 | R | <0.001 | 88 |
| SS | 0.11 | −1.58∼1.81 | 0.90 | F | 0.59 | 0 |
| PI-LL | −13.23 | −19.70∼−6.75 | <0.001 | R | 0.004 | 78 |
| SVA | −2.85 | −12.32∼6.62 | 0.56 | F | 0.24 | 28 |
| PJA | 11.47 | 8.21∼14.74 | <0.001 | R | 0.002 | 80 |

F, fix effect model; R, random effect model.

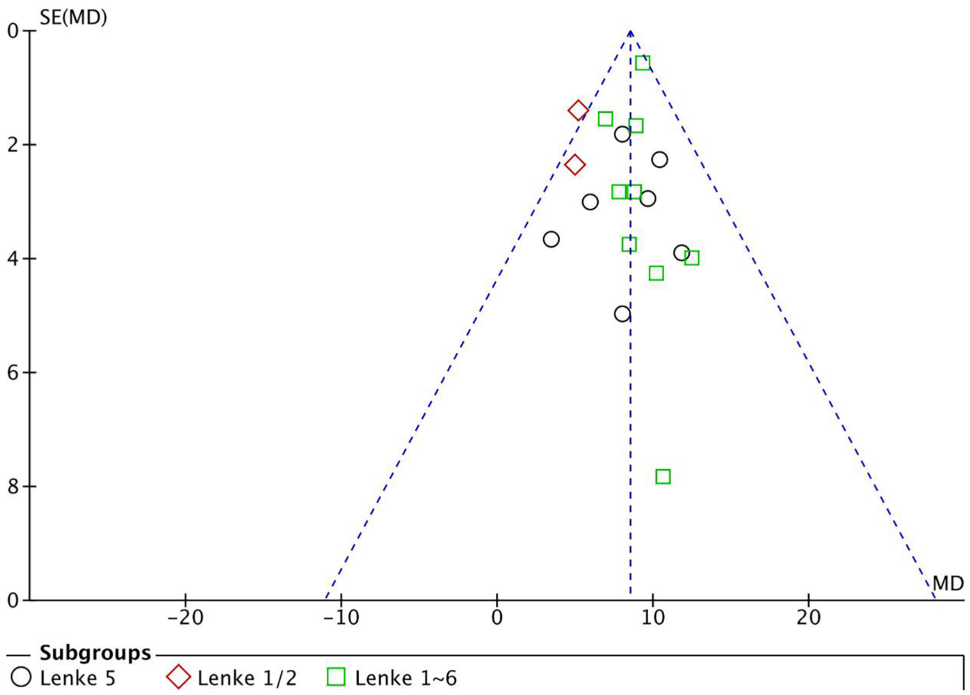


FIGURE 4
The funnel plot was symmetrical, which indicated no significant publication bias in this meta-analysis.

be used to clarify the PJK phenomenon in AIS patients. In adult spinal deformity, correction surgery mainly reconstructed the SVA, LL, and PT, while these parameters kept deteriorating with aging. The fixed segments failed to compensate for the sagittal spinal misalignment, and the increased PJA could compensate for the trunk forward (47). However, in AIS patients the proper sagittal balance is always maintained both before and after surgery and the PJA increase might be a manifestation of thoracic kyphosis. Furthermore, the larger PJA-RCA was detected in the PJK group, which also reflected that the PJA was mainly influenced by the adjacent segments rather than the whole sagittal alignment (27).

## Surgery factors associated with PJK in AIS individuals after PSF

In order to prevent PJK after surgery for adult spinal deformity, surgeons tried many surgical strategies, such as vertebral augmentation, ligament strengthening, semi-rigid structure at the proximal construct, and transverse process hook at UIV (47). However, there are not so many preventive measures in the AIS population. The most reported PJK prevention measure after PSF in AIS is to use lamina hook or transverse claws for UIV, and the reported results are inconsistent (28, 31, 40). The pooled results showed that the use of hooks for UIV (OR = 0.48, 95% = 0.31∼0.47, $p = 0.001$) could prevent PJK. In addition to proximal implants, other surgical-related PJK influencing factors have also been reported, such as disruption of junctional ligaments (25), exposure of adjacent joint (48), and thoracoplasty (42).

## Clinical outcome in AIS individuals after PSF

One of the main reasons why the phenomenon of PJK is getting more and more attention is that PJK can lead to poor clinical outcomes, which has been widely confirmed in adult degenerative spine deformity patients (49). However, for AIS, the researchers did not detect that PJK would have a significant impact on its clinical outcome (25, 35). These pooled results also did not find any difference in the preoperative and postoperative SRS-22 scores between the PJK group and the non-PJK group. The reason for this result may be that the current follow-up time is too short to show the effect of osteoporosis and muscle degeneration on the accelerated deterioration of PJK. We cannot be blindly optimistic that PJK patients after AIS still have no clinical symptoms after aging.

## Limitations

Even though the current meta-analysis retrieved papers on PJK after PSF in AIS patients, the following shortcomings should be taken into consideration. Firstly, the sample sizes were small for some papers included in this meta, which might lead to heterogeneity. Secondly, the current meta-analysis could not perform the subgroup analysis based on different curve types. Finally, only retrospective studies were included, and further prospective studies were needed to detect the primary risk factor of PJK in AIS.

# Conclusion

PJK was a common complication after PSF in AIS. The individuals with larger preoperative TK were more susceptible to PJK, and PJA was mainly influenced by the adjacent segments rather than the whole sagittal alignment. Using hooks or claws at UIV should be one measure to prevent PJK in AIS individuals.

# Author contributions

JZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CH: Data curation, Investigation, Resources, Writing – review & editing. YL: Data curation, Supervision, Validation, Writing – review & editing. DaL: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – review & editing. DoL: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Publisher's note

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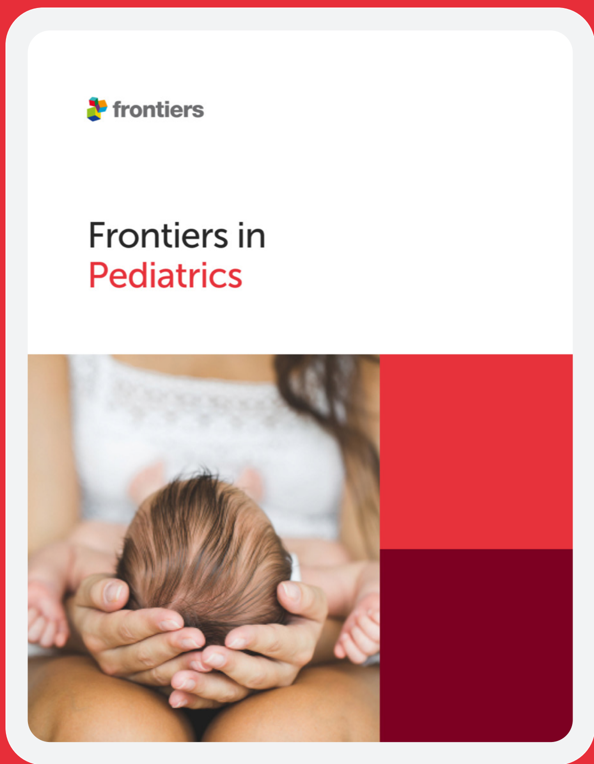


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