



Vertebra-disc ratio as a new predictor for curve progression in early thoracic AIS with bracing treatment[☆]



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ABSTRACT

Objectives: Previous studies have reported various predictors for curve progression in braced adolescent idiopathic scoliosis (AIS) patients. However, the reported predictors might be insufficient for patients with early AIS. The aim was to investigate whether the initial vertebra-disc ratio (VDR) could serve as an effective predictor for curve progression in early thoracic AIS (premenarchal and Risser 0) undergoing brace treatment.

Patients and methods: This study reviewed a consecutive series of early thoracic AIS girls with thoracic curve. All patients had accepted brace treatment and had regular follow-up. According to the bracing outcomes, patients were divided into two groups: Group P (progressed, curve progressed over six degrees or indicated for surgery) and Group NP (non-progressed).

Results: Totally 203 girls were included. There were 73 and 130 patients in Groups P and NP, respectively. The patients in Group P had greater initial VDR (1.9 ± 0.5 vs. 0.8 ± 0.4 , $P < 0.01$) than Group NP. During the follow-up, it showed continuous higher values in Group P than Group NP. The logistic regression analysis revealed that initial VDR had an effective value for predicting curve progression in the braced early AIS girls. The ideal cut-off point of initial VDR was 1.5 for the prediction of curve progression.

Conclusion: The initial VDR could serve as an effective predictor for curve progression in braced early AIS girls. Evaluation of this new parameter should be carefully performed at the bracing initiation.

1. Introduction

Brace treatment has been commonly used as an effective conservative management for adolescent idiopathic scoliosis (AIS) [1–4]. Among the braced candidates, early AIS (premenarchal and Risser 0) patients have been reported to progress most rapidly during the pubertal growth spurt [5,6]. The curve progression rate of non-treated early AIS was up to 80%, and even to 90% [7,8]. Thus, early intervention for this specific group is of great significance. Wiemann et al. [6] reported that 71% of the early AIS patients treated with nighttime brace showed curve progression during the follow-up. The high progression rate implied that longer wearing hours of brace might be of benefit for these patients [9]. Then, Sun et al. [5] conducted a study among the braced early AIS patients, they found that a lower percentage (38%) of them with longer wearing time demonstrated curve progression during the follow-up.

To better understand the causes and mechanisms of the unfavorable outcomes, several studies have investigated the predictors for curve

progression. Curve magnitude [3,10], growth potential [1,2,11–13], curve pattern [14], initial Cobb angle reduction velocity [15], and spinopelvic sagittal morphology [16] were identified as the predictors contributing to curve progression during bracing period. Among the braced early AIS girls with thoracic curve, Sun et al. [5] confirmed that the rib-vertebral angle measurements could serve as valid factors in predicting curve progression. However, for this specific group, it remains unclear whether there are any other factors that possess the predictive values for curve progression? Further insight into the investigation of effective predictors for curve progression in the early AIS patients is of importance. Previously, Will et al. [17] investigated the contributions of disc and vertebra wedging to curve progression in the braced early AIS patients. They found that curve progression initially increased from the disc wedging during the rapid growth spurt which was stratified by the Digital Skeletal Age (DSA) score. Namely, the aggravation of disc wedging took the major responsibility for curve progression. Hence, we tried to establish a new parameter, the vertebra-disc ratio (VDR), for predicting curve progression in the braced early

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AIS patients with a thoracic curve. VDR was computed as the ratio of the cumulative vertebra wedging angle to the cumulative disc wedging angle in the corresponding curve. If the VDR was greater than 1, the contribution of vertebra wedging angle was higher than the disc wedging angle, and vice versa.

After a series of pilot investigations, we hypothesized that the initial VDR might have a predictive value in predicting curve progression of braced early AIS patients. The aims of the present study were: (1) to identify the predictive value of the initial VDR for curve progression in braced early AIS patients; and (2) to evaluate the ideal cut-off value of initial VDR for prediction of curve progression.

2. Materials and methods

2.1. Patients

This study was approved by the Ethics Committee of our Hospital. A consecutive series of female patients who received brace treatment between January 2006 and May 2016 were identified from our AIS bracing database. The inclusion criteria were as follows: (1) aged from 8 to 12 years; (2) premenarchal with Risser grade of 0; (3) initial main right thoracic curve with the Cobb angle between 20° and 40°; (4) accepted a custom-made Milwaukee or Boston-type brace; (5) with regular follow-up for at least 1 year beyond weaning of bracing, or when the major curve progressed to > 40° Cobb angle with indication for surgery. Exclusion criteria were: (1) prior treatment before bracing; (2) alteration in brace type; (3) compliance of brace treatment (calculated as the ratio of the actual daily bracing time to the recommended daily time [18,19]) being less than 90%. In accordance with the protocol described previously [18,19], a daily bracing time of 22 h was prescribed initially.

The follow-up visit was scheduled at 6 month intervals [18,19]. Bracing was discontinued with a cessation process when patients reached skeletal maturity [18,19], which was defined as the growth status characterized with height gain less than 1 cm on two consecutive visits, Risser sign > 4 and 3 years after menarche [18,19]. According to the bracing outcomes at the latest follow-up, patients were divided into two groups: Group P (progressed, curve progressed over six degrees or indicated for surgery) and Group NP (non-progressed) [20,21].

2.2. Radiographs measurements

Right before bracing initiation and at each visit during bracing treatment, all girls were prescribed to take the posteroanterior radiographs of the whole spine out of brace in a standing position, and radiographs of the left hand and wrist.

All parameters were measured by two senior spinal surgeons (Z.C. and X.C.), and the mean values were adapted for further analyses. The following parameters were obtained from the anteroposterior radiographs: (1) Cobb angle; (2) discs and vertebrae wedging angles were measured according to the method described by Will et al. [17] (Fig. 1); (3) VDR was computed as the ratio of the discs wedging angle to the vertebrae wedging angle (Fig. 1); (4) the disc wedging percentage was the percent of discs wedging angles to the corresponding Cobb angle; The vertebrae wedging percentage was the percent of vertebrae wedging angles to the corresponding Cobb angle; (5) the convex rib-vertebral angle and rib-vertebral angle difference of the apex were measured with the methods described by Mehta et al. [5,22]; (6) the apical vertebra translation was defined as the horizontal distance from the center of the apical vertebra to the center sacral vertical line (CSVL). If the apex was located at the intervertebral disc, the vertebra inferior to the apical disc was chosen as the apical vertebra for the measurement; (7) coronal balance was measured by the deviation of the C7 plumb line from the CSVL; (8) sagittal vertical axis was measured as the distance from the C7 plumb line to the perpendicular line drawn from the superior posterior corner of the S1 vertebral body.

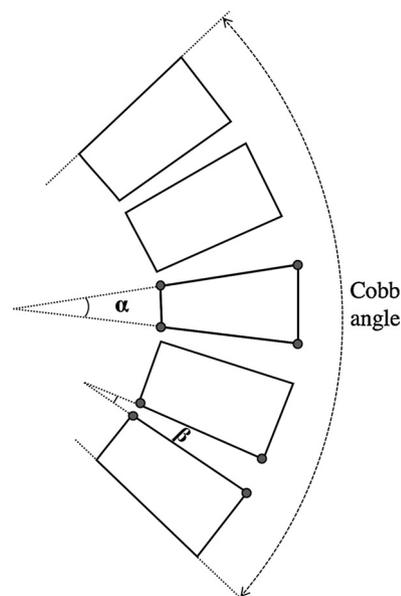


Fig. 1. Illustration of the method for measuring the vertebra and disc wedging angles as well as how the VDR was calculated. Cobb angle = $\Sigma\alpha + \Sigma\beta$; VDR = $(\Sigma\alpha)/(\Sigma\beta)$. α Vertebra wedging angle, β Disc wedging angle, VDR Vertebra-disc ratio, $\Sigma\alpha$ The sum of vertebra wedging angles in the corresponding curve, $\Sigma\beta$ The sum of disc wedging angles in the corresponding curve.

2.3. Skeletal age assessment

Skeletal age was evaluated on the radiograph of the left hand and wrist using the Tanner and Whitehouse (Tanner-Whitehouse-III) method [23]. The Tanner-Whitehouse-III method consisted of specifically scoring the individual bones with a letter correlated with a specific weighted score. The scores were constituted by the carpal bones and the radius, ulna, and small bones of the hand (RUS). As radius and ulna had the lowest correlation with CAP of the RUS scores, the DSA score was used in this study, which was defined as the RUS system without radius and ulna [24]. As described by Will et al. [17], three main stages of growth were defined by the DSA score: pre-growth spurt, growth spurt and post-growth spurt. Four DSA measurements were selected to define these three growth phases: less than 375 (pre-growth spurt), 375–450 (considered as the growth spurt period) and greater than 450 (post-growth spurt) [17].

All parameters were carried out by Surgimap (Spine Software, version 2.2.1, New York, NY). Two of the authors (Z.C. and X.C.) completed the measurements individually. In addition, all parameters were selected to determine the inter- and intra-observer variability of the measurement. All the radiographic parameters were measured by the authors and then repeated twice. There were strong inter-observer and intra-observer agreements for all the parameters with all the kappa correlation coefficients exceeding 0.8. Thus, the measured data were highly reliable, and the mean values of the parameters measured by the two investigators were used for further analyses.

2.4. Statistical analysis

Statistical analyses were performed using the SPSS software 19.0 (SPSS Inc., Chicago, IL). Paired-sample *t*-test was applied to compare the bracing changes in each group. Additionally, independent-sample *t*-test was used to compare the difference between the two groups. The statistical significance was set at $P < 0.05$. Logistic regression analysis of the selected variables from univariate analysis was performed to identify the factors independently associated with curve progression.

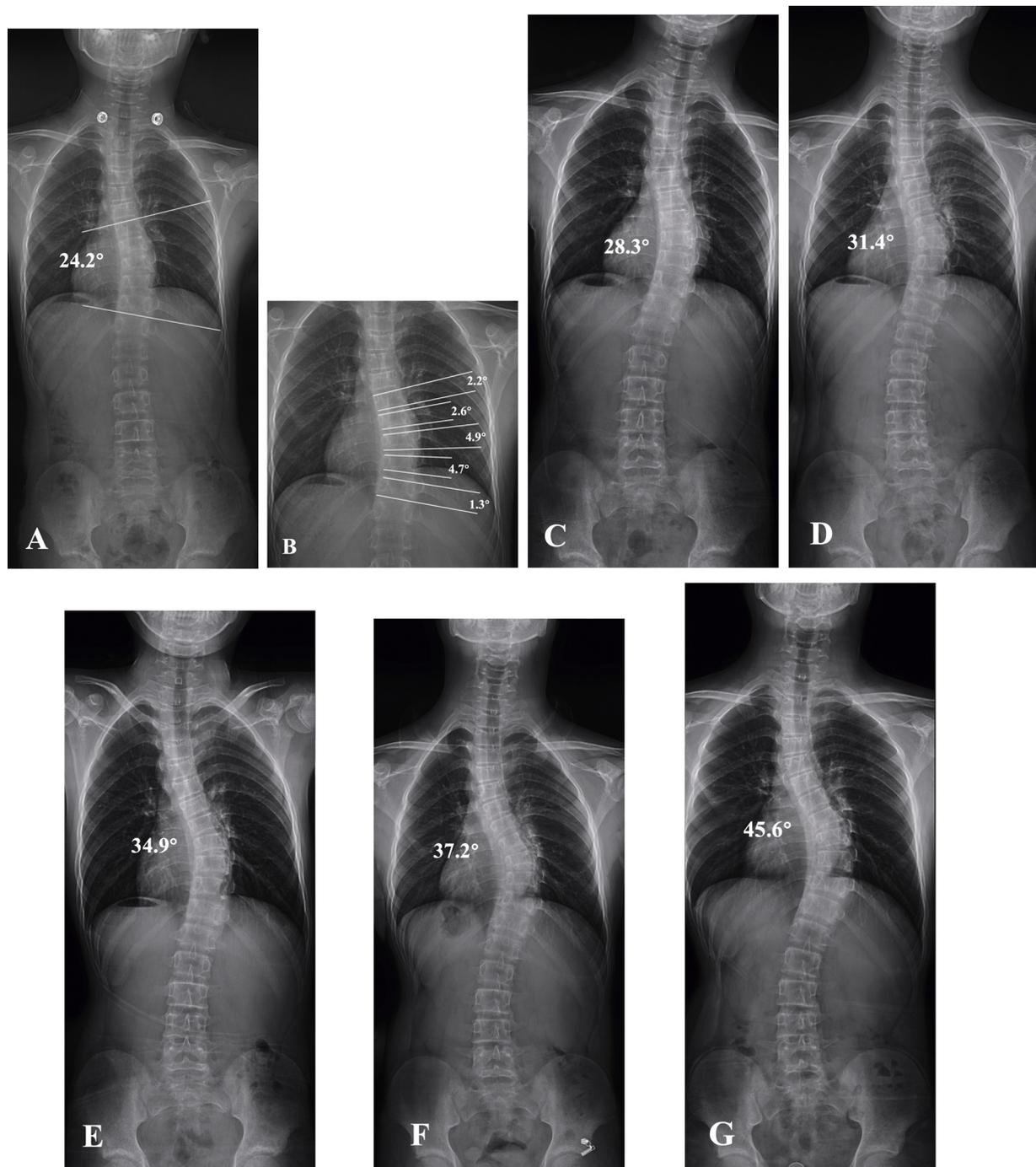


Fig. 2. A 10.1-year-old girl (premenarchal and Risser 0) accepted Boston brace treatment, however, the curve progressed. **1A** The Cobb angle and VDR were 24.2° and 1.85 at bracing initiation, respectively. **1B** Details of vertebra wedging angle in the corresponding curve at bracing initiation. The Cobb angle and VDR were 28.3° and 1.83 at 6 months (**C**); 31.4° and 1.77 at 12 months (**D**); 34.9° and 1.62 at 18 months (**E**); 37.2° and 1.3 at 24 months (**F**); 45.6° and 1.35 at 30 months (**G**), respectively. Finally, she received correction surgery for cosmetic concerns.

3. Results

A total of 203 patients were finally included in this study. They had a mean age of 10.1 ± 1.3 years (range, 8.0–11.9 years) at bracing initiation. They all had a right thoracic curve averaged $27.4 \pm 6.3^\circ$ (range, 20–40°). The apex located at T7 in 23, T7/8 disc in 21, T8 in 49, T8/9 disc in 10, T9 in 24, T9/10 disc in 37, T10 in 23, and T10/11 disc in sixteen cases. One hundred and nine patients had a compensatory left thoracolumbar/lumbar curve. At the latest follow-up, the average primary curve magnitude was $32.4 \pm 7.9^\circ$ (range, 15–56°). Thirty-four girls eventually accepted posterior correction surgery while the

remaining 169 cases were followed with a minimum of 1 year after brace weaning. Among the 169 cases, thirty-nine had worsening of the main curve of greater than six degrees. Overall, 73 (36%) patients were classified as Group P (**Fig. 2**), while the remaining 130 (64%) constituted Group NP (**Fig. 3**).

3.1. Comparison between group P and group NP

The comparison analyses revealed no significant differences between the two groups in terms of the age, Cobb angle or DSA score at the brace initiation (**Table 1**).

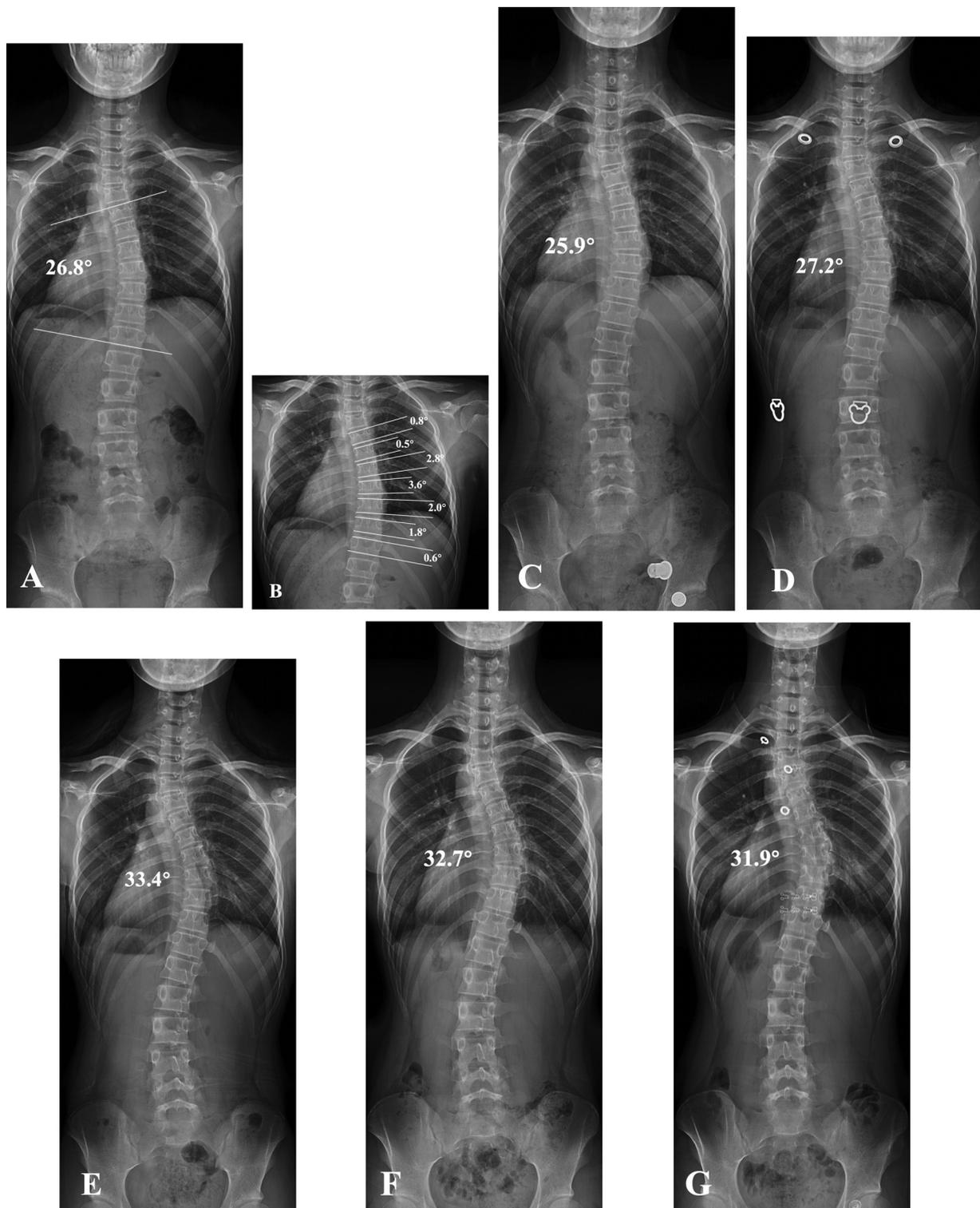


Fig. 3. A 10.5-year-old girl (premenarchal and Risser 0) accepted Boston brace treatment and her curve remained stable after 38 months of bracing. **2A** The Cobb angle and VDR were 26.8° and 0.82 at bracing initiation, respectively. **2B** Details of vertebra wedging angle in the corresponding curve at bracing initiation. The Cobb angle and VDR were 25.9° and 0.89 at 6 months (**C**); 27.2° and 0.81 at 12 months (**D**); 33.4° and 0.76 at 18 months (**E**); 32.7° and 0.82 at 38 months (**F**), respectively. Then the brace was discontinued. One year later, the thoracic curve was 31.9° (**G**).

Prior to the growth spurt, the average initial VDR in Group P was significantly greater than Group NP (1.9 ± 0.5 vs. 0.8 ± 0.4 , $P < 0.01$). During the growth spurt, the value of VDR decreased from 1.8 ± 0.6 to 1.2 ± 0.6 in Group P ($P < 0.01$), then it increased slightly from 1.2 ± 0.6 to 1.4 ± 0.6 after the growth spurt ($P = 0.152$). When compared with the baseline value, the DVR in

Group P slightly decreased at the time point of 375 (1.8 ± 0.6 vs. 1.9 ± 0.5 , $P = 0.494$), while it significantly decreased at the time point of 450 (1.2 ± 0.6 vs. 1.9 ± 0.5 , $P < 0.01$) and the end (1.4 ± 0.6 vs. 1.9 ± 0.5 , $P < 0.01$). However, it remained relatively stable in Group NP (**Fig. 4**). Besides, the VDR showed continuous higher values in Group P than Group NP during the bracing period. Similarly,

Table 1
General data of patients in two groups (± s).

	Goup P	Group NP
Age (years)		
Brace initiation	10.1 ± 1.2	10.2 ± 1.3
Latest FU	14.8 ± 1.2	16.7 ± 1.4
Cobb angle (°)		
Brace initiation	28.6 ± 6.2	26.2 ± 6.3
Latest FU	38.2 ± 8.3	26.5 ± 7.5
DSA score		
Brace initiation	309 ± 44	311 ± 48
Latest FU	523 ± 52	599 ± 7
Rsser sign		
Brace initiation	0	0
Latest FU	4.1 ± 1.0	4.8 ± 0.5
Years since menarche		
Brace initiation	0	0
Latest FU	2.6 ± 1.5	4.9 ± 1.7

DSA: Digital Skeletal Age.

the rib-vertebral angle difference and apical vertebra translation in Group P showed higher average initial values (18.9° ± 7.2° vs. 14.2° ± 6.7° and 26.4 mm ± 12.3 mm vs. 21.6 mm ± 10.9 mm, respectively; *P* < 0.05) than Group NP. At the same time, the initial convex rib-vertebral angle in Group P was significantly lower than Group NP. No significant differences were found between the two groups in terms of the coronal balance or sagittal vertical axis at brace initiation. (Table 2)

With regards to the contributions of vertebra and disc wedging to curve evolution, the patients in Group P had greater initial vertebra wedging angle and percentage (18.9° ± 4.5° vs. 11.7° ± 4.2° and 66.1% ± 9.5% vs. 44.7% ± 8.7%, respectively; *P* < 0.01) than Group NP. During the follow-up, they showed continuous higher values in Group P than Group NP. On the contrary, the disc wedging percentage showed continuous lower values in Group P than Group NP. For the disc wedging angle, it demonstrated an increasing trend in Group P, while it was relatively stable in Group NP. (Table 3, Fig. 4)

Table 2
Differences in parameters between two groups (± s).

	Initial	375	450	End
DSA score				
Initial				
375				
450				
End				
Cobb angle (°)				
Group P	28.6 ± 6.2	29.1 ± 6.5	34.4 ± 8.4	38.2 ± 8.3
Group NP	26.2 ± 6.3	24.9 ± 6.3	26.2 ± 6.5	26.5 ± 7.5
<i>P</i> value	0.071	< 0.001*	< 0.001*	< 0.001*
VDR				
Group P	1.9 ± 0.5	1.8 ± 0.6	1.2 ± 0.6	1.4 ± 0.6
Group NP	0.8 ± 0.4	0.8 ± 0.5	0.8 ± 0.6	0.9 ± 0.5
<i>P</i> value	< 0.001*	< 0.001*	< 0.001*	< 0.001*
Convex rib-vertebral angle (°)				
Group P	68.3 ± 7.2	66.1 ± 7.3	62.7 ± 7.8	61.5 ± 7.1
Group NP	73.4 ± 7.1	73.6 ± 7.4	74.4 ± 7.5	75.2 ± 7.3
<i>P</i> value	0.009*	< 0.001*	< 0.001*	< 0.001*
Rib-vertebral angle difference (°)				
Group P	18.9 ± 7.2	20.7 ± 7.2	27.1 ± 7.5	28.3 ± 7.7
Group NP	14.2 ± 6.7	13.6 ± 6.2	12.3 ± 6.1	13.1 ± 6.2
<i>P</i> value	0.012*	< 0.001*	< 0.001*	< 0.001*
Apical vertebra translation (mm)				
Group P	26.4 ± 12.3	27.2 ± 11.4	34.9 ± 13.7	36.2 ± 14.8
Group NP	21.6 ± 10.9	21.3 ± 10.5	22.6 ± 11.1	23.9 ± 12.5
<i>P</i> value	0.045*	< 0.001*	< 0.001*	< 0.001*
Coronal balance (mm)				
Group P	9.5 ± 8.7	9.3 ± 8.6	10.2 ± 8.4	10.6 ± 8.5
Group NP	9.8 ± 7.8	9.6 ± 8.2	9.9 ± 7.9	10.1 ± 8.1
<i>P</i> value	0.853	0.891	0.819	0.742
Sagittal vertical axis (mm)				
Group P	15.3 ± 9.4	15.9 ± 9.1	16.4 ± 9.3	15.8 ± 8.7
Group NP	16.1 ± 8.9	16.2 ± 9.2	15.7 ± 8.8	16.5 ± 8.6
<i>P</i> value	0.537	0.712	0.511	0.626

VDR: vertebra-disc ratio; DSA: Digital Skeletal Age; DSA score: less than 375 (pre-growth spurt), 375–450 (growth spurt period), greater than 450 (post-growth spurt).

* Statistically significant.

3.2. Logistic regression analysis of indicators for curve progression

The variables from the univariate analysis that were associated with curve progression included the initial VDR, convex rib-vertebral angle,

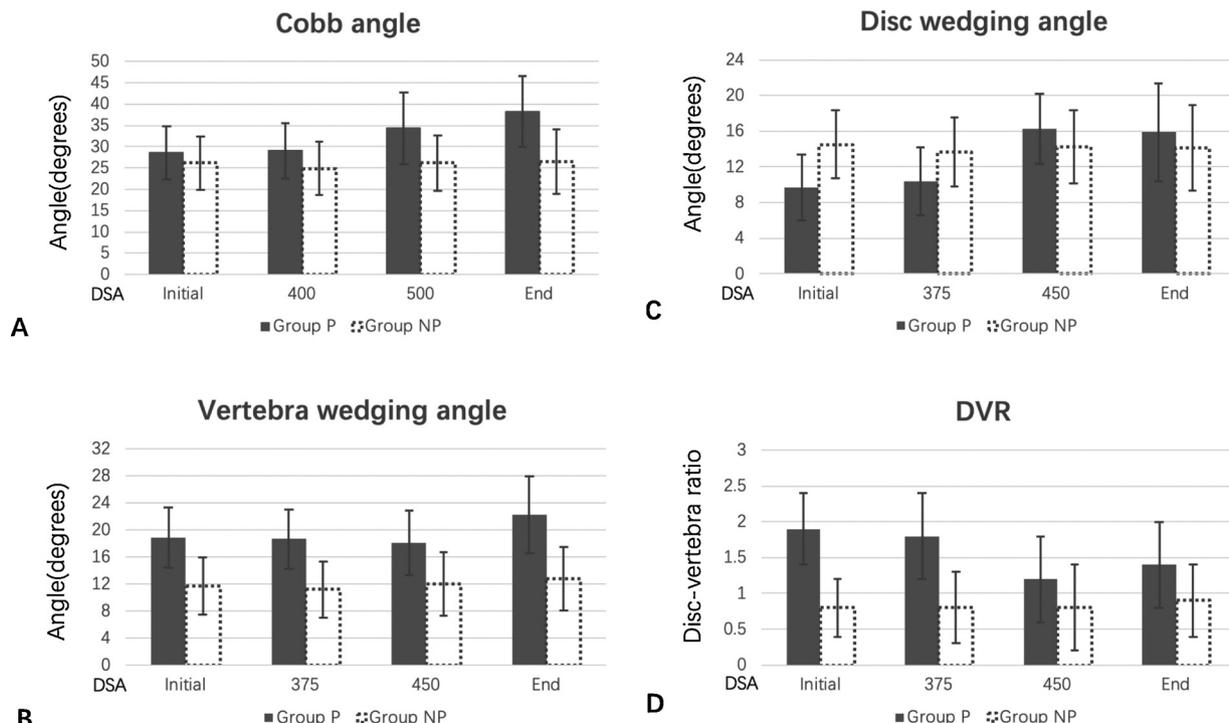


Fig. 4. The graphic representation of the evolution for Cobb angle(A), vertebra wedging angle (B), disc wedging angle (C) and VDR(D) during the 3 maturity phases stratified by DSA score. DSA score: less than 375 (pre-growth spurt), 375–450 (growth spurt period), greater than 450 (post-growth spurt).

Table 3
Contributions of discs and vertebrae wedging to curve evolution at different maturity points in the two groups.

DSA score	Initial	375	450	End
Vertebra wedging angle (°)				
Group P	18.9 ± 4.5	18.7 ± 4.4	18.1 ± 4.8	22.3 ± 5.7
Group NP	11.7 ± 4.2	11.2 ± 4.2	12.0 ± 4.7	12.8 ± 4.7
P value	< 0.001*	< 0.001*	< 0.001*	< 0.001*
Disc wedging angle (°)				
Group P	9.7 ± 3.7	10.4 ± 3.8	16.3 ± 3.9	15.9 ± 5.5
Group NP	14.5 ± 3.8	13.7 ± 3.9	14.2 ± 4.1	14.1 ± 4.8
P value	< 0.001*	0 < 0.001*	0.012*	0.006*
Vertebra wedging percentage (%)				
Group P	66.1 ± 9.5	64.3 ± 10.4	52.6 ± 10.6	58.4 ± 9.2
Group NP	44.7 ± 8.7	44.9 ± 10.1	45.8 ± 9.2	49.3 ± 8.9
P value	< 0.001*	< 0.001*	< 0.001*	< 0.001*
Disc wedging percentage (%)				
Group P	33.9 ± 9.5	35.7 ± 10.4	47.4 ± 10.6	41.6 ± 9.2
Group NP	55.3 ± 8.7	55.1 ± 10.1	54.2 ± 9.2	50.7 ± 8.9
P value	< 0.001*	< 0.001*	< 0.001*	< 0.001*

DSA: Digital Skeletal Age; DSA score: less than 375 (pre-growth spurt), 375–450 (growth spurt period), greater than 450 (post-growth spurt).

Table 4
Multivariate logistic regression for curve progression after bracing.

Risk factors	P value	Odds Ratio (95% CI)
VDR	< 0.001*	5.132(2.673–10.121)
Convex rib-vertebral angle	0.165	0.914(0.902–1.086)
Rib-vertebral angle difference	0.082	1.035(0.928–1.179)
Apical vertebra translation	0.154	1.033(0.988–1.080)

VDR: vertebra-disc ratio; CI: confidence interval.

* Statistically significant.

rib-vertebral angle difference and apical vertebra translation. Logistic regression analysis revealed that the initial VDR was an independent factor predicting curve progression during bracing treatment (Table 4). ROC curve analysis yielded good discrimination between the two groups, with an area under the curve of 0.835 (95% confidence interval 0.753–0.913) for the initial VDR. Based on the clinical application and the ROC curve analysis, the ideal cut-off value of the initial VDR predicting curve progression was determined at 1.5 finally. And at this point, the sensitivity and the specificity for curve progression was 79.2% and 83.9%, respectively.

4. Discussion

Previous studies have reported the natural history of the early AIS patients [7,8]. The high rate (80%–90%) of curve progression rendered the brace as a conservative management for this specific group. Even though, the unfavorable outcomes still could be observed in the braced early AIS girls with the incidence ranged from 38%–71% [5,6]. The current study revealed that the progression rate was 36% in the braced early patients during the follow-up. This was similar to the study performed by Sun et al. [5]. The unfavorable outcomes impelled the investigators to identify the factors of predicting curve progression among the early AIS patients.

The current study identified that the initial VDR could be severed as an effective predictor of the curve progression in the braced early thoracic AIS patients. Predictive factors related to curve progression in scoliosis have been reported in previous studies [2,3,5,10,14–16,25]. Although these factors shared the predicting significance in AIS patients, they were identified and investigated under various backgrounds, such as different age range, bracing types and curve patterns. For the early thoracic AIS patients, the associated predictive factors have seldom been addressed. Sun et al. [5] confirmed that the rib-vertebral angle measurements were predictive factors of curve

progression in this population. Will et al. [17] demonstrated that the aggravation of disc wedging was responsible for curve progression in the braced early AIS patients. However, the relevant predictors were not identified among this population. Hence, the present study proposed such a new parameter, the VDR, to predict the curve progression in the braced early AIS patients with thoracic curves.

The results (Table 4) of the current study illustrated that the braced early thoracic AIS patients with a higher initial VDR were inclined to have curve progression. This supported our hypothesis. The VDR was calculated as the ratio of cumulative vertebrae wedging angle to cumulative discs wedging angle in the corresponding curve. A higher initial VDR indicated that the vertebra wedging in Group P was higher than that in Group NP. Our results demonstrated that patients with such an unfavorable baseline showed curve progression during bracing. A possible explanation of this finding is asymmetrical growth of the spine. According to the Hueter-Volkman law [26,27], the unbalanced spinal growth may be pronounced due to the asymmetrical loading between the concave and convex side in the scoliosis. If the significant vertebra wedging emerges, the curve tends to experience unbalanced loading between the two sides despite of the bracing, which will result in asymmetrical spinal growth. Subsequently, the disc wedging and asymmetrical spinal growth aggravates in a vicious cycle especially during the growth spurt, and the scoliosis progresses. Our results confirmed this explanation with the evidence that the initial VDR and vertebra wedging angle were greater in Group P than Group NP. Thus, the theory that a potential higher initial VDR could predict the following curve progression is reasonable to be comprehended. Similar to many predictors, the cut-off point for initial VDR should be determined to accurately stratify and prognosticate the bracing outcome. Based on the clinical application and the ROC curve analysis, the present study identified that the ideal cut-off point of initial VDR was 1.5, which had the appropriate overall indicative value of predicting curve progression. Hence, careful evaluation of the initial VDR is of great significance. Besides, due to the higher progressive tendency among the early AIS patients with higher VDR, more attention should be paid to them. After a daily bracing time, exercise techniques for scoliosis such as Schroth method [28] which aims to strengthen or lengthen the asymmetrical muscles around the scoliosis may be benefit for reducing the likelihood of curve progression for these patients.

Aside from the identification of predictor for curve progression in the braced early thoracic AIS, the evolution of vertebra and disc wedging was also evaluated during different growth phases which were stratified by DSA score. For the vertebra wedging angle, it remained stabilized in Group NP during the bracing period. This might be attributed to the vertebra remodeling, which occurred mainly in the way of increasing the vertebral height on the convexity and concavity while not significantly changing the wedging angle. In Group P, the vertebra wedging showed stable magnitude before and during the growth spurt. However, it increased significantly after the growth spurt. This was in accord with the results of Will et al. [17]. The tension of discs that applied to the endplates on the convexity, thus triggered its growth or remodeling [17]. This might take the major responsibility for aggravation of vertebrae wedging. For the disc wedging angle, it showed the similar status in Group NP during the bracing period. While in Group P, the disc wedging demonstrated increasing trend especially during the growth spurt. Although this supported the conclusion of Will et al. [17] who reported that the disc wedging aggravation during the growth spurt was responsible for curve progression among the braced early AIS patients, our results further identified that the initial higher deformation of vertebra wedging was the initiator of disc wedging and curve progression for this specific group. Thus, as the explanation above, a greater initial VDR does have a predictive value in predicting curve progression among these patients.

This study has two limitations. First, since the patients were treated with braces, the natural history of untreated early thoracic AIS might not be accurately reflected. However, due to the ethical concerns, we

were unable to evaluate the natural history for the early AIS patients. Second, this study was limited by its retrospective nature. In the future, a prospective study focusing on the early AIS patients would be valuable. Despite the limitations, this study is the first, to our knowledge, to demonstrate that initial DVR could serve as one of the objective and important predictors for curve progression in the braced early thoracic AIS girls.

5. Conclusion

The clinical importance of the current study is that VDR may serve as an additional objective quantitative measurement for predicting the probability of curve progression and may help in selecting patients for appropriate treatment.

Acknowledgements

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