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DEFORMITY

Does ScoliScore Provide More Information Than Traditional Clinical Estimates of Curve Progression?

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Study Design. Retrospective study comparing ScoliScore and clinical risk estimates.

Objective. The purpose of this study was to compare risk stratification between ScoliScore and traditional clinical estimates to determine whether ScoliScore provides unique information.

Summary of Background Data. ScoliScore is a genetic prognostic test designed to evaluate the risk of curve progression in skeletally immature patients with adolescent idiopathic scoliosis with Cobb angles of 10° to 25°. Clinicians are currently trying to better understand the role this test may play in guiding clinical decision making because current standards of curve progression are largely based on radiographical markers, such as curve magnitude and bone age.

Methods. Ninety-one patients who received ScoliScore testing at our center and met study inclusion criteria were identified. Patients were given a "clinical risk" level using their Risser sign and Cobb angle. Assigned clinical risk levels were compared with the ScoliScore risk levels reported by the manufacturer's scoring algorithm.

Results. ScoliScore risk distribution in our population was 36% low risk, 55% intermediate risk, and 9% high risk. This compares with 2%, 51%, and 47%, respectively, for comparable clinical risk groupings. Only 25% of patients were in the same risk category for both systems. There were no significant correlations between ScoliScore and age, race, menarcheal status, Risser sign, or sex. There was a positive correlation between the Cobb angle and the ScoliScore ($r = 0.581$, $P < 0.001$). Cobb angle remained significant in the multivariate regression model ($P < 0.001$), and Cobb angle was found to account for 33.3% of ScoliScore's variance.

Conclusion. Only Cobb angle showed significant correlation with ScoliScore among the socioclinical variables studied. The risk distribution of the 2 risk estimation systems examined differed markedly: ScoliScore predicted nearly 16 times more low-risk patients and more than 5 times fewer high-risk patients. This demonstrates that ScoliScore provides unique information to traditional predictors of curve progression, advancing our understanding of the role of ScoliScore in the clinical setting.

Key words: adolescent idiopathic scoliosis, prognostic test, genetic markers, curve progression. **Spine 2012;37:2099–2103**

Although many theories currently exist, the etiology of curve progression in adolescent idiopathic scoliosis (AIS) has yet to be fully elucidated. Although the prevalence of curves more than 10° is 1.5% to 3.0%, the prevalence of curves more than 20° and 30° is only 0.3% to 0.5% and 0.2% to 0.3%, respectively.[1] Therefore, only a small subset of patients diagnosed with scoliosis progress to the point where surgical intervention becomes necessary. Risk of progression has been shown to correlate with multiple clinical risk factors, including sex, chronological age, menarcheal status, hand bone age, Risser sign, and curve pattern.[2–4] Unfortunately, the ability of these clinical risk factors to predict significant progression is limited, and there is great interest in developing more accurate methods of risk assessment.

Several genetic markers have been shown to be associated with the development and progression of curves in AIS,[5,6] including estrogen receptors,[7] melatonin,[8] and calmodulin.[9] Investigations conducted by Axial Biotech (Salt Lake City, Utah) of more than 9500 patients at more than 100 clinical sites led to the development of a 53-gene panel called "ScoliScore."[10] This saliva-based genetic test incorporates 28 progression and 25 protection-associated markers, along with the patient's Cobb angle at time of testing, into an algorithm used to determine the risk of curve progression requiring surgery in patients with AIS. This algorithm is used to calculate a numeric risk of progression on a scale between 1 and 200. Patients receiving low scores (1–50) were noted to

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have more than a 99% chance of not progressing to a severe curve (defined as a Cobb angle > 40°). The risk of progression in patients receiving intermediate scores (51–180) was 1% to 50%, whereas high-risk scores (181–200) were associated with a 50% to 99% chance of progression.[10] Current indications for the test include a diagnosis of AIS, a Cobb angle between 10° and 25°, skeletal immaturity, and Caucasian race.

The promising early results noted by the test's developers suggest that the ScoliScore could prove useful in various clinical scenarios. First, patients receiving low risk scores would ultimately require less frequent follow-up and may be able to avoid or discontinue bracing. This, in turn, would reduce health care expenses as well as allow patients to avoid unnecessary radiation exposure. Intermediate scores are less predictive and, therefore, unlikely to significantly impact clinician decisions regarding management of patients with AIS. High scores indicate a significant risk of progression, but how these scores should be interpreted is still under consideration. These patients may require more frequent follow-up, earlier initiation of bracing, or possibly early surgical intervention using newer growth modulation strategies, such as tethering or growing rods.

Although such implications of the test sound promising, considerations must be made for the scores returned by the test in actual practice. A high rate of intermediate scores would limit the test's clinical utility. Furthermore, given the costs of genetic testing, for this to be a clinically useful and economically justifiable test, high and low ScoliScores must provide unique information to the physician, not just reiterate knowledge that can already be divined from Cobb angle, skeletal maturity, and other established clinical risk factors. The purpose of this study was to describe the demographic and clinical characteristics of patients who have received ScoliScore testing at our institution and to compare ScoliScore risk stratification with previously used clinical risk estimates. We assumed the null hypothesis that the ScoliScore test will stratify patients similarly to clinical predictors of progression, limiting the utility of the test.

MATERIALS AND METHODS

Design and Study Setting

After appropriate institutional review board approval was obtained, a single-center retrospective analysis was performed for patients receiving ScoliScore testing at our institution. The study included patients seen at our institution's Scoliosis and Spine Deformity Center from March 5, 2009, to April 14, 2011.

ScoliScore Procedure

ScoliScore testing was performed at our institution on skeletally immature patients with AIS who met ScoliScore criteria and were willing to undergo testing. The indications for ScoliScore testing are (1) self-reported Caucasian boy or girl (North American, South American, European, Eastern European, Middle Eastern), (2) diagnosis of AIS, (3) aged 9 years until skeletal maturity (our group used a Risser grade of ≤4) at the time of ScoliScore testing, and (4) major curve Cobb angle between 10° and 25°. Saliva samples for DNA analysis are collected in the office and submitted to the testing center along with clinical and demographic information, including age, sex, and Cobb angle.

Participants

Inclusion criteria for this study were the same as the indications of the ScoliScore test. We did, however, opt to include 1 patient who had a ScoliScore test done 1 day prior to his or her ninth birthday. Patients were excluded if a ScoliScore had not been returned at the time of analysis or if radiographs from the time of ScoliScore testing were unavailable. Patients were also excluded if Risser grading was not possible on their anteroposterior spine radiographs or if they were of less than 50% Caucasian descent. During the study period, 155 patients submitted saliva samples for ScoliScore testing. Of these, 91 satisfied our inclusion criteria.

Data Collection

Demographic, clinical, and radiographical data were collected for each patient. Risser signs were determined using radiographs from the day closest to or the day of ScoliScore testing. Seventy-three of the 91 patients obtained radiographs on the same day as testing. Of the remaining 18 patients, the maximum time between radiograph and ScoliScore testing was 18 weeks, with a mean of about 5 weeks. All patients were assigned a ScoliScore risk level and a "clinical risk" category according to their Cobb angle and Risser sign as described by Lonstein and Carlson[2] (Table 1).

Statistical Analysis

Descriptive analyses were performed for ScoliScore, demographic, clinical, and radiographical variables. Pearson correlation analyses were performed to investigate the relationship between ScoliScore and continuous patient variables.

TABLE 1. Progression Risk Categories

Progression Risk System	Low Risk	Intermediate Risk	High Risk
Lonstein and Carlson[2]	Risser grades 2–5 + Cobb 10°–19°	Risser grades 0–1 + Cobb angle 10°–19° or Risser grades 2–5 + Cobb angle 20°–25°	Risser grades 0–1 + Cobb angle 20°–29°
ScoliScore[11]	1–50	51–180	181–200

Independent *t* tests were performed to examine differences in ScoliScores among categorical patient groups. A χ^2 analysis was conducted to determine how the risk stratification differed between the clinical risk and ScoliScore risk schema. Multivariate regression analysis was performed to identify factors predicting ScoliScore. All analyses were 2-tailed and were conducted using SPSS software version 18 (SPSS Inc., Chicago, IL). A *P* value of less than 0.05 was considered to be significant.

RESULTS

Patient Characteristics

After appropriate institutional review board approval was obtained, the charts of 91 patients matching the inclusion criteria for this study were reviewed. Study patients had a mean age of 11.7 years (range, 8.9–14.6 yr) and a mean Cobb angle of 18.8° (10°–25°). The patients were 91.2% female and 8.8% male. The majority of female patients (96.3%) were premenarcheal (Table 2).

Clinical Risk Estimates and ScoliScore Risk Stratification

The average ScoliScore in the cohort was 92.1 (1–199). All but 2 of the patients had clinical risks determined to be intermediate or high, whereas 91% of patients had ScoliScore risks of low or intermediate (Table 2). Chi-square analysis comparing ScoliScore and clinical risk distributions (Table 3) differed significantly ($P < 0.001$). The low clinical risk group (N = 2) had an average ScoliScore of 77.0. One of these patients had a low-risk ScoliScore (17) and the other had an intermediate risk ScoliScore (137). The intermediate clinical risk group (N = 46) had an average ScoliScore of 59.9 ± 55.9 (1–188). Nearly two-thirds of patients (N = 28) in this group received a low-risk ScoliScore and approximately one-third of patients (N = 16) received an intermediate risk ScoliScore. Only 2 patients in the intermediate clinical risk group had a high-risk ScoliScore. The high clinical risk group (N = 43) had an average ScoliScore of 127.2 ± 51.6 (8–199). Only 6 (14%) of these patients also received a high-risk ScoliScore level, whereas 33 (76.7%) of these patients fell into the intermediate ScoliScore level and 4 (9.3%) were low risk. The average ScoliScore of the intermediate clinical risk group was significantly lower than that of the high clinical risk group ($P < 0.001$). Because of the small sample size of the low clinical risk group (N = 2), we did not find a significant difference between the average ScoliScore of this group and the other 2 clinical risk groups. Only 25% of patients were in the same risk category for both systems.

Final Regression Analysis

Patients with low-risk ScoliScores had a significantly smaller average Cobb angle (15.2°) than those with intermediate (20.6°, $P < 0.001$) and high risk (22.5°, $P < 0.001$) ScoliScores. ScoliScore demonstrated significant correlation with Cobb angle ($r = 0.581$, $P < 0.001$) and clinical risk category ($r = 0.474$, $P < 0.001$). There were no significant associations noted between ScoliScore and age, race, menarcheal status, Risser sign, or sex. A multivariate regression analysis was conducted to adjust for possible confounding and/or interaction effects among the independent variables. The final model showed that only Cobb angle retained its significance and accounted for 33.3% of ScoliScore variance ($F = 23.4$, $P < 0.001$; $\beta = 6.4$, $P < 0.001$).

TABLE 2. Patient, Clinical, and ScoliScore Characteristics

	N = 91
Age at ScoliScore	11.5 ± 1.5 (8.9–15.8)
Cobb angle	18.8 ± 4.7 (10–25)
Sex	
Male	8 (8.8%)
Female	85 (91.2%)
Race	
Caucasian	83 (91.2%)
Hispanic	3 (3.3%)
Half-Hispanic	2 (2.2%)
Half-Asian	3 (3.3%)
Menarcheal status	
Premenarcheal	80 (96.3%)
Postmenarcheal	3 (3.7%)
N/A (male)	8
Risser sign	
0	72 (79.1%)
1	12 (13.2%)
2	3 (3.3%)
3	0 (0.0%)
4	4 (4.4%)
ScoliScore	92.1 ± 63.3 (1–199)
ScoliScore risk level	
Low (0–50)	33 (36.3%)
Intermediate (51–179)	50 (54.9%)
High (180–200)	8 (8.8%)
Clinical risk level	
Low	2 (2.2%)
Intermediate	46 (50.5%)
High	43 (47.3%)

DISCUSSION

The ScoliScore represents a promising but unduplicated new method of risk assessment in the field of pediatric orthopedics. Validating data from the manufacturer have been published,

TABLE 3. Clinical Risk and ScoliScore Risk Distributions (N = 91)

	ScoliScore Risk Categories		
	Low (33)	Intermediate (50)	High (8)
Clinical risk categories			
Low (2)	1 (50.0%)	1 (50.0%)	0 (0.0%)
Intermediate (46)	28 (60.9%)	16 (34.8%)	2 (4.3%)
High (43)	4 (9.3%)	33 (76.7%)	6 (14.0%)

but to our knowledge, no independent group has studied the test. We sought to compare ScoliScore risk stratification with commonly used clinical risk markers to determine the test's clinical utility. Our results indicate that ScoliScore provides novel clinical data that are unique from the clinical risk estimates commonly utilized in practice. This work advances our understanding of the potential role ScoliScore may serve in the clinical setting.

Risk distribution between the clinical criteria and the ScoliScore schema differed markedly. ScoliScore predicted nearly 16 times more low-risk patients and more than 5 times fewer high-risk patients than the clinical risk system. It is these groups in which ScoliScore may affect decision making most. Nearly 50% of ScoliScores predicted high or low risk of progression, indicating that the ScoliScore had potential to affect decision making in approximately half of our cohort.

A strong correlation was found between Cobb angle and ScoliScore, and Cobb angle was noted to account for 33.3% of ScoliScore variance. This was not unexpected, because the Cobb angle is included in the algorithm that generates each Scoliscore; however, we found a correlation of this magnitude with a dynamic variable surprising for what is marketed as a static genetic test. According to the development group, the Cobb angle is necessary in order to account for unmeasured genetic and environmental factors that contribute to curve progression.[10] Despite this, it is evident that ScoliScore still provided unique clinical information. In addition, no correlations were noted between ScoliScore and any of the other studied social or clinical markers. However, our population was fairly homogenous in regard to Risser grade, sex, and menarcheal status, making it more difficult to show significant differences that may have existed. Some of these clinical variables have shown correlations with risk of progression in other studies, so a greater diversity in the test population may uncover a correlation between these variables and the ScoliScore.

Interestingly, almost all of the studied patients had either intermediate or high clinical risk scores. This is because ScoliScore testing is most frequently offered to young, skeletally immature patients, most of whom were Risser grade 0. Based on the Lonstein risk of progression table,[2] Risser grade 0 patients can be classified only as intermediate or high risk. Therefore, this method of risk prediction tends to lump younger patients rather than stratify them. Hence, it is in this younger population where the ScoliScore may provide the most meaningful data, as it does stratify this group. In fact, the great majority of patients with a high clinical risk were classified as intermediate or low risk by ScoliScore. In practice, our institution sees a large number of skeletally immature patients with small curves, among whom it is difficult to determine who is likely to progress. The ability of the ScoliScore to more accurately risk stratify these patients would allow clinicians to lengthen the time confidently and appropriately between follow-up visits in some and watch others more closely.

In the data presented from the initial development and validation of ScoliScore, 52% to 64% of screened patients with mild scoliosis had ScoliScores of 40 and below.[10] Only 36.3% of our cohort fell within the low-risk ScoliScore category and only 27.5% of our cohort returned scores of less than 40. This may be related to the differences in the studied populations, because our study was conducted at a tertiary care referral center for scoliosis with an inherently higher risk population than the school screening or purely pediatrician referral-based population used in the initial test validation. However, such differences in patient score distributions under real testing conditions suggest the potential for limited utility in some practices; if the majority of ScoliScores return as intermediate and thus clinically indeterminate, physicians may opt to abandon the test because of an unfavorable cost/benefit ratio. Further work in larger cohorts of patients will be necessary to clarify these differences from the expected distribution of patient scores.

Although our data demonstrate a difference in the information obtained from clinical risk factors and the ScoliScore, it is still unclear whether this "different" information is accurate in its risk stratification of patients. Although the test's validation work demonstrated an excellent negative predictive value of low ScoliScores, further work is needed to determine the validity of the test's progression predictions in an independent cohort under real clinical conditions.[10]

One potential criticism of this study is the inclusion of 8 patients not fully categorizing as Caucasian. According to the manufacturer, ScoliScore testing is currently indicated only in self-reported Caucasian males and females, including North and South American, European, Eastern European, and Middle Eastern. These recommendations are based on the test's validation data having insufficient samples of other races to determine the validity of the test in those groups, noting specifically the black and Hispanic cohorts.[10] Such group distinctions can be vague particularly given the considerable heterogeneity of the "Hispanic" population. In addition, Hispanic is an ethnic distinction and not a racial grouping like Caucasian, and thus there exists considerable overlap between the 2. For this reason, we elected to include white-Hispanic patients (3 patients) and 50% or more of Caucasian descent patients (5 patients). Furthermore, because our study does not assess the validity of the ScoliScore predictions but rather discusses our experience

to date with the test, inclusion of these patients should not significantly impact the reported outcomes. They are also likely more reflective of how the test will be used in a real population, given the ambiguity of the test indications.

In this study, the 2 stratification systems used different definitions of progression, which could be perceived as a weakness. Lonstein's article defined progression as a Cobb angle increase of 5° to 10° beyond the measurement made at the time of diagnosis, whereas ScoliScore measures the risk that the curve will progress to 40° by skeletal maturity. However, we think that these different definitions of progression do not matter, because it is the perception of risk (high or low) that drives the physician's management decisions and patient's anxiety more so than the specific definition of that risk. We think this is especially true for younger children diagnosed with scoliosis who will automatically be placed into a clinical high-risk group because of their skeletal immaturity.

Sanders *et al*[11] recently described a simplified version of the Tanner-Whitehouse III classification of hand bone age studies, which categorizes patients into 8 stages of growth.[11] This method provides a more accurate assessment of remaining growth than the Lonstein staging because most patients have finished their peak growth velocity by the time they are Risser grade 1. If this staging had been used to classify clinical risk instead of the Lonstein classification, our findings might have demonstrated a different clinical risk stratification. However, many of our patients did not have a hand radiograph from the day of their ScoliScore, and it was not possible to include this in our analysis. Because of the ease of interpretation afforded by Sanders *et al*,[11] hand bone age is becoming more widely used at our institution to assess remaining growth potential, and its increased use will make its inclusion as a clinical risk predictor possible for future studies.

In conclusion, ScoliScore risk stratification differed markedly from traditional clinical estimates in patients tested at our institution, suggesting that ScoliScore provides additional information unable to be measured from radiographs and physical examination alone. Continued efforts are needed to justify the use of this test by following an independent cohort of tested patients to determine the clinical validity of ScoliScore's risk predictions. This validation is going to be particularly important for the high-risk group for whom there are various fusionless surgical interventions on the horizon.

➢ Key Points

- ScoliScore risk stratification differed from traditional clinical risk estimates in our population, suggesting that ScoliScore provides physicians with unique information that could be clinically meaningful.
- Of all studied clinical variables, only Cobb angle showed significant correlation with the ScoliScore.
- Continued efforts are needed to determine the use of this test by examining the clinical validity of ScoliScore's risk predictions in our population.

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