

Predictors of spine deformity progression in adolescent idiopathic scoliosis: A systematic review with meta-analysis

Andriy Noshchenko, Lilian Hoffecker, Emily M Lindley, Evalina L Burger, Christopher MJ Cain, Vikas V Patel, Andrew P Bradford

Andriy Noshchenko, Emily M Lindley, Evalina L Burger, Christopher MJ Cain, Vikas V Patel, Department of Orthopaedics, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

Lilian Hoffecker, Health Sciences Library, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

Andrew P Bradford, Department of Orthopaedics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

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Correspondence to: Andriy Noshchenko, PhD, Department of Orthopaedics, University of Colorado Anschutz Medical Campus, 13001 E. 17th Place, Mail Stop F432, Aurora, CO 80045, United States. andriy.noshchenko@ucdenver.edu
Telephone: +1-303-7247591
Fax: +1-303-7240919

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Abstract

AIM: To evaluate published data on the predictors of progressive adolescent idiopathic scoliosis (AIS) in order to evaluate their efficacy and level of evidence.

METHODS: Selection criteria: (1) study design: randomized controlled clinical trials, prospective cohort studies and case series, retrospective comparative and none comparative studies; (2) participants: adolescents with AIS aged from 10 to 20 years; and (3) treatment: observation, bracing, and other. Search method: Ovid MEDLINE, Embase, the Cochrane Library, PubMed

and patent data bases. All years through August 2014 were included. Data were collected that showed an association between the studied characteristics and the progression of AIS or the severity of the spine deformity. Odds ratio (OR), sensitivity, specificity, positive and negative predictive values were also collected. A meta-analysis was performed to evaluate the pooled OR and predictive values, if more than 1 study presented a result. The GRADE approach was applied to evaluate the level of evidence.

RESULTS: The review included 25 studies. All studies showed statistically significant or borderline association between severity or progression of AIS with the following characteristics: (1) An increase of the Cobb angle or axial rotation during brace treatment; (2) decrease of the rib-vertebral angle at the apical level of the convex side during brace treatment; (3) initial Cobb angle severity ($> 25^\circ$); (4) osteopenia; (5) patient age < 13 years at diagnosis; (6) premenarche status; (7) skeletal immaturity; (8) thoracic deformity; (9) brain stem vestibular dysfunction; and (10) multiple indices combining radiographic, demographic, and physiologic characteristics. Single nucleotide polymorphisms of the following genes: (1) calmodulin 1; (2) estrogen receptor 1; (3) tryptophan hydroxylase 1; (3) insulin-like growth factor 1; (5) neurotrophin 3; (6) interleukin-17 receptor C; (7) melatonin receptor 1B, and (8) ScolScore test. Other predictors included: (1) impairment of melatonin signaling in osteoblasts and peripheral blood mononuclear cells (PBMC); (2) G-protein signaling dysfunction in PBMC; and (3) the level of platelet calmodulin. However, predictive values of all these findings were limited, and the levels of evidence were low. The pooled result of brace treatment outcomes demonstrated that around 27% of patents with AIS experienced exacerbation of the spine deformity during or after brace treatment, and 15% required surgical correction. However, the level of evidence is also low due to the limitations of the included studies.

CONCLUSION: This review did not reveal any methods for the prediction of progression in AIS that could be recommended for clinical use as diagnostic criteria.

Key words: Orthopedics; Scoliosis; Adolescent idiopathic scoliosis; Spine deformity; Predictors

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Core tip: The systematic review with meta-analysis was performed for combining the published data on the predictors of progressive adolescent idiopathic scoliosis (AIS). Comprehensive literature search revealed 1391 citations, 25 of which were selected. All studies showed statistically significant or borderline association between severity or progression of AIS with the different characteristics such as: clinical, radiographic, physiologic, biochemical, genetic, and combinatorial. However, predictive values of all these findings were limited, and the levels of evidence were low. Current

study did not reveal any methods for the prediction of progression in AIS that could be recommended for clinical use as diagnostic criteria.

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INTRODUCTION

Description of the problem

Adolescent idiopathic scoliosis (AIS) is the most prevalent form of spinal deformity, accounting for 80% of pediatric scoliosis and impacts 2%-4% of children during their pubertal growth spurt^[1,2]. The disease affects girls predominantly and is defined by a lateral spinal curvature with a rotational component, lacking a known neuromuscular cause or genetic origin, typically diagnosed between age 10 and 16, prior to skeletal maturity^[3,4]. The total number of AIS patients in the United States is estimated at more than 4 million with approximately 1 million children exhibiting some degree of spinal deformity^[1,5]. Progressive scoliosis may result in cosmetic deformity, back pain and functional deficits, psychological problems and impaired social interactions^[6,7]. Severe cases are associated with cardiac dysfunction and pulmonary constraints^[8-10]. Treatment of AIS is largely pragmatic and includes orthotic braces and physiotherapy, as well as surgical interventions to arrest curve progression, correct the deformity, and limit pain and functional deprivations^[2,11]. Epidemiologic studies showed that among adolescents initially diagnosed with mild AIS, curve progression occurs in 10%-15%, while 22%-27% demonstrate spontaneous improvement^[1,12-14]. A recent prospective multicenter randomized clinical trial has demonstrated that brace-treatment allows the prevention of severe deformity before maturity in 72% of adolescents with initial curvatures of 20-40 degrees, while 28% experienced exacerbation of the curvature to more than 50 degrees necessitating surgical correction. In the observational group without brace treatment the rate of severe progression reached 52%^[15]. Approximately 29000 surgeries to correct AIS spine deformities are performed annually in the United States^[16]. The current standard of care suggests that spine deformities that exceed 45 degrees are an indication for surgical correction. Such deformities are typically associated with significant wedging of vertebral bodies and intervertebral discs requiring surgical intervention^[11,14,17,18].

Description of the methods being investigated

Currently, clinical criteria and features cannot ade-

quately predict which children, diagnosed with mild disease, will undergo subsequent curve progression requiring intervention. Research findings during the last two decades suggest that the etiology of AIS is likely multifactorial 26-28^[19]. Epidemiologic studies demonstrated that a single nucleotide polymorphism (SNP) at different chromosomal loci and possible susceptibility genes have an association with AIS with the following dysfunctions: connective tissue structural abnormalities^[20-23], calcium and bone metabolism dysfunctions^[24-26], and disorders in hormonal and growth factors signaling^[27-30]. However, these studies indicate that AIS is a complex genetic disorder likely determined by different patterns of genes SNPs^[19]. The functional role of these different genetic patterns in the pathogenesis and progression of AIS remains to be established. Axial Biotechnology has developed a ScolioScore™ test focused on identifying subjects with a low risk of curve progression in AIS, using a panel of 53 SNPs^[31,32]. The prognostic test was validated retrospectively using AIS cases of known outcome^[33], but its applicability to clinical practice remains to be proven^[34]. Moreover, due to ethnic variations in the frequency of SNP markers, the test is only valid for white subjects and is not applicable to Hispanic, Asian or African American patients^[33,35].

Some clinical and radiographic symptoms are associated with progression of spine deformity: thoracic and double or multiple thoracolumbar curves, occurrence of spine deformity prior to onset of menses, curve magnitude (Cobb angle $\geq 25^\circ$) at first presentation and delay in bone maturation^[14,36-38]. Severe curves are also associated with wedging of an intervertebral disc and adjacent vertebrae body^[11,14,17,39], and longitudinal overgrowth of vertebral bodies by endochondral ossification^[40,41]. However, attempts to use these indices as prognostic indicators of curve progression showed low sensitivity (Sn) and specificity (Sp), with a high number of both false positive and false negative results^[38].

Dysfunctional melatonin signaling was reported as a potentially informative index for prognosis of curve progression in scoliosis^[16,42-44]. Calmodulin (CaM) has also been implicated in the pathogenesis of AIS^[45-48]. However, the level of evidence in these studies was not defined, and the prognostic value and applicability of these characteristics, to clinical use, remain unclear.

How these methods might work

The ability to differentiate patients with a high risk of curve progression from those who do not have such risk or have high likelihood of spontaneous improvement at an early stage of their disease, could allow for optimal individualized treatment strategy, in particular, for less invasive surgical interventions in skeletally immature patients, reduced risk of complications and better treatment outcomes^[2]. Theoretically, different clinical, radiographic and laboratory tests can be used for this purpose, if we can define the individual and/or combinatorial prognostic value of each index. The most

valuable prognostic characteristics that have clinical implications are Sn, Sp and positive and negative predictive values.

Why it is important to do this review

Although AIS has been around for many years we have not advanced significantly in our ability to predict the outcome at first diagnosis. Despite contemporary methods, the follow up of AIS still consists of repeated visits with radiological imaging. Until the curve shows certain signs of progression we have no reliable method to predict the severity at the first presentation. Just because we can develop an index that shows a statistically significant difference between progressive and non-progressive curves in AIS, it does not necessarily mean that this index has a high predictive value. Theoretically, to be helpful for making a rational evidence based decision for early preventive surgery, a predictor should have at least the following predictive values: Sn $\geq 95\%$; Sp $\geq 95\%$; positive predictive value (+PV) $\geq 95\%$; and negative predictive value (-PV) $\geq 95\%$ and the corresponding odds ratio (OR) between progressive and non-progressive curves should exceed 100 with a *P* value ≤ 0.05 . The level of evidence should be strong or at least moderate allowing for the development of medical recommendations that can be applied in clinical practice. Previous reviews in this field were mainly narrative, and did not undertake an evaluation of predictive values or the evidence level of the reported findings^[1,2,19,49-51]. One systematic review with meta-analysis, demonstrated that school screening tests have a low predictive value for spine deformity progression in scoliotic adolescents^[52]. A comprehensive review is necessary to summarize the published data in this field, to define how strong is the evidence for selected risk factors for progression of spine deformity in AIS? and assess the applicability of the reported tests to clinical practice.

Objectives

The current review is focused on combining the published data, focusing on the predictors of progressive AIS, evaluation of their predictive values, and the level of evidence.

MATERIALS AND METHODS

Criteria for considering studies for this review

Types of studies: Studies with the following design were included: randomized controlled trials (RCTs), prospective cohort studies, prospective case series, and retrospective comparative and non-comparative studies.

Type of participants: (1) Human subjects; (2) Diagnosis: AIS, initial Cobb angle >10 degree; (3) Age: aged 10-20 years; (4) Gender: female or male and female; (5) Progression of spine deformity; and (6) Follow-up: > 0.3 year.

Table 1 Ovid medline search strategy: Ovid MEDLINE®, Ovid MEDLINE® In-Process and Other Non-Indexed Citations, Ovid MEDLINE®, Daily and Ovid OLDMEDLINE®

No.	Search syntax
1	"Adolescent idiopathic scoliosis".ab,ti.
2	(AIS and scoliosis).ab,ti.
3	Scoliosis/ and (exp adolescent/ or exp child/)
4	Or/1-3
5	"Curve progression".ab,ti.
6	"Disease susceptibility".ab,ti.
7	Prediction.ab,ti.
8	"Disease progression".ab,ti.
9	Exp disease progression/
10	Disease susceptibility/
11	"Predictive value of tests"/
12	Exp decision support techniques/
13	Or/5-12
14	Scoliosis/ra
15	(Ogilvie JW or Ward K*).au. and scoliosis.ab,ti.
16	"Scoliscore".mp.
17	"Axial biotech".mp.
18	Moreau A*.au. and scoliosis.ab,ti.
19	4 and 13
20	13 and 14
21	Or/15-20
22	(genetic adj2 test*).ab,ti.
23	"Genetic predisposition".ab,ti.
24	"Single nucleotide polymorphism".ab,ti. Or (SNP and polymorphism).ab,ti.
25	Genetic Testing/
26	Exp genetic predisposition to disease/
27	Polymorphism, single nucleotide/
28	Or/22-27
29	4 and 28
30	30. 21 or 29

Type of intervention: Observation, conservative treatment by bracing and/or physiotherapy, or surgery.

Exclusion criteria: (1) Neuro-axial abnormalities; (2) Juvenile/infantile onset curves; (3) Neuromuscular disorders; (4) Kyphotic deformities (Scheuermann's); and (5) Other musculoskeletal disease leading to deformity.

Type of outcome measure

Primary outcomes: (1) Method(s) of progressive AIS prediction including the following predictive values: Sn (%); Sp (%); positive prediction value (%); negative prediction value (%); (2) Characteristics that describe correlation/association between the studied parameters and progressive AIS, or severity of spine deformity including: OR; rate ratio; rate or number of correct predictions; correlation coefficient, and *P*-value; and (3) Characteristics that describe the difference between progressive and none progressive cases, or severe and mild AIS cases including: mean; standard deviation; standard error of the mean; 95%CI; and corresponding *P* values.

Secondary outcomes: (1) Fraction of AIS patients with curve progression after bracing; and (2) Fraction of AIS patients who required surgical correction during or

after bracing.

Search methods for identification of studies

Electronic searches: Studies and relevant publications were identified using the both bibliographic and patent databases. The bibliographic resources included: Ovid MEDLINE (1946-current), Embase *via* Embase.com (1980-current), and the databases of the Cochrane Library *via* the Wiley platform, Database of Systematic Reviews, Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects, Methodology Register, and Technology Assessment Database. No year limits were applied, therefore the review included all years through August 2014. No language or types of publication limits were applied. The search strategies were based on the concepts of "AIS", "curve progression", "prediction", "disease progression", "disease susceptibility", "predictive value of tests", "genetic testing", "SNP", and "genetic predisposition" with multiple subject headings (MeSH and Emtree), and text words to describe each concept, (see Table 1 for the MEDLINE search strategy). From the total retrieval, we identified systematic reviews including meta-analyses and controlled trials. The patent search involved the online databases of the United States Patent and Trademark Office (AppFT and PatFT), the European Patent Office (Espacenet), the Japanese Patent Office (PAJ), and the World Intellectual Property Organization. English language textwords were used to search these databases: the terms "scoliosis" and "AIS", combined with terms such as "prediction", "predisposition", "progression", and "markers" (*e.g.*, scoliosis AND predisposition). These searches were performed by a University of Colorado Health Sciences Library research Librarian (LH).

Searching other resources: A manual search of reference lists of review articles and any revisions was also performed to identify studies potentially eligible for our review.

Data collection and analysis

Two reviewers (Burger EL, Noshchenko A) screened the titles, abstracts, and when necessary full texts, to determine potentially eligible studies. Full text reports of selected studies were then analyzed by the two reviewers (EB and AN). Disagreements regarding inclusion were resolved by discussion. Excluded studies were listed with the reason for exclusion.

Data extraction and management: Data were extracted from the included studies by one reviewer (Noshchenko A) and checked by another (Burger EL). The following data were collected: (1) general information including: authors, title, publication status, year of publication, country, study design, sponsorship, and study objectives; (2) participants: inclusion and exclusion criteria (age, gender, type of spine deformity,

Risser sign, initial Cobb angle), number of participants in study groups, criteria of spine deformity progression; (3) trial characteristics: length of follow-up, dropout rate, randomization (if applicable), allocation concealment and blinding of assessors if applicable; (4) method of the spine deformity prediction, or differentiation between severe and mild deformities; and (5) characteristics of the prediction efficiency shown above.

Assessment of risk of bias in included studies

The risk of bias for each study included in the review was defined independently by two reviewers (Burger EL and Noshchenko A) taking into consideration the study design, and Cochrane Back Review Group recommendations for randomized clinical trials^[53] modified for observational studies and goals of the current review^[54]. Agreement between the two independent assessments was defined by Kappa test. Disagreements were resolved by discussion.

Measures of studied effects

OR, Sn, Sp, positive predictive values, and negative predictive values of studied characteristics were collected and analyzed. If authors of the selected studies did not calculate these parameters but presented primary data that allowed such calculations, we did that. If authors reported only mean values of studied characteristics in groups with progressive and none progressive AIS with corresponding indices of variability such as standard deviation, standard error of the mean, or 95% confident intervals with number of participants in each group, the data were binarized, assuming that distribution in each group was normal, Z-score probability was applied^[55], and the average between means in studied groups was used as cut off value for both groups. Then, OR and predictive characteristics were approximated using a standard 2 × 2 table.

Dealing with missing data

Studies with a dropout rate of more than 30% as well as those that did not report this information were classified as having risk of attrition bias; this was taken into consideration during the level of evidence evaluation.

Data synthesis

A Meta-analysis was performed, if it was applicable. An inverse-variance method was used for combining the data across studies. Pooled OR and predictive characteristics with 95%CI were calculated. To summarize the data, a random-effect model was applied. The GRADE approach was used to evaluate the quality of the revealed evidence^[53,56]. Grouping analysis was performed to assess the impact of potentially confounding factors and compare predictive values of different indices. The random effect modeling was applied in each group.

Assessment of heterogeneity

Statistical heterogeneity of the pooled data was defined by χ^2 test ($P < 0.05$ represented heterogeneity) and I^2

tests with the following interpretation of heterogeneity: less than 30% = low; 30% to 60% = moderate, greater than 60% = high^[57].

Assessment of publication bias

Funnel plots were used to evaluate the risk of publication bias^[57].

Sn analysis

Sn analysis was performed by extracting studies that showed results exceeding 95% confidence limits of the pooled result.

Meta-analysis was performed by a qualified biostatistician (Noshchenko A) using special program: Comprehensive Meta Analysis Version 2.2.057 (BIOSTAT, Englewood, NJ07631, United States; <http://www.meta-analysis.com/index.php>).

RESULTS

Description of studies

Electronic searches provided a total of 1391 citations and 21 were identified from other sources. After adjusting for duplicates, 1120 remained and were screened. Of these, 1054 were discarded because they did not meet the study criteria. The complete text of the remaining 66 publications was studied and 41 (Table 2) did not meet all of the inclusion criteria, leaving 25 studies that were included in the systematic review and meta-analysis, Figure 1.

Included studies

Twenty five studies selected for the review were published as full-text articles in English and were conducted in the following countries: the United States (4)^[46,47,58,59]; Canada (4)^[16,44,60,61]; Sweden (2)^[62,63]; Netherlands (1)^[64]; China (8)^[65-72]; Hong Kong (3)^[73-75]; Japan (1)^[76]; Singapore (1)^[36]; and South Korea (1)^[77]; Table 3. The search revealed no randomized controlled clinical trials meeting the inclusion criteria. Ten studies were nonRCTs: 5 compared the treatment effect of bracing vs observation^[46,47,60,63,74]; 1 bracing with electrical stimulation vs observation^[62]; 2 studies examined differences between patients with severe AIS who underwent surgical correction and healthy controls^[44,71]; and 2 studies compared patients with different severity of spine deformity^[58,61]. Eight retrospective case series studied the treatment effect of bracing^[59,66,70,73,77], and 1 presented results of observation^[75]. Three prospective case series reported the results of observation^[16,36,65]; and 3 case series did not specify the treatment of their participants^[64,72,76]. Fourteen studies enrolled patients with thoracic or thoracolumbar spine deformities^[44,46,47,62-67,69-71,73,77]; 1 study enrolled patients with a genetic predisposition to AIS but without clinical scoliosis (Cobb angle $< 10^\circ$)^[16]; and 10 studies did not specify the type of spine deformity in the enrolled patients^[36,58-61,68,72,74-76].

Table 2 Excluded publications

No.	Excluded publications
1	Buchan JG, Alvarado DM, Haller GE, Cruchaga C, Harms MB, Zhang T, Willing MC, Grange DK, Braverman AC, Miller NH, Morcuende JA, Tang NL, Lam TP, Ng BK, Cheng JC, Dobbs MB, Gurnett CA. Rare variants in FBN1 and FBN2 are associated with severe adolescent idiopathic scoliosis. <i>Hum Mol Genet</i> 2014; 23 : 5271-5282
2	Danielsson AJ, Nachemson AL. Radiologic findings and curve progression 22 years after treatment for adolescent idiopathic scoliosis: comparison of brace and surgical treatment with matching control group of straight individuals. <i>Spine (Phila Pa 1976)</i> 2001; 26 : 516-525
3	Grauers A, Danielsson A, Karlsson M, Gerdhem P: Familial heredity of idiopathic scoliosis unrelated to age at diagnosis and prognosis. <i>Eur Spine J</i> 2012; 21 : S314
4	Inoue M, Minami S, Nakata Y, Kitahara H, Otsuka Y, Isobe K, Takaso M, Tokunaga M, Nishikawa S, Maruta T, Moriya H. Association between estrogen receptor gene polymorphisms and curve severity of idiopathic scoliosis. <i>Spine (Phila Pa 1976)</i> 2002; 27 : 2357-2362
5	Lonstein JE, Carlson JM. The prediction of curve progression in untreated idiopathic scoliosis during growth. <i>J Bone Joint Surg Am</i> 1984; 66 : 1061-1071
6	Lowe TG, Burwell RG, Dangerfield PH. Platelet calmodulin levels in adolescent idiopathic scoliosis (AIS): can they predict curve progression and severity? Summary of an electronic focus group debate of the IBSE. <i>Eur Spine J</i> 2004; 13 : 257-265
7	Machida M, Dubousset J, Yamada T, Kimura J. Serum melatonin levels in adolescent idiopathic scoliosis prediction and prevention for curve progression—a prospective study. <i>J Pineal Res</i> 2009; 46 : 344-348
8	Miyake A, Kou I, Takahashi Y, Johnson TA, Ogura Y, Dai J, Qiu X, Takahashi A, Jiang H, Yan H, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, Taneichi H, Hosono N, Tsuji T, Suzuki T, Sudo H, Kotani T, Yonezawa I, Kubo M, Tsunoda T, Watanabe K, Chiba K, Toyama Y, Qiu Y, Matsumoto M, Ikegawa S. Identification of a susceptibility locus for severe adolescent idiopathic scoliosis on chromosome 17q24.3. <i>PLoS One</i> 2013; 8 : e72802
9	Nault ML, Mac-Thiong JM, Roy-Beaudry M, deGuise J, Labelle H, Parent S. Three-dimensional spine parameters can differentiate between progressive and nonprogressive patients with AIS at the initial visit: a retrospective analysis. <i>J Pediatr Orthop</i> 2013; 33 : 618-623
10	Nault ML, Mac-Thiong JM, Roy-Beaudry M, Turgeon I, de Guise J, Labelle H, Parent S: Three-Dimensional Spinal Morphology can Differentiate Between Progressive and Non-Progressive Patients With Adolescent Idiopathic Scoliosis at the Initial Presentation. <i>Spine (Phila Pa 1976)</i> 2014
11	Ogilvie JW. Update on prognostic genetic testing in adolescent idiopathic scoliosis (AIS). <i>J Pediatr Orthop</i> 2011; 31 : S46-S48
12	Ogura Y, Takahashi Y, Kou I, Nakajima M, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, Taneichi H, Yonezawa I, Tsuji T, Suzuki T, Sudo H, Kotani T, Watanabe K, Chiba K, Toyama Y, Matsumoto M, Ikegawa S. A replication study for association of 5 single nucleotide polymorphisms with curve progression of adolescent idiopathic scoliosis in Japanese patients. <i>Spine (Phila Pa 1976)</i> 2013; 38 : 571-575
13	Ogura Y, Takahashi Y, Kou I, Nakajima M, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, Taneichi H, Yonezawa I, Tsuji T, Suzuki T, Sudo H, Kotani T, Watanabe K, Chiba K, Toyama Y, Matsumoto M, Ikegawa S. A replication study for association of 53 single nucleotide polymorphisms in a scoliosis prognostic test with progression of adolescent idiopathic scoliosis in Japanese. <i>Spine (Phila Pa 1976)</i> 2013; 38 : 1375-1379
14	Patten SA, Moldovan F. Could genetic determinants of inner ear anomalies be a factor for the development of idiopathic scoliosis? <i>Med Hypotheses</i> 2011; 76 : 438-440
15	Peng Y, Liang G, Pei Y, Ye W, Liang A, Su P. Genomic polymorphisms of G-protein estrogen receptor 1 are associated with severity of adolescent idiopathic scoliosis. <i>Int Orthop</i> 2012; 36 : 671-677
16	Qiu XS, Tang NL, Yeung HY, Lee KM, Hung VW, Ng BK, Ma SL, Kwok RH, Qin L, Qiu Y, Cheng JC. Melatonin receptor 1B (MTNR1B) gene polymorphism is associated with the occurrence of adolescent idiopathic scoliosis. <i>Spine (Phila Pa 1976)</i> 2007; 32 : 1748-1753
17	Qiu XS, Tang NL, Yeung HY, Qiu Y, Cheng JC. Genetic association study of growth hormone receptor and idiopathic scoliosis. <i>Clin Orthop Relat Res</i> 2007; 462 : 53-58
18	Roye BD, Wright ML, Williams BA, Matsumoto H, Corona J, Hyman JE, Roye DP, Vitale MG. Does ScolioScore provide more information than traditional clinical estimates of curve progression? <i>Spine (Phila Pa 1976)</i> 2012; 37 : 2099-2103
19	Sanders JO, Khoury JG, Kishan S, Browne RH, Mooney JF, Arnold KD, McConnell SJ, Bauman JA, Finegold DN. Predicting scoliosis progression from skeletal maturity: a simplified classification during adolescence. <i>J Bone Joint Surg Am</i> 2008; 90 : 540-553
20	Soucacos PN, Zacharis K, Gelalis J, Soultanis K, Kalos N, Beris A, Xenakis T, Johnson EO. Assessment of curve progression in idiopathic scoliosis. <i>Eur Spine J</i> 1998; 7 : 270-277
21	Soucacos PN, Zacharis K, Soultanis K, Gelalis J, Xenakis T, Beris AE. Risk factors for idiopathic scoliosis: review of a 6-year prospective study. <i>Orthopedics</i> 2000; 23 : 833-838
22	Stokes IA, Aronsson DD. Disc and vertebral wedging in patients with progressive scoliosis. <i>J Spinal Disord</i> 2001; 14 : 317-322
23	Sun X, Qiu Y, Zhu Z, Zhu F, Wang B, Yu Y, Qian B. Variations of the position of the cerebellar tonsil in idiopathic scoliotic adolescents with a Cobb angle > 40 degrees: a magnetic resonance imaging study. <i>Spine (Phila Pa 1976)</i> 2007; 32 : 1680-1686
24	Sun X, Zhu ZZ, Qiu Y, Wang B, Li WC, Zhu F, Yu Y, Qian BP, Ma WW. [The role of initial bone mineral status in predicting the early outcome of brace treatment in girls with adolescent idiopathic scoliosis]. <i>Zhonghua Waike Zazhi</i> 2008; 46 : 1066-1069
25	Takahashi Y, Kou I, Takahashi A, Johnson TA, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, Taneichi H, Tsuji T, Suzuki T, Sudo H, Kotani T, Watanabe K, Chiba K, Hosono N, Kamatani N, Tsunoda T, Toyama Y, Kubo M, Matsumoto M, Ikegawa S. A genome-wide association study identifies common variants near LBX1 associated with adolescent idiopathic scoliosis. <i>Nat Genet</i> 2011; 43 : 1237-1240
26	Takahashi Y, Matsumoto M, Karasugi T, Watanabe K, Chiba K, Kawakami N, Tsuji T, Uno K, Suzuki T, Ito M, Sudo H, Minami S, Kotani T, Kono K, Yanagida H, Taneichi H, Takahashi A, Toyama Y, Ikegawa S. Lack of association between adolescent idiopathic scoliosis and previously reported single nucleotide polymorphisms in MATN1, MTNR1B, TPH1, and IGF1 in a Japanese population. <i>J Orthop Res</i> 2011; 29 : 1055-1058
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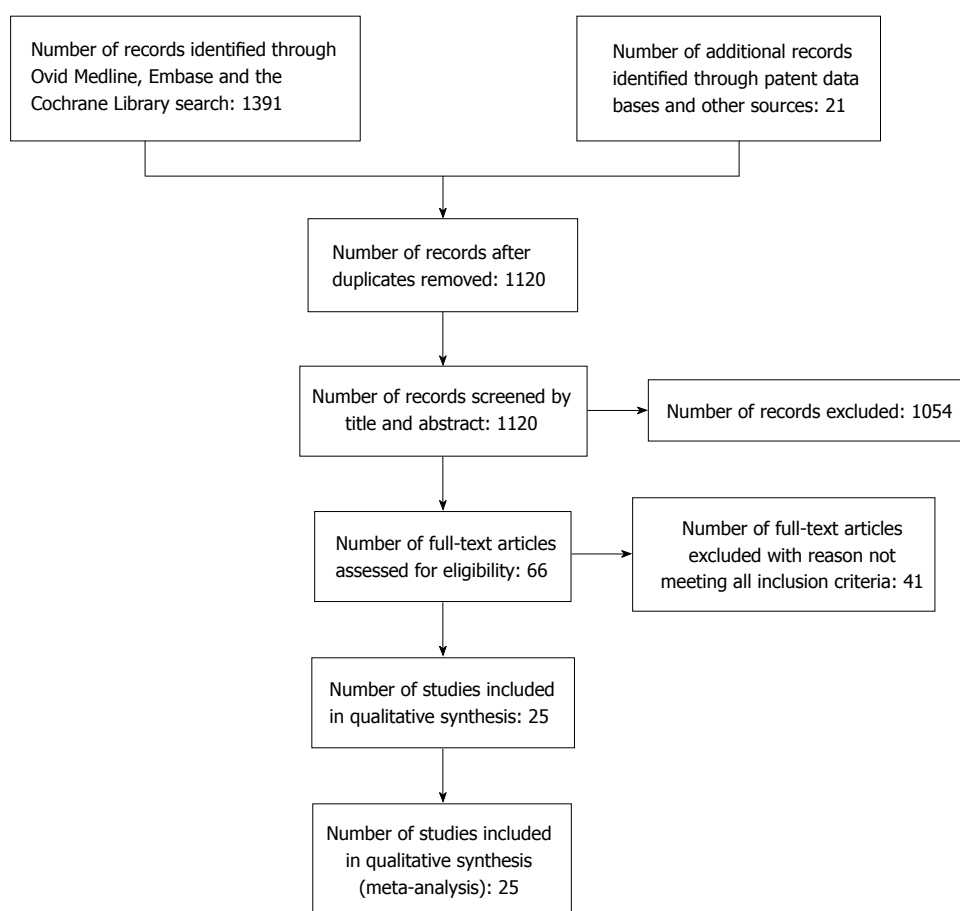


Figure 1 Flow diagram.

All included studies enrolled participants with an age range from 10 to 20 years, 9 included female only^[62,63,65-67,72,74-76], 13 included both sexes with a prevalence of females^[16,36,44,46,47,58-60,64,68,70,71,77], and 3 did not report the gender of the participants^[61,69,73]. The initial Cobb angle varied from 5 to 100 degrees (Table 3). The following criteria for progressive scoliosis were used: increase in the Cobb angle and/or vertebral rotation

of more than 4°-10° during the observation period, 12 studies^[16,47,60,62-65,69,73,74,77]; Cobb angle exceeding 30°, 3 studies^[36,68,71]; Cobb angle exceeding 40°^[58] or 45°^[59,61,67], 4 studies; a combination of different criteria including increase of Cobb angle and/or surgical correction, 3 studies^[46,66,70]; and 3 studies did not specify criteria for spine deformity progression^[44,72,75]. The follow-up period was reported by 13 studies ranging from 3 mo to 22

Table 3 Selected studies

Ref.	Study design	Publication	Spine deformity	Age (mean/range)	Gender	n	Treatment	Initial Cobb angle (degree)	Follow-up	Drop out	Progression of deformity criteria	Analysis/Method of prediction	Indices used	Prediction validity (progressive vs stable spine deformities)
Upadhyay <i>et al.</i> ^[73]	RCS	Art.	Thoracic, thoracolumbar, lumbar	< 18 Risser sign ≤ 2	NS	85	Brace	20-45	Until skeletal maturity or surgical treatment	NS	Cobb increasing ≥ 5°, and/or vertebral rotation ≥ 5°	Comparative analysis of progress vs stable cases	Predictor: Increase of Cobb angle and/or vertebral rotation ≥ 5° at 1-2 mo follow-up during brace treatment	OR = 33.2 ³ (95%CI: 4.0-270.4) P < 0.001 (1) Sensitivity: 39%; (2) Specificity: 98%; (3) +PV: 93%; and (4) -PV: 72%
Peterson <i>et al.</i> ^[63]	PChS	Art.	Thoracic, thoracolumbar	10-15	F (100%)	159	Observation (120) Electrical stimulation (39)	25-30	Until skeletal maturity	NS	Cobb increasing ≥ 6°	Multiple logistic regression modeling	Predictors: (1) Risser sign (0-1); (2) Apical level (upperTh12); (3) Imbalance (10 mm); and (4) Age	(1) Sensitivity: 81% ² ; (2) Specificity: 81%; (3) +PV: 82%; and (4) -PV: 80%
Ajamba <i>et al.</i> ^[60]	RChS	Art.	NS	12.3 (10-15)	F (87%) M (14%)	44	Observation (30) Brace (14)	18-49	1 yr - skeletal maturity	NS	Cobb increasing ≥ 5°	6 multiple support vector classifier models	Predictors: (1) 16 Lenke Rad. Indices; (2) Wrist X-ray; (3) Age; (4) Sex; and (5) Growing index	(1) Sensitivity: 67%-91% ² ; (2) Specificity: 22%-67%; (3) +PV: 73%-86%; and (4) -PV: 43%-67%
¹ Cheung <i>et al.</i> ^[64]	PCS	Art.	Right thoracic	10-16	F (87%) M (13%)	30	NS	10-60	4-5 mo	NS	Cobb increasing >10°	Multiple regression modeling, nomogram	Predictor: (1) Spinal grows velocity (≥ 11 mm/yr); (2) Paraspinial EMG activity concave/convex ≥ 1.3	(1) Sensitivity: 69%-79% ² ; (2) Specificity: 69%-79%; and (3) +PV: 60%-89%
¹ Danielsson <i>et al.</i> ^[65]	PChS	Art.	Thoracic, Thoracolumbar	10-15 (skeletal)	F (100%)	92	Observation Brace and electrical stimulation	25-35	16 yr	14%	Cobb increasing ≥ 6°	Rate comparison	Predictor: Premenarche at inclusion vs menarche at inclusion	OR = 2.52 ³ (95%CI: 1.0-6.11) P = 0.05 (1) Sensitivity: 60%; (2) Specificity: 63%; (3) +PV: 53%; and (4) -PV: 70%
Kindsfater <i>et al.</i> ^[66]	RCS	Art.	Thoracic, thoracolumbar	11-20	F (71%) M (29%)	17	Observation (7) Brace (10)	34 (15-90)	< 1 yr	NS	Cobb > 30°; Increasing > 10° /yr	Comparative analysis of progress vs stable cases	Predictor: Level of platelet calmodulin (ng/μg of protein); progressive 1.4-10.7; stable < 1.4 (P = 0.001)	OR = 275.0 ⁷ (95%CI: 4.8-15724.2) P = 0.007 (1) Sensitivity: 100%; (2) Specificity: 100%; (3) +PV: 100%; and (4) -PV: 100%

¹ Lowe <i>et al.</i> ⁽⁶⁷⁾	¹ Sun <i>et al.</i> ⁽⁶⁷⁾	¹ Sun <i>et al.</i> ⁽⁶⁸⁾	Hung <i>et al.</i> ⁽⁶⁵⁾	Lam <i>et al.</i> ⁽⁷⁴⁾	Lee <i>et al.</i> ⁽⁶⁸⁾	Tan <i>et al.</i> ⁽⁶⁹⁾
PChS	RCS	RCS	PCS	PChS	RCS	PCS
Art.	Art.	Art.	Art.	Art.	Art.	Art.
King I-V	Thoracic, thoracolumbar, lumbar	Thoracic, thoracolumbar	Thoracic, thoracolumbar, lumbar	NS	NS	NS
Adolescents	10-16	10-15	11-16	11-16	10-17	7-14
F (93%) M (7%)	F (100%)	F (100%)	F (100%)	F (100%) Chinese population	F (82.3%) M (17.7%)	F (84.9%) M (15.1%)
55	142	68	324	294	1858	186
Observation (28) Brace (17) Fusion(10)	Brace	Brace	Observation	Observation (192), Brace (102)	Brace (331) 450	Observation Brace
≤ 25	20-40	20-40	20-30	> 10; Mean: 26 (St. D, 8.2°)	10-30	> 10
1-3 yr	0.6-5.9 yr	3-6 mo	0.5-3.5 yr	Mean, 3.4 yr (St. D, 1.57°)	NS	1-8 yr
9,80%	NS	NS	NS	NS	NS	18%
Cobb increasing > 10° /yr	Cobb exceeding 45°, surgical treatment	Cobb increasing > 6°, or exceeding 45°	Cobb increasing > 6°	Cobb increasing > 6°	Cobb > 30°	Cobb ≥ 30°
Comparative analysis of progress vs stable cases	Multiple logistic regression modeling	Comparative analysis of progress vs stable cases	Multiple logistic regression modeling	Multiple logistic regression modeling	Risk assessment	Risk assessment
Predictor: Increasing of platelet calmodulin level during first year of observation	Predictors: (1) Premenarche; (2) Curve > 30°; and (3) Risser sign: 0-1	Predictors: (1) Premenarche; (2) Curve > 30°; (3) L2-L4 BMD < 0.76 g/cm ² ; and (4) Thoracic curve	Predictors: (1) Age at diagnosis < 13 yr; (2) Premenarche; (3) Risser sign: 0-1; (4) Curve pattern: thoracic or thoracolumbar; and (5) Initial Cobb angle > 30°; Osteopenia: decreased hip neck BMD at concave side	Predictors: (1) Age at diagnosis 11-13 yr, (2) Premenarche; (3) Initial Cobb angle > 25°; and (4) Ultrasound bone stiffness index (calcaneus) Z-score ≤ 0	Predictor: Initial Cobb angle ≥ 26° vs 8°-10°	Predictor: Initial Cobb angle ≥ 25° vs < 25°
OR = 11.0 ³ (95%CI: 1.7-69.9) P = 0.02 (1) Sensitivity: 69%; (2) Specificity: 83%; (3) +PV: 85%; and (4) -PV: 67%	OR: 5.1-11.5 ² P ≤ 0.002 (1) Sensitivity 72%-89% ³ ; (2) Specificity 48%-77% ³ ; (3) +PV: 20%-33%; and (4) -PV: 94%- 97%	OR: 6.6-11.2 ² (0.001 > P < 0.072) (1) Sensitivity: 74.5%; (2) Specificity: 64.7%	OR: 2.1-4.6 ² (0.001 > P < 0.044) (1) Sensitivity: 76% (95%CI: 69-83); (2) Specificity: 70% (95%CI: 62-77)	OR: 2.0-8.6 ² (0.0001 > P < 0.2) (1) Sensitivity: 84.7%; (2) Specificity: 66.5%	Hazard ratio, 8.8 ² (95%CI: 6.85-11.31)	OR = 24.6 ² (95%CI: 9.9-60.6) P < 0.001 (1) Sensitivity: 68% ³ ; (2) Specificity: 92% ³ ; (3) +PV: 68%; and (4) -PV: 92%

Author	RCS	Art.	Thoracic, thoracolumbar	10-15	F (84%) M (16%)	113	Brace	40-56	Until skeletal maturity (Risser sign \geq 4); average: 34 \pm 13 mo	NS	Cobb increasing \geq 5°	Comparative analysis of progress vs stable cases	Predictor:	OR = 5.6 ³ (95%CI: 2.2-13.9) <i>P</i> < 0.001
Modi <i>et al</i> ^[71]	RCS	Art.	thoracic, thoracolumbar	10-20	Chinese population	120	Brace	25-40	2.5 \pm 0.35 yr	NS	Cobb increasing \geq 5°	Comparative analysis of progress vs stable cases	Rib-vertebral angle at convex side of the curve apex after brace treatment (< 65° vs \geq 65°)	(1) Sensitivity: 45%; (2) Specificity: 87%; (3) +PV: 69%; and (4) -PV: 71%
Qiu <i>et al</i> ^[68]	RCS	Art.	thoracic, thoracolumbar	10-20	Chinese population	120	Brace	25-40	2.5 \pm 0.35 yr	NS	Cobb increasing \geq 5°	Comparative analysis of progress vs stable cases	<i>NTR3</i> gene: rs11063714, genotype GG vs AA	OR = 3.3 ³ (95%CI: 1.0-10.9) <i>P</i> = 0.08 (1) Sensitivity: 43%; (2) Specificity: 82%; (3) +PV: 56%; and (4) -PV: 72%
Xu <i>et al</i> ^[70]	RCS	Art.	Thoracic, thoracolumbar, lumbar	10-15	F (87%) M (13%)	312	Brace	20-40	0.6-2.2 yr	NS	Cobb increasing \geq 5° and/or surgical correction	Logistic regression modeling	Predictors: (1) <i>ERz</i> gene: rs9340799, allele G; (2) <i>TPH1</i> gene: rs10488682, allele A; (3) Risser sign O-1; and (4) Curve \geq 30°	OR: 1.2-3.6 ² 0.0001 > <i>P</i> < 0.1 (1) Sensitivity: 51%; (2) Specificity: 82%; and (3) Correct predictions: 75%
Yeung <i>et al</i> ^[53]	RCS	Art.	NS	12-16	F (100%) Chinese population	340	Observation	> 20	Until skeletal maturity, 16 years old or surgical intervention	NS	NS	Comparative analysis of Cobb angle in following genotypes of IGF1 SNP of IGF1 SNP: rs5742612, TT; TC; and CC	Predictor: TT (mean Cobb, 38 \pm 12.1, <i>n</i> = 169) vs CC (mean Cobb, 33° \pm 9.0, <i>n</i> = 33), <i>P</i> = 0.01 Cut-point: Cobb, 35.7°	OR = 2.1 ³ (95%CI: 1.0-4.4) <i>P</i> = 0.1 (1) Sensitivity: 88%; (2) Specificity: 22%; (3) +PV: 57%; and (4) -PV: 61%
¹ Ward <i>et al</i> ^[58]	RChS	Art.	Severe: 8% Moderate/mild: 92%	9-13 at diagnosis	F (100%) F (100%) M (100%)	277 257 163	NS	> 10	Till skeletal maturity or severe deformity	NS	Severe: Cobb > 40° Moderate: Cobb 25°-40°	Multiple logistic regression modeling	Predictor: Scale (1-200) based on 53 SNP markers; cut point, 40; 1-40 (\leq 1% risk of progression)	OR=16.8 ³ (95%CI: 6.6-42.7) <i>P</i> < 0.001 (1) Sensitivity: 91%; (2) Specificity: 63%; (3) +PV: 17%; and (4) -PV: 99%
¹ Bohl <i>et al</i> ^[59]	RCS	Art	NS	\geq 10	F (81%) M (19%)	16	Brace	20-40	1 yr after brace discontinuation or skeletal maturity	36%	Cobb > 45°	Comparative analysis: patients with Cobb > 45° vs Cobb < 45° logistic regression modeling	Predictor: Scale (1-200) based on 53 SNP markers and initial Cobb angle; cut-point, 160; 160-200 (high risk of curve progression with Cobb > 45°) vs < 160 (low risk of curve progression with Cobb > 45°)	OR = 21.0 ³ (95%CI: 1.5-293.3) <i>P</i> = 0.05 (1) Sensitivity: 78%; (2) Specificity: 86%; (3) +PV: 88%; and (4) -PV: 75%

Zhao <i>et al</i> ^[71]	RChS	Art	Double curves: thoracic, thoracolumbar or lumbar	10-20	Cases (AIS): F (90%) M (10%) Controls: 100 F (75%) M (25%) Chinese population	67 Surgical correction	30-90	NS	NS	Cobb $\geq 30^\circ$	Comparative analysis of cases <i>vs</i> healthy controls	Predictors: (1) ER1 gene: rs2234693, allele T; (2) CALM1 gene: rs12885713, allele T	OR: 1.7-1.8 ³ 0.01 > P < 0.05 (1) Sensitivity: 28%-69%; (2) Specificity: 44%-82%; (3) +PV: 45%-51%; and (4) -PV: 63%-68%
Zhou <i>et al</i> ^[72]	RCS	Art.	NS	11-18	F (100%) Chinese population	241 NS	20-100	54%	NS	Until skeletal maturity	Comparative analysis of severe cases (mean Cobb, 36° \pm 13°) <i>vs</i> moderate cases (mean Cobb, 29° \pm 7.4°)	Predictor: IL-17RC gene: rs708567, genotype GG, Cut-point: Cobb angle, 32.5°	OR = 3.4 ³ (95%CI: 1.4-8.3) P = 0.007 (1) Sensitivity: 94%; (2) Specificity: 17%; (3) +PV: 60%; and (4) -PV: 69%
Moreau <i>et al</i> ^[64]	RChS	Art.	Thoracic, thoracolumbar, lumbar	13-20	Cases (AIS): F (83%) M (17%) Controls: 17 F (65%) M (35%)	41 Surgical correction	30-90	NS	NS	NS	Comparative analysis of AIS cases (mean Cobb, 54° \pm 14°) <i>vs</i> controls (non- idiopathic deformities)	Predictor: low inhibition of forskolin stimulated cAMP by melatonin in osteoblasts <i>vs</i> significant inhibition of forskolin stimulated cAMP by melatonin in osteoblasts	OR=3.9 ³ (95%CI: 0.45-33.7) P = 0.3 (1) Sensitivity: 20%; (2) Specificity: 94%; (3) +PV: 89%; and (4) -PV: 33%
Akoume <i>et al</i> ^[65]	PCS	Art	Asymptomatic subjects at-risk of AIS	5-15	F (65%) M (35%)	31 Observation	≤ 10	NS	NS	Cobb > 10°	analysis of cases with developed AIS spine deformity (mean Cobb, > 10°) <i>vs</i> subjects at risk, but without deformity	Predictor: peripheral blood mononuclear cells electrical impedance	OR = 18.5 ³ (95%CI: 8.7-392.5) P = 0.03 (1) Sensitivity: 33%; (2) Specificity: 100%; (3) +PV: 100%; and (4) -PV: 70%
Akoume <i>et al</i> ^[61]	RChS	Art	NS	NS	NS	162 NS 794	NS	NS	NS	Cobb angle $\geq 45^\circ$ Cobb angle 10°-44°	Comparative analysis of the G proteins functional status	Predictor: type of peripheral blood mononuclear cells G protein response to electrical stimulation: FG2 <i>vs</i> FG1 or FG3	OR = 2.6 ³ (95%CI: 1.9-3.7) P < 0.001 (1) Sensitivity: 26%; (2) Specificity: 88%; (3) +PV: 56%; and (4) -PV: 67%

Yamamoto <i>et al.</i> ^[60]	RCS	Art.	NS	9-15	F (100%)	28	Analysis of curve history	5-59	05-2 yr	NS	Cobb increasing > 4°	Comparative analysis of progressive cases <i>vs</i> stable	Predictor: Brain stem function, abnormal vestibular-eye test <i>vs</i> normal	OR = 24.0 ³ (95%CI: 2.4-240.6) P = 0.007 (1) Sensitivity: 91%; (2) Specificity: 71%; (3) +PV: 67%; and (4) -PV: 92%
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¹Study used industrial or other sponsorship; ²Predictive characteristics reported in the collected publication; ³Predictive characteristics calculated by authors of current review using extracted results. PChS: Prospective cohort study; RCS: Retrospective cohort study; PCS: Prospective case series; +PV: Positive predictive value; -PV: Negative predictive value; NS: Not specified; EMG: Electromyography; SNP: Single nucleotide polymorphism; NTF3: Neurotrophin-3; IGF1: Insulin-like growth factor 1; ERα: Estrogen receptor alpha; IL-17RC: Interleukin 17 receptor C; CALM1: Calmodulin.

years^[16,36,46,47,63-67,69,70,74,76]. Eight studies declared that observation was performed until skeletal maturity of participants or surgical intervention^[58-60,62,72,73,75,77]. Four studies did not report a follow-up period^[44,61,68,71]. The dropout rate was reported by 3 prospective studies ranging from 9.8% to 18%^[36,47,63], and by 2 retrospective studies as 36%^[59] and 54%^[72]. The following main characteristics were reported as having an association with progressive AIS or severe spine deformity: (1) radiographic: increasing of Cobb angle during bracing^[73], rib-vertebral angle at the convex side of the curve apex after brace treatment^[77], and initial Cobb angle^[56,68]; (2) physiologic: pre-menarche at inclusion^[63], electrical activity of the paraspinal muscles (EMG) combined with spinal growth velocity^[64], and brain stem dysfunction by vestibular test^[76]; (3) multiple characteristics based on combining different radiographic indices such as: Risser sign, wrist X-ray, apical level of deformity, imbalance, Cobb angle, type of spine deformity, and bone or vertebral mineral density; with physiologic: menarche status, growing index, spinal growth velocity; and demographic: age and gender characteristics^[60,62,65-67,74]; (4) SNPs of different genes^[58,59,69-72,75]; (5) intracellular melatonin signaling dysfunction^[16,44]; (6) Gi and Gs proteins functional status in peripheral blood mononuclear cells (PBMC)^[61]; and (7) levels of platelet CaM^[46,47], Table 3.

Risk of bias in included studies

Two independent bias evaluations demonstrated good agreement (kappa coefficient, 0.85; standard error, 0.05; P = 0.71). Taking into consideration the observational design of the selected studies and revealed limitations, the general quality can be classified as moderate with a score range from 6 to 13 of 14 in 24 studies, and one study had low quality with a score of 2, (Table 4). Two studies did not clearly describe inclusion/exclusion criteria^[47,61]. Seven studies failed to identify potential confounders, and did not take them into consideration as selection criteria^[47,58,61,71,75-77]. Seventeen studies had retrospective or unclear design^[16,44,46,58-61,66-73,75-77]. Three studies did not report on the gender of the participants^[61,69,73]. Three studies did not specify criteria for curve progression^[44,72,75]. Four studies did not describe the method for measurement of curve progression^[47,59,61,76]. Four studies did not follow "intention to treat" analysis principles^[36,47,68,76]. All selected studies did not declare that those who performed data analysis were blinded to the patients' clinical outcome. Nine studies did not clearly report on the follow-up period^[44,58,59,61,62,68,71,75,77]. Only 5 studies reported dropout rates: ranging from 9.8% to 18%, 3 studies^[36,47,63]; and exceeding 30% in two studies^[59,72]. One study had some suggestion of selective outcome reporting^[58]. Eleven studies did not take in to consideration the impact of gender during their analysis^[16,44,47,61,64,68-71,73,77]. Seven studies used industrial or other financial support^[47,58,59,61,63,64,66]. In summary, 80% of the included studies were at risk of selection bias, 100% at risk of detection bias, 24% at risk of performance bias, 60% at risk of reporting bias, and 80% at risk of attrition bias.

Primary outcomes

Radiographic characteristics: One retrospective study (n = 85) demonstrated that the increase in the Cobb angle and/or vertebral rotation ≥ 5° at 1-2 mo follow-up during brace treatment was associated with further curve progression in skeletally immature patients^[73]. In particular, 73% of such patients required surgical correction. Corresponding OR was 33.2 (95%CI: 4.0-270.4; P < 0.001); SN, 39%; SP, 98%; +PV, 93%; and -PV, 72%.

Eight studies, 3 prospective^[36,65,74] and 5 retrospective^[66-68,70,73] reported an association between initial Cobb angle and progressive AIS in 3719 subjects. The criteria of progressive AIS were different: increasing of the Cobb angle more than 5° or 6°^[65,73,74]; Cobb angle exceeding 30°^[36,68]; Cobb angle exceeding 45° or surgical correction^[67,70];

Table 4 Risk of bias assessment

Ref.	Questions for evaluation														Score
Upadhyay <i>et al</i> ^[73]	Yes	Yes	Unsure	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	8
Peterson <i>et al</i> ^[62]	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	Yes	Yes	Yes	10
Ajemba <i>et al</i> ^[60]	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	Yes	10
Cheung <i>et al</i> ^[64]	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	Yes	10
Danielsson <i>et al</i> ^[63]	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Kindsfater <i>et al</i> ^[46]	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	Yes	10
Lowe <i>et al</i> ^[47]	No	No	Yes	Yes	Yes	No	Unsure	Yes	Yes	Yes	Yes	No	No	Yes	7
Sun <i>et al</i> ^[67]	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	Yes	10
Sun <i>et al</i> ^[66]	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	Yes	10
Hung <i>et al</i> ^[65]	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	No	Yes	10
Lam <i>et al</i> ^[74]	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	Yes	11
Lee <i>et al</i> ^[68]	Yes	Yes	No	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	No	Yes	Yes	7
Tan <i>et al</i> ^[36]	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12
Modi <i>et al</i> ^[77]	Yes	No	No	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	No	No	Yes	6
Qiu <i>et al</i> ^[69]	Yes	Yes	No	No	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	No	Yes	7
Xu <i>et al</i> ^[70]	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	Yes	9
Ward <i>et al</i> ^[58]	Yes	No	No	Yes	Yes	Yes	Unsure	No	No	Unsure	No	Yes	Yes	Yes	7
Bohl <i>et al</i> ^[59]	Yes	Yes	No	Yes	Yes	No	Unsure	No	Yes	No	Yes	Yes	Yes	Yes	9
Zhao <i>et al</i> ^[71]	Yes	No	Unsure	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	No	Yes	Yes	7
Zhou <i>et al</i> ^[72]	Yes	Yes	No	Yes	No	Yes	Unsure	Yes	Yes	No	Yes	Yes	Yes	Yes	10
Moreau <i>et al</i> ^[44]	Yes	Yes	No	Yes	No	Yes	Unsure	No	No	Unsure	Yes	No	Yes	Yes	7
Akoume <i>et al</i> ^[16]	Yes	Yes	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	Yes	9
Akoume <i>et al</i> ^[61]	No	No	No	No	Yes	No	Unsure	Unsure	No	No	Unsure	Yes	No	No	2
Yamamoto <i>et al</i> ^[76]	Yes	No	No	Yes	Yes	No	Unsure	Yes	No	Unsure	Yes	Yes	No	Yes	6
Yeung <i>et al</i> ^[75]	Yes	No	No	Yes	No	Yes	Unsure	No	No	Unsure	Yes	Yes	Yes	Yes	7

Questions for evaluation: (1) Were inclusion/exclusion criteria clearly described? (2) Were confounding factors identified, and taken into consideration as selection criteria? (3) Was study prospective? (4) Were number/rate of male and female enrolled into the study reported? (5) Were criteria of curve progression clearly identified? (6) Was measurement of curve progression clearly described? (7) Were enrolled patients analyzed in the same treatment group (bracing, observation, physiotherapy) to which they were allocated? (8) Was statistician blind to the status of subjects enrolled into the study? (9) Was follow-up period clearly identified? (10) Was drop out rate reported? (11) Was drop out rate acceptable? (< 25%); (12) Are reports of the study free of suggestion of selective outcome reporting? (13) Was impact of gender taken into consideration during analysis? and (14) Was impact of confounding factors taken into consideration during analysis?

and using of several criteria^[66]. The following cut off values for the initial Cobb angle were applied: 25° or 26°, 3 studies^[36,68,74]; and 30°, 5 studies^[65-67,70,73]. All studies showed statistically significant ($P < 0.02$) associations between a higher initial Cobb angle and a risk of further severe spine deformity. The OR varied from 2.2 to 34.5, the pooled OR was 7.6 (95%CI: 4.2-13.6; $P < 0.001$; high heterogeneity, $I^2 = 79.2\%$). The grouping analysis did not reveal significant differences between prospective and retrospective studies, or between studies using different cut off values. The pooled prognostic characteristics were low with a lack of statistical significance of +PV: Sn, 69% (95%CI: 62%-74%; $P < 0.001$; high heterogeneity, $I^2 = 89\%$); Sp, 73% (95%CI: 65%-79%; $P < 0.001$; high heterogeneity, $I^2 = 92\%$); +PV, 62% (95%CI: 48%-74%; $P = 0.096$; high heterogeneity, $I^2 = 97\%$); and -PV, 81% (95%CI: 73%-87%; $P < 0.001$; high heterogeneity, $I^2 = 94\%$).

Four retrospective studies reported an association of curve pattern with progression of spine deformity in 607 AIS patients, in particular thoracic vs thoracolumbar, lumbar, or double^[66,67,70,73]. Criteria for progression were Cobb angle increase > 5°, exceeding 45°, or surgical correction. All studies demonstrated that cases with thoracic curves showed a higher risk of progression than

cases with other types of deformity. The OR ranged from 1.3 to 11.3. Two studies showed a statistically significant association, $P \leq 0.03$ ^[66,67], while 2 others were not significant, $0.1 > P < 0.3$ ^[70,73]. The pooled OR was 2.3 (95%CI: 1.2; 4.6; $P = 0.017$; moderate heterogeneity, $I^2 = 59\%$). The pooled prognostic values were low with statistically insignificant Sn and +PV: Sn, 60% (95%CI: 48%-72%; $P = 0.098$; high heterogeneity, $I^2 = 87\%$); Sp, 59% (95%CI: 52%-66%; $P = 0.01$, high heterogeneity, $I^2 = 62\%$); +PV, 40% (95%CI: 22%-60%; $P = 0.30$; high heterogeneity, $I^2 = 91\%$); and -PV, 77% (95%CI: 66%-86%; $P < 0.001$; high heterogeneity, $I^2 = 85\%$).

Four studies (1 prospective^[65] and 3 retrospective^[67,70,77]) reported an association between skeletal maturity by Risser sign and progressive AIS in 1891 subjects. The Risser grade of 1 or 2 was used as a cut off. The criteria of progressive AIS were an increase of Cobb angle > 5°, Cobb angle > 45° or surgical correction. The OR ranged from 1.5 to 5.1. Three studies showed a statistically significant association between Risser grade 0-1 and progressive AIS ($P \leq 0.01$)^[65,67,70], while 1 study did not find a significant association of Risser grade 0-2 with progressive AIS ($P = 0.3$)^[77]. The pooled OR was 2.8 (95%CI: 1.6-4.8; $P < 0.001$, moderate heterogeneity, $I^2 = 50\%$). The

pooled predictive characteristics were relatively low, in particular Sn and +PV showed lack of statistical significance: Sn, 64% (95%CI: 43%-81%; $P = 0.165$; high heterogeneity, $I^2 = 96\%$); Sp, 66% (95%CI: 52%-77%; $P = 0.018$; high heterogeneity, $I^2 = 92\%$); +PV, 43% (95%CI: 22%-66%; $P = 0.565$; high heterogeneity, $I^2 = 98\%$); and -PV, 82% (95%CI: 60%-93%; $P < 0.005$; high heterogeneity, $I^2 = 97\%$).

One retrospective study ($n = 113$) revealed that a rib-vertebral angle of less than 65° at the apical level of the convex side, after a few months of brace treatment, is associated with further curve progression in patients with initial Cobb angle of 40° to 56° ^[77]. The approximated OR was 5.6 (95%CI: 2.2-13.9; $P < 0.001$). The prognostic values were low: Sn, 45%; Sp, 87%; +PV, 69%; and -PV, 71%.

Three studies, 2 prospective^[65,74] and 1 retrospective^[66], reported an association of osteopenia with progressive AIS in 686 subjects. The criteria of progression were an increase of Cobb angle $> 6^\circ$ or exceeding 45° in spite of brace treatment. Two studies used dual energy X-ray absorptiometry to define bone density: one in the femoral neck^[65] and one in L2-L5 vertebrae^[66]. One study used bone stiffness index by ultrasound in the calcaneus^[74]. All 3 studies demonstrated a statistically significant association between markers of osteopenia and progression of spine deformity in AIS. The OR ranged from 2 to 11.3, $P \leq 0.03$. The pooled OR was 2.6 (95%CI: 1.4-5.6; $P = 0.005$; moderate heterogeneity, $I^2 = 51\%$). The pooled prognostic values were low and highly heterogeneous, in particular, the pooled Sp was not statistically significant: Sn, 73.8 (95%CI: 53.8%-87.2%; $P = 0.021$; $I^2 = 96\%$); Sp, 62% (95%CI: 47.4%-74.8%; $P = 0.1$; $I^2 = 93\%$); +PV, 69% (95%CI: 56%-78.3%; $P = 0.004$; $I^2 = 90\%$); -PV, 68% (95%CI: 55.9%-77.1%; $P = 0.003$; high heterogeneity, $I^2 = 89\%$).

Demographic and physiologic characteristics:

Three studies (two prospective^[65,74] and one retrospective^[67]) reported results with an association between the age at diagnosis of AIS with a progressive form of the disease in 760 girls. The criteria of progressive AIS were the following: increase of the Cobb angle $> 6^\circ$ ^[65,74], and Cobb angle exceeding 45° or surgical correction^[67]. All 3 studies showed that patients < 13 years of age at diagnosis, had a higher risk of curve progression than those who were older, OR ranged from 2.1 to 3.1, $P \leq 0.06$. The pooled OR was 2.7 (95%CI: 1.9-3.9; $P < 0.001$; low heterogeneity, $I^2 = 0\%$). The pooled prognostic values were low and heterogeneous with statistically insignificant Sp and positive prediction value: Sn, 66% (95%CI: 45%-77%; $P = 0.009$; high heterogeneity, $I^2 = 90\%$); Sp, 54% (95%CI: 49%-59%; $P = 0.077$; moderate heterogeneity, $I^2 = 43\%$); +PV, 45% (95%CI: 24%-69%; $P = 0.705$; high heterogeneity, $I^2 = 97\%$); -PV, 73% (95%CI: 55%-86%; $P = 0.013$; high heterogeneity, $I^2 = 95\%$).

Six studies (3 prospective^[63,65,74] and 3 retrospective^[66,67,77]) reported an association between pre-

menarche status at diagnosis and progressive AIS in 980 girls. Five studies enrolled patients with Cobb angle $< 40^\circ$ ^[63,65-67,74], and one with Cobb angle 40° - 56° ^[77]. Criteria for progression were different: increase of Cobb angle $> 5^\circ$, 4 studies^[63,65,74,77]; Cobb angle exceeding 45° , 1 study^[67]; and both of these criteria, 1 study^[66]. All studies showed that pre-menarche at diagnosis was associated with a higher risk of progressive AIS. The OR ranged from 1.5 to 11.5 and was statistically significant in studies that enrolled patients with Cobb angle $< 40^\circ$. The pooled OR was 4.0 (95%CI: 2.0-7.9; $P < 0.001$; high heterogeneity, $I^2 = 64\%$). Grouping analysis confirmed that studies that enrolled patients with Cobb angle $< 40^\circ$, showed significantly ($P = 0.023$) higher association between pre-menarche status and curve progression than those that enrolled patients with more severe deformity. The pooled predictive values were low and heterogeneous with statistically insignificant positive predictive value: Sn, 60% (95%CI: 50.7%-67.9%; $P = 0.034$; high heterogeneity, $I^2 = 85\%$); Sp, 74.3% (95%CI: 50.7%-67.9%; $P = 0.001$; high heterogeneity, $I^2 = 93\%$); +PV, 52.3% (95%CI: 37.8%-66.5%; $P = 0.758$; high heterogeneity, $I^2 = 94\%$); -PV, 75% (95%CI: 66.8%-81.5%; $P < 0.001$; high heterogeneity, $I^2 = 89\%$).

One retrospective study reported data showing a significant association between brain stem vestibular dysfunction and spine deformity progression (increase of Cobb angle $> 4^\circ$), in a case series of 28 girls with AIS^[76]. Initial Cobb angle ranged from 5° to 59° . The OR was 24 (95%CI: 2.4-240.6), $P = 0.007$; Sn, 91%; Sp, 71%; +PV, 67%; and -PV, 92%.

Combining of radiographic, demographic and physiologic characteristics:

Seven studies: 4 prospective^[62,64,65,74], and 3 retrospective^[60,66,67] applied multiple regressions modeling to combine selected radiographic, demographic, and physiological characteristics to generate an index with maximal prognostic value for progressive AIS. These studies enrolled 1057 participants. Five studies included patients with initially mild or moderate spine deformities with Cobb angle ranging from 10° to 40° ^[62,65-67,74] and two studies also included patients with a Cobb angle of $> 45^\circ$ ^[60,64]. Criteria for AIS progression were: an increase in Cobb angle of more than 5° - 10° , 5 studies^[60,62,64,65,74]; Cobb angle exceeding 45° , one study^[67]; and both criteria, one study^[66]. The following radiographic indices were used: skeletal maturity by Risser sign^[62,65,67] or wrist X-ray^[60]; different characteristics of curve pattern^[60,62,65,66]; initial Cobb angle^[65-67,74]; imbalance^[62]; spine growth velocity^[64]; and osteopenia by different markers^[65,66,74]. Demographic characteristics included age^[60,62,65,74], and gender^[60]. Physiologic indices included: menarche status^[65-67,74]; growth index^[60]; and asymmetry of the paraspinal muscles electrical activity by electromyography^[64]. From 2 to 6 characteristics were combined to generate prognostic indices. All studies showed a high association of developed indices with the AIS progression. The

OR ranged from 4.5 to 24.7 with $P \leq 0.1$. The pooled OR was 9.6 (95%CI: 6.1-15.2; $P < 0.001$; moderate heterogeneity, $I^2 = 34\%$). The funnel plot analysis revealed a small publication bias towards overestimation of this association. However, exclusion of two studies with the highest association (OR > 20) from the analysis decreased heterogeneity to low, without a significant change in the pooled OR, 7.2 (95%CI: 4.8-10.7; $P < 0.001$). The pooled prognostic values were moderate: Sn, 82.1% (95%CI: 77.4%-86.2%; $P < 0.001$, high heterogeneity, $I^2 = 66\%$); Sp, 71.1 (95%CI: 66.9%-76.7%; $P < 0.001$; high heterogeneity, $I^2 = 62\%$); +PV, 77.2% (95%CI: 72.9%-81.1%; $P < 0.001$, moderate heterogeneity, $I^2 = 52\%$); -PV, 81.9% (95%CI: 74.5%-87.9%; $P < 0.001$; high heterogeneity, $I^2 = 83.4\%$).

SNP of different genes: One retrospective study reported a significant association between estrogen receptor (*ER1*) gene SNP at locus rs2234693 and progressive AIS with severe spine deformity (Cobb angle > 40°) and different curve patterns, $P < 0.05^{[71]}$. The result was obtained in the Chinese population by analysis of 67 AIS patients and 100 healthy controls. The approximated OR was 1.8 (95%CI: 1.1-2.8); Sn, 69%; Sp, 44%; +PV, 45%; -PV, 68%. Another retrospective study reported significant association between curve progression after brace treatment and estrogen receptor gene (*ER1*) SNP at locus rs9340799, $P < 0.001^{[70]}$. The result was obtained in 312 AIS patients of the Chinese population. The approximated OR was 2.7 (95%CI: 1.77-4.6); Sn, 27%; Sp, 87%; +PV, 44%; -PV, 76%.

One retrospective study showed an association between different forms of progressive AIS and calmodulin 1 (*CALM1*) gene SNP at locus rs12885713, $P = 0.034^{[71]}$. The result was obtained in 67 AIS patients and 100 healthy controls (Chinese population). The approximated OR was 1.7 (95%CI: 1.0-2.93); Sn, 28%; Sp, 82%; +PV, 51%; -PV, 63%.

One retrospective study reported an association between progressive AIS and tryptophan hydroxylase 1 (*TPH1*) gene SNP at locus rs10488682, $P = 0.033^{[70]}$. The result was obtained in 312 AIS patients treated by brace wearing (Chinese population). The approximated OR was 1.9 (95%CI: 1.0-3.5); Sn, 17%; Sp, 90%; +PV, 38%; -PV, 76%. The same study reported an association between progressive AIS and SNP of melatonin receptor 1B gene (*MTNR1B*) at locus rs4753426 with borderline significance, $P = 0.074$. The approximated OR was 1.5 (95%CI: 1.0-2.4); Sn, 72%; Sp, 37%; +PV, 29%; -PV, 79%.

One retrospective study reported significant association between SNP in the neurotrophin 3 (*NTF3*) gene promoter at rs11063714 locus and curve severity in 362 AIS patients (Chinese population), $P = 0.008^{[69]}$. In particular, patients with AA genotype demonstrated more successful brace treatment than those patients with GG genotype, $P = 0.043$, the OR was 3.3 (95%CI: 1.0-2.9); Sn, 56%; Sp, 72%; +PV, 43%; -PV, 82%.

One retrospective study reported a significant association between the interleukin-17 receptor C (*IL17RC*) gene SNP at rs708567 locus and curve severity in 529 Chinese girls with AIS^[72]. In particular, skeletally mature patients with GG genotype ($n = 215$) showed a higher mean Cobb angle ($36.0^\circ \pm 13.1^\circ$) than those patients with AG genotype ($n = 26$; mean Cobb angle, $28.9^\circ \pm 7.4^\circ$), $P = 0.007$. The approximated OR with Cobb angle cut off 32.5° was 3.4 (95%CI: 1.4-8.3); Sn, 94%; Sp, 17%; +PV, 60%; -PV, 69%.

One retrospective study showed an association between the Insulin-like growth factor 1 (*IGF1*) gene SNP at rs5742612 locus and curve severity in AIS girls with Cobb angle > 20° (Chinese population)^[75]. In particular, patients with TT genotype ($n = 169$) had mean Cobb angle ($38.1^\circ \pm 12.1^\circ$) higher than those who had TC ($n = 138$; mean Cobb angle, $35.6^\circ \pm 12.0^\circ$) or CC ($n = 33$; mean Cobb angle, $33.3^\circ \pm 9.0^\circ$) genotypes. The approximated OR (TT vs CC, with Cobb angle cut off 35.6°) was 2.1 (95%CI: 1.0-4.4; $P = 0.1$); Sn, 88%; Sp, 22%; +PV, 57%; -PV, 61%.

Two retrospective studies reported an association of a multiple index developed by combining 53 different gene SNPs and initial Cobb angle (ScoliScore test) with non-progressive or progressive AIS^[58,59]. OR between the selected SNPs and different forms of the AIS ranged from 0.26 to 1.94 suggesting low association^[58]. However, the developed multiple index had a positive correlation with severity of spine deformity ranging from 0 to 200. In particular, one study presented results obtained in 697 Caucasian AIS patients with Cobb angle > 10°^[58]. It was shown that the index value of < 41 is associated with a small spine deformity. Correspondingly, the index values ranged from 40 to 200 showed significant association with severe spine deformity (Cobb angle > 40°): OR, 16.8 (95%CI: 6.6-42.7; $P < 0.001$). However, Sp and positive prediction value of this test were low: Sn, 91%; Sp, 63%; +PV, 17%; -PV, 99%. The second study demonstrated that the index values > 160 associated with severe spine deformity (Cobb angle > 45°) in 16 AIS patients with initial Cobb angle $\geq 20^\circ$: OR, 21.0 (95%CI: 1.5-293; $P = 0.05$); Sn, 78%; Sp, 86%; +PV, 88%; -PV, 75%^[59]. The pooled OR was relatively high: 17.2 (95%CI: 7.1-41.5); $P < 0.001$; low heterogeneity, $I^2 = 0\%$). However, the pooled prognostic characteristics were moderate and highly heterogeneous with statistically insignificant Sp and positive predictive value: Sn, 87.3% (95%CI: 71.8%-94.9%; $P < 0.001$; high heterogeneity, $I^2 = 79\%$); Sp, 73.2% (95%CI: 44.8%-90.2%; $P = 0.101$; high heterogeneity, $I^2 = 70\%$); +PV, 53.4% (95%CI: 3.3%-97.4%; $P = 0.940$); high heterogeneity, $I^2 = 96\%$); -PV, 94.6% (95%CI: 36.4%-99.8%; $P = 0.1$; high heterogeneity, $I^2 = 97\%$).

Melatonin signaling: Two studies 1 prospective^[16] and 1 retrospective^[44] reported an association of AIS spine deformity with changes in intracellular melatonin signaling^[16,44]. One study demonstrated that a reduced inhibition of forskolin stimulated cAMP by melatonin

in osteoblasts, harvested during surgery, was more typical in patients with severe AIS (41 cases who underwent surgical correction) compared to patients with other types of scoliosis, or non-scoliotic controls ($n = 17$)^[44]. The approximated OR was 3.9 (95%CI: 0.5-33.7; $P = 0.3$) with the corresponding prognostic characteristics: Sn, 20%; Sp, 94%; +PV, 89%; -PV, 33%. A second study showed that electrical impedance of PBMC < 120 ohms after melatonin or iodomelatonin administration associated with progression of the initially small spine deformity with Cobb angle < 10° to clinically significant deformities with Cobb angle > 10° in children genetically predisposed to AIS ($n = 31$), $P = 0.03$ ^[16]. The approximated OR was 18.5 (95%CI: 0.8-392), corresponding predictive values: Sn, 33%; Sp, 100%; +PV, 100%; -PV, 70%. The pooled OR was 6.5 (95%CI: 1.1-38.2; $P = 0.037$; low heterogeneity, $I^2 = 0$), corresponding predictive values showed low Sn, but relatively high Sp and positive predictive value: Sn, 25.4% (95%CI: 15%-39.8%; $P = 0.001$; moderate heterogeneity, $I^2 = 44%$); Sp, 94.9% (95%CI: 87.2%-98.1%; $P < 0.001$; low heterogeneity, $I^2 = 0%$); +PV, 93.5% (95%CI: 70%-98.9%; $P = 0.004$; moderate heterogeneity, $I^2 = 47.6%$); -PV, 51.1% (95%CI: 18.6%-82.8%; $P = 0.954$; high heterogeneity, $I^2 = 90.4%$).

Gi and Gs proteins functional status in PBMC: One retrospective study reported that Gi and Gs proteins functional status in PBMC, defined by cellular dielectric spectroscopy, allowed classification of AIS patients into three functional groups (FG1, FG2, and FG3) according to the profile of imbalance between the responses to Gi and Gs stimulation. Activation of Gs, by isoproterenol, predominated in FG1, while FG3 was characterized by Gi dominant, somatostatin, responses^[61]. It was suggested that FG2 group, which exhibited balanced responses to Gs and Gi, had significantly higher risk of severe spine deformity (Cobb angle $\geq 45^\circ$) than FG1 or FG3 groups. In particular, among 162 patients with a Cobb angle of $\geq 45^\circ$, 56% related to the FG2 group, 31% to the FG3 group, and 13% to the FG1 group; while among 794 patients with Cobb angle ranging from 10° to 44° the distribution was different: the FG2 group, 33%; the FG3 group, 39%; and the FG1, 28%. Corresponding OR (FG2 vs FG3 + FG1) was 2.6 (95%CI: 1.9-3.7; $P < 0.001$) with relatively low prognostic values: Sn, 26%; Sp, 88%; +PV, 56%; -PV, 67%.

Platelet CaM: Two studies (1 retrospective^[46] and 1 prospective^[47]) studied the level of platelet CaM in AIS with different progression and healthy controls. The retrospective study reported that platelet CaM defined by radioimmune analysis and measured as nanograms of CaM per microgram of protein (ng/ μ g protein) was more than twice higher in patients with AIS ($n = 17$) than in healthy controls ($n = 10$), but this difference was not statistically significant by the standard student's t -test ($P > 0.05$)^[46]. However, all 5 patients

with progressive scoliosis (increase of Cobb angle > 10° during observation) had levels of platelet CaM ranging from 1.46 to 10.67 ng/ μ g protein, while 12 patients with stable deformities had platelet CaM from 0.09 to 1.16 ng/ μ g protein. Theoretically it means that there could be a strong association between the level of platelet CaM and progressive AIS by χ^2 -test ($P = 0.007$) with high predictive values; Sn, 100%; Sp, 100%; +PV, 100%; -PV, 100%. The prospective study used enzyme-linked immunosorbent analysis developed for the study to evaluate the platelet CaM level in 55 AIS patients^[47]. The authors noted a high variability of the platelet CaM levels making results of quantitative statistical analysis not significant. However, it was revealed that among patients without treatment (observational group; $n = 28$) the progressive AIS cases (increase of Cobb angle $\geq 10^\circ$ per year of observation) were associated with an increase of platelet CaM levels during the first year of observation, while in patients with stable curvatures such increases were not observed: OR, 11 (95%CI: 1.7-69.9; $P = 0.02$); Sn, 69; Sp, 83; +PV, 85; -PV, 67. Combining the results of these two studies showed significant association between platelet CaM levels, and progressive AIS: the pooled OR was 32.6 (95%CI: 1.7-643; $P = 0.022$; $n = 45$; moderate heterogeneity, $I^2 = 50%$); the pooled predictive values showed moderate level: Sn, 86% (95%CI: 31%-99%; $P = 0.17$; high heterogeneity, $I^2 = 71%$); Sp, 89% (95%CI: 60%-98%; $P = 0.015$; moderate heterogeneity, $I^2 = 40%$); +PV, 90% (95%CI: 66%-98%; $P = 0.005$; low heterogeneity, $I^2 = 29%$); -PV, 86% (95%CI: 29%-99%; $P = 0.194$; high heterogeneity, $I^2 = 73%$).

Secondary outcomes

Eight studies (1 prospective^[63], and 7 retrospective^[46,66,67,69,70,73,77]) reported on the number/rate of AIS patients who experienced progression of spine deformity in spite of brace treatment, in 907 participants. The initial Cobb angle exceeded 15° in all 8 studies. Criteria for curve progression were different: increasing of the initial Cobb angle with more than 5° or 6° during or after treatment, 4 studies^[63,70,73,77]; Cobb angle exceeding 45°, 2 studies^[67,69]; and using of a few criteria, 2 studies^[46,66]. The rate of progressive cases ranged from 19% to 39% with $P \leq 0.05$ in all studies. The pooled rate was 26.9% (95%CI: 22.9%-31.2%; $P < 0.001$; moderate heterogeneity, $I^2 = 42%$). Group analysis did not reveal a significant difference between prospective and retrospective studies.

Four studies: 1 prospective^[63] and 3 retrospective^[66,67,70] reported the number/rate of AIS patients requiring surgical correction, due to progression of spine deformity, during or after brace treatment in 579 AIS patients. The initial Cobb angle ranged from 20° to 45°. Rates of surgical treatment ranged from 10.5% to 19.2% with $P < 0.001$ in all studies. The pooled rate was 15% (95%CI: 11.0%-41.6%; $P < 0.001$; moderate heterogeneity, $I^2 = 41%$).

Table 5 Summary table of meta-analysis of association between studied characteristics and progressive adolescent idiopathic scoliosis

Studied characteristics	Study (n)	Participants (n)	Heterogeneity		Summary statistics			P value	Level of evidence (GRADE)
			I ² (%)	Level	Pooled odds ratio	95% confident limits			
						Lower	Upper		
Age (< 13 yr)	3	760	59	Moderate	2.7	1.8	4.6	0.001	Low
Osteopenia	3	686	51	Moderate	2.8	1.4	5.6	0.005	Low
Brain stem dysfunction	1	28	NA	NA	24.0	2.4	240.3	0.007	Very low
Multiple indices ¹	7	1057	35	Moderate	9.6	6.1	15.2	< 0.001	Low
Curve pattern	4	607	59	Moderate	2.3	1.2	4.6	0.017	Low
Curve progression during bracing	1	85	NA	NA	33.2	4.0	272.9	0.001	Very low
Initial Cobb angle	8	3719	90	High	7.6	4.2	13.6	< 0.001	Low
Melatonin signaling	2	89	0	Low	6.5	1.1	38.2	0.037	Low
Platelet calmodulin	2	72	39.9	Moderate	39.9	2.2	735.9	0.013	Low
Premenarche	6	980	64	High	4.0	2.0	7.9	< 0.001	Low
Rib-vertebral angle	1	113	NA	NA	5.6	2.2	13.9	< 0.001	Very low
Skeletal immaturity	4	891	50	Moderate	2.8	1.6	4.8	< 0.001	Low
SNP CALM1	1	67	NA	NA	1.7	1.0	2.9	0.036	Very low
SNP ER1	2	379	63	High	2.4	1.3	4.7	0.009	Low
SNP IGF1	1	340	NA	NA	2.1	0.9	4.5	0.054	Very low
SNP IL17RC	1	312	NA	NA	1.5	0.9	2.4	0.074	Very low
SNP NTF3	1	120	NA	NA	3.3	1.0	10.9	0.050	Very low
SNP TPH1	1	312	NA	NA	2.1	1.0	4.4	0.052	Very low
SNPs(53), ScolioScore test	2	713	0	Low	17.2	7.1	41.5	< 0.001	Low
Gi proteins functional status	1	956	NA	NA	2.6	1.9	3.7	< 0.001	Very low

¹Multiple indices included combinatorial radiographic, demographic, and physiologic characteristics. NA: Not available; SNP: Single nucleotide polymorphism; CALM1: Calmodulin 1; ER1: Estrogen receptor 1; IGF1: Insulin-like growth factor 1; IL17RC: Interleukin-17 receptor C; NTF3: Neurotrophin 3; TPH1: Tryptophan hydroxylase 1.

DISCUSSION

In the present review, we have systematically collected and analyzed the available evidence from published data evaluating the predictive values of various characteristics and parameters for the prediction of severe spine deformity in AIS. The prediction values of various indices were collected from published data, if necessary, additional calculation were performed. Methods of meta-analysis were applied, to summarize results of different publications. This was an independent study, performed without industrial or commercial support.

Summary of main results

Twenty five observational clinical studies were included in the current review.

One retrospective study demonstrated that the increase of spine deformity with more than 5° (Cobb angle and/or vertebral rotation) at 1-2 mo follow-up after starting brace treatment had a significant association with risk of further curve progression and requirement for surgical correction^[73]. However, despite a high association (Table 5) the prognostic values of this index were limited. The level of evidence is very low because only one retrospective study reported this finding^[53].

It was shown by one retrospective study that a rib-vertebral angle of less than 65°, at the apical level of convex side after a few months of brace treatment, had a significant association with the risk of further curve progression (Table 5)^[77]. The predictive values of this index were low. The level of evidence is very low due to the same reason.

Eight studies (3 prospective and 5 retrospective) showed that severity of the initial spine deformity (Cobb angle more than 25°-30°) demonstrated significant association with a risk of further curve progression^[36,65-68,70,73,74]. The pooled OR was relatively high (Table 5), nonetheless prognostic values were low. The level of evidence is low due to the high heterogeneity of the pooled results and limitations of the included studies (Tables 3 and 4).

Four retrospective studies examined spinal curve patterns and found that thoracic deformities had a significantly higher risk of progression than thoracolumbar, lumbar or double curvatures (Table 5)^[66,67,70,73]. However, prognostic values of this index were low. The level of evidence is low due to high heterogeneity of the pooled results and the limitations of the included studies (Tables 3 and 4).

Four studies (1 prospective and 3 retrospective) showed that skeletally immature patients (based on radiographic criteria), had significantly higher risks of curve progression than those who were skeletally mature (Table 5)^[65,67,70,77]. However, the pooled predictive values were low. The level of evidence is also low due to the high heterogeneity of the pooled results and limitations of the included studies (Tables 3 and 4).

Three studies (2 prospective and 1 retrospective) have found that osteopenia, defined by radiographic or ultrasound methods, is significantly associated with progressive spine deformity in AIS (Table 5)^[65,66,74]. However, the predictive values were low. The high heterogeneity of the pooled results and limitations of the included studies suggested a low level of evidence (Tables 3 and 4).

One prospective cohort study has reported that 3-dimensional morphological parameters of spine at the first visit significantly differed in patients with progressive and non-progressive AIS^[78]. However, reported data did not allow evaluation of the predictive values of these characteristics, therefore these results were not included in our review.

Three retrospective studies showed that patients' age < 13 years old at diagnosis have a significant associated risk for spine deformity progression (Table 5), but with low predictive values^[65,67,74]. The level of evidence is low due to the lack of significance and the high heterogeneity of the pooled prognostic values and the limitations of the included studies (Tables 3 and 4).

Six studies 3 prospective^[63,65,74] and 3 retrospective^[66,67,77] showed that the premenarche status at diagnosis had a significant association with risk of curve progression, particularly in girls with mild and moderate spine deformity (Table 5). However, this index showed low predictive values. The level of evidence is low due to the lack of significance and high heterogeneity of the pooled prognostic values, and limitations of the included studies (Tables 3 and 4).

It was demonstrated by one retrospective study that brain stem vestibular dysfunction had a significant association with progressive AIS (Table 5) with moderate Sn, but low Sp and positive predictive value^[76]. This finding has very low level of evidence.

Seven studies (4 prospective^[62,64,65,74] and 3 retrospective^[60,66,67]) showed that use of multiple indices, based on a combination of radiographic, bone densitometry, demographic and physiologic characteristics, demonstrates a significant association with progressive AIS (Table 5). However, the prognostic values of these combinatorial indices did not exceed moderate level. The level of evidence is low due to the limitations of the included studies (Tables 3 and 4), high heterogeneity of the pooled prognostic values, and the risk of the publication bias.

SNPs of the following genes have been reported as having significant association with progressive AIS: *CALM1*^[71]; *ER1*^[70,71]; *TPH1*^[70]; *IGF1*^[75]; *NTF3*^[69]; *IL17RC*^[72]; and *MTNR1B*^[70]. However, the levels of association were relatively low (Table 5) with small predictive capacity. All these findings have very low level of evidence due to the limitations of the studies design (Tables 3 and 4) and that fact that only one study reported each finding. Of note, results concerning association between SNPs and AIS have low replicability in different populations^[19,49]. It was also reported that rare variants in fibrillin-1 and fibrillin-2 genes^[79], and rs12946942 on chromosome 17q24.3^[80] have significant association with severity of spine deformity in AIS. These studies did not match the inclusion criteria of our review, and thus were not included in the detailed analysis. However, the level of revealed associations was not high (OR: 1.6-2.6) corresponding with low prognostic values. Retrospective design of these studies and other limitations suggest a low level of evidence.

It has been reported by two retrospective, industry sponsored studies that a complex index based on 53 SNPs and initial Cobb angle (ScoliScore test) had significant association with progressive or stable AIS^[58,59]. The pooled OR was relatively high (Table 5); but the pooled predictive characteristics ranged between low and moderate level with limited statistical significance. To note, these predictive values are similar to those obtained by other complex indices which included initial Cobb angle as an input parameter (Table 5). The level of evidence is low due to the limitations in the studies design (Tables 3 and 4), and the high heterogeneity of the pooled prognostic values. Of note, replicability of this method was low in the Japanese population^[35].

The results of two studies, 1 retrospective^[44] and 1 prospective^[16], from the same group of researchers suggested a significant association between impairment of melatonin signaling and development of AIS (Table 5). That fact that this defect was revealed in cells of different tissues (osteoblasts and blood mononuclear cells), means that the defect is likely systemic, and thus can impact the functionality of different systems in the body. Potential physiological and biochemical mechanisms of this association have been discussed elsewhere^[19,50]. The pooled prognostic values showed relatively high Sp and positive predictive value, but low Sn, and negative predictive value. Of note, the design of these studies does not allow evaluation of the predictive values of the melatonin signaling impairment as a predictor of severe spine deformity in AIS. The level of evidence is low due to the small number of studied cases and the limitations in the studies design (Tables 3 and 4).

One retrospective study from the same research group reported a significant association between the functional status of Gi and Gs proteins in PBMC and severity of spine deformity in idiopathic scoliosis^[61]. In spite of this significant association (Table 5) the results suggested low predictive capacity. Thus, G-proteins dysfunction is likely involved in the pathogenesis of idiopathic scoliosis, corresponding with melatonin signaling impairment, but this index cannot currently be used as diagnostic criteria for treatment strategy selection. The level of evidence is very low due to the limitations the presented results (Table 2) and the fact that only one study reported this finding.

Combining the results of two studies 1 retrospective^[46] and 1 prospective^[47] suggested that platelet CaM levels also have a significant association with progressive AIS (Table 5)^[46,47]. Potential mechanisms of this association have been discussed elsewhere^[19]. The pooled prognostic values were moderate. The level of evidence is low due to the small number of studied cases and the limitations of the studies reported this finding (Tables 3 and 4).

The pooled results of 8 studies suggested that around 27% of the AIS patients with initial Cobb angle exceeding 15 degrees had exacerbation of the spine

deformity in spite of brace treatment^[46,63,66,67,69,70,73,77], and pooled results of 4 studies demonstrated that 15% of patients treated by bracing required surgical correction^[63,66,67,70]. However, the level of evidence is low due to the limitations of the studies presented these findings (Tables 3 and 4).

Strength and weakness of the review

To our knowledge this is first systematic review, with a meta-analysis, focused on summarizing the published results and analyzing the reported predictive values of different characteristics in progressive AIS, the risk of severe spine deformity during and after brace treatment, and in particular, the risk of requiring surgical correction. The review was conducted independent of industry following contemporary requirements for systematic reviews and meta-analysis of studies that evaluate diagnostic methods and health care interventions^[81,82]. Comprehensive searches were performed to identify relevant studies. Unfortunately, no randomized controlled clinical trials met the inclusion criteria. Therefore, we had to include nonrandomized studies, while taking into consideration the risk of corresponding biases^[56]. The results of the meta-analysis are limited by the quality of the studies identified in the review. In spite of a comprehensive search, studies relevant to the review may have been missed, which should be regarded as a potential limitation.

Unfortunately, studies included in the review used different criteria for the progression of AIS, making the results of the meta-analysis less certain. In particular, such criteria as Cobb angle exceeding 45° an important potential indication for preventive surgical treatment, was used by only 4 of 25 studies. OR and predictive values were approximated based on the assumption that the studied indices were normally distributed. This is a potential source of inaccuracy, as in reality, all parameters may not exhibit a normal distribution. However, we think that this potential error was accounted for by considering 95%CI and thus did not significantly affect the results.

Overall, the presented findings have low or very low level of evidence due to the limitations typical of observational studies; high heterogeneity and lack of significance of the some pooled results suggesting inconsistency, and due to the fact that some findings were reported by only one study suggesting imprecision and have yet to be validated or reproduced^[53].

Implication for practice

The current review did not reveal any methods for the prediction of severe spine deformity progression in AIS that could be recommended as diagnostic criteria for selection of treatment strategy, in particular, preventive surgical intervention.

Implication for research

The current review revealed a paucity of high quality studies such as: randomized controlled clinical trials

or prospective cohort studies focused on evaluation or development of diagnostic criteria, which would allow selection of patients, with a high risk of severe spine deformity, for preventive surgical intervention at the earlier stage of the AIS. Further research is needed in this field. Such studies should incorporate multiple criteria and integrate different characteristics linked with potential pathogenetic mechanisms, taking into consideration the contemporary concept of the multifactorial etiology of AIS.

COMMENTS

Background

Adolescent idiopathic scoliosis (AIS) is the most prevalent form of spinal deformity, accounting for 80% of pediatric scoliosis and impacts 2%-4% of children during their pubertal growth spurt. The disease affects girls predominantly and diagnosed between age 10 and 16, prior to skeletal maturity. Severe spine deformity occurs in 10%-15%, while 22%-27% demonstrates spontaneous improvement. Medical care depends on the curve progression including observation, none surgical treatment, and surgical correction. Accurate prediction of the spine deformity progression at first patient's visit would significantly improve selection of treatment strategy making it more efficient.

Research frontiers

Over the past 3 decades different indices were reported as having significant association with progression or severity of spine deformity including demographic, radiographic, physiologic, biochemical, genetic, and their combinations. However, published data concerning prognostic value of these findings and their level of evidence have not been systematically collected and evaluated yet.

Innovations and breakthroughs

Current publication is first systematic review with meta-analysis which summarize published data concerning predictive value and level of evidence of different findings that were presented as predictors of progressive or severe spine deformity in AIS. It was shown that all published predictors have low level of evidence and limited predictive capability. The current review did not reveal any methods for the prediction of severe spine deformity progression that could be recommended as diagnostic criteria for selection of treatment strategy, in particular, preventive surgical intervention.

Applications

The study results suggest that further high quality researches are needed in this field.

Terminology

Meta-analysis is a statistical methodology that allows pooling together results of different studies. Low level of evidence means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Peer-review

The authors present a highly interesting and diligently performed, important meta-analysis aiming at the identification of factors predicting progression of scoliosis in idiopathic adolescent cases. The review apparently includes all relevant studies published in the field, it represents a detailed, open and rigorous analysis, and finally draws conclusions demonstrating all results in the appropriate level of evidence.

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