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EDITORIAL

Arthroscopic approach to the posterior compartment of the knee using a posterior transseptal portal

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Abstract

Arthroscopic surgery of the posterior compartment of the knee is difficult when only two anterior portals are used for access because of the inaccessibility of the back of the knee. Since its introduction, the posterior transseptal portal has been widely employed to access lesions in the posterior compartment. However, special care should be taken to avoid neurovascular injuries around the posteromedial, posterolateral, and transseptal portals. Most importantly, popliteal vessel injury should be avoided when creating and using the transseptal portal during surgery. Purpose of the present study is to describe how to avoid the neurovascular injuries during establishing the posterior three portals and to introduce our safer technique to create the transseptal portal. To date, we have performed arthroscopic surgeries *via* the transseptal portal in the posterior compartments of 161 knees and have not encountered nerve or vascular injury. In our procedure, the posterior septum is perforated with a 1.5-3.0-mm Kirschner wire that is protected by a sheath inserted from the posterolateral portal and monitored from the posteromedial portal to avoid popliteal vessel injury.

Key words: Arthroscopic surgery; Knee; Posterolateral portal; Posteromedial portal; Transseptal portal

Core tip: Arthroscopic surgery in posterior compartment of the knee *via* the transseptal portal is less invasive to the patient compared to open surgery for access to the back of the knee. However, special care should be taken to avoid neurovascular injury when creating the three posterior portals. We have not encountered neurovascular injury with our procedure for creating a posterior transseptal portal in 161 treated knees, and conclude that it is safe and reliable.

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INTRODUCTION

Prior to introduction of the posterior transseptal portal, arthroscopic surgery for lesions located in the posterior compartment of the knee was difficult because both the cruciate ligaments and curvature of the femoral condyles obstructed the advance of the arthroscope or other instruments to the back of the knee. Additionally, posterior lesions such as a posterior periphery or posterior horn of the medial meniscus might be missed when using an anterior approach alone[1,2]. Trans-notch views from anterior portals have allowed us to obtain clear views of the posterior compartment[1-3]. However, a particular "blind zone" on the medial meniscus that could not be viewed remained even with a 70-degree arthroscope[4,5]. The treatment of lesions located in the posterior compartment introduces further difficulty. The addition of posteromedial and posterolateral portals together with a 70-degree arthroscope facilitated treatment procedures for posterior lesions[2,6-9]. Nevertheless, the cruciate ligaments, femoral condyles, and prominence of the tibial spine limited the maneuverability of the arthroscope or other instruments advanced through the intercondylar notch from the anterior portals[1,3]. Ideally, either the posteromedial or posterolateral portal would be used as a viewing portal, while the other would be used as a working portal. However, the posterior compartment of the knee is divided into two compartments by a posterior septum comprising a thin synovial membrane between the posterior cruciate ligament (PCL) and the posterior capsule. In 1997, Kim first reported arthroscopic surgery in the posterior compartment of the knee through two posterior portals created after perforating the posterior septum[10]. Since then, many authors have demonstrated their techniques for transseptal portal creation[10-12]. However, important neurovascular or tendon structures lie just posterior to the posteromedial, posterolateral, and transseptal portals. Special care must be taken to avoid injuries to those structures[13,14]. To date, arthroscopic surgeries *via* transseptal portal have been employed more frequently along with broadening indications for arthroscopic surgery for posterior lesions of the knee, including synovectomy[15], meniscectomy[16], repair of the posterior horn of the medial meniscus[17-20], PCL reconstruction[21], PCL avulsion fracture fixation[22], loose body removal[23-26], cystic lesion removal[27-29], posterior capsular release[30], repair of posterior capsular tears[31], and synovectomy of a prosthetic knee[32]. We have also performed arthroscopic surgery *via* the transseptal portal to approach lesions located in the posterior compartment of the knee since 2006. In this paper, we present the techniques for creating posteromedial, posterolateral, and transseptal portals and for avoiding neurovascular injuries around the portal site reported by several authors as well as those performed at our institute.

ANATOMY AND CLINICAL RELEVANCE

The triangular posterior septum borders the dorsal aspect of the PCL anteriorly, femoral intercondylar notch superiorly, and posterior capsule posteriorly and divides the posterior compartment into the posteromedial and posterolateral compartments[11,12] (Figure 1). The septum comprises adipose tissue surrounded by a synovial membrane that contains blood vessels and nerve endings[33]. The medial genicular artery, which originates from the popliteal artery, enters the proximal portion of the septum, which accordingly features a richer vasculature than the distal portion. Mechanoreceptors are also abundant in the proximal septum[33]. Therefore, recommendations regarding limited resection or penetration of the septum indicate that this procedure should be performed at the distal portion, just behind the PCL, rather than at the proximal or femoral side to reduce bleeding while creating the transseptal portal. Immediately behind the septum, the popliteal artery lies outside of the posterior capsule[34-36]. The popliteal artery lies approximately 10 mm laterally to the septum[15,37]. Regarding the posteromedial portal, a sartorial branch of the saphenous nerve is located immediately inferoposteriorly to the portal site (Figure 2A). The common peroneal nerve and long head of the biceps femoris are immediately posterior to the posterolateral portal site, whereas the lateral collateral ligament and popliteal tendon are immediately anterior to this site[36,38-41] (Figure 2B).

ESTABLISHMENT OF THE TRANSSEPTAL PORTAL

In 1997, Kim first introduced an arthroscopic approach to lesions located in posterior compartment of the knee *via* the transseptal portal. According to Kim's technique, the posterior septum was perforated *via* the posteromedial portal using a blunt obturator with a sheath[10]. Ahn *et al*[11]. described a limited resection of the septum using a shaver introduced from the anteromedial portal through the intercondylar notch, which was viewed from the posteromedial portal. Louisia *et al*[12] penetrated the septum from the medial to lateral direction using a blunt obturator, which was followed by a skin incision to create a posterolateral portal. These authors demonstrated a "back and forth" technique in which each posterior portal is used alternately for the arthroscope and other instruments placed through the transseptal portal. Kim *et al*[15] penetrated the septum in the posterolateral to posteromedial direction to create a transseptal portal for complete synovectomy in a patient with rheumatoid arthritis.

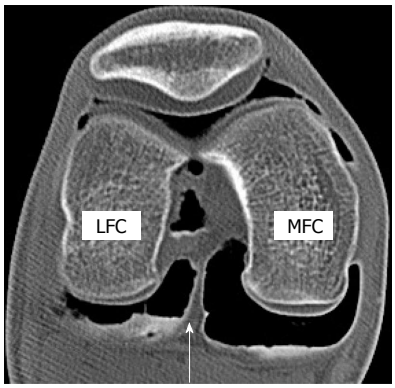

Figure 1 Axial image of double contrast arthrography of the knee. The white arrow indicates a posterior septum that borders the posterior cruciate ligament anteriorly and posterior capsule posteriorly. Note that posteromedial compartment is larger than posterolateral compartment. LFC: Lateral femoral condyle; MFC: Medial femoral condyle.

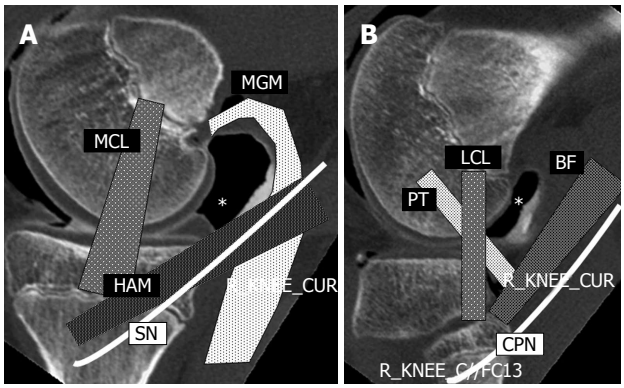

Figure 2 Sagittal images of double contrast arthrography at the levels of the medial (A) and lateral (B) femoral condyle of the knee. Posteromedial (A) and posterolateral (B) sites are indicated by asterisks (*). The portal site is surrounded by important structures. MCL: Medial collateral ligament; MGM: Medial head of the gastrocnemius muscle; HAM: Hamstrings; SN: Saphenous nerve; LCL: Lateral collateral ligament; PT: Popliteus tendon; BF: Biceps femoris; CPN: Common peroneal nerve.

RISKS INVOLVING NERVES AND VESSELS

Special care should be taken to avoid popliteal neurovascular injuries during transseptal portal creation and subsequent arthroscopic surgery *via* this portal. The posterior compartment, which is enlarged upon knee flexion, is enlarged to an even greater extent during arthroscopic surgery under irrigation pressure[34]. The distances between the PCL and popliteal artery at different knee positions were measured in cadavers[34,35,38,41]. A flexion of 90 degrees resulted a greater distance (17-29 mm) between the PCL and popliteal artery than that observed at 30 degrees of flexion. As the popliteal neurovascular bundle lies laterally to the septum, posterolateral capsule injuries should be avoided during surgery[12,37]. Perforation of the septum in the posterolateral to the posteromedial direction, as described by Kim *et al*[15], is a safer technique. Arthroscopic procedures in the posteromedial compartment are easier than those in the posterolateral compartment because the former is 1.5 times larger and bulges a bit more posteriorly under irrigation pressure during surgery relative to the latter[15,37] (Figure 1). Fortunately, popliteal vessel injuries during arthroscopic surgery *via* the transseptal portal have not yet been reported in the literature.

Care should be taken not only to avoid popliteal vessel injury when creating the transseptal portal, but also to avoid neurovascular injury when creating the posteromedial and posterolateral portals[35-38,40,41]. Oglivie-Harris *et al*[13] reported five complications related to the posteromedial portal that involved the saphenous nerve and vein. McGinnis *et al*[40] reported a so-called "anatomical soft spot", which is surrounded by the posterior edge of the medial condyle of the femur, hamstrings, and medial tibial plateau, as a safe area in which to place the posteromedial portal. The posteromedial portal could be created more safely with the knee at a flexion of 90 degrees than in an extended position because the saphenous nerve and vessels move more posteriorly in the former position[36,38,41]. The mean distance between the posteromedial portal site and saphenous nerve is 22-26 mm at a 90-degree flexion[36,38,41]. The distance between the posterolateral portal site and common peroneal nerve at a 90-degree knee flexion is relatively wide: 40 mm as reported by Pace *et al*[41], and 25.4 mm according to Ahn *et al*[21]. When creating a posterolateral portal, palpation of the fibular head as an identifiable landmark is recommended if the posterolateral capsule is not visible in the intercondylar posterior view[38]. However, excess knee flexion (*e.g.,* > 120°) is not acceptable because this reduces the distance between the common peroneal nerve and posterolateral portal to a greater extent[36].

OUR TECHNIQUE

In our method, the patient is placed under spinal or general anesthesia and the knee is flexed beyond 90 degrees on the operating table using a footrest and lateral post. As a precaution, a tourniquet is applied but not inflated. No arthropump is used. The procedure begins with the creation of the posteromedial and posterolateral portals through the anterior two portals according to the approach reported by Schreiber[9], although our method uses a 30-degree rather than 70-degree arthroscope. The arthroscope is introduced into the posteromedial compartment through the intercondylar notch from the anterolateral portal. If osteophytes block the advance of the arthroscope through the intercondylar notch, knee extension facilitates the advance to the posteromedial compartment. A 23-gauge spinal needle is subsequently inserted just behind the posterior medial condyle and 5 mm above the tibial articular surface under guidance from a cutaneous trans-illumination arthroscopic light, as described by Schreiber[9] (Figure 3A). If a condition such as obesity prevents identification of the posterior

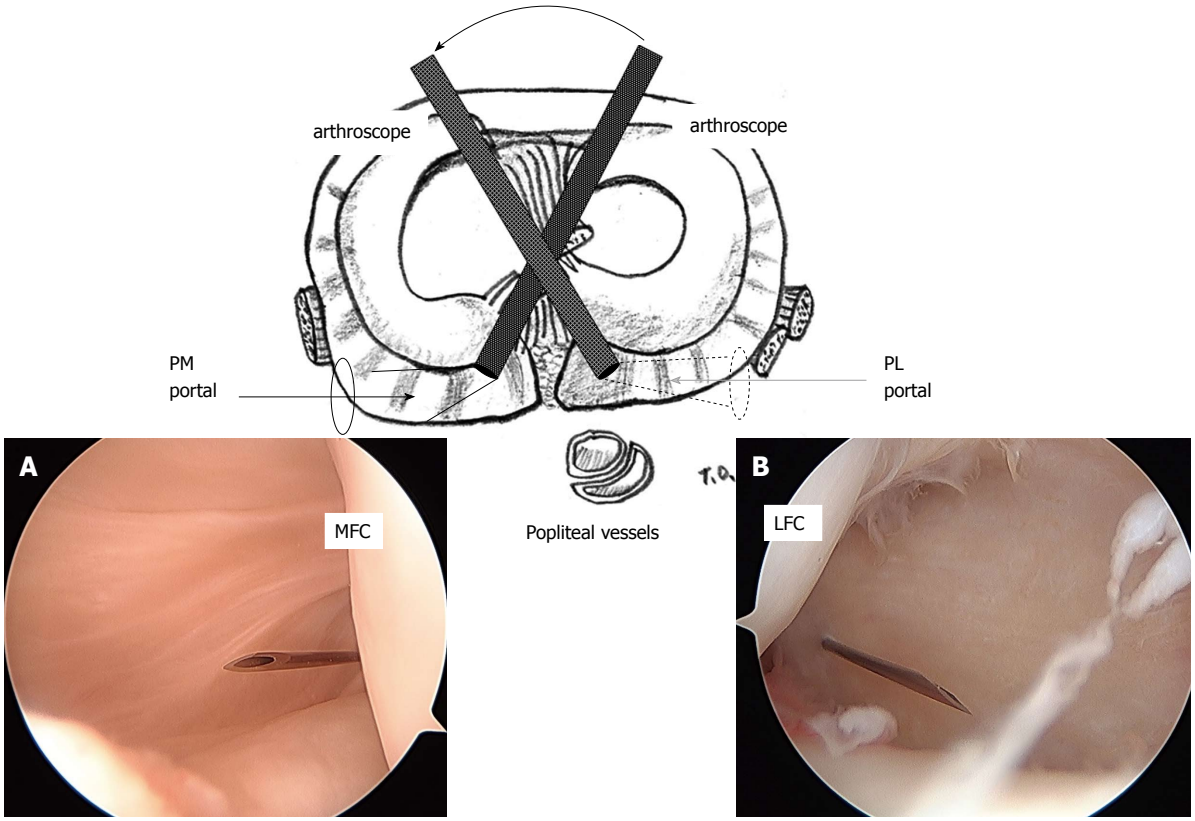

Figure 3 Arthroscopic view of the posteromedial (A) and posterolateral (B) compartment through the intercondylar notch from the anterolateral (A) and anteromedial (B) portals. A 23-gauge spinal needle is inserted just posterior to the medial (A) and lateral (B) femoral condyle at 5 mm above the tibial articular surface. PM: Posteromedial; PL: Posterolateral; MFC: Medial femoral condyle; LFC: Lateral femoral condyle. (Permission for reproduction was obtained from Nankodo Co., Ltd.).

edge of the medial femoral condyle, a 23-gauge spinal needle is first inserted to the medial aspect of the femoral condyle first, and the needle insertion site is then moved posteriorly to identify the posterior edge of the medial femoral condyle. The cutaneous trans-illumination arthroscopic guide helps to avoid injuries of the saphenous nerve and adjacent vein[9]. The entry point skin and capsule are incised with a No. 11 knife just anterior to and along with the 23-gauge needle. The posteromedial portal opening is subsequently maintained with a hemostat. Next, an arthroscope is introduced into the posterolateral compartment through the intercondylar notch from the anteromedial portal. A posterolateral portal is then created in the same manner as the posteromedial portal, using a 23-gauge spinal needle to determine the posterolateral portal site (Figure 3B). Palpation of the common peroneal nerve and fibular head may help to avoid common peroneal nerve injuries. Next, a switching rod with a sheath is inserted through the posterolateral portal to the septum. The camera head of the 30-degree arthroscope is turned to the septum so the operator can confirm that the tip of the rod is attached to the septum (Figure 4). The rod is then removed while the sheath is kept in place. The sheath is pushed into the septum, and the arthroscope is inserted into the posteromedial portal. While maintaining a view of the medial side of the septum using the arthroscope introduced through the posteromedial portal, 1.5-mm (Figure 5A) and 3.0-mm Kirschner wires (Figure 5B) are sequentially pushed to the septum from the posterolateral portal through the sheath while in close contact with the posterior femoral condyle, after which the septum is perforated. The sheath is expected to protect the posterolateral capsule. The Kirschner wires are pushed several times into the septum to enlarge the initial hole and allow the switching rod to pass easily through the septum (Figure 5C). The switching rod is then inserted from the posterolateral portal to the posteromedial portal *via* the transseptal portal. Once the transseptal portal has been created, the arthroscope and instruments can be easily interchanged through the two posterior portals using the posterior "back and forth" approach described by Louisia *et al*[12] (Figure 6). It is not necessary to remove the septum with a motorized shaver.

OUR EXPERIENCE OF THR TECHNIQUE

Using our procedure, we performed arthroscopic surgery for lesions in the posterior compartments of 161 knees between December 2006 and March 2015 (Figure 7). Some of these cases were reported elsewhere to demonstrate the use of the transseptal portal[42-47]. The arthroscopic procedures conducted using our

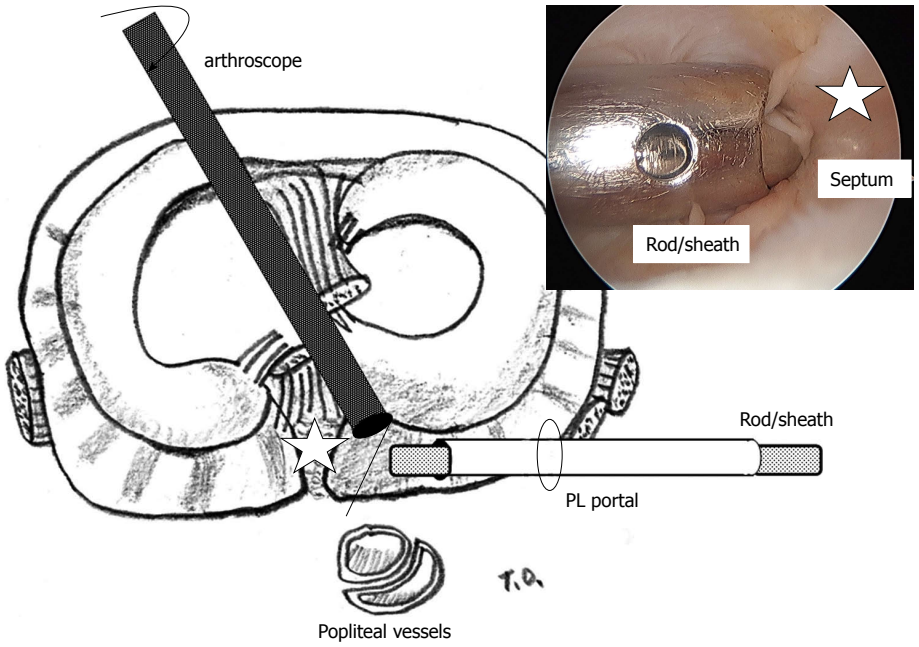

Figure 4 Rod with a sheath is inserted from the posterolateral portal. The camera head of the 30-degree arthroscope is turned toward the septum so that the operator can confirm attachment of the tip of the rod to the septum (white star). PL: Posterolateral. (Permission for reproduction was obtained from Nankodo Co., Ltd.).

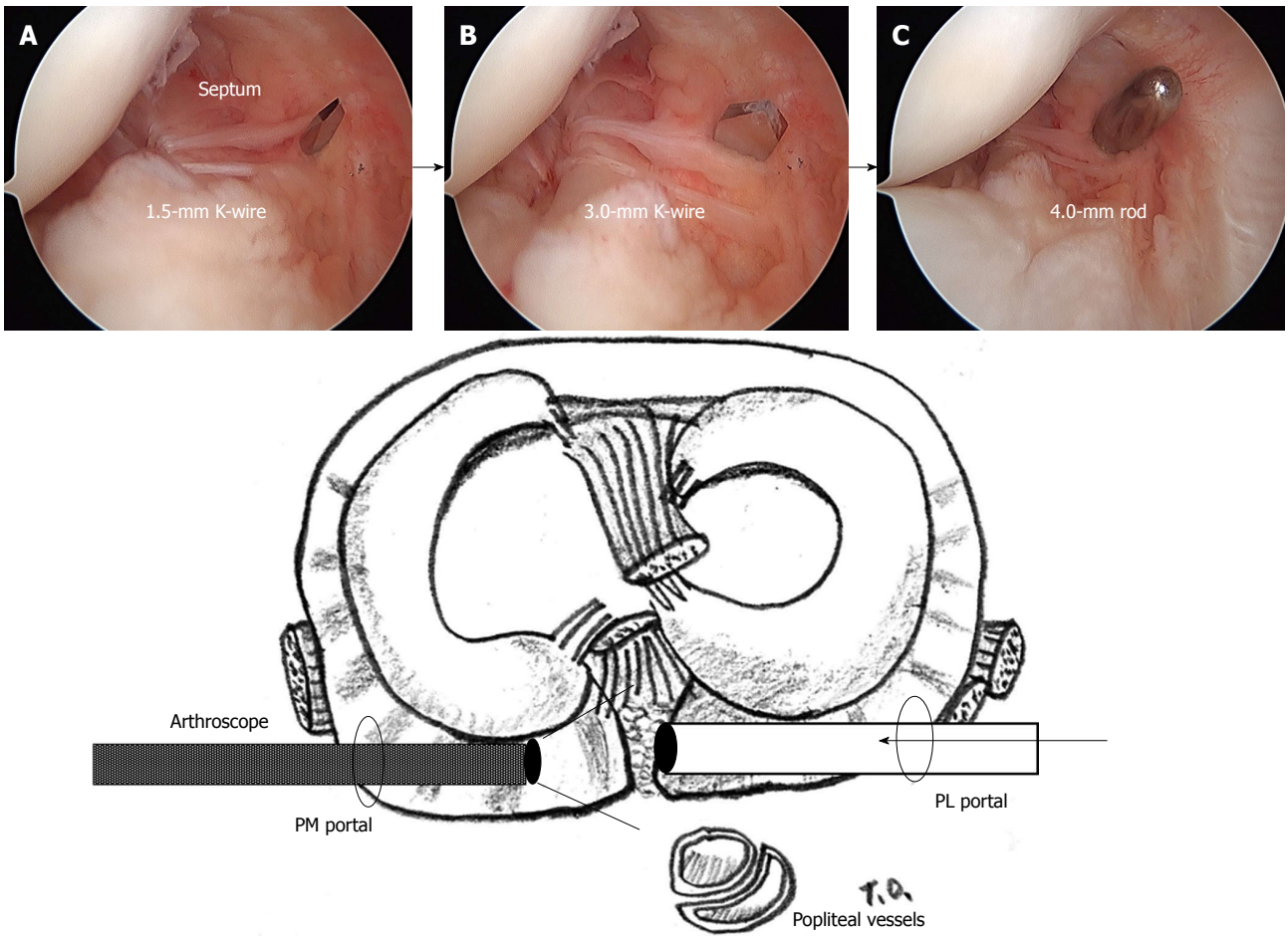

Figure 5 Arthroscopic views from the posteromedial portal. While maintaining a view of the medial side of the septum using an arthroscope introduced through the posteromedial portal, 1.5-mm (A) and 3.0-mm Kirschner wires (B) are pushed sequentially to the septum through the sheath from the posterolateral portal, finally, a 4.0-mm switching rod is passed through the septum (C). PM: Posteromedial; PL: Posterolateral. (Permission for reproduction was obtained from Nankodo Co., Ltd.).

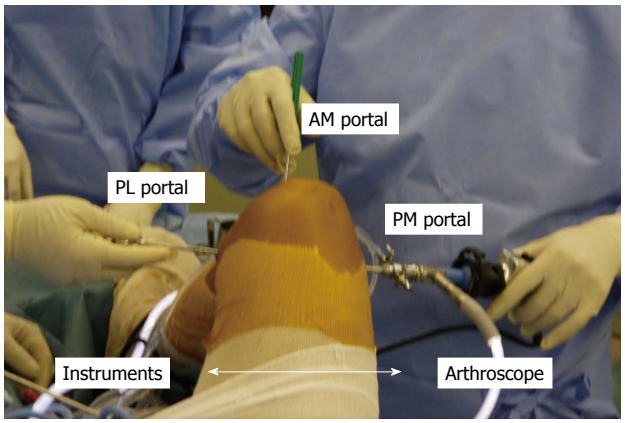

Figure 6 Image taken during an operation involving the posterior transseptal portal. One of the posterior two portals is used as a viewing portal; the other is used as a working portal. Anterior portals can be also used as working portals. PM: Posteromedial; PL: Posterolateral; AM: Anteromedial.

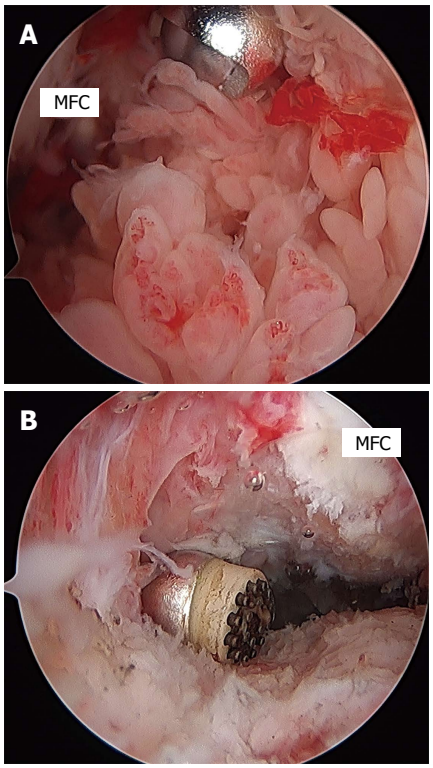

Figure 7 Arthroscopic views of the posterior compartment of the knee in a patient with rheumatoid arthritis. The posteromedial compartment was filled with synovial villi prior to synovectomy. A shaver is introduced from the posterolateral portal through the transseptal portal (A). An arthroscopic view from the posterolateral portal through the transseptal portal after synovectomy (B). A radiofrequency device is introduced from the posteromedial portal. MFC: Medial femoral condyle.

established transseptal portal technique are listed in Table 1. Postoperative complications were encountered in four knees (2.5%), including superficial infection of the posteromedial portal in two knees, subcutaneous hematoma in one knee, and deep infection of the posterolateral portal in one knee. Treatment for the latter case required open debridement of the affected knee. No popliteal neurovascular, peroneal nerve, or saphenous nerve injuries or postoperative deep vein thromboses occurred in any knee during these operations.

Table 1 List of procedures using our transseptal portal technique

Procedure	*n*
Synovectomy	57
Meniscal resection	20
Thermal shrinkage	1
Resection of PCL ganglion	1
Meniscal cyst decompression	1
Popliteal cyst decompression	53
Repair of PCL avulsion fracture	5
Free body resection	5
Repair of the posterior horn of the medial meniscus	5
PCL reconstruction	2
Probing only	11

PCL: Posterior cruciate ligament.

ADVANTAGES OF OUR TECHNIQUE

We have modified the procedures reported in previous papers[10-12,15] as follows. First, the knee is flexed beyond 90 degrees on the operating table, with a footrest placed at the heel, so that the popliteal vessels move posteriorly. Flexion beyond 90° is better achieved when the lower leg is not suspended from the side of the table. Moreover, the operator can work freely when the lower leg is on the operating table, as this provides more available space for working around the knee (Figure 6). Second, we perforated the septum while protecting the posterolateral capsule with a sheath to avoid popliteal vessel injury, as a popliteal neurovascular bundle is located just lateral to the septum (Figure 4). Finally, septum perforation using only a rod or blunt obturator might be difficult and could confer the risk of posterior rod or blunt obturator slippage, as the septum is very elastic and easily stretched. It is therefore safer to perforate the septum initially with a 1.5-mm Kirschner wire to determine the proper placement, followed by a 3.0 mm Kirschner wire to enlarge the hole and subsequent switching rod placement, rather than rod placement alone (Figure 5). However, the operator should ensure that the tip of the Kirschner wire is properly positioned just behind the PCL and is not directed towards the posterior capsule. It is essential that the operators use an arthroscope introduced through the opposite portal to maintain direct visibility of the tip of the Kirschner wire or the switching rod as it passes through the perforated septum.

CONCLUSION

An arthroscopic approach *via* a transseptal portal for posterior lesions of the knee confers several advantages upon patients and operators, including less invasive technique compared to the open surgery for access to

the back of the knee. However, the risk of neurovascular injuries should be considered. It is important for operators to understand the anatomy around the posterior three portals.

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ORIGINAL ARTICLE

Retrospective Study

Cost analysis and outcomes of simple elbow dislocations

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Author contributions: Panteli M, Kanakaris NK and Giannoudis PV designed the research; Panteli M, Pountos I and Tosounidis TH performed the research; Panteli M, Pountos I and Tosounidis TH analysed the data; Panteli M, Pountos I and Giannoudis PV wrote the paper.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at michalispanteli@gmail.com. Consent for identifiable data sharing was not obtained but the presented data are anonymized and risk of identification is low. No additional data are available.

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Abstract

AIM: To evaluate the management, clinical outcome and cost implications of three different treatment regimes for simple elbow dislocations.

METHODS: Following institutional board approval, we performed a retrospective review of all consecutive patients treated for simple elbow dislocations in a Level Ⅰ trauma centre between January 2008 and December 2010. Based on the length of elbow immobilisation (LOI), patients were divided in three groups (Group I, < 2 wk; Group Ⅱ, 2-3 wk; and Group Ⅲ, > 3 wk). Outcome was considered satisfactory when a patient could achieve a pain-free range of motion ≥ 100° (from 30° to 130°). The associated direct medical costs for the treatment of each patient were then calculated and analysed.

RESULTS: We identified 80 patients who met the inclusion criteria. Due to loss to follow up, 13 patients were excluded from further analysis, leaving 67 patients for the final analysis. The mean LOI was 14 d (median 15 d; range 3-43 d) with a mean duration of hospital engagement of 67 d (median 57 d; range 10-351 d). Group Ⅲ (prolonged immobilisation) had a statistically significant worse outcome in comparison to Group Ⅰ and Ⅱ (P = 0.04 and P = 0.01 respectively); however, there was no significant difference in the outcome between groups Ⅰ and Ⅱ (P = 0.30). No statistically significant

difference in the direct medical costs between the groups was identified.

CONCLUSION: The length of elbow immobilization doesn't influence the medical cost; however immobilisation longer than three weeks is associated with persistent stiffness and a less satisfactory clinical outcome.

Key words: Elbow dislocations; Simple; Management; Outcome; Cost analysis

Core tip: Our study demonstrates that prolonged immobilisation following simple elbow dislocations may lead to detrimental effects. We therefore stress the need for increased vigilance to the duration of immobilisation and that every effort should be taken to ensure that without associated fractures, the elbow should not be immobilised for more than three weeks. In addition, our study supports that the direct medical cost from treating these injuries may be substantial regardless of the type of treatment, and this should be known both by commissioners and providers of health care.

Panteli M, Pountos I, Kanakaris NK, Tosounidis TH, Giannoudis PV. Cost analysis and outcomes of simple elbow dislocations. *World J Orthop* 2015; 6(7): 513-520 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i7/513.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i7.513

INTRODUCTION

Elbow dislocations represent the second most common dislocation in the adult population following shoulder dislocation, and the most common type of dislocation in the paediatric population[1]. In the United States population alone, the incidence of elbow dislocation has been reported as high as 5.21 per 100000 habitants, with males 10-19 years of age, having the highest risk for dislocation[2]. Seventeen per cent of these dislocations are associated with fractures[3], with nearly half of them occurring in sports[2]. Falls represent the primary mechanism of injury being responsible for 56.5% of elbow dislocations overall[2].

The most commonly used classification system of elbow dislocation is based on the presence of concomitant fractures in the region. Simple dislocations are characterised by the absence of fractures (except from avulsion fractures)[4], whereas complex dislocations are those accompanied by fractures[5,6]. The terrible triad describes a complex posterior dislocation with an intra-articular fracture of the radial head and of the coronoid process[6]. Elbow dislocations are also defined by the direction and topography of the dislocated parts[7].

To date, there is no general consensus regarding the protocol of management of simple elbow dislocations with different protocols being suggested. These include surgical treatment with exploration and repair of the joint ligaments; non-surgical treatment with immobilisation of the elbow joint (varying from few days to more than 3 wk)[5,8-14]; and non-surgical, functional treatment with just a short period of immobilisation of only a few days[5,9-13]. The primary functional outcome has been defined as achieving early active motion within the limits of pain with or without the use of a sling or a hinged brace[5,10].

Numerous complications of simple elbow dislocation have been described including neurovascular injury, joint instability, heterotopic ossification, occult distal radio-ulnar joint disruption and post-traumatic stiffness, most commonly defined as an arc of elbow motion less than 100°[3,5,15-18]. Biomechanical studies have shown that arcs of motion between 30° to 130° are required for most daily activities[19] and that a loss of 50° in the arc of motion, can cause up to an 80% loss of function[18].

Limited information is available with regards to the cost of the management of simple elbow dislocations. To the best of our knowledge, direct medical cost pertaining to National Health Service (NHS) including hospitalisation, imaging, outpatient follow-ups, need for physiotherapy and medication, have not been previously reported.

We hypothesized that prolonged elbow immobilisation (longer than three weeks) yields inferior outcomes. Thereafter, the purpose of this study was to determine the optimal length of elbow immobilisation (LOI) following a simple elbow dislocation. Direct medical costs were also determined.

MATERIALS AND METHODS

Following institutional board approval (Leeds Teaching Hospitals Institutional Review Board; ID3050; 23/11/2010), we performed a retrospective review of all consecutive patients treated for elbow dislocations in a large United Kingdom Level I trauma centre between January 2008 and December 2010. Inclusion criteria comprised of skeletally mature patients with clinically and/or radiologically confirmed acute "simple" elbow dislocations, having at least one year of follow-up. "Simple" dislocation were defined as dislocations that involved soft tissue disruption (Figure 1)[4]. Exclusion criteria included: associated fractures, with the exception of avulsion fractures ("complex" elbow dislocations; Figure 2); open wounds requiring debridement in the operating room; and patients with inadequate follow-up, defined as patients not attending three consecutive appointments at the outpatients clinic, or being followed up by another institution.

All patients were managed at the emergency department according to a standardised protocol. After a careful clinical and radiological evaluation, reduction was attempted under analgesia and conscious sedation or administration of Nitrous Oxide and Oxygen (Entonox®). If the dislocation was obvious and access to radiography

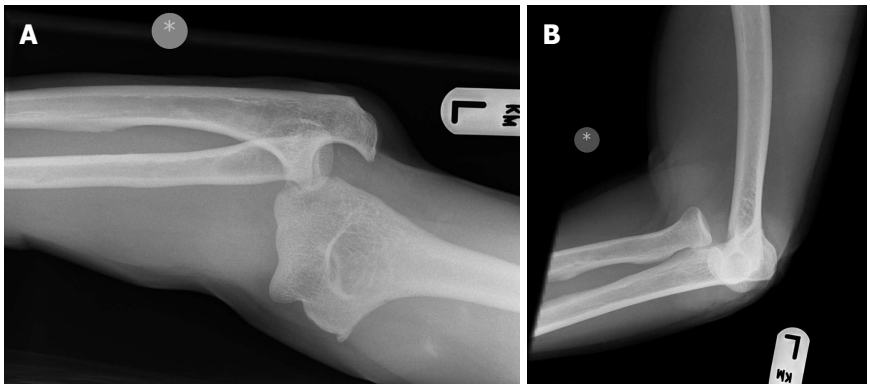

Figure 1 Simple elbow dislocation. A: Anteroposterior view; B: Lateral view.

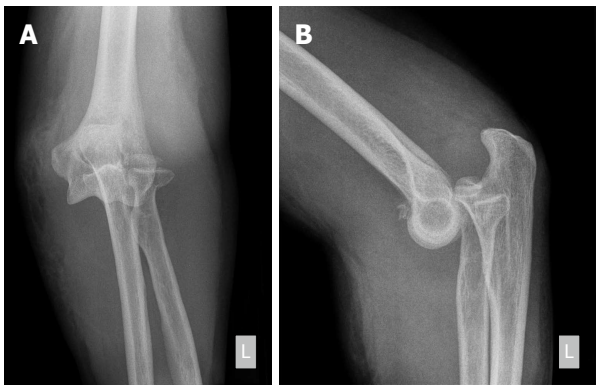

Figure 2 Complex elbow dislocation. A: Anteroposterior view; B: Lateral view.

was expected to significantly prolong time to reduction, reduction was performed before radiographs were obtained in order to relief the pressure to the soft tissues, thus reducing the risk of neurovascular injury. In case of failed closed reduction, the elbow was reduced in theatres under general anaesthetic. Once reduction was achieved, the stability of the joint and the neurovascular status were checked and documented, and the elbow was immobilised with a backslap and a collar and cuff. Finally, the patients were discharged and a follow-up appointment was arranged, or admitted where indicated. Further imaging [computed tomography (CT) and/or magnetic resonance imaging (MRI)], was performed only in patients with high clinical suspicion of occult fractures and/or complex injury patterns.

Patient demographics including age, gender, mechanism of injury, side and type of dislocation[20], method of treatment, time to mobilisation, clinical outcome, complications, secondary procedures, outpatient reviews, need for physiotherapy and time of discharge from the clinic were recorded.

The decision for the LOI and the need for formal physiotherapy were guided purely by the surgeon's preference and indirectly by the compliance of patients to attend their allocated appointments. Based on the LOI, patients were divided into three groups (Group Ⅰ, < 2 wk of immobilisation; Group Ⅱ, 2-3 wk of immobilisation; and Group Ⅲ, > 3 wk of immobilisation). The major cause of the prolonged LOI of patients in Group Ⅲ was the lack of adherence to their scheduled outpatient trauma clinic appointments. The criteria for discharge from physiotherapy were the ability to perform daily living activities, an achievement of satisfactory arc of elbow motion (30° to 130°), or the reach to a plateau in range of motion despite continuing physiotherapy and home exercises. In terms of the clinical outcome, a good/satisfactory result was defined as the achievement of a range of motion $\geqslant$ 100° (from 30° to 130°)[19]. If a residual deficit in elbow motion was evident or if the patient reported any significant post-traumatic stiffness, outcome was considered poor/unsatisfactory and the patient was referred back to the treating surgeon.

Cost estimation and analysis methods

The associated direct medical costs for the treatment of each patient were calculated and analysed. The costs represent the actual treatment that each patient received, including admission costs where applicable, hospital stay, investigations, outpatient attendances and physiotherapy sessions. The cost of each individual entry was obtained from the appropriate department (Trauma and Orthopaedics finance department and inter-provider tariff list), (Table 1). Costs were given in GPB (£).

Statistical analysis

This was undertaken using IBM SPSS Statistics version 22.0 software (SPSS inc., Chicago, IL). Continuous data were analysed for differences using a two-tailed independent samples *t*-test, whereas for parametric data a χ^2 was used to examine associations between variables. Yates' correction was applied where appropriate and confidence intervals were calculated when necessary. A *P*-value < 0.05 was considered significant.

RESULTS

Eighty consecutive patients met the inclusion criteria and were included in the study. The mean age was 36.49 years (median: 32 years; SD 15.68 years).

Table 1 Costs of treatment, investigations and support services

Category	Item	Cost (£)
Hospital Services	A and E attendance leading to admission	95
	A and E attendance not leading to admission	76
	Minor Injuries leading to admission	34
	Minor Injuries not leading to admission	42
	Walk in centre leading to admission	31
	Walk in centre not leading to admission	34
	Theatre session (including recovery)	880
Hospitalisation/day	Acute Care Adult wards admission per day	269
Follow-up	Outpatient clinic (new)	116
	Outpatient clinic (follow-up)	93
Support Services	Physiotherapy/session in clinic	34
Radiology	X-ray	59.5
	Computed tomography scan	225
	Magnetic resonance imagingscan	280
	Radiographer per twenty minutes clinic visit (includes A and E)	13

Table 2 Demographic details of patients in each group

	Group Ⅰ	Group Ⅱ	Group Ⅲ
No. of patients	26	27	14
Age (yr)	34.80 ± 15.04	41.36 ± 17.84	35.41 ± 12.23
	Median: 30	Median: 37	Median: 37
Male/female	18/8	17/10	8/6
Right/left	12/14	9/18	7/7
No. of patients admitted	5 (19%)	3 (11%)	3 (21%)
LOS (h)	29.59 ± 19.41	37.42 ± 36.28	33.07 ± 15.03
	Range: 19-68	Range: 15-79	Range: 17-46
Patients referred to physiotherapy	21	20	11
Patients seen by physiotherapy	14	17	5
No. of physiotherapy sessions	2.43 ± 0.76	2.76 ± 1.60	2.60 ± 1.34
	Median: 2	Median: 2	Median: 2
No. of clinic appointments	3.31 ± 1.72	3.15 ± 1.10	3.21 ± 1.48
	Median: 3	Median: 3	Median: 3
Time of follow-up (d)	59.00 ± 38.75	67.32 ± 62.62	81.66 ± 58.80
	Median: 53	Median: 58	Median: 62
Time to mobilisation (d)	5.82 ± 3.57	16.69 ± 4.32	24.37 ± 8.97
	Median: 6	Median: 16	Median: 23
Good outcome	21 patients	23 patients	6 patients

Admitted: Patients had an overnight stay in hospital. LOS: Length of stay; Follow-up: From time of injury to time of discharge or referral to upper limb specialist.

Fifty-one patients in the cohort were male (63.8%), and 33 dislocations (41.3%) involved the right side. The most common mechanism of injury was fall to an outstretched hand from a standing height (30 patients, 37.5%), followed by sport related injuries (26 patients, 32.5%). Common sports associated with the elbow injuries sustained included: rugby (eight patients), football (six patients), skateboarding (three patients), biking and kickboxing (two patients respectively). The rest of the patients were involved in different sports (acrobatics, cricket, rollerblading, rounders and ice-skating). Eighteen patients (22.5%) sustained their injuries following a fall from height, three patients (3.8%) were assaulted and three patients (3.8%) were involved in road traffic accidents.

Posterior or posterior lateral dislocations were the most frequent presentations (63 patients, 78.8%). Medial or posterior medial dislocation was evident in six patients (7.5%), whereas lateral dislocation was diagnosed in three patients (3.8%). In eight patients (10.0%) the direction of dislocation was not documented due to the fact that the reduction of the dislocated joint was performed as an emergency procedure with no pre-reduction radiographic imaging being available.

Thirteen patients had inadequate follow-up (16.3%) and were therefore excluded from the final analysis of the study, leaving 67 patients who formed the study cohort. Group Ⅰ consisted of 26 patients (median LOI 6 d; range 3-11 d), Group Ⅱ of 27 patients (median LOI 16 d; range 15-21 d) and Group Ⅲ of 14 patients (median LOI 23 d; range 22-43 d). The three groups were comparable in terms of age, gender, side, type of dislocation, need for hospital admission and length of follow-up. Table 2 summarises the demographic details

Table 3 Comparisons of the three groups

Variable	Group Ⅰ *vs* Group Ⅱ		Group Ⅰ *vs* Group Ⅲ		Group Ⅱ *vs* Group Ⅲ		Test
	P	95%CI	*P*	95%CI	*P*	95%CI	
Gender	0.630	0-3.841	0.677[1]	0-3.841	0.717	0-3.841	χ^2 test
Age	0.155	-15.66-2.56	0.898	-10.09-8.88	0.271	-4.83-16.73	*t*-test
Side	0.340	0-3.841	0.816	0-3.841	0.300	0-3.841	χ^2 test
Admission	0.659[1]	0-3.841	0.868[1]	0-3.841	0.674[1]	0-3.841	χ^2 test
Follow-up	0.541	-37.69-20.02	0.143	-54.32-8.17	0.485	-55.13-26.65	*t*-test
Outcome	0.669	0-3.841	0.037[1]	0-3.841	0.014[1]	0-3.841	χ^2 test
Medical Costs	0.200	-98.62-460.17	0.401	-215.08-526.57	0.884	-368.78-318.72	*t*-test

[1]Yates' correction was employed. The results in bold indicate statistical significance (level of 0.05). LOI: Length of immobilisation.

Table 4 Cost analysis per patient

	Group Ⅰ	Group Ⅱ	Group Ⅲ
No. of X-rays	8.38 ± 4.57 Median: 7	6.48 ± 2.53 Median: 6	7.93 ± 4.58 Median: 7
CT scans	2 patients	1 patient	1 patient
MRI scans	1 patient	-	-
Need for theatre reduction	2 patients	2 patients	-

CT: Computed tomography; MRI: Magnetic resonance imaging.

and the treatment course according to LOI.

Four patients (6.0%) underwent a closed reduction of the dislocation under general anaesthesia (two from Group Ⅰ and two from Group Ⅱ). Ten patients (14.9%) were admitted for social reasons. No statistical significant difference was recorded regarding the length of follow-up in the three groups (Table 3). Patients from Group Ⅰ and Group Ⅱ had a significantly better outcome compared to Group Ⅲ, but we did not detect any difference between the first two groups (Table 3). No patient re-attended the emergency department of our institution with a recurrent dislocation within 12 mo from the initial injury.

Patients in Group Ⅲ were more likely not to attend their scheduled physiotherapy appointments compared to Groups Ⅰ and Ⅱ (P = 0.23 and P = 0.02 respectively). Though, there was no difference in the number of patients referred to physiotherapy by the treading surgeon, or the number of physiotherapy sessions attended by the patients in all groups.

With regards to the outcome, 17 patients (25.4%) were recorded as having an unsatisfactory outcome (Group Ⅰ: 5 patients; Group Ⅱ: 4 patients; Group Ⅲ: 8 patients). Two patients suffered from post-traumatic neurapraxia (median nerve: one patient in Group Ⅱ; ulnar nerve: one patient in Group Ⅰ), which has however improved during the follow-up period.

The direct medical cost per patient according to treatment used was in Group Ⅰ £1184, in Group Ⅱ £1005, and in Group Ⅲ and £1068. The costs were then further broken down to the main components that contributed to the total cost (Tables 4 and 5). Analysis of the total costs per patient failed to indicate any statistically significant difference between the three groups.

DISCUSSION

There is insufficient evidence in the current literature from well-designed randomised controlled trials to determine the best method of treatment of simple elbow dislocations in adults. Historically, these were treated with prolonged casting followed up by physiotherapy[5]. It has also been suggested by several studies that the reduction should be followed-up by an up to 2-wk period of immobilisation[5,12]. Recent evidence however, supports the early active mobilisation within two weeks post-injury and as soon as pain allows[1,13,16,21]. The final functional outcomes obtained with early mobilisation are reported to be significantly better when compared to immobilisation[5,16,22,23]. The results of the present study are in agreement with the above findings. In particular, the final outcome of the patients managed with immobilisation not exceeding three weeks, was significantly better compared to the outcome of patients managed with prolonged immobilisation (more than three weeks). Of note is the observation that immobilisation for less that two weeks had the same outcome compared to immobilisation for 2-3 wk.

The characteristics of the patients sustaining simple elbow dislocations were also found to be comparable to the international literature. Taylor *et al*[4] reported that more than 90% of simple elbow dislocations occur in a posterior or posterior lateral direction, compared to 87.5% in the herein study. Anakwe *et al*[24] suggested that the epidemiology of simple elbow dislocation is different between men and women, particularly with respect to the mechanism of injury, and that it correlated with patient's age. We have also found that the predominant gender in this group of injuries is young male patients, who are also more likely to have a sports related injury. Stoneback *et al*[2] separated sports activities by gender, reporting that males sustained elbow dislocations most often in association with football, wrestling, and basketball and females in gymnastics and skating activities. Even though an association between type of sports and gender was obvious with men being involved in sports such as rugby and football, the relatively small number of patients in our series did not allow us to draw any robust conclusions.

Table 5 Costs of treatment (£) analysis per patient

Treatment description	Group Ⅰ	Group Ⅱ	Group Ⅲ
Hospital[1]	219.77 ± 318.27	197.62 ± 398.65	174.79 ± 204.79
	Median: 76.00	Median: 76.00	Median: 76.00
Radiology	590.12 ± 334.96	424.96 ± 156.73	539.36 ± 350.21
	Median: 528.00	Median: 396.00	Median: 429.00
Outpatients	330.62 ± 158.96	315.78 ± 102.21	321.93 ± 137.35
	Median: 302.00	Median: 302.00	Median: 203.00
Physiotherapy	44.46 ± 44.98	59.19 ± 62.97	31.57 ± 8.97
	Median: 68.00	Median: 68.00	Median: 0
Total cost of treatment	1184.96 ± 534.82	1004.19 ± 477.67	1067.64 ± 641.91
	Median: 1166.50	Median: 867.00	Median: 842.00

[1]Hospital costs include emergency department's costs, admission costs and theatre costs. Any further costs after the patient's referral to an upper limb specialist were not included in the cost analysis.

Previous research suggests that patients complete their recovery and return to normal activity by six months after such an injury[24]. We followed-up our patients for a longer period and advised them to contact the treating consultant in case of any concern. We therefore believe that the duration of follow-up in our study allowed us to assess accurately the final outcome in terms of range of motion of the affected elbow joint. The rates of residual pain and stiffness with early elbow motion have been reported to be 62% and 56% respectively, even though the functional outcome and patient reported satisfaction were favourable[23,24]. Residual pain restricting the function of the elbow did not seem to be of significant concern in our cohort, in contrast to significant stiffness limiting daily living activities that was reported as high as 25%[23,24]. Functional instability was less common involving four patients (6%) compared to 8% that was previously reported in the literature[24].

No re-dislocation or late instability was noted in the patients who were treated with early mobilisation. Similar studies in the literature agree with our findings and suggest that early mobilisation does not contribute to residual instability[5,12,13,20]. Other complications seen at the final follow-up included complaints of increasing pain during physical activities, which we believe could be related to the residual joint stiffness and stressing of the joint. None of our patients with a simple elbow dislocation was treated with an early surgical reconstruction. Noteworthy, the existing evidence does not suggest that surgical repair of elbow ligaments for simple elbow dislocation improves long-term function[4,20].

The current literature is limited in terms of the health economics of treating simple elbow dislocations. To the best of our knowledge there is only one study by Yang *et al*[3] reporting on the direct medical costs of these injuries. More specifically, the authors published a retrospective series of 428 simple and complex elbow dislocations treated in Taiwan, calculating the direct medical cost to be $504 per patient (included inpatient expenditure by admission and ambulatory care expenditure by visit)[3]. This is much lower compared to our estimated costs (average of £1088). We believe what accounts for this divergence are the different costs in a completely different national health care system, as well as the former timing at which these costs were obtained (between 2000 and 2005).

Even though one would expect that the direct medical costs of patients with prolonged immobilisation are higher because of higher incidence of post-traumatic stiffness and associated complications[5,16,22,23], this was not observed in our cohort. Possible explanations of this finding may include: two patients in Group Ⅰ and two patients in Group Ⅱ required a reduction in theatre compared to none in Group Ⅲ, thus increasing the overall costs; patients in Group Ⅲ were more likely not to attend their physiotherapy sessions, therefore reducing their overall costs. At the same time, the relatively small number of patients included in our study increases the risk of a type Ⅱ error.

Limitations of this study include its retrospective nature and the small number of subjects, meaning that there is a risk of a type Ⅱ statistical error. Yet, our findings are in line with the literature, thus providing sufficient evidence to support changes even with comparatively low numbers. Another limitation is the fact that elbow "stiffness" and loss of function was defined as an arc of elbow motion less than 100°[3,5,15-19]. Nevertheless, recent studies report that the functional elbow range of motion that is necessary for activities of daily living may actually be greater than this[25]. We also believe that this study could have been further enhanced by the collection of patient reported outcome measures, which probably reflects better on the loss of function from a patient's perspective. On the positive side, this study was performed in a level Ⅰ Trauma Centre, with no attempt for patient selection. Another improvement of the herein study was the inclusion of the associated costs for each group, a parameter that has not been previously adequately reported.

This study clearly underlines the fact that prolonged immobilization adversely affects the clinical outcome following a simple elbow dislocation. Despite the limita-

tions and the retrospective nature of this study, the small number of patients included, and the 16.3% of lost to follow-up, we are confident that this cohort is representative of the actual clinical reality of a large United Kingdom hospital. In addition, this study depicts that the financial cost of treating elbow dislocations to the NHS may be substantial, regardless of the type of treatment. However, for the correct evaluation of each treatment modality a full prospective economic evaluation is desirable. This should include not only the direct medical and non-medical costs, but also the indirect costs associated with the duration of therapy, the final functional outcome, the loss of productivity and any disability payments of each patient[26].

The findings of our study stress the need for increased vigilance to the duration of immobilisation following simple elbow dislocations. Treating physicians (either orthopaedic surgeons or general practitioners) should be aware of the detrimental effects of prolonged immobilisation, and every effort should be taken to ensure that without associated fractures the elbow is not immobilised for more than three weeks. The direct medical cost from treating these injuries is substantial, and this should be known to both commissioners and providers of health care.

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COMMENTS

Background

Elbow dislocations represent the second most common dislocation in the adult population following shoulder dislocation, and the most common type of dislocation in the paediatric population. To date, there is no general consensus regarding the protocol of management of simple elbow dislocations with different protocols being suggested. In this study the authors determined the optimal length of elbow immobilisation following a simple elbow dislocation, along with their associated direct medical costs.

Research frontiers

The duration of immobilisation following simple elbow dislocations is directly associated to the final functional outcome. Treating physicians (either orthopaedic surgeons or general practitioners) should be aware of the optimal immobilisation period required and of the associated direct medical costs for treating these injuries.

Innovations and breakthroughs

This study clearly underlines the fact that immobilization longer than three weeks adversely affects the clinical outcome following a simple elbow dislocation. In addition, the financial cost of treating elbow dislocations to the NHS may be substantial, regardless of the type of treatment.

Applications

An increased vigilance to the duration of immobilisation is required when treating these injuries, ensuring that without associated fractures, the elbow should not be immobilised for more than three weeks. Additional prospective studies evaluating the direct medical and non-medical costs, as well as the indirect associated costs could shed more light to the optimal treatment method.

Terminology

"Simple" elbow dislocations include the dislocations that involve soft tissue disruption without any associated fractures, with the exception of avulsion fractures.

Peer-review

Very well done and useful study, which contributes to existing literature on this subject and clearly tells us that an unnecessary and prolonged immobilization is not only harmful to the patient but the hospital economics.

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ORIGINAL ARTICLE

Prospective Study

Can tranexamic acid change preoperative anemia management during total joint arthroplasty?

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Author contributions: Phan DL performed the data collection, statistical analysis, and wrote the paper; Rinehart JB designed the research study and revised the paper; Schwarzkopf R designed the research study and revised the paper.

Institutional review board statement: The study was reviewed and approved by the UCI Institutional Review Board.

Clinical trial registration statement: Because all study participants received the same treatment, the project was not registered as a clinical trial.

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Data sharing statement: All technical data is available from the corresponding author at phandl@uci.edu. Consent was not obtained, but the presented data is anonymized and the risk of identification is low.

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Abstract

AIM: To investigate the postoperative transfusion and complication rates of anemic and nonanemic total joint arthroplasty patients given tranexamic acid (TXA).

METHODS: A cross-sectional prospective study was conducted of primary hip and knee arthroplasty cases performed from 11/2012 to 6/2014. Exclusion criteria included revision arthroplasty, bilateral arthroplasty, acute arthroplasty after fracture, and contraindication to TXA. Patients were screened prior to surgery, with anemia was defined as hemoglobin of less than 12 g/dL for females and of less than 13 g/dL for males. Patients were divided into four different groups, based on the type of arthroplasty (total hip or total knee) and hemoglobin status (anemic or nonanemic). Intraoperatively, all patients received 2 g of intravenous TXA during surgery. Postoperatively, allogeneic blood transfusion (ABT) was directed by both clinical symptoms

and relative hemoglobin change. Complications were recorded within the first two weeks after surgery and included thromboembolism, infection, and wound breakdown. The differences in transfusion and complication rates, as well as the relative hemoglobin change, were compared between anemic and nonanemic groups.

RESULTS: A total of 232 patients undergoing primary joint arthroplasty were included in the study. For the total hip arthroplasty cohort, 21% (18/84) of patients presented with preoperative anemia. Two patients in the anemic group and two patients in the nonanemic group needed ABTs; this was not significantly different (P = 0.20). One patient in the anemic group presented with a deep venous thromboembolism while no patients in the nonanemic group had an acute complication; this was not significantly different (P = 0.21). For nonanemic patients, the average change in hemoglobin was 2.73 ± 1.17 g/dL. For anemic patients, the average change in hemoglobin was 2.28 ± 0.96 g/dL. Between the two groups, the hemoglobin difference of 0.45 g/dL was not significant (P = 0.13). For the total knee arthroplasty cohort, 18% (26/148) of patients presented with preoperative anemia. No patients in either group required a blood transfusion or had an acute postoperative complication. For nonanemic patients, the average change in hemoglobin was 1.85 ± 0.79 g/dL. For anemic patients, the average change in hemoglobin was 1.09 ± 0.58 g/dL. Between the two groups, the hemoglobin difference of 0.76 g/dL was significant (P < 0.001).

CONCLUSION: TXA administration results in low transfusion and complication rates and may be a useful adjunct for TJA patients with preoperative anemia.

Key words: Total knee replacement; Tranexamic acid; Total hip replacement; Preoperative anemia

Core tip: Patients with preoperative anemia presenting for total joint arthroplasty (TJA) have an increased risk of requiring allogeneic blood transfusion (ABT). Current methods to increase preoperative hemoglobin is expensive, limited in efficacy, and have side effects. In this study, we found that intraoperative tranexamic acid (TXA) safely and effectively decreases blood loss and limits the rate of ABT after TJA for anemic patients. We recommend TXA for all patients without contraindications who have preoperative anemia.

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INTRODUCTION

Approximately 20% of patients presenting for total joint arthroplasty (TJA) have preoperative anemia and are at a relatively higher risk of needing allogeneic blood transfusion (ABT)[1-6]. This rate reflects the overall prevalence of anemia in the general elderly population, defined by the World Health Organization as hemoglobin (Hb) < 12 g/dL in females and < 13 g/dL in males, and can be contributed to by causes such as nutritional deficiency or chronic disease[7,8]. Preoperative and perioperative blood management is of considerable importance for these patients, especially given the influence of postoperative anemia on functional recovery, complications, and outcome[1,2]. Although there have been no large studies examining the effect of preoperative anemia on mortality after TJA, studies in the hip fracture[9,10], cardiac[11], vascular[12], and general surgery[13] patient populations have shown an increase in mortality rates. It is likely that there may be a similar effect with TJA.

Multiple authors have proposed preoperative screening and treatment protocols to limit the potential for perioperative anemia[14-17]. General factors such as patient weight, comorbidities, and nutritional deficiencies should be addressed to optimize hematologic status[18]. Preoperative Hb should be routinely obtained and a thorough analysis performed for moderate to severe levels of anemia to determine the etiology of the disorder[18]. A preoperative Hb of 13 g/dL has historically been held as the gold standard to minimize the rate of symptomatic perioperative anemia[1].

Tranexamic acid (TXA) has gained popularity as an intraoperative adjunct to help decrease blood loss and perioperative anemia. TXA is a lysine analog that competitively inhibits the activation of plasminogen to plasmin, slowing the rate of fibrinolysis[19]. It can be applied intravenously or topically[20] has a short half-life, and preferentially affects fibrinolysis in the surgical field[21]. Although there have been sporadic case reports about side-effects, there have been no large-scale studies that show a significant increase in complications such as symptomatic thromboembolism[22-25]. When compared to other treatments, most specifically erythropoietin, TXA can be cost-effective[26]. The analog has been well documented as efficacious in orthognathic[27], cardiac[28], and spine[29] procedures. Multiple studies have shown a decrease in blood loss and ABT with TXA application for both primary and revision TJA[22-25,30,31]. The effect of TXA on patients presenting with preoperative anemia has been less well examined.

The purpose of this study was to compare rates of transfusion and postoperative complications between anemic and nonanemic patients given TXA who underwent primary total hip arthroplasty (THA) and total knee arthroplasty (TKA). Our hypothesis was that there would be no significant difference in the rates of trans-

Table 1 Patient demographics and outcome

	Anemic THA	Nonanemic THA	Anemic TKA	Nonanemic TKA
Number	18	66	26	122
Gender (M/F)	10/8	33/33	10/16	48/74
Age	63.0 (± 15.6)	60.0 (± 13.8)	68.2 (± 8.6)	67.0 (± 10.2)
Preoperative Hb (g/dL)	11.45 (± 0.82)	13.85 (± 0.92)	11.43 (± 0.72)	13.66 (± 0.94)
Hospital day 1 Hb (g/dL)	9.17 (± 1.26)	11.11 (± 1.35)	10.34 (± 0.91)	11.81 (± 1.09)
Hb change (g/dL)	2.28 (± 0.96)	2.73 (± 1.17)	1.09 (± 0.58)[1]	1.85 (± 0.79)[1]
Transfusions	2	2	0	0
Complications	1	0	0	0

[1]Significant difference in hemoglobin change between anemic TKA and nonanemic TKA patients ($P < 0.001$).
THA: Total hip arthroplasty; TKA: Total knee arthroplasty; Hb: Hemoglobin.

fusion and complications for both groups of patients. If supported, this could lead to changes in preoperative management for anemic TJA patients.

MATERIALS AND METHODS

A prospective cross-sectional study was performed from 11/2012 to 6/2014 at a tertiary university academic institution. Patients undergoing elective primary THA or TKA by the lead author were eligible. Exclusion criteria included revision or bilateral TJA, TJA after hip fracture, or patients with contraindications towards receiving TXA.

Preoperative

Preoperative Hb was measured within 3 wk prior to surgery and patients were classified as anemic *vs* nonanemic based on World Health Organization guidelines (< 12 g/dL in females and < 13 g/dL in males). Patients were not prescribed supplemental treatment, such as iron supplementation or erythropoietin, and were advised to stop blood-thinning medications such aspirin or nonsteroidal anti-inflammatory medications 1 wk prior to surgery.

Intraoperative

All patients received two doses of intravenous TXA in the perioperative period: 1 g prior to incision and 1 g during wound closure. Spinal anesthesia was used for all eligible patients as determined by the anesthesia team; patients deemed ineligible received a general anesthetic with endotracheal tube. TKA patients were placed in the supine position, had a tourniquet applied prior to incision, and a standard parapatellar approach utilized to implant a cemented metal-on-polyetheylene system. THA patients were placed in the lateral decubitus position with a standard posterior approach utilized to implant a non-cemented metal or ceramic-on-polyethylene system. Fluid resuscitation and transfusion requirement was managed by the anesthesia team following standard guidelines. A cocktail for pain control, including 80 mcg clonidine, 30 mg ketorolac, 0.5 mL 1:1000 epinepherine, and 49.25 mL 0.5% ropivicaine, combined with normal saline to a total volume of 100 mL, was injected into the joint capsule and surrounding tissues prior to final closure in both groups.

Postoperative

Patients were admitted to the Orthopaedics unit and followed a standardized postoperative protocol, including aggressive multimodal pain control with oral medications and physical therapy starting on the day of surgery. Coumadin and a sequential compression device were used to prevent thrombus formation. Hb was measured for all patients on the first postoperative day, as well as for the majority of patients on subsequent days as required. Transfusion was dictated by a significant decrease in Hb combined with clinical symptoms or changes in physiologic parameters. An absolute Hb threshold for transfusion was not used. Discharge was typically on the third postoperative day. Any postoperative complications up to the first postoperative visit, typically at two weeks, were recorded. Complications included superficial hematoma formation, deep joint effusion, wound breakdown, thromboembolism, and acute infection.

Statistical analysis

Patients were divided into one of four groups based on preoperative Hb and type of arthroplasty performed (nonanemic *vs* anemic, TKA *vs* THA). In each surgical group (TKA and THA), the nonanemic patients were used as controls and the anemic patients as the study groups. A two-sample T test was used to compare the average change in Hb between each of the groups (*e.g.,* anemic TKA *vs* nonanemic TKA). A Fisher exact test was used to compare the rate of complications between each of the groups as well as the rate of transfusion between each of the groups. Significance was set at the P value of $\leqslant 0.05$. Statistical analysis was performed using Microsoft Excel (Microsoft, Richmond WA).

RESULTS

A total of 232 patients met inclusion criteria and were enrolled in the study (Table 1).

THA

Eighty-four patients had THA performed. Twenty-one percent (18/84) of the patients presented with

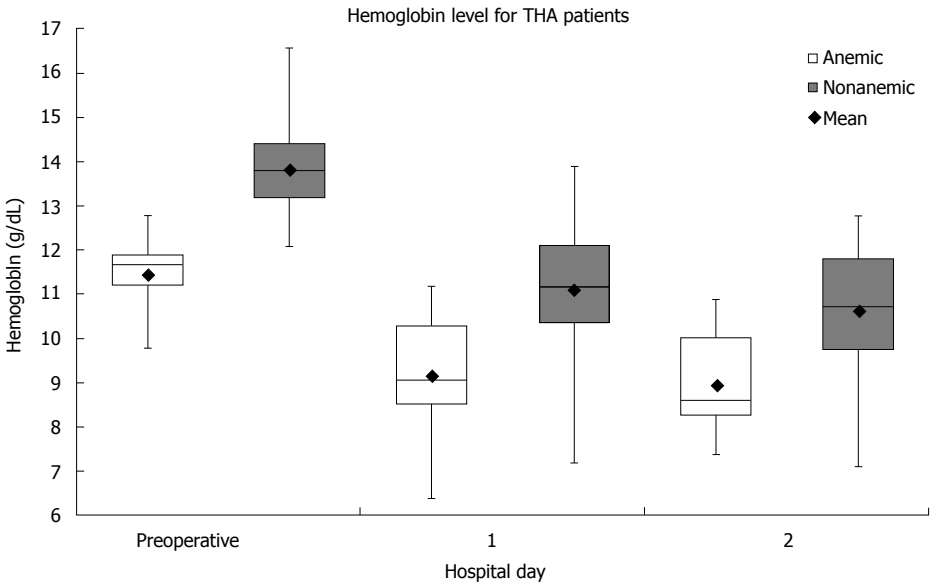

Figure 1 Hemoglobin levels in total hip arthroplasty using tranexamic acid. Boxplots showing median and interquartile ranges for hemoglobin levels in each group on each hospital day are shown. Both groups experienced a fall in hemoglobin following surgery and both groups had at least one patient who required transfusion on the first postoperative day. Despite the differences in starting hemoglobin, there was no significant difference between groups in rate of transfusion. THA: Total hip arthroplasty.

preoperative anemia. For nonanemic patients, the average change in Hb from preoperative to the first postoperative day was 2.73 ± 1.17 g/dL. For anemic patients, the average change in Hb from preoperative to the first postoperative day was 2.28 ± 0.96 g/dL (Figure 1). Between the two groups, the Hb difference of 0.45 g/dL was not significant (P = 0.13). Two patients in the nonanemic group and two patients in the anemic group required ABT. There was no significant difference in the rate of ABT (P = 0.20). One patient in the anemic group presented with a deep venous thrombosis at the fourth postoperative day; there were no complications for patients in the nonanemic group. There was no significant difference in the rate of all immediate postoperative complications (P = 0.21).

TKA

One hundred and forty-eight patients had TKA performed. Eighteen percent (26/148) of the patients presented with preoperative anemia. For nonanemic patients, the average change in Hb from preoperative to the first postoperative day was 1.85 ± 0.79 g/dL. For anemic patients, the average change in Hb from preoperative to the first postoperative day was 1.09 ± 0.58 g/dL (Figure 2). Between the two groups, the Hb difference of 0.76 g/dL was significant (P < 0.001). No patients in either group required ABT. No patients in either group presented with complications within the first post-operative visit.

DISCUSSION

Current methods to increase Hb in patients with preoperative anemia have disadvantages. The results of iron supplementation are inconclusive, with studies showing diverging effects on preoperative Hb[6,32-34]. Common side effects such as constipation, and abdominal pain can lower the adherence rate[32]. Recombinant human erythropoietin has been shown to be efficacious[35-37], but is only available *via* an intravenous or subcutaneous route and is relatively expensive[14,38]. Preoperative autologous donation provides the patient a safe supply of blood[39] but physiologic compensation after donation may be inadequate[40] and a significant amount of donated blood is unused[1,40,41]. As such, the goal of this study was to determine if TXA would be useful as an alternative strategy for patients with preoperative anemia to limit the rate of blood loss and ABT.

As expected from undergoing a TJA, all patients had a decrease in Hb at the first postoperative day. Anemic and nonanemic patients who underwent THA had a similar decrease in Hb, with anemic patients averaging only an additional 0.45 g/dL of blood loss. This supported the hypothesis that TXA would result in equivalent rates of blood loss, regardless of preoperative Hb levels. However, nonanemic patients who underwent TKA averaged a decrease in Hb that was significantly greater than that for anemic patients, at 0.76 g/dL; this was unexpected. It is not entirely clear what caused this difference in Hb change, but it may simply be that nonanemic patients lose more red cells per ml of blood lost than anemic patients (due to intraoperative fluid resuscitation), so for equivalent volumes lost between groups the nonanemic group would be expected to have lost more red cell mass overall and therefore experience a bigger drop in Hb. As all patients received fluids during the perioperative period according to strict guidelines following anesthesia protocol based on patient weight and hemodynamic status, it is unlikely that differences in fluid administration were contributive.

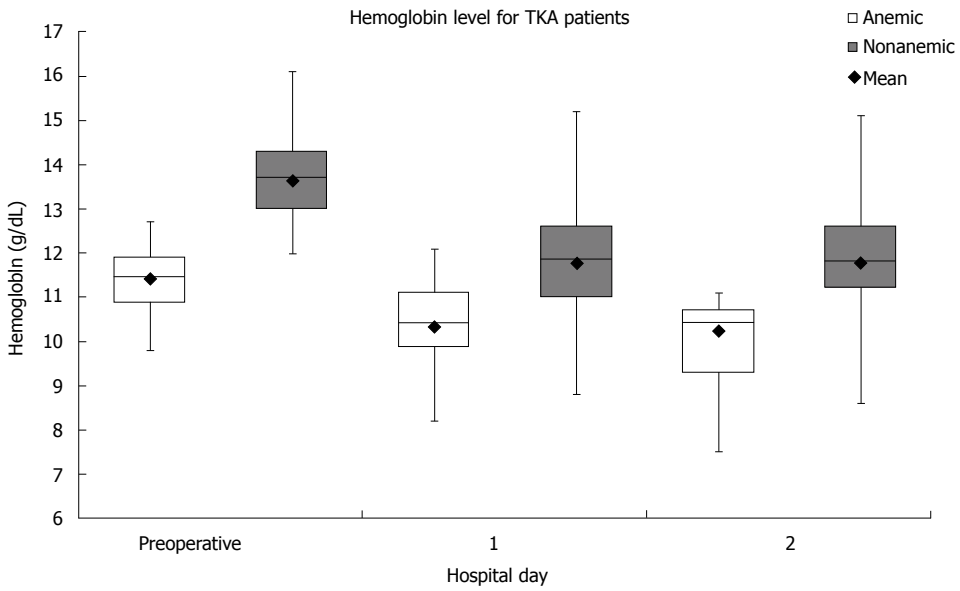

Figure 2 Hemoglobin levels in total knee arthroplasty using tranexamic acid. Boxplots showing median and interquartile ranges for hemoglobin levels in each group on each hospital day are shown. Both groups experienced a fall in hemoglobin following; in this case the nonanemic patients had a significant greater fall then the anemic patients at the first postoperative day (but still had a higher median hemoglobin). None of the patients in either group required transfusion. TKA: Total knee arthroplasty.

Finally, only one patient, in the anemic THA group, had a postoperative complication, well within the normal occurrence rate reported for THA[42]. The thrombosis was treated with anticoagulation and did not result in symptomatic embolism. This low rate of complications reaffirms the safe use of TXA as seen in the current literature.

There was no significant difference in the rate of ABT for anemic and nonanemic patients treated with TXA during THA, and none of the TKA patients required transfusion. This supports the hypothesis that use of TXA would result in equivalent rates of perioperative transfusion, regardless of preoperative blood levels. Given that patients with preoperative anemia generally require a higher rate of transfusion, the results suggest that TXA may actually decrease the rate of ABT for this patient population. The potential significance of this finding is two-fold. First, patients with a mild level of anemia may not require any preoperative or perioperative adjunct treatment aside from TXA, such as PO or Ⅳ iron supplementation or erythropoietin. Limiting the use of these treatments may decrease concerns about patient compliance and reduce overall surgical costs, as well as rare but real complications from the therapies themselves. In addition, the threshold to operate on patients may be lowered, increasing the availability of TJA for patients with anemia. For these patients, a preoperative course combining multiple treatment modalities in addition to perioperative TXA may be sufficient to minimize significant blood loss and ABT requirements.

This study has several limitations. All procedures were performed by a single surgeon and thus operative blood loss may not be equivalent to that of other surgeons using alternative TJA techniques. Because the study highlighted the relative change (as opposed to absolute values) in Hb, the overall impact of this limitation should be small. In addition, the same approach and same implant system was used by the surgeon for the procedures, which limited variation in surgical technique. The study population was not large, which resulted in a low number of patients with anemia, and thus power could have been increased by enrolling additional patients. However, the percentage of patients presenting with preoperative anemia was equivalent to the rates seen in the existing literature, suggesting that the study population was a suitable representation of the patient population. As such, a formal power analysis was not performed. Another limitation was with regard to the rates of transfusion; with only four ABT's in the study it is possible that a much larger sample may have demonstrated differences, though even here the conclusion that TXA may allow safe TJA at lower Hb levels would not have changed. Finally, the decision for ABT was not dictated by a single factor, such as postoperative Hb. The current literature is increasingly supportive of using a restrictive transfusion threshold similar to that used in this study, but it is possible that other centers with more liberal transfusion practices may have different results.

In this study, there was no significant difference in the rate of autologous blood transfusion and postoperative complications for anemic and nonanemic patients presenting for lower-extremity TJA when TXA was used. These results support the use of TXA as a safe and effective agent to limit perioperative blood transfusion in patients with preoperative anemia. Potentially, TXA may be used as the single treatment for patients with mild anemia, in place of preoperative methods such as iron supplementation

and erythropoietin. TXA may also be helpful when combined with these adjuncts for patients with more severe anemia. Further investigations concerning TXA in patients with preoperative anemia are recommended. Topics to be considered, or are currently under examination, include comparing efficacy and analyzing cost-benefit of TXA *vs* different preoperative treatments (*e.g.,* iron supplementation, erythropoietin). These studies will ideally lead to a standardized and cohesive protocol for TJA patients with preoperative anemia.

COMMENTS

Background

Total joint arthroplasty (TJA) of the hip and knee are successful surgeries that can dramatically reduce pain and increase function for patients with end-stage joint arthritis. However, despite changes in surgical approaches, techniques, and implants, intraoperative blood loss requiring blood transfusion is still prevalent, especially for patients presenting with anemia. Currently, the therapeutic options to treat preoperative anemia are limited and not commonly used.

Research frontiers

Tranexamic acid (TXA) has been highlighted in the last half-decade as a way to decrease intraoperative blood loss. Application during surgery, *via* intravenous or topical, has been shown to decrease the rate of blood transfusion in THA patients. TXA use has also expanded to other fields of orthopaedics, such as spine surgery.

Innovations and breakthroughs

To the authors' knowledge, no previous study has closely examined TXA use on THA patients presenting with preoperative anemia. The current study is the first to directly compare blood loss, transfusion rate, and complication rate for anemic THA patients given TXA *vs* nonanemic controls. With the results shown, it may be possible to use TXA as the sole treatment for patients with mild anemia and as a adjunct with other treatment options for patients with severe anemia.

Applications

The current study shows the efficacy and safety of TXA use for THA patients presenting with preoperative anemia and suggests that routine use in anemic patients with no contraindications is warranted to limit the rate of blood transfusion.

Terminology

TXA - synthetic lysine analog that competitively inhibits the activation of plasminogen to plasmin. Anemia - Defined by the World Health Organization as hemoglobin < 12 g/dL in adult females and < 13 g/dL in adult males.

Peer-review

This is a manuscript which compares rates of transfusion and postoperative complications between anemic and nonanemic patients given TXA who underwent primary total hip arthroplasty and total knee arthroplasty. This is an interesting paper on a relevant issue. The paper is well written and well structured.

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SYSTEMATIC REVIEWS

Persistent post-surgical pain and neuropathic pain after total knee replacement

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Abstract

AIM: To study the prevalence of persistent post-surgical pain (PPSP) and neuropathic pain (NP) after total knee replacement (TKR).

METHODS: MEDLINE and Embase databases were searched for articles published until December 2014 in English language. Published articles were included if they referred to pain that lasts at least 3 mo after primary TKR for knee osteoarthritis, and measured pain with pain specific instruments. Studies that referred to pain caused by septic reasons and implant malalignment were excluded. Both prospective and retrospective studies were included and only 14 studies that match the inclusion criteria were selected for this review.

RESULTS: The included studies were characterized by the heterogeneity on the scales used to measure pain and pre-operative factors related to PPSP and NP. The reported prevalence of PPSP and NP seems to be relatively high, but it varies among different studies. There is also evidence that the prevalence of post-surgical pain is related to the scale used for pain measurement. The prevalence of PPSP is ranging at 6 mo from 16% to 39% and at 12 mo from 13.1% to 23% and even 38% of the patients. The prevalence of NP at 6 mo post-operatively is ranging from 5.2% to

13%. Pre-operative factors related to the development of PPSP also differ, including emotional functioning, such as depression and pain catastrophizing, number of comorbidities, pain problems elsewhere and operations in knees with early grade of osteoarthritis.

CONCLUSION: No firm conclusions can be reached regarding the prevalence of PPSP and NP and the related factors due to the heterogeneity of the studies.

Key words: Total knee replacement; Pain; Chronic pain; Neuropathic pain; Post-operative pain; Persistent post-surgical pain

Core tip: Persistent post-surgical pain (PPSP) is reported in a significant proportion of patients after total knee replacement. This proportion varies between the different studies and different factors have been implicated including the instrument used to measure pain. It is also obvious that in some of these patients the pain is neuropathic (NP) in origin or the NP pain coexists. Nevertheless, due to the heterogeneity of the studies, mainly on the scales used to assess pain and preoperative factors, we are unable to reach firm conclusions concerning the prevalence, and the risk factors of PPSP pain after total knee replacement. Additional studies focused on the prevalence and risk factors related to PPSP are needed.

Drosos GI, Triantafilidou T, Ververidis A, Agelopoulou C, Vogiatzaki T, Kazakos K. Persistent post-surgical pain and neuropathic pain after total knee replacement. *World J Orthop* 2015; 6(7): 528-536 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i7/528.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i7.528

INTRODUCTION

Total knee replacement (TKR) is a treatment of knee osteoarthritis to alleviate pain symptoms and improve mobility and physical functioning when other conservative treatments have failed[1-3]. It is a very common and successful procedure since 1970s for late stage osteoarthritis and there is a continuously increasing number in demand for primary TKR performed worldwide each year[4,5]. However, not all patients are satisfied after TKR. Pain after TKR is stronger determinant of satisfaction than function[6]. An unfavorable pain outcome was seen in at least 8.0% and up to 26.5% of patients[7] and contribute to functional disability after TKR[6,8-10].

Apart from the post-surgical pain that is a result of a specific cause, some patients suffer from a persistent post-surgical pain (PPSP) with no specific origin that represents an important cause for patients' dissatisfaction. Although the cause of PPSP is not known, it seems that some of the patients with PPSP after TKR suffer from neuropathic pain (NP)[11]. The International Association for the Study of Pain (IASP) defines: (1) as PPSP the pain that is being developed after surgery and exists beyond the time for normal healing and is present for at least 3-6 mo[12]; and (2) NP is also defined by the IASP as the pain caused by a lesion or a disease of the somatosensory nervous system (IASP website, http://www.iasp-pain.org/)[13]. A wide variety of scores–tools have been used in order to assess the outcome postoperatively. Almost all scores or instruments -either objective (clinician-based)[14] or subjective (patient-reported)[15] or disease specific[3,16] - being used for the study of the outcome, function and satisfaction after TKR, include some kind of pain assessment[17]. However, a standard definition of pain severity at follow-up considered a difficult issue to be applied and the need to improve assessment and measurement of musculoskeletal pain in the clinical setting is recognized[18].

The purpose of this study is to present a review of the existing literature concerning the existence of PPSP and NP after TKR for at least 3 mo, including studies with main purpose the prevalence of the PPSP and NP after TKR using pain-specific instruments and not through other scores or instruments measuring functional outcome.

MATERIALS AND METHODS

Literature search

MEDLINE and Embase databases were searched for articles published until December 2014. The keywords "TKR", "total knee arthroplasty", "chronic postoperative pain", "NP" and synonyms were used to maximize the efficiency of the search. Both prospective and retrospective studies were included.

Inclusion and exclusion criteria

Published articles were included only if they referred to pain that lasts at least 3 mo after primary TKR and if the main reason of TKR was knee OA. Studies were excluded if they were abstracts, case studies, reviews, editorials and if they referred to pain caused by septic reasons and implant malalignment. Studies that assessed a mixed cohort of patients (*e.g.*, knee and hip replacement patients) were included in the review and only data relevant to the TKR patients were extracted. Studies in other language than English were excluded.

A total of 112 articles were found. Only 14 studies that match the inclusion criteria and measured pain with pain specific instruments were selected for this review.

RESULTS

PPSP after TKR (Table 1)

Studies: We identified 5 prospective[19-23], and 3 retrospective[9,24,25] studies. Three of the studies found to have as primary aim the documentation of the existence and the prevalence of PPSP after TKR[19,20,25], while another

Table 1 Total knee replacement and chronic (persistent) post-surgical pain

Ref.	Design/patients	Aim of the study	Scores-scales	Follow-up	Pain	Factors
Brander *et al*[19]	Prospective *n* = 116	To describe the natural history of pain after TKR To identify factors predicting excessive post-surgical pain	VAS and other measures of patient health	Pre-op. Post-op.: (1) 1 mo; (2) 3 mo; (3) 6 mo; and (4) 12 mo	Pre-op.: 72.3% Post op.: (1) 44.4%; (2) 22.6%; (3) 18.4%; and (4) 13.1%, respectively	Factors related with post-op pain at 12 mo (1) Pre-operative pain; and (2) Pre-operative depression and anxiety
Forsythe *et al*[20]	Prospective *n* = 55	To document: the prospective pain experience following TKR To determine if: (1) comorbidities; (2) preoperative pain; or (3) preoperative pain catastrophizing scores are predictors of chronic pain after TKR	MPQ PCS	Pre-op. Post-op.: (1) 3 mo; (2) 12 mo; and (3) 24 mo	Significant reduction only between pre-op and 3-mo post-op values. After 3-mo pain had reached a plateau Pain catastrophizing scores didn't show any significant differences	Predictive of chronic postoperative pain: (1) No. of comorbidities; and (2) Pre-operative pain catastrophizing scores
Ritter *et al*[24]	Retrospective *n* = 7326	To quantify the effect of sex on the clinical outcome and survivorship of a specific TKR (AGC, Biomet, Warsaw, Ind)	KSS PS FS	Clinical scores: Throughout 5 yr Survival data: Up to 17 yr	Pain after TKR was less for men but there was no statistically significant difference between men and women	Improvement after TKR is similar for men and women No significant difference in post-operative pain between men and women
Wylde *et al*[9]	Retrospective *n* = 632	To assess the (1) prevalence; (2) severity; (3) sensory qualities; and (4) postoperative determinants of persistent pain after primary THR and TKR	WOMAC Pain Scale SFMPQ pD-Q Two-item Patient Health Questionnaire (PHQ-2)	Median: 41 mo Range: 34-49 mo	Persistent post-surgical pain (PPSP): 44% Severe-extreme PPSP: 15% Constant PPSP: 5% Likely neuropathic pain: 6%	Significant and independent postoperative determinants of number of PPSP: (1) No. of pain problems elsewhere; and (2) The presence of major depression
Polkowski *et al*[23]	Prospective *n* = 309	To explore the relationship between early-grade preoperative OA with pain and dissatisfaction after TKR	Group A: Pain after TKR Group B: Consecutive series of 100 TKR's performed the same period by the same surgeon Group C: Asymptomatic TKR Group D: Symptomatic TKR performed the same period	1-5 yr	Early-grade OA pre-op: Group A: 49% Group B: 5% Group C: 6% Group D: 10%.	A high percentage of patients referred for unexplained pain after TKR had early-grade OA pre-operatively
Noiseux *et al*[21]	Prospective *n* = 215	To discover whether any preoperative assessment could predict high pain scores and functional limitations postoperatively	Pain Intensity rating: NRS QST Anxiety Form of the State Trait Anxiety Inventory GDS PCS	Pre-op. Post-op.: 6 mo	Moderate to severe pain At rest: Pre-op.: 17% Post-op.: 5% With range-of-motion: Pre-op.: 52% Post-op.: 16%	Significant predictors (for moderate or severe TKR pain with knee motion after 6 mo): (1) Severe preoperative knee pain with range-of motion; and (2) Anxiety
Pérez-Prieto *et al*[22]	Prospective *n* = 716 Depressed: *n* = 200	To evaluate quality of life, function, pain and satisfaction outcomes in patients, with and without depression, undergoing TKR	GDS KSS Medical Outcomes Study 36-Item Short Form Health (SF-36) MCS VAS	12 mo	Depressed patients reported significant higher pain scores than non-depressed patients pre- and post-operatively Net changes (postoperative - preoperative): No significant difference	Depression leads to (1) Poorer preoperative and postoperative scores in all but the mental domains; and (2) But similar net score changes (improvement) with a high rate of patient satisfaction

W-Dahl *et al*[25]	Non-depressed: *n* = 516 retrospective	To evaluate how the instruments used to measure pain affected the number of patients who reported no relief of pain or worse pain, and the relative effect of potential risk factors	Osteoarthritis Outcome Score (KOOS) VAS EQ-5D	Pre-operatively 1 year post-operatively	No pain relief: 10.1% Only KOOS pain: 25% Only VAS knee pain: 52% Both: 23%	The observed proportion of patients with unchanged or worse pain one year after TKR differed depending on the method of pain measurement used Risk factors for no pain relief are: (1) less pre-operative pain; and (2) higher degree of anxiety Charnley category C was a risk factor for unchanged or worse pain as measured by the VAS but not for the KOOS

OA: Osteoarthritis; TKR: Total knee replacement; Pre-op: Preoperatively; Post-op: Postoperatively; PPSP: Persistent post-surgical pain; VAS: Visual Analogue Scale; EQ-5D: Euro-Qol 5 Dimension; MCS: Mental Composite Score; KSS: Knee Society Score; GDS: Geriatric Depression Scale; PCS: Pain Catastrophizing Scale; QST Quantitative Sensory Testing; NRS: Numerical Rating Scale; SFMPQ: Short-Form McGill Pain Questionnaire; pD-Q: PainDETECT Questionnaire; WOMAC: Western Ontario and McMaster Universities Index of Osteoarthritis; FS: Function score; PS: Pain score; KSS: Knee Society knee score; MPQ: McGill Pain Questionnaire.

one assessed PPSP retrospectively in patients after both TKR and THR[9].

Factors-variables related to PPSP: Multiple variables have been considered to play an important role at persistent postoperative pain. At times, different aspects of risk factors have been examined. In these studies, preoperative factors that were examined were comorbidities[20], preoperative pain[19,20] and pain catastrophizing scores[20,21]. But only one study found to quantify the effect of sex on postoperative pain outcomes[24] while another one assessed the relationship of PPSP and the Grade of knee osteoarthritis according to the scale of Kellgren and Lawrence[23]. Quality of life, pain and satisfaction were measured in depressed and non-depressed patients to identify differences that might exist in the scores[22].

Pain scales or scores: Pain intensity mainly was measured using validated patient reported measures of pain, the most common were the Visual Analogue Scale (VAS)[19,25] which is a well evaluated tool, the McGill pain questionnaire (MpQ)[9,20], the Knee Society Score[22,24] and the Numerical Rating Scale (NRS)[21].

To cover the influence of psychological factors on TKR outcomes Pain Catastrophizing Scale (PCS) was used to measure pain catastrophizing[20,21], while the Two-item Patient Health Questionnaire (PHQ-2)[9], Geriatric Depression Scale[21,22], Medical Outcomes Study 36-Item Short Form Health, Mental Composite Score[22] and Anxiety Form of the State Trait Anxiety Inventory (STAI)[21] were used to measure depression and anxiety.

A recent study[25] evaluated the tools that used to measure pain intensity, Knee injury and Osteoarthritis Outcome Score (KOOS) and VAS and how they affect the pain outcomes.

Pain assessment times and post-operative follow-up: At the most of the studies there was a continuous follow-up. Assessments took place preoperatively[19-21,25] and postoperatively at 1 mo[19], 3 mo[19,20], 6 mo[19,21], 12 mo[19,22,23,25] and up to 1 year postoperatively[19,22,23,25].

Prevalence of pain: A significant reduction of pain after TKR was observed between preoperative scores and postoperative scores; from 72% to 44%[19]. A further reduction was observed up to 3 mo postoperatively where pain reached a plateau[20].

At 6 mo post-operatively, pain at movements was found in 16% of patients[21] while pain at rest was significantly reduced in 5% of the patients.[21]. Others found PPSP in 18.4% of the patients at 6 mo[19]. PPSP has been reported at 1 year post-operatively in 13.1% of the patients[19] while in another study, 44% of the patients reported to had PPSP at a mean of 4 years after TKR[9].

Interestingly, in one study where the same patients were tested using two different scales at one year post-operatively, the prevalence of PPSP was different; in 25% of the patients using the KOOS and in 52% using the VAS[25].

Factors related to PPSP: Preoperative factors that affected pain scores were depression scores[9,19], affecting both preoperative and postoperative pain scores[22], early grade

of osteoarthritis[23], number of comorbidities[20] and pain problems elsewhere[9]. Gender didn't seemed to affect postoperative outcomes at all[24]. A high correlation was found between preoperative pain catastrophizing scores and the existence of PPSP and its intensity[20]. Which is in accordance with other reviews that is referred that patient's pain catastrophizing might play an important role in chronic pain intensity[26,27].

NP after TKR (Table 2)

Studies: The existence and prevalence of NP have been reported by a small number of studies[9,28,29]. Three prospective studies[9,28,29] with the study population ranged from 77 to 120 patients, and 1 retrospective study[9] with a number of 632 patients were designed for this purpose. However, other studies that aimed to evaluate specific treatments for NP recorded its prevalence too[30].

Pain scales or scores: Scores, initially were used to establish the existence of pain in some of these studies. These scores were MpQ[9,28], VAS[29] and NRS[30].

Additionally, NP was assessed by painDetect Questionnaire (PD-Q)[9,29], Leeds Assessment of Neuropathic Symptoms and Signs scale[30] and MpQ[28]. The contribution of depression's and anxiety's presence and severity to the existence of NP were examined. PHQ-2[9], Beck Depression Inventory (BDI)[28], the Hospital Anxiety and Depression score[29] and the STAI[28] were used for this purpose.

Pain assessment times and post-operative follow-up: Pain assessment at these studies took place preoperatively[29,30] and postoperatively at 3-5 d[29], 6 wk[29], 1 mo[28], at 3, 6 and 9 mo[28-30] and up to 1 year postoperatively[9,29].

NP prevalence: A high correlation was found between VAS pain scores and NP at 3 mo, 1 year and 3 years post-op[29]. Six weeks postoperatively a peak at the graph was observed with 27% having possible and 8% of the patients having likely NP. At 3 mo that proportion reduced to 19% with possible and 4% with likely NP[29].

Buvanendran *et al*[30], identified a rate of NP of 5% at 6 mo postoperatively, while in another study[28] was found 13% of the patients having Complex Regional Pain Syndrome after TKR at both 3 and 6 mo. It is reported that at mean 4 years after TKR 6% of the patients have pain of likely neuropathic origin[9,29]. The use of perioperative pregabalin reduced the incidence of NP at 0%, while placebo pregabalin didn't seem to reduce NP[30].

Studies including TKR patients concerning the existence, prevalence and etiology of NP (Table 3)

Studies: A retrospective study assessed the existence and the preoperative predictors of NP in 632 TKR patients and 662 THR patients[9], and two prospective studies in 100 TKR patients and 89 patients after breast surgery[31,32]. Another prospective study, also examined the relationship between postoperative trajectories and NP, in 112 TKR and UKR patients[33].

Pain scales or scores: Scores that used to assess NP were PD-Q[9] and Diagnosing Neuropathic 4[31-33]. Shortform McGill Pain Questionnaire[9], NRS[31,33] and Brief Pain Inventory[32] were used to define the existence of pain postoperatively.

Factors studied: Preoperative factors of NP that were examined were depression[9,31,32], anxiety[31,33], pain catastrophizing[31,33], cognitive and emotional functioning[32]. Depression was assessed with PHQ-2[9] and 13-item BDI[31,32]. Spielberger STAI and PCS were used to assess anxiety and pain catastrophizing[31,33]. Cognitive functioning was assessed with Trail-Making Test A + B, Rey-Osterrieth Complex Figure-copy and immediate recall, Coping Strategies Questionnaire and Brief Version of the Survey of Pain Attitudes[32].

Pain assessment times and post-operative follow-up: Assessments took place preoperatively[9,31-33], 2 d postoperatively[31,32], at day 1 to 8[33], 3 mo[31,33], 6 mo, 12 mo[32] and 3 to 4 years postoperatively[9].

Factors: Acute postoperative pain [31], cognitive functioning, pain coping[32], emotional functioning[9,32] and problems of pain elsewhere[9] found to be predictors of PPSP and NP.

Prevalence: Seventy five percent of the patients seemed to have NP preoperatively, according to Attal *et al*[32], 2014, while in another study NP seemed to appear on 30.7% of the patients[31]. At 3 mo postoperatively, NP ranged between 11%[33] and 42.2%[31] of the patients. Six and 12 mo postoperatively patients with NP reduced at 32% and 26%, respectively[32]. At 3 to 4 years postoperatively only 6% of TKR patients had NP[9].

DISCUSSION

The number of the 14 studies that used pain-specific instruments to measure pain after TKR is small and studies that approach and record NP after TKR are much less.

According to these studies, a significant proportion of patients have persistent post-operative pain for years after TKR and part of these patients suffer from pain of neuropathic origin.

Factors found to be related to persistent postoperative pain after TKR include emotional functioning such as depression and pain catastrophizing, number of comorbidities and pain problems elsewhere and operations in knees with early grade of osteoarthritis.

Nevertheless, due to the heterogeneity of the studies, mainly on the scales used to assess pain and

Table 2 Total knee replacement and neuropathic pain

Ref.	Design	No. of patients	Aim of the study	Scores-scales	Follow-up	Pain	Factors
Harden *et al*[28]	Prospective	77	Preoperative emotional distress and pain intensity and would predict the occurrence of signs and symptoms of CRPS following TKR	CRPS: IASP criteria (signs/symptoms) Beck Depression Inventory State Trait Anxiety Inventory McGill Pain Questionnaire-Short Form	Pre-op. Post-op.: (1) 1 mo; (2) 3 mo; and (3) 6 mo	1 mo: 21.0% 3 mo: 13.0% 6 mo: 12.7%	CRPS-like phenomena: (1) In a significant number of patients after TKR; and (2) No association with significantly greater complaints of postoperative pain Prediction by preoperative distress and pain: Modest utility
Buvanendran *et al*[30]	Prospective	Control: 120 Pregabalin: 120	To examine if perioperative treatment with pregabalin, would reduce the incidence of postsurgical NP	11-point NRS LANS scale Osteoarthritis Outcome Score–Physical function Short-form (KOOS-PS)	Pre-op. Post-op.: (1) 3 mo; and (2) 6 mo	Study group: 0% Placebo group: (1) 3 mo: 8.7%; (2) 6 mo: 5.2%	Perioperative pregabalin administration reduces the incidence of chronic NP after TKR In the doses tested, it is associated with a higher risk of early postoperative sedation and confusion
Wylde *et al*[9]	Retrospective	632	To assess: (1) prevalence; (2) severity; (3) sensory qualities; and (4) postoperative determinants of persistent pain after primary THR and TKR	WOMAC Pain Scale SF-MPQ PainDETECT Questionnaire Two-item PHQ-2	Median: 41 mo Range: 34-49 mo	Persistent postsurgical pain (PPSP): 44% Severe-extreme PPSP: 15% Constant PPSP: 5% Likely NP: 6%	Significant and independent postoperative determinants of number of PPSP: (1) No. of pain problems elsewhere; and (2) The presence of major depression
Phillips *et al*[29]	Prospective	94	To record the prevalence of pain and NP To establish predictive factors that could be used to identify patients who were likely to have high levels of pain or NP	VAS HADS score pD-Q score OKS	Pre-op. Post-op.: (1) 3-5 d; (2) 6 wk; (3) 3 mo; (4) 6 mo; (5) 9 mo; (6) 1 yr; and (7) 46 mo	VAS (value) Pre-op.: 5.8 Post-op.: (1) 3-5 d: 4.5; (2) 6 wk: 3.2; (3) 3 mo: 2.4; (4) 6 mo: 2.0; (5) 9 mo: 1.7; (6) 1 yr: 1.5; and (7) 46 mo: 2.0 Frequency (%) VAS moderate-severe/painDETECT possible -likely Pre-op.: 41-50/5-1 Post-op.: (1) 3-5 d: 47-19/5-3; (2) 6 wk: 39-9/27-8; (3) 3 mo: 21-10/19-4; (4) 6 mo: 16-6/17-3; (5) 9 mo: 16-4/13-6; (6) 1 yr: 14-3/9-2; and (7) 46 mo: 15-7/7-6	High correlation between the mean VAS scores for pain and the mean painDETECT scores at 3 mo, 1 yr and 3 yr post-operatively No correlation between the pre-operative scores and any post-operative scores at any time point NP is an underestimated problem in patients after TKR

CRPS: Complex regional pain syndrome; NP: Neuropathic pain; Pre-op: Preoperatively; Post-op: Postoperatively; LANS: Leeds Assessment of Neuropathic Symptoms and Signs; NRS: Numerical Rating Scale; WOMAC: Western Ontario and McMaster Universities Index of Osteoarthritis; SF-MPQ: Short-Form McGill Pain Questionnaire; PHQ-2: Patient Health Questionnaire; VAS: Visual Analogue Score; HADS: Hospital Anxiety and Depression; pD-Q: PainDETECT; OKS: Oxford Knee score.

Table 3 Studies including total knee replacement patients concerning the prevalence and etiology of neuropathic pain

Ref.	Design	No. of patients	Aim of the study	Scores-scales	Follow-up	Pain	Factors
Wylde *et al*[9]	Retrospective	632	To assess: (1) prevalence; (2) severity; (3) sensory qualities; and (4) postoperative determinants of persistent pain after primary THR and TKR	Western Ontario and McMaster Universities Index of Osteoarthritis Pain Scale Short-Form McGill Pain Questionnaire PainDETECT Questionnaire Two-item Patient Health Questionnaire	Median: 41 mo Range: 34-49 mo	PPSP: 44% Severe-extreme PPSP: 15% Constant PPSP: 5% Likely NP: 6%	Significant and independent postoperative determinants of number of PPSP: (1) No. of pain problems elsewhere; and (2) The presence of major depression
Masselin-Dubois *et al*[31]	Prospective	TKR patients: 89 breast cancer surgery patients: 100	To assess the predictive value of: (1) Anxiety; (2) Depression; (3) Pain catastrophizing; and (4) Baseline pain intensity for chronic post-surgical pain. The existence of neuropathic pain	BPI NRS Neuropathic Pain Diagnostic Questionnaire (DN4) Spielberger STAI 13-item BDI PCS	Pre-op. Post-op: (1) 2 d (2) 3 mo	TKR patients: (1) Pre-op: 84% at least moderate pain (2) 2 d: 46.9%; and (3) 3 mo: 50.6% Neuropathic pain TKR patients: (1) Pre-op: 30.7% (2) 3 mo: 42.2%	Regardless the type of surgery, state anxiety, pain catastrophizing (especially pain magnification) and acute post-surgical pain are predictive of persistent post-surgical pain Acute post-surgical pain was also predictive of NP pain. Baseline pain intensity, trait anxiety and depression had no independent impact on post-surgical pain (considering low baseline scores for depression in this study)
Lavand' homme *et al*[33]	Prospective	TKR and UKR patients: 120	To examine the relationship between postoperative pain trajectories and persistent pain, specifically neuropathic pain.	NRS Neuropathic Pain Diagnostic Questionnaire (DN4) PCS Spielberger STAI for Adults	Pre-op. Post-op: (1) Day 1 to day 8; (2) 3 mo	At 3 mo post-op: (1) 42% patients were pain free (2) 47% patients with persistent pain without NP pain; and (3) 11% patients with persistent pain involving neuropathic component	Patients with neuropathic pain displayed higher pain scores, particularly during mobilization No differences found among pain trajectories for pain at rest
Attal *et al*[32]	Prospective	TKR patients: 89 breast cancer surgery patients: 100	If: (1) cognitive functioning (2) emotional functioning and pain coping are predictors of persistent post-surgical pain and neuropathic pain	BPI Neuropathic Pain Diagnostic Questionnaire (DN4) TMT A TMT B ROCF-copy ROCF-immediate recall BDI Spielberger STAI CSQ Brief Version of the SOPA-B	Pre-op: (1) 1 mo; and (2) 1 d Post-op: (1) 2 d; (2) 6 mo, 12 mo	TKR patients (1) Pre-op: 84%; (2) 6 mo: 39%; and (3) 12 mo: 38% Neuropathic pain TKR patients: (1) Pre-op: 75 patients; (2) 6 mo: 32 patients; and (3) 12 mo: 26 patients	Cognitive functioning, emotional functioning and pain coping made an independent contribution to the prevalence and severity of persistent post-surgical pain, as well as its neuropathic quality. Results at ROCF-copy and ROCF-immediate recall test seemed to be predictors of pain with neuropathic nature

PPSP: Persistent postsurgical pain; BPI: Brief Pain Inventory; NRS: Numerical Rating Scale; STAI: State-Trait Anxiety Inventory; PCS: Pain Catastrophizing Scale; BDI: Beck Depression Inventory; TMT A: Trail-Making Test A; ROCF-copy: Rey-Osterrieth Complex Figure-copy; ROCF-immediate recall: Rey-Osterrieth Complex Figure-immediate recall; CSQ: Coping Strategies Questionnaire; SOPA-B: Survey of Pain Attitudes.

preoperative factors, we are unable to reach firm conclusions concerning the prevalence, and the risk factors of persistent post-operative pain after TKR. Additional studies focused on the prevalence and risk factors related to persistent postoperative pain are needed.

COMMENTS

Background

Persistent-post-surgical pain of unknown origin and neuropathic pain (NP) is considered a major underestimated problem for patients and for clinicians too. There are several studies that measure pain with a wide variety of scores-tools.

Research frontiers

According to our acknowledgment this is the first review that analyses the prevalence of both persistent post-surgical pain (PPSP) and NP after total knee replacement (TKR), while pain is measured only with pain-specific instruments. Risk factors that might play an important role in the prediction and the prevalence of persistent postoperative pain were also analyzed.

Innovations and breakthroughs

PPSP measured by pain- specific instruments only by a few studies. From this review, it is obvious that post-surgical pain and NP exists in a significant

proportion of patients, for years after TKR. Risk factors that might affect its prevalence and its intensity, found to be emotional functioning, such as depression and pain catastrophizing, number of comorbidities and early grade of osteoarthritis.

Application

Although it became recognizable the existence and the prevalence of PPSP and NP after TKR, these studies did not lead us to firm conclusions. There was mainly heterogeneity on the scales used to measured pain. Thus, further studies concerning the prevalence of PPSP and NP and their risk factors are needed, with pain-specific instruments.

Terminology

PPSP is the pain that is being developed after surgery, exists beyond the time for normal healing and is present for at least 3-6 mo. NP is defined as the pain caused by a lesion or a disease of the somatosensory nervous system.

Peer-review

This is a nice review article concerning postoperative knee pain after total knee arthroplasty.

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META-ANALYSIS

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

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Data sharing statement: No additional data are available.

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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°); (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) ScoliScore 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

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.

Noshchenko A, Hoffecker L, Lindley EM, Burger EL, Cain CMJ, Patel VV, Bradford AP. Predictors of spine deformity progression in adolescent idiopathic scoliosis: A systematic review with meta-analysis. *World J Orthop* 2015; 6(7): 537-558 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i7/537.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i7.537

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 ScoliScore™ 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 $\geqslant 25^{\circ}$) 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 $\geqslant$ 95%; Sp $\geqslant$ 95%; positive predictive value (+PV) $\geqslant$ 95%; and negative predictive value (-PV) $\geqslant$ 95% and the corresponding odds ratio (OR) between progressive and non-progressive curves should exceed 100 with a *P* value $\leqslant$ 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°)[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. *Hum Mol Genet* 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. *Spine* (Phila Pa 1976) 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. *Eur Spine J* 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. *Spine* (Phila Pa 1976) 2002; **27**: 2357-2362
5	Lonstein JE, Carlson JM. The prediction of curve progression in untreated idiopathic scoliosis during growth. *J Bone Joint Surg Am* 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. *Eur Spine J* 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. *J Pineal Res* 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. *PLoS One* 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. *J Pediatr Orthop* 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. *Spine* (Phila Pa 1976) 2014
11	Ogilvie JW. Update on prognostic genetic testing in adolescent idiopathic scoliosis (AIS). *J Pediatr Orthop* 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. *Spine* (Phila Pa 1976) 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. *Spine* (Phila Pa 1976) 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? *Med Hypotheses* 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. *Int Orthop* 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. *Spine* (Phila Pa 1976) 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. *Clin Orthop Relat Res* 2007; **462**: 53-58
18	Roye BD, Wright ML, Williams BA, Matsumoto H, Corona J, Hyman JE, Roye DP, Vitale MG. Does ScoliScore provide more information than traditional clinical estimates of curve progression? *Spine* (Phila Pa 1976) 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. *J Bone Joint Surg Am* 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. *Eur Spine J* 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. *Orthopedics* 2000; **23**: 833-838
22	Stokes IA, Aronsson DD. Disc and vertebral wedging in patients with progressive scoliosis. *J Spinal Disord* 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 & gt; 40 degrees: a magnetic resonance imaging study. *Spine* (Phila Pa 1976) 2007; **32**: 1680-1686
24	Sun X, Zhu ZZ, Qiu Y, Wang B, Li WG, 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]. *Zhonghua Waike Zazhi* 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. *Nat Genet* 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. *J Orthop Res* 2011; **29**: 1055-1058
27	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. Replication study of the association between adolescent idiopathic scoliosis and two estrogen receptor genes. *J Orthop Res* 2011; **29**: 834-837
28	Tang NL, Yeung HY, Hung VW, Di Liao C, Lam TP, Yeung HM, Lee KM, Ng BK, Cheng JC. Genetic epidemiology and heritability of AIS: A study of 415 Chinese female patients. *J Orthop Res* 2012; **30**: 1464-1469
29	Vijvermans V, Fabry G, Nijs J. Factors determining the final outcome of treatment of idiopathic scoliosis with the Boston brace: a longitudinal study. *J Pediatr Orthop B* 2004; **13**: 143-149
30	Wiley JW, Thomson JD, Mitchell TM, Smith BG, Banta JV. Effectiveness of the boston brace in treatment of large curves in adolescent idiopathic scoliosis. *Spine* (Phila Pa 1976) 2000; **25**: 2326-2332

31 Wise CA, Gao X, Shoemaker S, Gordon D, Herring JA. Understanding genetic factors in idiopathic scoliosis, a complex disease of childhood. *Curr Genomics* 2008; **9**: 51-59
32 Wu H, Ronsky JL, Cheriet F, Harder J, Küpper JC, Zernicke RF. Time series spinal radiographs as prognostic factors for scoliosis and progression of spinal deformities. *Eur Spine J* 2011; **20**: 112-117
33 Yamauchi Y, Yamaguchi T, Asaka Y. Prediction of curve progression in idiopathic scoliosis based on initial roentgenograms. A proposal of an equation. *Spine* (Phila Pa 1976) 1988; **13**: 1258-1261
34 Yang T, Jia Q, Guo H, Xu J, Bai Y, Yang K, Luo F, Zhang Z, Hou T. Epidemiological survey of idiopathic scoliosis and sequence alignment analysis of multiple candidate genes. *Int Orthop* 2012; **36**: 1307-1314
35 Yang T, Xu JZ, Jia QZ, Guo H, Luo F, Ye Q, Bai Y. [Comparative analysis of sequence alignment of SH3GL1 gene as a disease candidate gene of adolescent idiopathic scoliosis]. *Zhonghua Waike Zazhi* 2010; **48**: 435-438
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37 Ylikoski M. Spinal growth and progression of adolescent idiopathic scoliosis. *Eur Spine J* 1993; **1**: 236-239
38 Ylikoski M. Growth and progression of adolescent idiopathic scoliosis in girls. *J Pediatr Orthop B* 2005; **14**: 320-324
39 Yu Ws, Chan Ky, Yu FWP, Yeung Hy, Ng BKW, Lee Km, Lam Tp, Cheng JCY: Abnormal bone quality versus low bone mineral density in adolescent idiopathic scoliosis: a case-control study with in vivo high-resolution peripheral quantitative computed tomography. *Spine Journal* 2013
40 Zhang HQ, Lu SJ, Tang MX, Chen LQ, Liu SH, Guo CF, Wang XY, Chen J, Xie L. Association of estrogen receptor beta gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. *Spine* (Phila Pa 1976) 2009; **34**: 760-764
41 Zhao D, Qiu GX, Wang YP, Zhang JG, Shen JX, Wu ZH, Wang H. Association of calmodulin1 gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. *Orthop Surg* 2009; **1**: 58-65

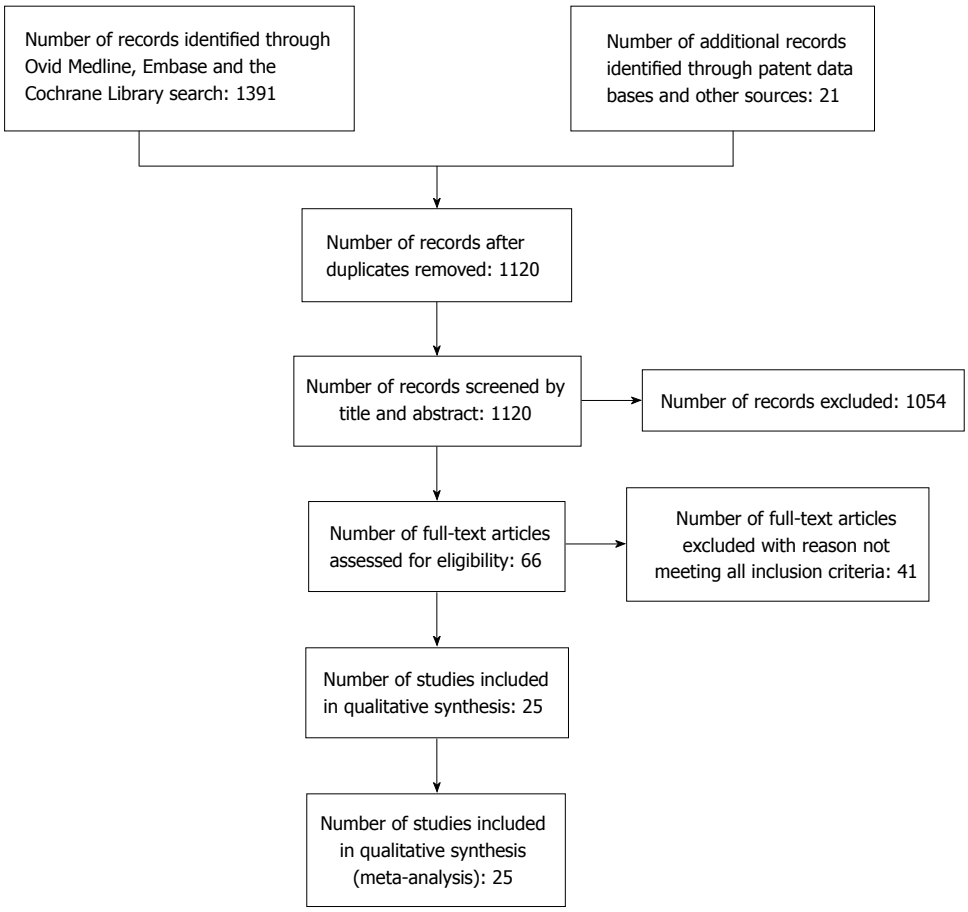

Figure 1 Flow diagram.

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 *et al*[73]	RCS	Art.	Thoracic, thoracolumbar, lumbar	< 18 Risser sign ⩽ 2	NS	85	Brace	20-45	Until skeletal maturity or surgical tretment	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 *et al*[62]	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 (uperTh12); (3) Imbalance (10 mm); and (4) Age	(1) Sensitivity: 81%[2]; (2) Specificity: 81%; (3) +PV: 82%; and (4) -PV: 80%
Ajemba *et al*[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 *et al*[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) Paraspinal EMG activity concave/convex ⩾ 1.3	(1) Sensitivity: 69%-79%[2]; (2) Specificity: 69%-79%; and (3) +PV: 60%-89%
[1]Danielsson *et al*[63]	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 *et al*[46]	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[3] (95%CI: 4.8-15724.2) P = 0.007 (1) Sensitivity: 100%; (2) Specificity: 100%; (3) +PV: 100%; and (4) -PV: 100%

[1]Lowe *et al*[47]	PChS	Art.	King I-V	Adolescents	F (93%) M (7%)	55	Observation (28) Brace (17) Fusion(10)	⩽ 25	1-3 yr	9.80%	Cobb increasing > 10° /yr	Comparative analysis of progress *vs* stable cases	Predictor: Increasing of platelet calmodulin level during first year of observation	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%
Sun *et al*[67]	RCS	Art.	Thoracic, thoracolumbar, lumbar	10-16	F (100%)	142	Brace	20-40	0.6-5.9 yr	NS	Cobb exceeding 45°, surgical tretment	Multiple logistic regression modeling	Predictors: (1) Premenarche; (2) Curve > 30°; and (3) Risser sign: 0-1	OR: 5.1-11.5[2] $P \leqslant 0.002$ (1) Sensitivity 72%-89%[3]; (2) Specificity 48%-77%; (3) +PV: 20%-33%; and (4) -PV: 94%- 97%
[1]Sun *et al*[66]	RCS	Art.	Thoracic, thoracolumbar	10-15	F (100%)	68	Brace	20-40	3-6 mo	NS	Cobb increasing > 6°, or exceeding 45°	Comparative analysis of progress *vs* stable cases	Predictors: (1) Premenarche; (2) Curve > 30°; (3) L2-L4 BMD < 0.76 g/cm^2; and (4) Thoracic curve	OR: 6.6-11.2[2] (0.001 > *P* < 0.072) (1) Sensitivity: 74.5%; (2) Specificity: 64.7%
Hung *et al*[65]	PCS	Art.	Thoracic, thoracolumbar, lumbar	11-16	F (100%)	324	Observation	20-30	0.5-3.5 yr	NS	Cobb increasing > 6°,	Multiple logistic regression modeling	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	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)
Lam *et al*[74]	PChS	Art.	NS	11-16	F (100%) Chinese population	294	Observation (192), Brace (102)	> 10; Mean: 26 (St. D, 8.2°)	Mean, 3.4 yr (St. D, 1.57°)	NS	Cobb increasing > 6°	Multiple logistic regression modeling	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	OR: 2.0-8.6[2] (0.0001 > *P* < 0.2) (1) Sensitivity: 84.7%; (2) Specificity: 66.5%
Lee *et al*[68]	RCS	Art.	NS	10-17	F (82.3%) M (17.7%)	1858 450	Brace (331)	10-30	NS	NS	Cobb > 30°	Risk assessment	Predictor: Initial Cobb angle ⩾ 26° *vs* 8°-10°	Hazard ratio, 8.8[2] (95%CI: 6.85-11.31)
Tan *et al*[36]	PCS	Art.	NS	7-14	F (84.9%) M (15.1%)	186	Observation Brace	> 10	1-8 yr	18%	Cobb ⩾ 30°	Risk assessment	Predictor: Initial Cobb angle ≥ 25° *vs* < 25°	OR = 24.6[2] (95%CI: 9.9-60.6) *P* < 0.001 (1) Sensitivity: 68%[3]; (2) Specificity: 92%; (3) +PV: 68%; and (4) -PV: 92%

Modi *et al*[77]	RCS	Art.	Thoracic, thoracolumbar	10-15	F (84%) M (16%)	113	Brace	40-56	Until skeletal maturity (Risser sign ⩾ 4); average: 34 ± 13 mo	NS	Cobb increasing ⩾ 5°	Comparative analysis of progress *vs* stable cases	Predictor: Rib-vertebral angle at convex side of the curve apex after brace treatment (< 65° *vs* ⩾ 65°)	OR = 5.6[3] (95%CI: 2.2-13.9) *P* < 0.001 (1) Sensitivity: 45%; (2) Specificity: 87%; (3) +PV: 69%; and (4) -PV: 71%
Qiu *et al*[69]	RCS	Art.	Thoracic, thoracolumbar	10-20	Chinese population	120	Brace	25-40	2.5 ± 0.35 yr	NS	Cobb increasing ⩾ 5°	Comparative analysis of progress *vs* stable cases	Predictor: *NTF3* gene: rs11063714, genotype GG *vs* AA	OR = 3.3[3] (95%CI: 1.0-10.9) *P* = 0.08 (1) Sensitivity: 43%; (2) Specificity: 82%; (3) +PV: 56%; and (4) -PV: 72%
Xu *et al*[70]	RCS	Art.	Thoracic, thoracolumbar, lumbar	10-15	F (87%) M (13%)	312	Brace	20-40	0.6-2.2 yr	NS	Cobb increasing ⩾ 5° and/or surgical correction	Logistic regression modeling	Predictors: (1) *ERα* gene: rs9340799, allele G; (2) *TPH1* gene: rs10488682, allele A; (3) Risser sign O-1; and (4) Curve ⩾ 30°	OR: 1.2-3.6[2] 0.0001 > *P* < 0.1 (1) Sensitivity: 51%; (2) Specificity: 82%; and (3) Correct predictions: 75%
Yeung *et al*[75]	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 rs5742612: TT; TC; and CC	Predictor: TT (mean Cobb, 38 ± 12.1, *n* = 169) *vs* CC (mean Cobb, 33° ± 9.0, *n* = 33), *P* = 0.01 Cut-point: Cobb, 35.7°	OR = 2.1[3] (95%CI:1.0-4.4) *P* = 0.1 (1) Sensitivity: 88%; (2) Specificity: 22%; (3) +PV: 57%; and (4) -PV: 61%
[1]Ward *et al*[58]	RChS	Art.	Severe: 8% Moderate/ mild: 92%	9-13 at diag-nosis	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 (⩽ 1% risk of progression)	OR=16.8[3] (95%CI: 6.6-42.7) *P* < 0.001 (1) Sensitivity: 91%; (2) Specificity: 63%; (3) +PV: 17%; and (4) -PV: 99%
[1]Bohl *et al*[59]	RCS	Art	NS	⩾ 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) *P* = 0.05 (1) Sensitivity: 78%; (2) Specificity: 86%; (3) +PV: 88%; and (4) -PV: 75%

Zhao *et al*[71]	RChS	Art	Double curves: thoracic, thoracolumbar or lumbar	10-20	Cases (AIS): F (90%) M (10%) Controls: F (75%) M (25%) Chinese population	67 100	Surgical correction	30-90	NS	NS	Cobb ⩾ 30°	Comparative analysis of cases *vs* healthy controls	Predictors: (1) *ER1* gene: rs2234693, allele T; (2) *CALM 1* 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 *et al*[72]	RCS	Art.	NS	11-18	F (100%) Chinese population	241	NS	20-100	Until skeletal maturity	54%	NS	Comparative analysis of severe cases (mean Cobb, 36° ± 13°) *vs* moderate cases (mean Cobb, 29° ± 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 *et al*[44]	RChS	Art.	Thoracic, thoracolumbar, lumbar	13-20	Cases (AIS): F (83%) M (17%) Controls: F (65%) M (35%)	41 17	Surgical correction	30-90	NS	NS	NS	Comparative analysis of AIS cases (mean Cobb, 54° ± 14°) *vs* controls (non- idiopathic deformities)	Predictor: low inhibition of forskolin stimulated cAMP by melatonin in osteoblasts *vs* 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 *et al*[16]	PCS	Art	Asymptomatic subjects at-risk of AIS	5-15	F (65%) M (35%)	31	Observation	⩽ 10	2 yr	NS	Cobb > 10°	Comparative analysis of cases with developed AIS spine deformity (mean Cobb, > 10°) *vs* subjects at risk, but without deformity	Predictor: peripheral blood mononuclear cells electrical impedance after melatonin or iodomelatonin administration: < 120 ohms *vs* ⩾ 120° homs	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 *et al*[61]	RChS	Art	NS	NS	NS	162 794	NS	NS	NS	NS	Cobb angle ⩾ 45° 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 *vs* 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 *et al*[76]	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 *vs* stable	Predictor: Brain stem function, abnormal vestibular-eye test *vs* 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%

[1]Study used industrial or other sponsorship; [2]Predictive characteristics reported in the collected publication; [3]Predictive characteristics calculated by authors of current review using extracted results. PChS: Prospective cohort study; RChS: Retrospective cohort study; PCS: Prospective case series; RCS: Retrospective case series; +PV: Positive predictive value; -PV: Negative predictive value; NS: Not specified; EMG: Electromyography; SNP: Single nucleotide polymorphism; NTF3: Neurotropin-3; IGF1: Insulin-like growth factor 1; ERα: Estrogen receptor alpha; Il-17RC: Interleukin 17 receptor C; CALM1: Calmodulin1.

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[36,68]; (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 $\geqslant 5°$ 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 *et al*[73]	Yes	Yes	Unsure	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	8
Peterson *et al*[62]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	Yes	Yes	10
Ajemba *et al*[60]	Yes	Yes	No	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	10
Cheung *et al*[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	10
Danielsson *et al*[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	13
Kindsfater *et al*[46]	Yes	Yes	No	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	10
Lowe *et al*[47]	No	No	Yes	Yes	Yes	No	No	Unsure	Yes	Yes	Yes	Yes	No	No	7
Sun *et al*[67]	Yes	Yes	No	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	10
Sun *et al*[66]	Yes	Yes	No	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	10
Hung *et al*[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	No	10
Lam *et al*[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	Yes	Yes	11
Lee *et al*[68]	Yes	Yes	No	Yes	Yes	Yes	No	Unsure	No	No	Unsure	Yes	No	Yes	7
Tan *et al*[36]	Yes	Yes	Yes	Yes	Yes	Yes	No	Unsure	Yes	Yes	Yes	Yes	Yes	Yes	12
Modi *et al*[77]	Yes	No	No	Yes	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	No	No	6
Qiu *et al*[69]	Yes	Yes	No	No	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	No	7
Xu *et al*[70]	Yes	Yes	No	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	9
Ward *et al*[58]	Yes	No	No	Yes	Yes	Yes	Yes	Unsure	No	No	Unsure	No	Yes	Yes	7
Bohl *et al*[59]	Yes	Yes	No	Yes	Yes	No	Yes	Unsure	No	Yes	No	Yes	Yes	Yes	9
Zhao *et al*[71]	Yes	No	Unsure	Yes	Yes	Yes	Yes	Unsure	No	No	Unsure	Yes	No	Yes	7
Zhou *et al*[72]	Yes	Yes	No	Yes	No	Yes	Yes	Unsure	Yes	Yes	No	Yes	Yes	Yes	10
Moreau *et al*[44]	Yes	Yes	No	Yes	No	Yes	Yes	Unsure	No	No	Unsure	Yes	No	Yes	7
Akoume *et al*[16]	Yes	Yes	No	Yes	Yes	Yes	Yes	Unsure	Yes	No	Unsure	Yes	No	Yes	9
Akoume *et al*[61]	No	No	No	No	Yes	No	Unsure	Unsure	No	No	Unsure	Yes	No	No	2
Yamamoto *et al*[76]	Yes	No	No	Yes	Yes	No	No	Unsure	Yes	No	Unsure	Yes	Yes	No	6
Yeung *et al*[75]	Yes	No	No	Yes	No	Yes	Yes	Unsure	No	No	Unsure	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, $P \leqslant 0.03$[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 ($P \leqslant 0.01$)[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° 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, $P \leqslant 0.03$. 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°[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, $P \leqslant 0.06$. 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 premenarche status at diagnosis and progressive AIS in 980 girls. Five studies enrolled patients with Cobb angle < 40° [63,65-67,74], and one with Cobb angle 40°- 56°[77]. Criteria for progression were different: increase of Cobb angle > 5°, 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°. 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°, 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°), 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°[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 $P \leqslant 0.1$. 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%; +PV43%; -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° ± 13.1°) than those patients with AG genotype ($n = 26$; mean Cobb angle, 28.9° ± 7.4°), $P = 0.007$. 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° ± 12.1°) higher than those who had TC ($n = 138$; mean Cobb angle, 35.6° ± 12.0°) or CC ($n = 33$; mean Cobb angle, 33.3 ± 9.0°) 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%; -PV61%.

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 ⩾ 20°: 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 ⩾ 45°) than FG1 or FG3 groups. In particular, among 162 patients with a Cobb angle of ⩾ 45°, 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/μg 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/μg protein, while 12 patients with stable deformities had platelet CaM from 0.09 to 1.16 ng/μg 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 ⩾ 10° 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 ⩽ 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), ScoliScore 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

[1]Multiple 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 (Tale 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 fibrilin-1 and fibrilin-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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CASE REPORT

Florid reactive periostitis ossificans of the humerus: Case report and differential diagnosis of periosteal lesions of long bones

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Abstract

A case of florid reactive periostitis ossificans (RPO) arising in a long bone is presented. This is a rare bone proliferation with a pronounced periosteal reaction. Less than 100 cases have been described in the literature with far fewer outside the bones of the hand, feet, fingers, and toes. Although the etiology is unknown, a relationship to preceding trauma is suggested. The imaging and histologic features show an overlap with other bone lesions including bizarre parosteal osteochondromatous proliferation, subungual exostosis, and malignant surface tumors of bone and cartilage which include, periosteal and parosteal osteosarcoma. It is important to recognize the clinical presentation and diagnostic features of RPO as a benign entity so that it is not mistaken for a more aggressive neoplasm. We present a case of a right distal humeral lesion that on histopathological review revealed florid RPO. This diagnosis was not suspected on imaging studies, but was made on open biopsy of the mass. The patient remains disease free, years postoperatively. In addition to presenting this unique case report, we review the pertinent literature, and offer a differential diagnosis and treatment strategy for its management.

Key words: Bizarre parosteal osteochondromatous proliferation (Nora's lesion); Reactive tumor-like lesions of long bones; Florid reactive periostitis ossificans; Periosteal and parosteal osteosarcomas

Core tip: Florid reactive periostitis ossificans (RPO) is a rare benign entity that is classically localized to the phalanges of the distal extremities. This lesion is often clinico-radiologically and histologically confused for malignant entities, like osteosarcoma and chondrosarcoma. We report a rare presentation of this lesion arising from the posterior aspect of the right elbow in a 38-year-old woman, diagnosed on biopsy. Recognizing the key similarities and differences between florid RPO, and other similar appearing disorders discussed in this paper, can prevent the pitfall of misdiagnosis and unnecessary aggressive surgery.

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INTRODUCTION

Reactive or reparative lesions of bone, which historically have been related to trauma, include subungual exostosis, giant cell reparative granuloma, florid reactive periostitis, and bizarre parosteal osteochondromatous proliferation (BPOP)[1]. Spjut and Dorfman[2] first identified reactive periostitis in 1981 within small tubular bones (phalanges, metacarpals, metatarsals) of the hands and feet. Typically florid reactive periostitis occurs in adolescent or young adults and presents as a small area of painful swelling and erythema over the affected bone[3,4]. As noted, these tumors typically occur in the bones of the hands and feet, but they may also present in long bones of the axial skeleton, as in our case[3-5]; when they occur in the phalanges, they are clinically reassuring, because such lesions are more likely to be benign than malignant (21:1)[4,5]. Regardless, it is important to recognize them so that they are not misdiagnosed. In this case report, we present an unusual presentation of this lesion, discuss its clinical, radiologic, and histologic appearance, review the pertinent literature, and offer a differential diagnosis and treatment strategy for its management.

CASE REPORT

A 38-year-old woman presented with a 2-mo interval of throbbing pain in her right elbow, which was aggravated by bending and lifting. The first time the patient noticed pain was soon after completing a half marathon where she carried her phone in her right hand. On physical examination she was found to have moderate swelling in the posterior aspect of her elbow along with a mild effusion and significant tenderness in the posterior-lateral compartment.

Conventional radiographs revealed an irregular mass posterior to the distal humerus just superior to the olecranon fossa (Figure 1). Magnetic resonance imaging showed extensive edema in the distal triceps muscle adjacent to the mass. A CT scan showed diffuse calcifications within the mass. No bony destruction was seen (Figure 2). At this point the differential diagnosis included atypical myositis ossificans or a neoplastic process. A repeat CT after 11 wk showed a 2.0 cm × 1.9 cm osseous excrescence arising from the posterior distal humeral metaphysis (Figure 3). The differential considerations broadened to include BPOP, a low-grade parosteal osteosarcoma, or less likely a periosteal chondroma. An open biopsy was performed through a posterior excision.

Operative findings revealed pallor of the anterior deep triceps and significant edema of the distal triceps. The specimen was removed piece-meal. The gross appearance was of loosely adherent tan-gray fibrous tissue. The distal portion of humerus showed focal necrosis and hemorrhage. Based on this appearance, an infectious etiology was considered and a fragment of the lesion was submitted for aerobic, anaerobic, mycobacterial, and fungal cultures. Histologic examination revealed mixed bland spindle cells adjacent to osteoblastic proliferation with reactive (woven) new bone formation (Figure 4). Zonation was seen suggestive of myositis ossificans (heterotopic ossification). Osteomyelitis was ruled out because of a lack of a significant inflammatory infiltrate. Osteosarcoma was ruled out because of lack of cellular atypia or tumor osteoid. There were no cytomorphologic features of a parosteal (low grade) osteosarcoma.

After surgery, her elbow motion improved from 30-degree flexion to full flexion and full forearm rotation over several weeks. The wrist and hand motion were judged to be normal with normal neuromuscular function. Neither recurrent heterotopic bone nor osteoblastic proliferation of the posterior humerus was seen radiographically. She was discharged home on a supportive Dynasplint with follow up on an outpatient basis.

DISCUSSION

Florid reactive periostitis is a benign bone lesion characterized by an aggressive periosteal reaction and soft-tissue inflammation[2,3]. This rare tumor has been identified by various names such as, pseudomalignant osseous tumor of the soft tissue, fasciitis ossificans, parosteal fasciitis and benign fibro-osseous pseudotumor[6]. For classification purposes this diagnosis is often grouped with either pseudomalignant osseous tumors of the soft tissue or myositis ossificans. Due to its mild course, it is generally managed by observation after initial biopsy, but rarely it can be locally aggressive and recurrent[7]. The imaging and histologic features of this benign bone lesion, show an overlap with other

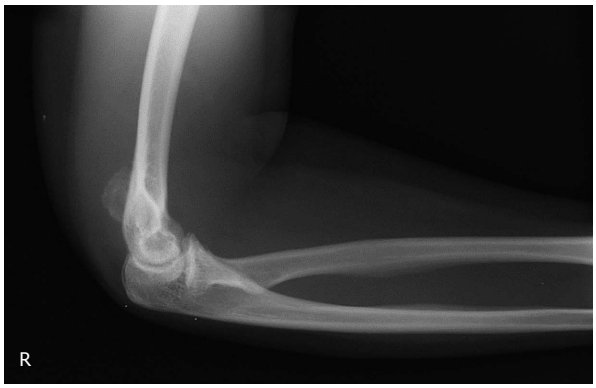

Figure 1 Conventional radiograph at two months from onset revealing an irregular mass posterior to the distal humerus superior to the olecranon fossa.

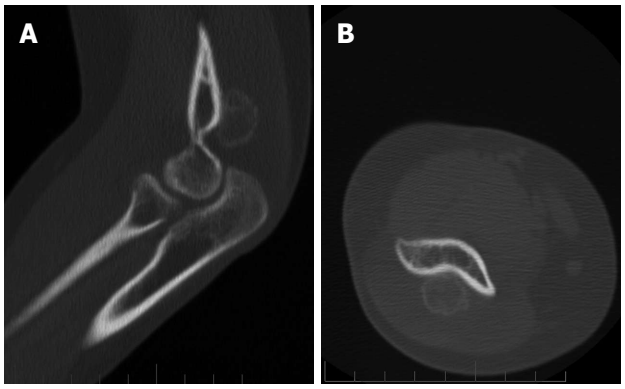

Figure 2 Sagittal (A) and axial (B) views demonstrating fine calcifications within the mass; no boney destruction was seen.

bone lesions including BPOP, subungual exostosis, osteomyelitis, myositis ossificans, and malignant surface tumors of bone and cartilage which include, conventional, periosteal and parosteal osteosarcoma.

Like florid reactive periostitis, BPOP (also known as Nora's lesion) is also a rare entity that is grossly described as an exophytic outgrowth of the cortical surface of the phalanges of the hands and feet[6,8]. It is composed of a disorganized mixture of bone, cartilage, and fibrous tissue and the upper extremities are four times more affected than the lower extremities[8-10]. This lesion can present itself at any age, but individuals in their 20's and 30's are higher at risk[10-12]. It is sometimes mistaken for a malignant process due to its high rate of recurrence, proliferative nature, and atypical microscopic appearance[12]. However, unlike osteosarcoma, on imaging BPOP lacks cortical flaring and communication with the underlying medullary canal[12-15]. On histology, the exophytic bone mass has a characteristic dark blue tinctorial quality, especially at the interface with the cartilage. The intertrabecular spaces contain proliferating spindle cells that lack cytological atypia. The cartilaginous component is hypercellular and contains irregular groups of binucleated and "bizarre" chondrocytes. Although double-nucleated chondrocytes are common, hyperchromasia and cytological atypia are typically not present[13,16].

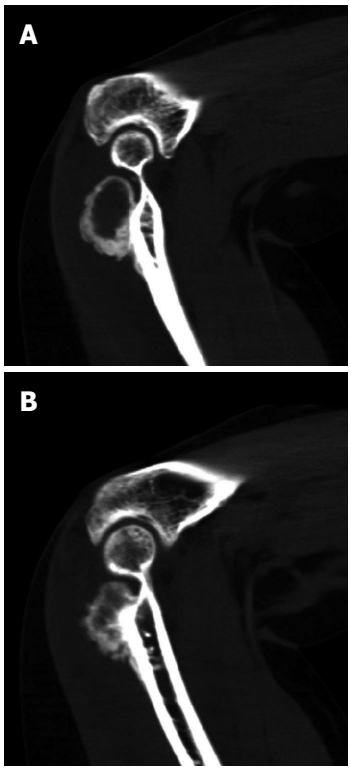

Figure 3 Computed tomography scan 11 wk after the initial imaging showing a 2.0 cm × 1.9 cm osseous excrescence arising from the posterior distal humeral metaphysis.

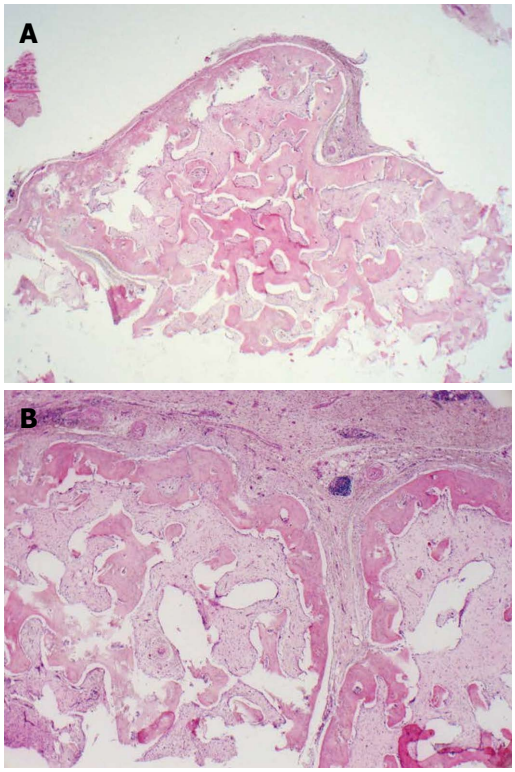

Figure 4 Histologically the lesion was composed of woven bone in the background of mildly cellular bland spindle cells [haematoxylin and eosin, original magnification x 40 × (A), and × 100 (B)].

Another benign lesion that occurs in relation to the long bones (and shows overlapping radiologic and histologic findings with reactive periostitis) is myositis ossificans traumatica[17]. This lesion most commonly occurs in the muscles of the arms or in the quadriceps following covert or overt trauma[17]. On imaging, soft tissue calcifications are visible within 2–6 wk of the inciting incident. Peripheral ossification is the characteristic feature noted on CT[17,18]. This lesion is generally not biopsied as it rapidly resolves, but if clinical and imaging studies are inconclusive, an open biopsy may be indicated. There are three phases of myositis ossificans: acute (fibroblastic zone), subacute (osteoblastic zone), and late (calcified zone). Detection of this zonal phenomenon on histology is diagnostic of myositis ossificans[17,18].

Chronic osteomyelitis may also be in the differential diagnosis. This diagnosis is made radiologically by the presence of an osteolytic center with a ring of sclerosis on conventional imaging[19]. Additionally, a culture of the biopsy tissue is needed to support the diagnosis and identify the specific pathogen. Histology often only shows sclerotic bone with chronic inflammatory cells[20]. Due to its infectious etiology, treatment involves surgical debridement and prolonged antibiotic therapy.

Furthermore, subungual exostoses can also mimic florid reactive periostitis. These are bony projections that protrude from the dorsal aspect of the distal phalanx[21]. The reason it occurs on the dorsal aspect is thought due to the fact that the periosteum is relatively loose dorsally, but very tightly adherent on its volar aspect[22]. Due to its location, this lesion may lead to the destruction of the nail bed causing considerable pain or discomfort. There is a reproducible translocation [t(x; 6) (q13; q22)] associated with this diagnosis and thus, it may be considered a true neoplasm. Surgical excision is the mainstay of therapy.

Lastly, malignant osteoblastic tumors including parosteal, periosteal, and conventional osteosarcoma are considered in the differential diagnosis. These tumors are most prevalent in children and young adults[23,24]. They are localized at the end of long bones. Most often they affect the proximal end of the tibia or humerus, or the distal end of the femur. Of the three types, parosteal osteosarcoma has the best prognosis, followed by periosteal and then conventional. Periosteal osteosarcoma is the most uncommon among the three types[25]. This lesion most commonly appears in the diaphysis or metadiaphysis of the tibia and femur. Grossly, the tumor may form a cavity deep in the cortex with radiating striations that may break into the medullary cavity as the disease progresses. Histologically, there is a prominent cartilaginous component to this tumor with a small amount of osteoid production. Treatment depends on grade. Low-grade lesions may be treated with wide surgical excision alone, while higher-grade lesions may require chemotherapy in addition to surgery[25]. Parosteal osteosarcoma is the most frequently occurring osteosarcoma and thus it is crucial to diagnostically separate this entity from reactive periostitis. Seventy percent of the time, it arises in the metaphysis of the posterior aspect of the distal femur and less frequently involves the proximal tibia and humerus. It is composed of a dense osteoid component that extends from the outer cortex *via* a narrow zone[26,27]. Histologically, it exhibits an extensive boney matrix with a hypocellular stroma and mild to minimal fibroblastic cellular atypia. Radiologically, it takes the appearance of a firm, lobulated "cauliflower-like", lesion encircling the bone. A thin radiolucent line delineating the tumor from the cortex, known as the "string sign", is seen radiologically in 30% of cases. Treatment for parosteal osteosarcomas usually involves surgical resection without neoadjuvant chemotherapy, as these tumors are commonly low-grade in nature[26,27]. Conventional osteosarcoma can usually be easily separated from reactive periostitis. Histologically, these tumor cells are very pleomorphic with numerous atypical mitoses that are entrapped in the osteoid matrix. Complete radical surgical *en bloc* resection with chemotherapy is the treatment of choice for conventional osteosarcoma[25].

It can be appreciated from the above differentials that the diagnosis of florid reactive periostitis is often challenging. Therefore, a careful assessment of clinical history, radiology, and pathology are helpful in reaching an accurate diagnosis. Although rare, this entity should be considered in the differential diagnosis of any osteogenic growth in long bones. Being aware of the above differentials can assist in separating this benign entity from its malignant mimickers. Once the malignant and infectious imitators of this lesion are ruled out, treatment can be discussed. When presenting early, this process can be treated conservatively with rest and nonsteroidal anti-inflammatory medication. When presenting late, with an aggressive nature and/or with recurrence, wide local resection is considered treatment of choice.

COMMENTS

Case characteristics

A 38-year-old woman with no significant medical history presented with a 2-mo history of throbbing pain in her right elbow, which was aggravated by bending and lifting.

Clinical diagnosis

Moderate swelling in the posterior aspect of her elbow along with a mild effusion and significant tenderness in the posterior-lateral compartment.

Differential diagnosis

Atypical myositis ossificans, bizarre parosteal osteochondromatous proliferation, low-grade parosteal osteosarcoma, periosteal chondroma or chondrosarcoma.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

CT showed a 2.0 cm × 1.9 cm osseous excrescence arising from the posterior distal humeral metaphysis.

Pathological diagnosis

Florid-reactive periostitis ossificans.

Treatment
Complete surgical excision of lesion.

Related reports
Reactive periostitis ossificans is a benign entity that classically present in the hands/feet, very rarely it has been reported in long bones with an etiology related to trauma. This entity is commonly confused for a neoplastic process due to its unusual location and can at times even histologically mimic sarcoma.

Term explanation
Benign parosteal osteochondromatous proliferations (BPOP) is a rare cartilaginous neoplasm that like reactive periostitis ossisficans (RPO) presents in the hands/feet. BPOP is known to be locally aggressive and requires extensive surgical resection.

Experiences and lessons
This is entity is commonly confused for a neoplastic process due to its unusual location and can at times even histologically mimic sarcoma. Recognizing this as a diagnostic pitfall can prevent misdiagnosis and eliminate the need for aggressive surgical treatment.

Peer-review
The paper is well written.

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