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EXPERT CONSENSUS

Consensus Delphi study on guidelines for the assessment of anterior cruciate ligament injuries in children

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Abstract

Background: Knee examination guidelines in minors are intended to aid decision-making in the management of knee instability. Clinical question: A Delphi study was conducted with a formal consensus process using a validated methodology with sufficient scientific evidence. A group consensus meeting was held to develop recommendations and practical guidelines for use in the assessment of instability injuries in children. Key findings: there is a lack of evidence to analyse anterior cruciate ligament injuries in children and their subsequent surgical management if necessary. Diagnostic guidelines and clinical assessment of the patient based on a thorough examination of the knee are performed and a guide to anterior cruciate ligament exploration in children is developed. Clinical application: In the absence of a strong evidence base, these established guidelines are intended to assist in that decision-making process to help the clinician decide on the most optimal treatment with the aim of benefiting the patient as much as possible. Following this expert consensus, surgical treatment is advised when the patient has a subjective sensation of instability accompanied by a pivot shift test ++, and may include an anterior drawer test + and a Lachman test +. If these conditions are not present, the conservative approach should be chosen, as the anatomical and functional development of children, together with a physiotherapy programme, may improve the evolution of the injury.

Key Words: Anterior cruciate ligament; Diagnoses and examinations; Sports injuries; Knee; Injury to minors

Core Tip: A Delphi study was conducted with a formal consensus process using validated methodology with scientific evidence to develop recommendations and practical guidelines for the assessment of instability injuries in children. Following this expert consensus, surgical treatment is advised when the patient has a subjective sensation of instability accompanied by a pivot shift test ++, and may include an anterior drawer test + and a Lachman test +. If these conditions are not present, the conservative approach should be chosen, as the anatomical and functional development of children, together with a physiotherapy programme, may improve the evolution of the injury.

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INTRODUCTION

Physiopathology of the anterior cruciate ligament

The anterior cruciate ligament (ACL) has a viscoelastic capacity that provides the possibility of dissipating the energy received through adjustments in its length and in the internal distribution of loads[1,2], that is, it has the capacity to generate microscopic adjustments in relation to the internal stresses it has to withstand[3].

ACL injury occurs as a result of excessive force in the anterior translational direction of the tibia or rotation of the femur on the tibia[4].

The most common mechanism of ligament failure is the sequential rupture of bundles of collagen fibres distributed throughout the ligament and not located in a specific area. As it does not have the plastic capacity to deform, ruptures of the ligament are defined as total or partial. There is controversy regarding what is a partial rupture, and there are studies that define it as a hemorrhage in the femoral insertion while others define it as a rupture of the anteromedial and posterolateral fascicles. The American Medical Association establishes a classification in which partial tears correspond to second-degree ligament injuries. Another way of estimating the type of injury is in relation to the percentage of the ligament injured. Partial tears are considered to be between 25% and 75%[5-8]. Partial tears in turn can be classified as high grade when more than 50% of the fibres of the ligament are involved or low grade when the involvement is less than 50%[8].

In general, a partial ACL injury can be defined as a combination of the following factors[8]: (1) Asymmetrical Lachman test result; (2) Pivot Shift negative; (3) Measurement with KT-1000 less than or equal to 3 mm; and (4) Arthroscopic evidence of partial ACL injury.

Adults more frequently suffer ruptures in the medial substance while lesion settlement in children is more frequently observed between the layers of mineralized and non-mineralized fibrocartilage[9].

Once the histological rupture occurs, the ACL goes through four phases: inflammatory, epiligamentous regeneration, proliferative and remodeling. These states are similar to those occurring in other connective tissues but with peculiarities, probably related to two facts: Firstly, the ACL is immersed in the synovial fluid which, due to its characteristics, modifies cell metabolism and the inflammatory response, also preventing the formation of the fibrin clot necessary for the union of the ends of the rupture; furthermore, the vascularization of the ACL after rupture is compromised as the vascular branches that irrigate it also break[10-13]. The flow of synovial fluid is responsible for the fibrin clot not forming by dispersing the blood in the form of hemarthrosis[13]. As a consequence of this lack of fibrin clot there is a decrease in proteins of the extracellular matrix and cytosines such as fibrinogen and fibronectin and Willebrand factor within the ACL wound[14,15].

In injuries of tibial eminence fractures it has been observed that ACL fibres suffer plastic deformation with permanent elongation of the fibers. This fact may be responsible for residual clinical laxity even in cases where surgical reduction or healing has occurred[16].

Ethiopathogenesis of anterior cruciate ligament injuries

The mechanisms of injury are multifactorial and include both extrinsic and intrinsic causes[17-24].

The type of pattern of ACL injury depends on the degree of skeletal maturity, this fact may be related to differences in skeletal rigidity and conditions the type of injury in both groups. Tibial avulsion injuries and partial ACL ruptures are more frequent in patients with skeletal immaturity and complete ruptures are more frequent in mature or partially mature patients[25].

The ACL can be injured by two mechanisms, direct contact or non-contact. Approximately 70% of them are due to non-contact injury mechanisms[24-26]. Not all authors define ACL contact injuries in the same way; while some authors define them in relation to those that occur in the absence of contact between players, others define them as the absence of a direct blow to the knee. In fact, there are authors who define "non-contact injuries with disturbance" by referring to injuries resulting from body-body contact, but without direct trauma to the knee[25]. Contact injuries involve injurious mechanisms of hyperextension or excessive valgus stress while the mechanisms that occur in non-contact injuries occur during the development of rapid decelerations or rotations performed in gestures involving pivoting on a fixed foot[27]. In addition, non-contact injuries are often accompanied by an internal hip rotation. This body position in non-contact injuries leads to a collapse in knee valgus or "dynamic knee valgus"[28-30]. It has also been observed that in non-contact injuries the centre of body mass is delayed in relation to the supporting base[24]. Although, as indicated above, the type of injury may be influenced by the degree of skeletal maturity, the injury mechanisms are the same in children and adults[25].

Several studies have shown that non-contact injuries from team ball sports occur at a bending angle of less than 30°. Modifications of the knee valgus angle were observed: in basketball where there was an increase from 4° to 15° in 30 ms, in handball from 3° to 16° in 40 ms, and these periods coincide with the maximum vertical force[31-33]. From this it can be deduced that the valgus position in a relatively straight leg (15°-40°) may be a key factor in the risk of ACL injury. It has also been observed that female athletes with a higher risk of injury land in a position of higher dynamic valgus and high loads of separation. In alpine skiing, other situations are observed such as phantom foot mechanisms, boot-induced anterior drawer mechanisms or external valgus-rotation mechanism[34,35].

It is also important to know the injury mechanisms affecting the posterolateral complex (PCL) of the knee as they represent 16% of all ligament injuries of the knee; of the total PCL injuries only 28% occur in isolation, the rest being associated with ACL injury[36,37]. The common mechanisms of injury of this complex are related to forces in the posterolateral direction of the tibia, hyperextension of the knee and elevated external rotation of the tibia when the knee is in a position of partial flexion. The most frequent contexts in which these injuries occur are sports injuries, road accidents and falls[38].

Biochemical and structural changes following injuries to the ACL

After an injury at the level of the ACL, a significant increase in metalloproteinases and interleukins at the level of the matrix is observed. Due to the existence of poor vascularization of the articular cartilage and tendons of the knee, the possibility and capacity to eliminate these inflammatory cytokines is diminished. The effects of this difficulty in elimination, causes an increase in the activity of the same that can be translated with irreversible alterations at the level of the collagen and the anchorage points of the ACL[39].

Modifications have also been observed in terms of muscle mass and volume, with significant atrophy in the knee musculature of the injured extremity, mainly in the quadriceps, which may be related to the presence of edema in the knee joint[40]. Altered quadriceps activation and the appearance of asynchronous contractions of the medial and lateral ischiotibial muscles have been reported after these injuries[40]. The changes produced in the quadriceps muscle mass may be due to adaptations of the muscle fibres together with the formation of alternative substances at the level of the matrix[39]. Some of the adaptations that occur at the level of the muscle fibre are the transition from type I to type IIa or IIb muscle fibres. These adaptations are not suffered in the same way by the different muscles[39]. Together with this, the lack of use decreases the size of the myofibre and stimulation at the level of the motor neuron[39].

At the biochemical level, alterations have been found in alpha-2 macroglobulin, myostatin, protein-72, mechano GF-C24E, synovial fluid and histochemical alterations at the level of collagen and cartilage [39].

In relation to the alteration of collagen after ACL injury, studies by Li *et al*[41] reveal that the degradation of collagen after ACL injury is irreversible and is replaced by another type of less structured collagen, thus affecting the integrity of the structure as a whole. This alteration in the synthesis of the correct collagen may be related to a greater probability of developing post-traumatic osteoarthritis.

Most knees with ACL injury experience altered levels of anti-inflammatory chemotactic cytosines causing longer periods of inflammation. In addition, pro-inflammatory and proteoglycan chemicals have been identified with consequent deterioration of the knee joint in patients with ACL injury[41].

Variations in the levels of certain chondrocyte-degrading interleukins have also been observed[42]. In addition, these biochemical modifications can also influence the level of bone tunnels in ACL reconstructions[43]. Therefore, the synovial fluid will have a significant and important effect on knee recovery[41].

Risk factors for anterior cruciate ligament injury

Risk factors for injury are classified into extrinsic and intrinsic causes[17-24]. Intrinsic causes are related to factors specific to the individual such as genetic, hormonal, anatomical factors, gender, neuromuscular and cognitive function, as well as previous injury to the knee. Extrinsic causes are external to the individual and among these factors the most studied are the level and type of activity, the type and surface of play, environmental conditions and the material used for the development of the sport or activity[44].

It is interesting that trained athletes have a high risk of breakage[45]. This fact may be related to situations in which there is an increase in joint efficiency. This occurs in situations where the individual acquires a greater degree of skill after practicing joint movements, which causes a decrease in antagonistic coactivation, making the ACL the only joint stabilizer in these circumstances[46]. Other studies also show the synergy between the stabilizing function of the rotational laxity of the ACL and the antagonistic coactivation of the hamstrings[47].

Anatomical changes in the knee in relation to age and gender

The anatomical region with the highest number of injuries in children and adolescents is the knee, which suffers up to 60% of injuries in the sports environment[31]. Among knee injuries, ACL ruptures have a 10 times higher incidence than the rest of the injuries. The relationship between specific anatomical characteristics and the risk of ACL injury has been studied, as well as the relationship with changes in anatomical characteristics during the stages of growth and skeletal maturation. Kiapour Ata [48] in 2016 conducted a study in which he observed significant differences in both the size and orientation of the age-dependent ACL in both females and males in healthy knees. They presented preliminary results indicating that changes in ACL size in relation to length, cross-section and area are significantly different in boys than in girls. Although it was observed that the ACL became more vertical in both the sagittal and coronal planes with similar patterns in boys and girls, the area of the ACL (cross-section) increased more in boys during early school age and late adolescence while girls showed this modification only when they became adolescents[48]. The same author also studied modifications of femoral condyles in relation to age and sex: Both bicondylar width and intercondylar notch increased continuously in boys after becoming adolescents, remaining constant in young adolescents; girls showed a higher medial femoral condyle curvature in late adolescents compared to boys of the same age and a more curved lateral femoral condyle compared to boys. They also found age-related anatomical modifications of the tibial plateau in both girls and boys. There was a difference in size, more pronounced in boys; slope, greater in girls; and depth, greater in boys, of the tibial plateau between girls and boys in the stages following skeletal maturation[49-52].

Risk factors for ACL rupture in skeletally immature patients

Risk factors for ACL rupture in skeletally immature patients are divided into intrinsic and extrinsic factors.

The most studied, and therefore best known, intrinsic factors are those related to anatomy: increased pelvic tilt, increased femoral anteversion, increased Q-angle, increased tibial slope fall, increased foot pronation, scaphoid fall and decreased intercondylar notch[48,50]. Also very important as a risk factor is female gender where ACL ruptures are 6 times more frequent compared to men[50]. In relation to this data, it is known that female patients are usually accompanied by data on hypermobility-hyperlaxity together with genu valgus and genu recurvatum[51].

In relation to hormonal factors, the relationship between the phase of the menstrual cycle and rupture of the ACL has been observed to be greater in the follicular phase where the concentration of estrogen is higher[50].

In relation to extrinsic factors, the most important are climatic conditions, footwear and its interaction with the playing field and court.

During summer conditions of light rain followed by evaporation of the same, this causes the surface to harden increasing ACL injuries in these conditions. It has also been studied how certain characteristics of footwear such as size, height and position of the lateral margin of the sole may increase ACL injuries[48,50,52].

Risk factors for injury to the anterior cruciate ligament in relation to its size

As previously mentioned, anatomical conditions are important in ACL injuries. The size of the ACL may be a risk factor for injury in those cases where there is a decrease in the size of the ACL. Davis *et al* [53] and Dienst *et al*[54] have presented studies relating the size of the ACL to greater risk of injury in load situations.

Intercondylar notch is another factor to be taken into account. Narrow intercondylar notches are associated with risk of ACL injury. Narrow intercondylar notches cause increased loading on the ACL [55-59]. With the consequent risk of injury; the correlation between narrow intercondylar notches and small ACLs has also been observed, with the width of the intercondylar notch being connected to the area of the ACL cross-section in pediatric populations, and is responsible for 24%-26% of the variations in the ACL cross-section area[48]. Narrow intercondylar notches produce a mechanical impact on the ACL and may have a tearing effect on the ACL when subjected to repetitive and high-risk movements, reducing the structural properties of the ligament over time[48].

Female sex in young adolescents is a risk factor for ACL injury, giving them a different anatomical profile[38]. One of the causes that may explain this fact may be related to a decrease in the inter-conditional space in this population of young adolescents compared to boys of the same age. Young adolescents also present steeper lateral tibial slopes and deeper tibial columns with the consequent greater risk of ACL injury[60-67].

As mentioned above, increased load on the ACL is associated with increased risk of ACL injury. The steep slopes of the posterior tibial plateau are related to this fact[68-74]. In activities involving weight loading, the posterior tibial slope causes a component of anterior shear force due to axial compression force[70].

The increase in the posterior tibial slope is found to be increased in adolescent girls[48] and may cause an increase in anterior tibial shear force[71-73] due to an acceleration of anterior tibial translation [74] with consequent damage to the ACL. Smaller tibial columns will stabilize less the femoral external rotation and femoral translation and may also cause an increase in ACL load[75,76].

Tibial depth has also been associated with the risk of ACL injury in cases where there is less medial tibial depth by providing less resistance to anterior tibial translation[71,72].

Risk factors related to the muscular state

There is no unanimity among the various authors on the correlation between an alteration at the muscular level and ACL injuries. Authors such as Zaínos *et al*[26] present a direct relationship between imbalances in the agonist-antagonist muscles of the knee together with muscle fatigue as with ACL injury. This author states that high levels of fatigue can lead to altered motor control leading to muscle imbalances, although there are not many studies that prove these claims. In the same vein, Orchard *et al* [77] indicate that excessive extensor force of the quadriceps muscles together with a decrease in the flexor force of the posterior femoral muscles are related to ACL injury. For Malinzak *et al*[78], motor control may be related to postures that put the ACL at risk in fact when a rapid lower limb maneuver will cause an angular change and an imbalance of the knee and hip; these modifications cause muscle adjustments that increase the risk of ACL injury. However, Garrido[79] and Benell *et al*[80] state that there is no relationship between knee muscle imbalances and ACL injury.

Associated injuries in anterior cruciate ligament injury

ACL injury may occur in isolation or be associated with injuries to other structures. In general, the structures most commonly associated with ACL injuries are: Meniscal injuries: These may appear in conjunction with ACL injury in 30% to 60% of individuals. The external meniscus injury is the most frequent in acute ACL injuries and the internal meniscus injury in patients with chronic instabilities[80-82]. Chondral injuries: from bone edema to impacted fractures and even osteochondral fragments[83]. Capsuloligamentous lesions: Usually appear when there are combined injury mechanisms.

Different authors have identified the appearance of associated lesions in relation to sex and age. Posterolateral contusion of the tibial plate tends to appear more frequently in women, while involvement in the external femoral condyle and soft tissue is more prevalent in men. Similarly, a higher rate of patellar tendon rupture has been observed in the adolescent population[84-86].

MATERIALS AND METHODS

A national group of surgeons, physiotherapists, basic scientists, orthopaedic surgeons and paediatric orthopaedic surgeons with experience in ACL instability was convened. A formal consensus process was conducted using a validated methodology. We reviewed the existing literature, held a consensus group meeting to develop recommendations, followed by a broader consultation meeting with an open invitation for final ratification. We conducted an iterative consensus (Delphi) study involving national and international experts in anterior cruciate ligament diagnosis. Group members were recruited through expressions of interest and specific invitations from experts. The Delphi study consisted of four rounds of anonymous surveys. Rounds 1 and 2 involved the generation and ranking of an extensive list of possible characteristics. In rounds 3 and 4, participants were presented with the results of previous rounds and asked to agree on a set of preliminary criteria. Panel participants (n = 34, range by Round 28-30) were predominantly highly experienced clinicians, representing a variety of clinical experience and all inhabited continents. Based on the initial rounds, a set of preliminary criteria was developed, incorporating three levels of diagnostic certainty: healthy ligament, partial rupture and suspected complete rupture. Consensus was reached in Round 4, with a very high level of agreement (> 89%) for all levels of criteria and subcategories. The adoption of the criteria was supported by 96% of the panel members and the guidelines were reviewed and authorised by the NEUMUSK research group, followed by the trauma and orthopaedic specialists of the CEMTRO clinic in Madrid before final publication.

RESULTS

Following the literature review and the multidisciplinary group meeting, an assessment including the following screening tests is proposed.

ACL evaluation

The assessment of ACL injury is mostly clinical[87-92]. Different exploration tests have been described to assess the integrity or insufficiency of the ACL throughout history.

Georges K Noulis in 1875 first described the Trillat-Lachman test to evaluate ACL integrity with the knee in extension. In 1938, Palmer first discussed the "drawer sign" indicating that the positivity of this sign is a pathognomonic sign of ACL rupture. In 1960, Ritchei described Trillat-Lachman's technique again and 1976 Torg *et al*[93] (Lachman's student) described the test and made it known. The test described by John Lachman and released by Torg demonstrated the biomechanical superiority of the test over the previous drawer test. In 1976, Hughston *et al*[49] presented a classification of knee ligament instabilities and indicated that the ACL increases in association with ACL tear and posterior oblique ligament injury. In 1968, Slocum *et al*[101] defined and described a technique for "rotational instability" of the knee in relation to injury of the medial and ACL components[94-102]. Also in this year, Galway and Macintosh described the phenomenon of pivot shift in relation to rupture of the external capsule with injury of the ACL[98].

The Lachman test has a sensitivity of 62% and a specificity of 82% and is a sign of laxity. It is more sensitive for fibres in the posterolateral beam. The anterior drawer test has a sensitivity of 56% and a specificity of 82% and is a sign of ACL rupture. It is more sensitive for fibres in the anteromedial beam [99,100]. There is a variety of the anterior drawer test that is externally rotated and specifically allows assessment of posterior-internal structures[102].

The pivot shift test, Jerk test, has a sensitivity of about 90%. The existence of concomitant lesions such as LLI rupture, iliotibial strap rupture or mechanical interposition may make this test difficult[99].

For a correct diagnosis it is necessary to establish the difference between laxity and instability[102]: Laxity: Objective and quantifiable exploratory sign in relation to capsuloligamentous insufficiency. Instability: Subjective symptom of discomfort experienced by the patient.

The loss of stability of the knee is objectified according to the existence of laxity in the knee. The AOSSM (American Orthopaedic Society for Sports Medicine) Committee on Research and Education classifies them as follows[103]: Non-rotating, single plane linear: There are several types (anterior, posterior, internal and external). It is graded from 0 to 3 through the anterior drawer tests: 0: Normal laxity; 1 +: Anterior translation less than 0.5 cm; 2 ++: Anterior translation between 0.5 cm and 1 cm; 3 +++: Anterior translation between 1 cm and 1.5 cm.

Rotary, single or two-plane: they can be: Anterointernal: Abduction, external rotation and tibial anterior translation. It causes the internal tibial plate to move or sublux anteriorly in relation to the femur. Posterointernal: This occurs when there is a posterior translation of the internal tibial plate in relation to the femur. Anteroexternal: Excessive anterior translation of the external tibial plate. Postero-external: posterior translation of the external tibial plate.

Combined: all types of combinations can be found, the most common being: Anterointernal/antero-external, anterointernal/posterointernal and anterointernal/posteroexternal. Considering the approach followed by Guillén García *et al*[104] and his team regarding the diagnosis of knee stability, different criteria should be followed: (1) Anatomical: The proximal and distal insertion of the ACL is behind the femoral axis. This is why when the lesion mechanism is produced by a knee rotation and the foot is fixed, the ACL and menisci are broken; (2) Biomechanical: It is impossible for the PCL to be the axis of the knee. The PCL changes its angular arrangement on the tibial platform between 20º and 85º in relation to the knee's flexo-extension angle; and (3) Clinical: Both the healing and the tolerance of the patient to the ACL rupture are bad in contrast to the PCL in which maintaining a state of rest produces its healing and the tolerance of isolated injuries of the same by the patient are good.

In relation to the above, the classification of knee instabilities is as follows: Anterior laxity: Anterior laxity: Isolated ACL tear (very rare); Anteromedial laxity: ACL rupture next to the medial system; Antero-posterolateral laxity: ACL rupture next to the posterolateral system. Posterior laxity: Posterior laxity: Isolated PCL tear; Posteromedial laxity: Rupture of the PCL next to the posteromedial system; Posterolateral laxity: LCP rupture together with the posterolateral system. Combined antero-posterior laxity: ACL, PCL rupture along with medial or lateral systems.

Description of ACL assessment test

Before performing the specific tests, the healthy knee should be explored as a control for guidance. The tests that produce the least pain should be started first to prevent the muscle spasm from interfering with the rest of the tests.

Lachman test: This is the main test to be carried out on an acute injury[100]. It is performed with the knee in a 30° knee flexion position and a force is applied in an anterior direction. It is considered positive in cases where the anterior displacement of the tibia is increased compared to the contralateral knee. It is important to note the end point of tibial displacement. This end point is soft or weak when there is a break in the ACL[100-105].

Anterior drawer flex/rotate test: Combines Lachman's test and lateral pivot shift. Both hands are used to firmly grip the calf and move the knee in a 15° to 30° flexion arc. When the ACL is broken, at 15° of flexion there is an anterior subluxation of the tibia and an external rotation of the femur. Increasing the flexion to 30° produces a posterior reduction of the tibia and an internal rotation of the femur[106]. There are authors who claim that this test has less sensitivity than Lachman's test, although it has more sensitivity than the tibial shift tests[107].

Anterior drawer test: This test assesses the anteroposterior femorotibial displacement with a starting position of 90º knee flexion and 45º hip flexion and the foot fixed on the table. From this position, traction and pressure movements are performed in a neutral anterior and posterior position, respectively; to put the capsuloligamentous structures in tension, the test is performed in internal rotation and external rotation. An important detail is to check the initial tibial starting point; if there is an injury at the level of the PCL it could give a false anterior tibial displacement when performing the technique[108].

Hughston *et al*[109] in 1976 described this technique by performing a proximal measurement in the tibia between the thumb and other fingers; the hamstrings are palpated to see if they are relaxed. From this position, an anterior tibial traction is performed to evidence the existence of laxity. If an end point is seen at the limit of the displacement, it is indicative of the continuity of the ACL. If the consistency of the endpoint is spongy and lacking in firmness, it is indicative of rupture of the ACL.

Anterior Neutral Box: The starting position is with the tibia in neutral position. If the test is positive it may be due to injury in: ACL, ACL and internal complex, ACL and external complex or both complexes [110].

Anterior drawer-external rotation: The starting position is with the external rotation of the tibia. In this position the structures of the internal complex are tightened. A moderate positive test result indicates injury of the internal complex, while a strong positive test result indicates injury of the posterior internal angle[101].

Anterior drawer test-Internal Rotation: The starting position is with tibial internal rotation. In this position the structures of the external complex are tightened. A moderate positive result indicates injury to the structures of the external complex. If it is intense positive, we must also think of injury of the PCL together with the structures of the external compartment (LCE, external capsule and posterior-external angle). In this case a further assessment of the postero-external capsule can be made by testing the external rotation recurvatum[109].

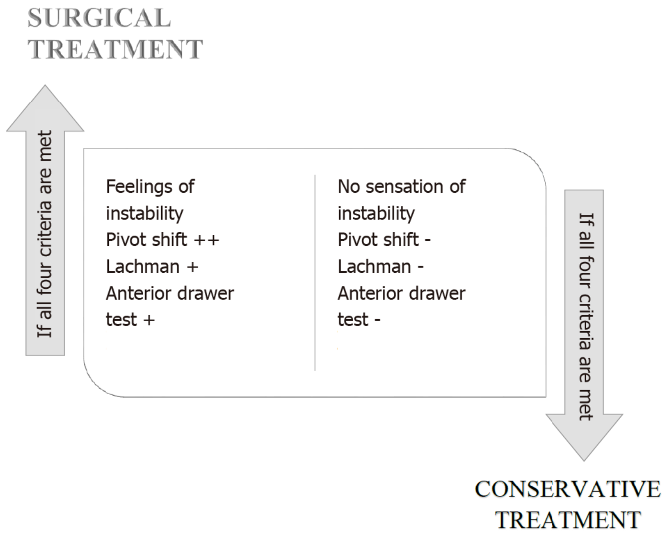
Pivot shift test: The starting position is in knee extension and valgus along with internal rotation of the tibia. A progressive flexion of the tibia is performed and towards 30° a posterior displacement of the tibia is felt on the femur. This displacement appears as a consequence of the reduction of the anterior subluxation of the tibia[110].

Hughston's jerk test: A 45° hip flexion is performed with the knee at 90°. A valgus force is applied and the knee is extended with the tibia in internal rotation. The test is positive when there is a transitory anterior subluxation of the tibia on the femur over the 30° of flexion, with a spontaneous reduction occurring as the knee is extended[109].

Test of internal rotation of the tibia: The starting position is with flexion of 45° or more of the knee and external rotation of the tibia. From this position, the leg is progressively extended, allowing internal rotation to occur while applying a valgus force with anterior pressure applied behind the head of the fibula. This produces anterior subluxation of the anterolateral tibia. As the knee approaches full extension, the tibia is reduced, producing an audible "snap"[111].

Slocum test: The patient is placed in the lateral position with the knee and hip of the healthy lower limb flexed. The pathological knee is placed in contact with the table in an extended position. Palpation of the fibula head is performed with the index finger of the left hand while the index finger of the right hand contacts the external femoral condyle. To perform the technique, a valgus force is applied to the knee in flexion. When the ACL is insufficient, the anterior subluxation of the tibia is reduced by reaching 30° of knee flexion. The reduction is felt with the fingers[112].

Figure 1 shows the summary diagram of the decision-making process regarding the assessment of the ACL and the decision to carry out conservative or surgical treatment.



DOI: 10.5312/wjo.v13.i9.777

Figure 1 Diagram of the decision-making process regarding the assessment of the anterior cruciate ligament.

Capsuloligamentary complex and meniscus evaluation

In order to assess the existence of an associated lesion, together with the analysis of the stability of the knee, an exploration of the rest of the structures of the knee should be performed, paying special attention to the menisci and the internal and external collateral ligaments[100].

Evaluation of capsuloligamentous structures

When there is an ACL lesion, the study and assessment of the capsuloligamentary structures should include the assessment of both the external/internal collateral complex and the postero-internal and postero-external capsular complex. For this purpose, both the valgus and the forced varus must be evaluated both in full extension and in 30º flexion. It is important to increase strength progressively to the point of onset of pain to verify maximum laxity without the appearance of muscle spasm[112,113].

Valgus in extension: When the test is positive, the structures that may be damaged are: the superficial and deep portion of the LCM, posterior oblique ligament, PAPI, peripheral disinsertion of the medial meniscus and ACL. If it is very severe there could be injury of the PCL[85].

Valgus in 30° flexion: A slight positivity in the test will indicate a rupture of the superficial portion of the LLI. If the result is a severe yawn, other structures of the internal complex besides the ACL and PCL will also be affected[85].

Varus in extension: When the test is positive it will indicate injury of the LLL, middle capsule, arcuate ligament and Maissiat band, in addition to the ACL. If it is very severe, the PCL will also be injured[85].

Varus at 30° flexion: Mild external yawning indicates injury to the CLL. If the test result is very severe there will be injury to the medial capsule, the Maissiat band and the arcuate ligament[85].

Meniscal evaluation

It is essential to assess the presence or absence of meniscal pathology concomitant to ACL injuries. The diagnosis will obviously be clinical through evaluative tests that can be divided into[114]: (1) Tests that cause pain or clicks with palpation of the interline; (2) Tests that generate pain with rotation of the tibia on the femur.

With regard to the reliability of the meniscal tests, several studies have tried to prove the effectiveness of the different meniscal tests. There are differences in results between the researchers. Both types of evaluation tests have low diagnostic value when applied individually, increasing their usefulness when combined with the clinical history[114]. A cross-sectional study by Gobbo *et al*[115] in 2011, studied the sensitivity and specificity of the McMurray, Steinmann I, Steinmann II, Childress and Apley tests for both the medial and lateral meniscus. The analysis showed that the sensitivity for the medial meniscus was 89% and the specificity was 31% while for the lateral meniscus the sensitivity was 85% *vs* a specificity of 24%. This study corroborates the data presented previously that tests performed in isolation have a lower diagnostic value. In relation to the independent analysis of each test, the Apley test has the best specificity for both the medial and the lateral meniscus. In relation to the precision for detecting lesions, greater precision was obtained in the evaluation of lesions in the medial meniscus than in the lateral meniscus, except for the Apley test which showed the same predictive value for both the lateral and medial meniscus lesions[115].

Genufonía

The knee has its own language with which it communicates what is happening to it. This language does so through sound. It is important to listen to the sounds that the knee shows us during its movement, which will help us to extract information about your injury[116].

DISCUSSION

ACL injuries are common in sports. Most ACL injuries are non-contact in nature and usually occur in certain athletic tasks. Complete ACL tears can lead to chronic knee problems, such as knee instability, damage to the meniscus and chondral surface, and osteoarthritis. Due to the increasing participation of children and adolescents in both organized sports and intense sports training at an early age, the number of ACL injuries in this age group has increased, accounting for 3.3% of ACL injuries[68-74].

Practice is not yet standardised and the literature to guide decision-making in children is very limited. This consensus process has been based on the expert experience of a diverse group of professionals treating and dealing with this injury, their thorough examination and subsequent decision-making focused on the prior assessment of the patient, and sometimes based on the experience of the healthcare professional conducting the patient study.

Although there is level 1 clinical evidence on screening for ACL rupture, this process is based on the practical and clinical experience of the examiner. However, there are few manuscripts that include screening for this injury in minors, so these guidelines have been developed in the healthcare setting. This consensus has been developed by a large group of experts in the field and has resulted in a solid and established method for the development of guidelines in the healthcare of the pathology in question. We believe that the knee has its own language with which it communicates what is happening to it. This language is expressed through sound, which is why the term genufonia is coined[116]. It is important to listen to the sounds that the knee shows us during its movement, which will help us to extract information about its injury.

It can be seen that the consensus statements cover the assessment and screening of ACL rupture in children. A decision is made in the evaluation of patients, depending on whether surgical treatment [117] or conservative treatment will be chosen.

CONCLUSION

ACL rupture is a complex pathology with multiple approaches that should be based primarily on patient assessment and evaluation. In the absence of a solid evidence base and the lack of consensus in the literature on the approach and exploration of this injury in minors, these established guidelines aim to contribute to that decision-making process to assist the clinician in performing the most optimal treatment with the goal of benefiting the patient as much as possible. Following this expert consensus, surgical treatment is advised when the patient has a subjective sensation of instability accompanied by a pivot Shift ++ test, and may include an anterior drawer + test and Lachman + test. If these conditions are not present, the conservative approach should be chosen, as the anatomical and functional development of the children, together with a physiotherapy programme, can improve the evolution of the injury.

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ORIGINAL ARTICLE

Case Control Study

Histological difference in ligament flavum between degenerative lumbar canal stenosis and non-stenotic group: A prospective, comparative study

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Abstract

BACKGROUND

Ligament flavum (LF) hypertropy is the main etiopathogenesis of lumbar canal stenosis (LCS). The purely elastic LF undergoes a morphological adaptation including a reduction in the elastic fibers and a consequent increase in the collagen content, fibrosis, cicatrization, and calcification. However, the morphometric analysis can delineate the LF in patients with LCS from those without LCS, which would help in better understanding LCS pathogenesis.

AIM

To compare the histopathological changes in LF between the degenerative LCS and non-stenotic (non-LCS) group.

METHODS

The present prospective study was conducted in 82 patients who were divided into two groups, namely LCS and non-LCS. Demographic details of the patients such as duration of symptoms, level of involvement, and number of segments were recorded. The LF obtained from both groups was histopathologically examined for the fibrosis score, elastic fiber degeneration, calcification, and chondroid metaplasia. Morphometrical details included a change in elastin and collagen percentages, elastin/collagen ratio, elastic fiber fragmentation, and ligamentocyte numbers. All parameters were compared between the two groups by using the independent t test, Chi-square test, and Pearson's correlation test.

RESULTS

Out of 82 cases, 74 were analysed, 34 in LCS and 40 in non-LCS group. The mean ± SD age of presentation in LCS and non- LCS group was 49.2 ± 8.9 and 43.1 ± 14.3 respectively. The LCS group (n = 34) exhibited significant differences in fibrosis (P = 0.002), elastic fiber degeneration (P = 0.01), % elastic fragmentation (66.5 ± 16.3 *vs* 29.5 ± 16.9), % elastic, content (26.9 ± 6.7 *vs* 34.7 ± 8.4), % collagen content (63.6 ± 10.4 *vs* 54.9 ± 6.4), reduction of elastic/collagen (0.4 ± 0.1 *vs* 0.6 ± 0.1), and ligamentocyte number (39.1 ± 19.1 *vs* 53.5 ± 26.9) as compared to non-LCS group (n = 40). The calcification (P = 0.08) and Pearson's correlation between duration and loss of elastin was not significant. The difference in LF morphology is consistent in patient's ≥ 40 years of age among the groups as found in subgroup analysis. Similarly in the patents < 40 and > 40 in the non-LCS group.

CONCLUSION

LF is vital in the pathogenesis of LCS. The purely elastic LF undergoes a morphological adaptation that includes a reduction in the elastic fibers with a consequent increase in the collagen content, fibrosis, cicatrization, and calcification. The present study provides a detailed morphometric analysis to semiquantitatively delineate the LF changes in patients with LCS from those in patients without LCS.

Key Words: Spinal stenosis; Lumbar spine; Ligamentum flavum; histopathology; Morphometry

Core Tip: The ligament flavum (LF) is vital in the pathogenesis of lumbar canal stenosis (LCS). The purely elastic LF undergoes a morphological adaptation that includes a reduction in the elastic fibers with a consequent increase in the collagen content, fibrosis, cicatrization, and calcification. The present study provides a detailed morphometric analysis to semiquantitatively delineate the LF changes in patients with LCS from those in patients without LCS.

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INTRODUCTION

Lumbar canal stenosis (LCS) is a common spinal disorder that affects elderly patients, leading to lower back pain, leg pain, and neurogenic claudication, which rarely ends in paresis[1,2]. Because the ligamentum flavum (LF) covers most of the posterior and lateral part of the lumbar spinal canal, the hypertrophied facets and LF hypertrophy (LFH) are responsible for LCS despite the disc complex, contributing to spinal canal narrowing[2,3]. Thus, morphological and histological changes in developing lumbar spinal canal encroachment must be studied[4,5]. With aging of the global population, a paradigm shift toward symptomatic LCS that requires surgical treatment is observed[6].

LF contains the purest form of elastic tissue among ligaments. These elastic fibers decrease with age and are replaced by collagen fibers[2]. The causes of LFH are multifactorial, including the activity levels, age, and mechanical stress[7,8]. Based on transmission electron microscopy findings, Postacchini *et al*[9] concluded that the reduced elasticity might cause bulging of the LF into the spinal canal even in the standing position.

Studies have exhibited a qualitative transformation in the dynamics of the LF components with degeneration[1,6,10-12]. The LFH exhibited loss of elastic fibers, increased content of collagen fibers, and chondrometaplasia, leading to calcification. A few studies have suggested this association of calcification[10], whereas two other studies have suggested a decrease in the elastin/collagen ratio[2,4]. Electron microscopy has revealed fragmentation and changes in the quality of elastic fibers.

Therefore, the present study attempted to explain the LF structure histologically in a semi-quantitative manner by using advanced imaging software.

MATERIALS AND METHODS

The present prospective study was conducted following the Helsinki Declaration principles and approved by the local institutional review board (T/IM/18-19/43 dated 04/01/2019). Valid written informed consent was obtained from all participants.

Study population

The present study was conducted in 74 adult patients undergoing lumbar spine surgery between January 2019 and March 2020 in the departments of orthopedics or neurosurgery in a tertiary care center. Patients with characteristic clinical and radiological findings of spinal stenosis were grouped as the LCS study group. Simultaneously, patients with lumbar disc herniation, infective etiology (tubercular or non-tubercular), trauma, and malignancy constituted the non-LCS study group. Patients with prior lumbar surgery were excluded from the study. Clinical details such as age, sex, duration of symptoms, and level of involvement were recorded.

LF samples were obtained from 82 patients who underwent decompressive laminectomy in piecemeal by using a Kerrison's rounger and sent for histopathological assay in neutral buffer formalin. Of these, eight samples were excluded due to sufficient tissue availability. Thus, the final analysis was conducted in 74 patients.

Histology

The harvested LF components were kept in a solution containing 10% neutral buffered formalin for 24 h. The tissues were processed overnight on an automatic tissue processor (Leica Biosystems Ltd.) and embedded in paraffin. Multiple 4-μm thick sections were cut. All sections were stained with haematoxylin and eosin (H & E), Verhoef-Van-Gieson stains (VVG), Masson trichrome stain (MTS), reticulin, and Von-krossa stains.

Light microscopy

The histological evaluation was performed by two experts who were blinded to the nature of the groups. Light microscopy was used to examine LF sections for elastic degeneration, fibrosis, metaplasia (chondroid or osteoid), hemorrhage, and calcification. Elastic degeneration was graded depending upon the percentage of elastic fibers exhibiting degenerative changes and elastin fiber fragmentation (1+: 0%–33%, 2+: 33%–66%, and 3+: > 67% of elastic fibers). Fibrosis was graded as per the criterion described previously[2].

Image acquisition and morphometric analysis

Digital images were obtained using a commercial imaging system (ZEN blue edition on ZEISS Scope A.1 microscope) at 200X magnification for H & E, VVG, and MTS stains in the tagged image file format. For each case, at least two areas from different LF regions were captured randomly. All images were imported in Image J software java windows-64 application (ImageJ bundled with 64-bit Java 1.8.0_172) for morphometric analysis.

The morphological analysis of the digital images of different stains was performed for elastin content (VVG), collagen content (MTS), and the number of ligamentocytes (H & E). The tool was used to estimate the percentage of collagen and elastic fibers, elastic to collagen fiber ratio, number of ligamentocytes, and elastic fiber width. Each parameter was estimated three times, and two independent observers recorded the average.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD). Differences in the mean between the groups were tested using the independent t test. The Chi-square test was used to compare the categorical variables between the two groups. Correlation between various morphological parameters and duration of symptoms was determined using the Pearson's correlation test for the stenotic group. Subgroup analysis was also performed for patients aged ≥ 40 years and for patients aged < 40 and ≥ 40 years in the non-LCS group. All differences associated with a chance probability of ≤ 0.05 were considered. Data were analyzed using the IBM Statistical Package for Social Sciences ver. 17 (SPSS Inc., Chicago, IL, United States).

RESULTS

Clinical features

Of the 74 cases, 34 cases constitute the LCS group and 40 cases constituted the non-LCS group (Figure 1). The mean ± SD age of presentation in the LCS and non-LCS groups was 49.2 ± 8.9 and 43.1 ± 14.3 years, respectively. The percentage of patients in the stenotic group aged > 40 years was 91%, whereas that in the non-stenotic group was 57.5%. This difference was statistically significant (P = 0.001) (Fischer exact test). Although the non-stenotic group included permanent lumbar disc herniation, other pathologies were also observed (Table 1). Single-level involvement was observed in majority of cases. L4-5 involvement was observed in 43.5% patients, followed by L3-4 and L5-S1 involvement (23% patients each). The remaining patients exhibited involvement in L1-2 and L2-3 levels.

Histological differences between LCS and non-LCS groups

The histological differences in elastin fibers, collagen content, and ligamentocytes were compared between the two groups. The LCS group exhibited higher elastic degeneration and fibrosis than the non-LCS group (P = 0.01 and 0.002, respectively) (Table 2; Figures 2-4). On the other hand, the extent of calcification, chondroid metaplasia, and hemorrhage was statistically nonsignificant between the groups.

LF exhibited a significant reduction in the elastin content in the LCS group (P < 0.0001, independent t test) and an increase in the collagen content (P < 0.0001, independent t test) compared with those in the non-LCS group. The elastin/collagen ratio, width of elastic fibers, and ligamentocyte number were also significantly lower in the LCS group than in the non-LCS group (Table 3).

Correlation of clinicopathological features between the LCS and non-LCS groups

The Pearson's correlation test indicated a moderate correlation between decrease in the number of ligamentocytes and age in both groups (non-LCS-R: −0.52, P < 0.001 and LCS-R: −0.578, P < 0.001). All other morphological changes were statistically nonsignificant. The duration of symptoms in the LCS group was not significantly correlated with morphological changes in both groups.

The ligamentocyte number was moderately correlated with the elastin content in the LCS group (R: −0.450, P = 0.008), (Figure 5). On the other hand, the collagen content was moderately correlated with the elastic content in the non-LCS group (R: −504, P: 0.001). The LCS group exhibited an inverse correlation between the elastin and collagen contents. However, this difference was statistically nonsignificant.

Subgroup analysis

Subgroup analysis exhibited a statistically nonsignificant difference between the patients aged < 40 years and those aged > 40 years in the LCS group. Additionally, the difference between the LCS and non-LCS groups in the percentage of patients aged > 40 years was statistically significant (Table 4).

DISCUSSION

The LF, which envelops the spinal canal, is a highly elastic structure that contains four times pure elastin than collagen[6]. If the LF surrounding the spinal canal becomes hypertrophic, it will compress the dural sac containing the cauda equina or the nerve root. Elsberg[13] first reported a case of LFH causing sciatica. Several clinical studies have reported that LFH is the primary pathology in LCS[1,2,4,6-10]. Although surgical excision is the only therapeutic management for patients with LFH in LCS, a deeper understanding of the pathophysiology can encourage future nonsurgical or prophylactic treatment modalities. Thus, the present study attempted to study the pathological changes in LF and compare the LCS and non-LCS study groups.

Etiology

Sairyo *et al*[1] had proposed that LFH occurs due to degenerative changes with aging process, and also due to increased mechanical stress occurring in instability. Wang *et al*[14] have experimentally demonstrated increased motion in lumbar spine induced LFH. Chuang *et al*[15] have found that age-related LFH occurred due to activation of the Akt and MAPK (apoptotic) pathways. The authors also postulated that hypertrophy is initiated in all subjects after the second decade of life. Zaki *et al*[16] also found that older individuals had some loss and rupture of elastic fibres with abnormal collagen, increase in vascularity and ossification particularly in the lumbar region as compared to the thoracic and cervical spine. Postacchini *et al*[9] observed that although older individuals with disc herniation exhibited some elastic fiber loss, the stenotic group of similar age exhibited more collagen and chondroid metaplasia and were strikingly different. However, the authors noted that there was no difference was observed in stenotic changes related to age and listhesis (degenerative), implying that instability does not accelerate hypertrophic changes[9]. The present study also exhibited no LCS-

Table 1 Demographic profile of the groups

Categories		LSS (*n* = 34)	Non-LSS (*n* = 40)	*P* value
Age in years, mean (SD)		49.2 (8.9)	43.1 (14.3)	
Sex in %		M:F – 59:41	M:F – 60:40	
Duration in weeks, mean (SD)		44.1 (11.6)	9.4 (8.1)	
Level	One	30 (88.2)	32 (80)	0.553
	Two	3 (8.8)	7 (17.5)	
	Three	1 (2.9)	1 (2.5)	
Diagnosis		Lumbar canal stenosis	PIVD – 18	
			Trauma – 8	
			Potts spine – 7	
			Tumour – 5	
			Epidural abscess (non-TB) – 2	

Table 2 Histological differences between the groups

Variable	Histological features	Stenotic (*n* = 34)	Non stenotic (*n* = 40)	*P* value (Chi square test)
Elastin degeneration	1+ and 2+	9 (26.5)	22 (55)	**0.010**
	3+	25 (73.5)	18 (45)	
Fibrosis	1+ and 2+	10	17	**0.002**
	3+	24	13	
Calcification	Absent	28	38	0.081
	Present	6	2	
Chondroid metaplasia	Absent	22	26	0.979
	Present	12	14	
Haemorrhage	Absent	17	23	0.519
	Present	17	17	

induced morphological changes in the non-LCS group of similar age. Similarly, no difference was observed in the non-LCS group with age < 40 years, whereas a statistically significant difference was observed from age > 40 years.

Levels and age

Sairyo *et al*[1] exhibited that LF thickness increased with age; however, the changes with age exhibited spinal level dependence. The increment at L4/5 and L3/4 levels was more extensive than that at L2/3 and L5/S1 levels. Similar changes in magnetic resonance imaging (MRI) were also reported by Kolte *et al*[7]. Okuda *et al*[10] exhibited that thickening was correlated to calcification, which was prime in LCS. A positive correlation was also observed by authors between calcification and clinical scoring (Japanese orthopedic association scores). The present study did not measure the thickness, either grossly, histologically, or radiologically. The present understanding of LCS has evolved from a pure 'static compression' (dependent on width) to a more "dynamic compression" that arises from the imbalance in LF components rather than actual width. Altun *et al*[2] hypothesized that the loss of elasticity is the contributing factor for LF infolding, leading to spinal canal narrowing[2].

Schräder *et al*[12] also studied 41 Ligaments in 21 patients and reported single-level stenosis in five patients, bi-segmental stenosis in 24 patients, and stenosis on three levels in 12 patients. Additionally, Hulmani *et al*[4] exhibited more double-level stenosis in their series. However, the present study exhibited more single-level involvement (*n* = 32) than double-level (*n* = 7) or multilevel (*n* = 1) involvement. This may be due to the higher age group cohort in the study by Hulmani *et al*[4] compared to that in the present study (72 *vs* 49) due to the preferential selection. The present study exhibited that L4-5 was the most common involvement, followed by L3-4. Sairyo *et al*[1] proposed that high mechanical stress might be responsible for the preferential increase in thickness at the L4-5 level.

Table 3 Morphometric differences between the groups

Factor		mean	SD	*t*	df	*P* value
% Elastin fragmentation	NS (40)	29.50	16.9	-9.51	71	**< 0.0001**
	S (34)	66.47	16.3			
Collagen content (area %)	NS (40)	54.94	6.41	-4.38	53.2	**< 0.0001**
	S (34)	63.59	10.36			
Elastic content (area %)	NS (40)	34.73	8.36	4.36	72	**< 0.0001**
	S (34)	26.94	6.71			
Elastin/Collagen ratio	NS (40)	0.63	0.14	6.01	71.27	**< 0.0001**
	S (34)	0.43	0.13			
Width of elastin fibers	NS (39)	4.37	1.07	5.44	71	**< 0.0001**
	S (34)	3.27	0.54			
Ligamentocyte numbers	NS (40)	53.45	26.85	2.6	72	**< 0.0001**
	S (34)	39.11	19.05			

Table 4 Subgroup analysis among groups > 40 years

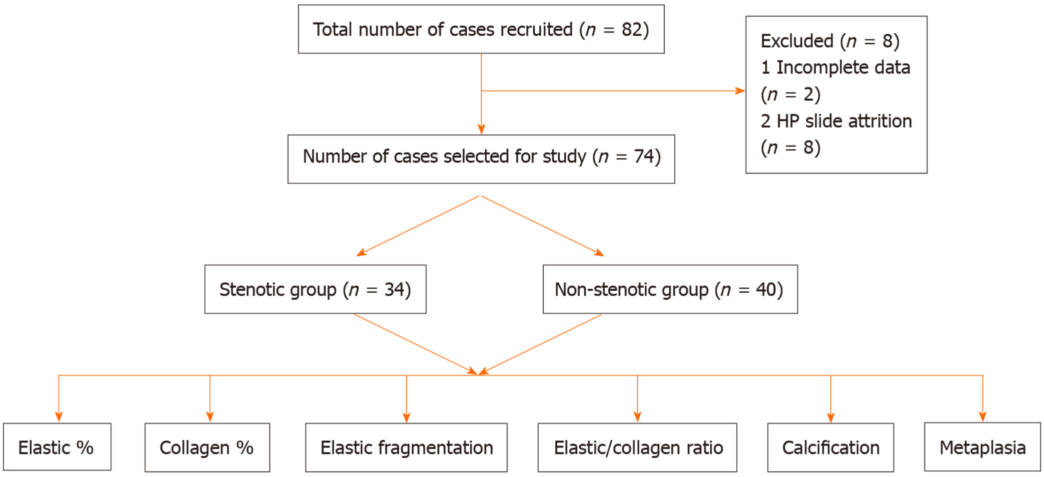
Factor		mean	SD	*t*	df	*P* value
% Elastin fragmentation	NS (25)	31.80	18.123	-7.4	43.93	**< 0.0001**
	S (31)	67.10	16.96			
Collagen content (area %)	NS (25)	55.12	7.62	-3.4	53.19	**0.001**
	S (31)	63.58	10.75			
Elastic content (area %)	NS (25)	34.898	7.92	4.20	46.6	**< 0.0001**
	S (31)	26.57	6.60			
Elastin/Collagen ratio	NS (25)	0.63	0.14	5.54	50.09	**< 0.0001**
	S (31)	0.43	0.13			
Width of elastin fibers	NS (25)	3.75	0.98	4.42	31.94	**< 0.0001**
	S (31)	2.77	0.49			
Ligamentocyte numbers	NS (25)	46.56	22.4.0	1.88	41.03	**0.66**
	S (31)	36.612	15.41			

Histology

Okuda *et al*[10] and Elsberg *et al*[13] observed that nearly all ligaments were calcified in LCS. Calcium deposition within the ligament significantly aggravated the symptoms, and this process increased with age. The increase in the formation of calcium crystals is a significant factor for LF thickening. Okuda *et al* [10] observed that the mean age of patients with calcification and those without calcification was 74 ± 2.0 and 68 ± 1.4 years, respectively. Therefore, patients with calcification were significantly older than those in the LCS group. No reactive granulomatous tissue formation was noticed in the calcification focus. Other researchers have reiterated a smooth transition between calcific zones and surroundings[10,17]. Okuda *et al*[10] reported focal and dispersion-type calcification in their patients with LCS and correlated calcification with a low clinical score.

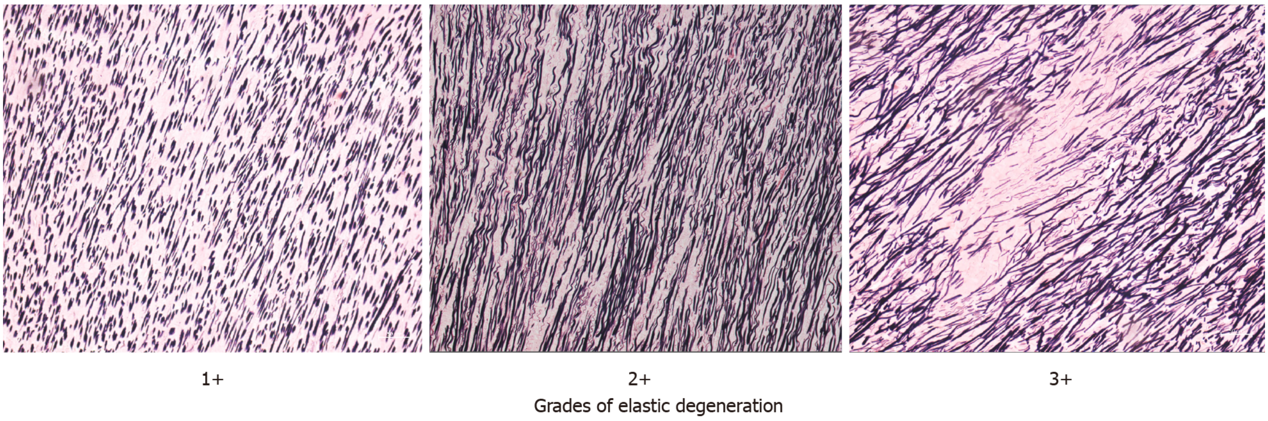
Altun *et al*[2], Hulmani *et al*[4], and Reyes-Sánchez *et al*[18] exhibited contrasting findings regarding calcification. No statistical difference was observed in calcification between the LCS group and the lumbar disc herniation (LDH) group in these studies.

Schräder *et al*[12] exhibited calcification of all the ligaments, and the patients also exhibited relevant fibrosis with decrease in the elastic/collagenous fiber ratio. Additionally, Sairyo *et al*[1] reported that the LCS group exhibited increased LF thickness and fibrosis with reduced elastic fibers. These transformations were more predominant along the dorsal side than those along the middle of the dural side. Sato tel. also found that dorsal side is affected 30 more than the dural side[19] Peng *et al*[20] revealed that the dorsal fibers of the LF were subjected to higher stress than the dural fibers that have a fluid-filled tube,



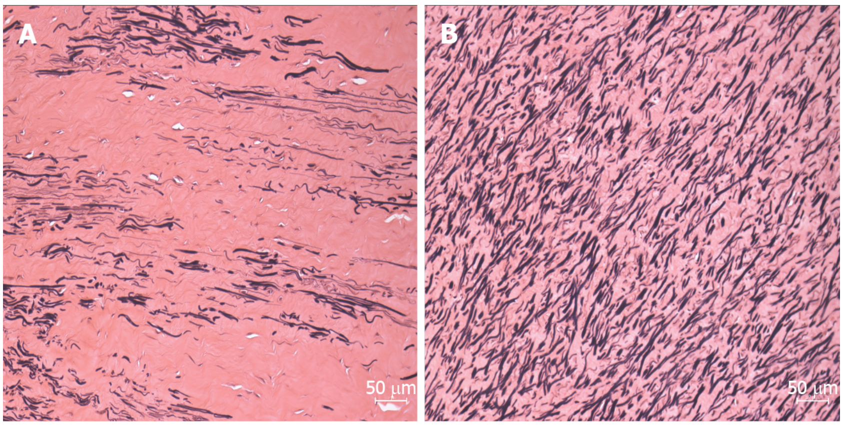
DOI: 10.5312/wjo.v13.i9.791

Figure 1 Flow diagram of patients.



DOI: 10.5312/wjo.v13.i9.791

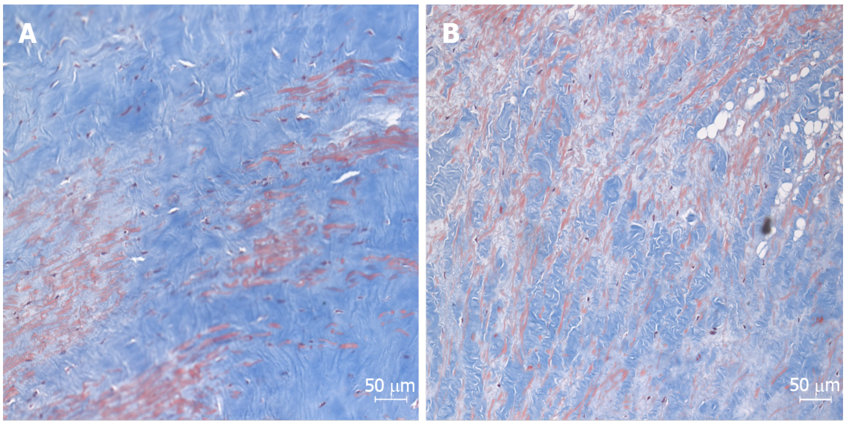
Figure 2 The three grades of elastic degeneration.



DOI: 10.5312/wjo.v13.i9.791

Figure 3 Von Geisson's stain showing the difference between lumbar canal stenosis & Non-lumbar canal stenosis in the number of elastic fibers. A: Lumbar canal stenosis; B: Non-lumbar canal stenosis.

which keeps it smooth. Hamdan *et al*[11] exhibited that the LCS changes were more in the central portion than in the attachments. Yabe *et al*[21] reported a severe reduction in elastic fibres on the dorsal hypertrophied LF. We did not differentiate among the sides as the stenotic effect was due to in-toto changes in LF. Moreover, the LF was removed piecemeal in most of our cases. Hence, such differences



DOI: 10.5312/wjo.v13.i9.791

Figure 4 Masson's Trichrome stain showing the difference in the number of collagen fibers. A: Lumbar canal stenosis; B: Non-lumbar canal stenosis.

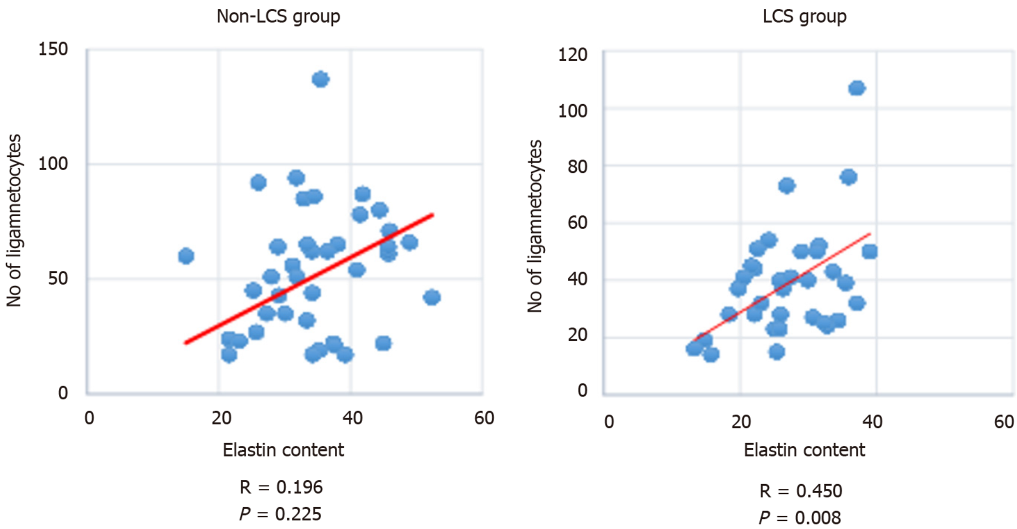


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Figure 5 Scatter plot showing the correlation between the elastic fibers and ligamentocyte numbers in the groups. LCS: Lumbar canal stenosis.

were not observed in the present study.

Fuertes *et al*[22] were first to comment on the anatomical and fiber arrangements on different layers. The authors realized that aging and repetitive stress altered the elastic fiber organization, causing disarray, derangement, and even complete transformation with no elastic fibers. In the present study, morphologic changes such as diameter irregularity, orientation turbulence, and extent of fragmentation were observed in elastic fibers. A similar finding was observed though electron microscopy in the study by Hulmani *et al*[4]. The image software was used to perform the morphometric study based on light microscopy. The present study did not exhibit significant ganglionic cystic changes or chondroid metaplasia despite substantial fibrosis. The present study noted a statistically significant reduction in the elastin percentage, increase in collagen, and reduction in the elastin/collagen ratio. This finding is in contrast to that of other studies. Additionally, a significant change was observed in the elastic fibers (4.37 ± 1.07 *vs* 3.27 ± 0.54; $P < 0.001$), fragmentation, and decrease in the number of ligamentocytes. Altun *et al*[2] reported that elastic fiber reduction or collagen increase was not significant, except for calcification. Okuda *et al*[10] first described elastic fiber degeneration, and it was accompanied by a proliferation of collagen fibers among elastic fibers. Additionally, Hulmani *et al*[4] reported findings such as ganglion-like cystic lesion, mucinous degeneration, and vascularization that were confirmed through electron microscopy. Reyes-Sánchez *et al*[18] exhibited more cystic degeneration, fibrillar appearance, and hypercellularity in the degenerative listhetic group than in the degenerative stenotic group. These results could be caused by instability rather than a degenerative disease in the spine. Schräder *et al*[12] noted that the parallel arrangement of LF elastic fibers was lost in degenerative LCS. This finding is concurrent with that of the present study and the study by Altun *et al*[2].

Significant fibrosis was observed in the LCS group in the present study[2,4]. This finding is in contrast to that of Hulmani *et al*[4] or Altun *et al*[2], and Cheung *et al*[23] exhibited a positive correlation between fibrosis and LFH in the LCS group. On the other hand, the developmental stenotic group exhibited paradoxically less fibrosis[23]. Okuda *et al*[10] also exhibited graded fibrosis in their LCS patients. However, the correlation with the clinical symptoms of patients was not significant. Additionally, the authors exhibited a large number of chondroid cells in patients with spondylolisthesis [10]. These findings are similar to those of Fukuyama *et al*[8], who postulated that unstable lumbar spine accelerates LF degeneration and chondrometaplasia.

LFH etiology is multifactorial. The morphological transformation that includes reduction in the elastin/collagen ratio, degeneration, fragmentation of the residual elastic fibers, fibrosis, cicatrization, and calcification leads to a loss in elasticity that can infold into the spinal canal, causing narrowing. Future studies can evaluate the correlation between symptom duration and progression of specific changes.

Several inflammatory cytokines have been studied which are responsible for the growth and reproduction and some of these plays' crucial role in inflammatory response and progressive LF fibrosis [24]. However, we have not studied any such markers.

Limitation

The present study exhibited that morphometric findings can be studied satisfactorily even in the absence of an electron microscope, which can be reproduced even in less sophisticated setups. However, it could not differentiate between the dorsal and dural aspects as we removed the LF piecemeal and not as a whole. The central and peripheral parts could not be segregated, which could allow more in-depth understanding, particularly of chondroid metaplasia. Clinical scoring, occupational activity, and MRI measurement were also ignored to keep the study simple. Additionally, gene expression was not studied in the present study.

CONCLUSION

The LCS and non-LCS groups differ in clinical parameters, mainly symptom duration. Histopathologically, the two groups exhibited significant differences in elastin degeneration, fragmentation, elastic/collagen ratio, fibrosis, and number of ligamentocytes. However, calcification was not significant between the groups.

ARTICLE HIGHLIGHTS

Research background

Ligament flavum (LF) hypertropy is the main etiopathogenesis of lumbar canal stenosis (LCS). The purely elastic LF undergoes a morphological adaptation including a reduction in the elastic fibers and a consequent increase in the collagen content, fibrosis, cicatrization, and calcification. However, the morphometric analysis can delineate the LF in patients with LCS from those without LCS, which would help in better understanding LCS pathogenesis.

Research motivation

The research is motivated due to high footfall of these patient on Orthopedic outpatient department. An interdepartmental meeting was made to analyze these patients and funds were provided by the institute.

Research objectives

To compare the histopathological changes in LF between the degenerative LCS and non-stenotic (non-LCS) group.

Research methods

The present prospective study was conducted in 82 patients who were divided into two groups, namely LCS and non-LCS. Demographic details of the patients such as duration of symptoms, level of involvement, and number of segments were recorded. The LF obtained from both groups was histopathologically examined for the fibrosis score, elastic fiber degeneration, calcification, and chondroid metaplasia. Morphometrical details included a change in elastin and collagen percentages, elastin/collagen ratio, elastic fiber fragmentation, and ligamentocyte numbers. All parameters were compared between the two groups by using the independent *t* test, Chi-square test, and Pearson's correlation test.

Research results

Of the total, we selected 74 patients. The number of patients in the LCS and non-LCS groups was 34 and 40, respectively. The mean ± standard deviation of age of presentation in the LCS and non-LCS groups was 49.2 ± 8.9 and 43.1 ± 14.3 years, respectively. The difference in fibrosis (P = 0.002), elastic fiber degeneration (P = 0.01), elastic fragmentation percentage (66.5% ± 16.3% *vs* 29.5% ± 16.9%), elastic content percentage (26.9% ± 6.7% *vs* 34.7% ± 8.4%), collagen content percentage (63.6% ± 10.4% *vs* 54.9% ± 6.4%), reduction of elastic/collagen ratio (0.4 ± 0.1 *vs* 0.6 ± 0.1), and ligamentocyte number (39.1 ± 19.1 *vs* 53.5 ± 26.9) between the LCS and non-LCS groups was statistically significant. The difference in calcification (P = 0.08) and Pearson's correlation between duration and loss of elastin was statistically nonsignificant. Subgroup analysis exhibited a consistent difference in LF morphology in patients aged ≥ 40 years between the two groups. A similar finding was observed in patients aged < 40 and > 40 years in the non-LCS group.

Research conclusions

The quality change in elastin fibers and an increase in the collagen content and fibrosis cause loss of elasticity in LF, contributing to LCS pathogenesis. However, calcification did not play a significant role in LCS pathogenesis.

Research perspectives

Tne study compare the histopathological changes in LF between the degenerative LCS and non-stenotic (non-LCS) group.

FOOTNOTES

Author contributions: Jain M, Sable B, Tirpude AP, and Sahu RN conceived the idea; Jain M got the ethical clearance and grant for the study; Jain M, Sahu RN, and Das G collected the sample; Sable M and Tirpude AP performed the histological analysis; The data were compiled by Jain M and Samanta SK; Sable M and Jain M performed the statistical analysis; Jain M, Samanta SK, and Das G wrote the manuscript, whereas the other authors provided critical inputs; All authors have read and agree to the content of the manuscript.

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Conflict-of-interest statement: There is no conflict of interest.

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ORIGINAL ARTICLE

Clinical Trials Study

Short arm cast is as effective as long arm cast in maintaining distal radius fracture reduction: Results of the SLA-VER noninferiority trial

Giovanni Dib, Tommaso Maluta, Matteo Cengarle, Alice Bernasconi, Giulia Marconato, Massimo Corain, Bruno Magnan

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Abstract

BACKGROUND

Distal radius fractures (DRFs) are a common challenge in orthopaedic trauma care, yet for those fractures that are treated nonoperatively, strong evidence to guide cast treatment is still lacking.

AIM

To compare the efficacy of below elbow cast (BEC) and above elbow cast (AEC) in maintaining reduction of manipulated DRFs.

METHODS

We conducted a prospective, monocentric, randomized, parallel-group, open label, blinded, noninferiority trial comparing the efficacy of BEC and AEC in the nonoperative treatment of DRFs. Two hundred and eighty patients > 18 years of age diagnosed with DRFs were successfully randomized and included for analysis over a 3-year period. Noninferiority thresholds were defined as a 2 mm difference for radial length (RL), a 3° difference for radial inclination (RI), and volar tilt (VT). The trial is registered at Clinicaltrials.gov (NCT03468023).

RESULTS

One hundred and forty-three patients were treated with BEC, and 137 were treated with AEC. The mean time of immobilization was 33 d. The mean loss of RL, RI, and VT was 1.59 mm, 2.83°, and 4.11° for BEC and 1.63 mm, 2.54°, and

3.52° for AEC, respectively. The end treatment differences between BEC and AEC in RL, RI, and VT loss were respectively 0.04 mm (95%CI: -0.36-0.44), -0.29° (95%CI: -1.03-0.45), and 0.59° (95%CI: -1.39-2.57), and they were all below the prefixed noninferiority thresholds. The rate of loss of reduction was similar.

CONCLUSION

BEC performs as well as AEC in maintaining the reduction of a manipulated DRF. Being more comfortable to patients, BEC may be preferable for nonoperative treatment of DRFs.

Key Words: Distal radius fracture; Immobilization; Below elbow cast; Above elbow cast; Short arm cast; Long arm cast

Core Tip: Currently, there is no general agreement on how best to immobilize a distal radius fracture (DRF) although classic teaching was that immobilization of the elbow would ensure better control of fracture instability. This has been recently challenged by a number of new randomized controlled trials (RCTs) but no one was designed as a non-inferiority RCT, which is the most appropriate way to evaluate the hypothesis that blocking the elbow is unnecessary. We devised a large population noninferiority RCT to give statistical evidence that short arm cast is as effective as long arm cast to treat DRFs using predetermined noninferiority thresholds.

Citation: Dib G, Maluta T, Cengarle M, Bernasconi A, Marconato G, Corain M, Magnan B. Short arm cast is as effective as long arm cast in maintaining distal radius fracture reduction: Results of the SLA-VER noninferiority trial. *World J Orthop* 2022; 13(9): 802-811

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INTRODUCTION

Distal radius fractures (DRFs) are a common clinical challenge in orthopaedic trauma care. Traditionally, it was thought that immobilization including the elbow would ensure better control of fracture instability, prevent loss of reduction, and result in better clinical outcomes. However, long arm casts are cumbersome and treatment with lighter short arm casts is generally considered a more comfortable option for patients. Currently, there is no general agreement on how best to immobilize a DRF. Various methods have been described, but no one approach has been identified as being more effective than another[1-4]. According to the latest clinical practice guidelines from the American Academy of Orthopaedic Surgeons, released in 2009, the evidence available for and against elbow immobilization in patients treated with a cast is "inconclusive" and the choice between them is down to the clinician's judgment[5]. The hypothesis that short arm casts might perform as well as long arm casts in maintaining the reduction of DRFs has been tested in a number of previous studies. These superiority randomized controlled trials (RCTs) have not found a significant difference in outcome and risk of loss of reduction between below elbow cast (BEC) and above elbow cast (AEC)[6-11]. However, the absence of any significant difference in these studies does not necessarily indicate equivalence[12]. To compare the efficacy and tolerability of these two treatment approaches, we designed a noninferiority randomized trial using predefined minimal clinically important difference thresholds.

In this paper, the terms short arm cast and BEC or long arm cast and AEC are used interchangeably.

MATERIALS AND METHODS

Design

The SLA-VER trial is a prospective, monocentric, randomized, parallel-group, open label, blinded, noninferiority trial (PROBE design), comparing the efficacy of BEC and AEC in maintaining reduction of manipulated DRFs. This study was approved by the local institutional review board (CE\1165CESC), conducted in accordance with the Declaration of Helsinki, and registered on ClinicalTrials.org (NCT03468023). All patients enrolled gave written informed consent.

Outcomes

The primary outcome was fracture reduction maintenance, measured as variation in radial length (RL), radial inclination (RI), and volar tilt (VT). The secondary outcomes included disability of arm, shoulder and hand (DASH) scores and short form 12 (SF-12) scores as measures of cast tolerability.

Population

All patients admitted to the emergency room with a diagnosis of DRF were enrolled according to the following inclusion criteria: Age ≥ 18 years; candidates for nonoperative treatment; displaced fracture requiring manipulation. The exclusion criteria were: Skeletally immature patients (less than 18); undisplaced fracture; fracture requiring surgical treatment; open fracture; hand/wrist/forehand skin lesion on fractured limb; vascular or neurological deficit; bilateral fracture; association with homolateral upper limb fracture. Patients with any medical comorbidity were included, but pregnant patients or patients requiring urgent or life-saving procedures were excluded. Patients were excluded from the study (*i.e.* dropouts) if reduction could not be achieved after two attempts (after which surgical treatment was offered), the cast was damaged or removed during treatment, or consent was withdrawn [13].

Procedures

Randomization was carried out by a statistician with no involvement in the clinical care of patients. Software random allocation in blocks of 4 resulted in 353 sequentially numbered opaque sealed envelopes. When a patient was eligible for enrollment, an envelope was opened to assign the participant to a treatment group. Closed manipulation was performed under hematoma block, and the forearm was immobilized in an opposite-to-dislocation position. The arm cast was a radial gutter made of plaster of Paris (POP) that was left open on the volar side to allow for swelling and then circumferentially closed 5-7 d later by applying an extra layer of POP (Figure 1). BEC patients were treated with a BEC extending from the metacarpal heads to 2-4 cm from the elbow crease. AEC patients were treated with an AEC extending from the metacarpal heads to the middle third of the arm. Posteroanterior (PA) and lateral view X-rays were taken pre and post manipulation and at 7 and 35 d. The radial gutter was closed at the first office visit and removed at the final visit. If closed manipulation failed to achieve satisfactory reduction, patients were offered surgical treatment and excluded from the study. If reduction was lost at 7 d, patients were offered surgical treatment. These patients were still considered for analysis as subjects who did not maintain satisfactory reduction at the final follow-up. Radiographic parameters were determined at each X-ray examination. RL was measured on the PA view as the distance between two lines drawn perpendicularly to the radial shaft long axis: one at the tip of the radial styloid and one at the ulnar border of the radius articular surface at the central reference point, which is a point midway between the volar and dorsal ulnar corners to eliminate variation caused by dorsal angulation as described by Slutsky[14]. RI was measured on the PA view by determining the angle between a line passing through the tip of the radial styloid and the medial corner of the articular surface of the radius and a line perpendicular to the shaft of the radius. VT was measured on the lateral view by the angle between the line of the distal articular surface (passing through the two most distal points of the dorsal and volar lips of the radius) and the longitudinal axis of the radius[14,15]. Fracture stability was assessed according to Lafontaine (dorsal angulation > 20°, dorsal comminution, articular involvement, associated ulnar fracture, and age > 60 years): If three or more of these criteria were present, the fracture was defined unstable[16]. The casting technique was assessed by means of cast index and three-point index[17,18]. Reduction was considered to be maintained when the following criteria, described by Graham, were met[13]: Loss of radial length < 5 mm, radial inclination ≥ 15°, and volar tilt between +15° and -20°. Given the variability of the criteria used to assess acceptability of reduction, we decided to further test the dataset against three other sets of criteria (combinations of different thresholds of RL, RI, and VT). All measurements were performed by three investigators, none of whom were involved in patient recruitment and all of whom were blinded to patient group assignment. Patients were stratified by age, sex, presence of osteoporosis (indirectly assessed by osteoporosis-specific drug consumption), fracture type (according to AO classification), and fracture stability (according to Lafontaine's criteria) [19]. At the final follow-up visit, patients were asked to complete DASH and SF-12 questionnaires and elbow range of movement (ROM) after cast removal was also recorded[20,21]. Protocol details have been published previously[22] and are available at https://clinicaltrials.gov/ct2/show/NCT03468023.

Statistical analysis

For the study to have 80% power to show a difference between the treatments with a two-sided type 1 error rate of 5%, we calculated that approximately 150 patients would be required for each group using a 2 mm difference in RL and a 3° difference in RI and VT as noninferiority thresholds. These estimates of minimal clinically important differences were based on previous reports of interobserver variability of up to 3° in radiographic parameter measurement and considerable deterioration of clinical outcome when shortening of RL was > 5 mm[15,23,24]. We included 53 additional patients to make up for a predicted 15% dropout rate. Since our aim was to identify the real treatment efficacy under optimal conditions, we conducted a per-protocol analysis. In noninferiority trials, both intention-to-treat and

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Figure 1 Above elbow cast (long arm cast) on the left side and below-elbow cast (short arm cast) on the right side. A and C: Long arm cast; B and D: Short arm cast.

per-protocol analyses are recommended[25]. In this trial, we did not include dropouts in the final analysis, since doing so would have introduced a confounding effect of surgery. We did not use baseline differences to decide whether and which covariates should be used to adjust treatment effect because we assumed that, in RCTs, any baseline difference between the two groups is attributable to chance and thus negligible[26]. The 95%CI was calculated for continuous variables following a normal distribution. Noninferiority *t*-tests were used to compare radiological parameters, and chi-squared tests were used to compare percentages of loss of reduction between the two groups. DASH and SF-12 scores between the BEC and AEC groups were compared using superiority *t*-tests. All variables included in the analysis were complete, with no missing data. Analyses were performed using SAS 9.4.

RESULTS

Between March 2017 and February 2020, 353 eligible patients were enrolled in the trial. Of these, 180 patients were randomly assigned to treatment group A (BEC) and 173 were randomly assigned to treatment group B (AEC). In group A, 29 patients dropped out of the study, and 8 did not complete the follow-up. In group B, 25 patients dropped out from the study, and 11 did not complete the follow-up (Figure 2). Dropouts (and dropout reasons) were similar between the groups. A total of 280 patients (143 in group A and 137 in group B) completed the study and were included in the analysis. The study groups were similar with respect to age, sex, osteoporosis, type of fracture (AO classification), and stability of fracture, as shown in Table 1. Cast index and three-point index were homogeneous between the groups (χ^2 = 1.72, P = 0.19 and χ^2 = 0.06, P = 0.79, respectively). Randomization resulted in two well-balanced study groups. The mean time of immobilization was 33 d (95%CI: 31.88-34.10) for BEC patients and 32.6 d (95%CI: 31.5-33.63) for AEC patients. Nine patients treated with BEC and ten treated with AEC lost reduction at 7 d. Seven were treated surgically, and two continued nonoperative treatment in the BEC group; seven were treated surgically, and three continued nonoperative treatment in the AEC group. Upon removal of cast at the final follow-up, the mean loss of RL was -1.59 mm for BEC *vs* -1.63 mm for AEC (between-group difference: 0.04 mm; 95%CI: -0.36-0.44); the mean loss of RI was -2.83° in BEC *vs* -2.54° in AEC (between-group difference: -0.29°; 95%CI: -1.03-0.45); the mean loss of VT was 4.11° in BEC *vs* 3.52° in AEC (between-group difference: 0.59°; 95%CI: -1.39-2.57). Differences in loss of RL, RI, and VT during treatment between the groups reached statistical significance when tested for noninferiority (P < 0.0001 for RL, P < 0.0001 for RI, and P = 0.0087 for VT), and all differences were below the prefixed thresholds outlined above. Differences between the final and baseline radiographic parameters are reported in Table 2. According to Graham's criteria, 99 (69%) out of 143 patients treated with BEC maintained satisfactory reduction as opposed to 106 (77%) out of 137 patients treated with AEC. This difference was not significant (P = 0.12; Table 3). Considering that the percentage of fractures labelled as "maintained" varies according to the criteria of acceptability of reduction used, we tested a further three sets of criteria as described above. In all cases, no statistically significant difference was

Table 1 Baseline patient demographics

Characteristic	Group A (below-elbow cast)	Group B (above-elbow cast)	*t*-test (*t*) or Chi-squared test (χ^2)	*P* value
Age (yr), mean ± SD	70.2 ± 13.7	69.5 ± 15.4	$t = 0.42$	$P = 0.68$
Sex, *n* (%)			$\chi^2 = 0.02$	$P = 0.89$
Male	19 (13)	19 (14)		
Female	124 (87)	118 (86)		
Osteoporosis, *n* (%)			$\chi^2 = 1.53$	$P = 0.46$
Yes	44 (31)	78 (57)		
No	84 (59)	38 (28)		
Missing	15 (10)	21 (15)		
Type of fracture (AO classification), *n* (%)			$\chi^2 = 0.20$	$P = 0.90$
Type A	48 (34)	43 (31)		
Type B	17 (12)	18 (13)		
Type C	78 (55)	76 (55)		
Stability of fracture (Lafontaine), *n* (%)			$\chi^2 = 0.12$	$P = 0.73$
Stable	68 (48)	68 (50)		
Unstable	75 (52)	69 (50)		

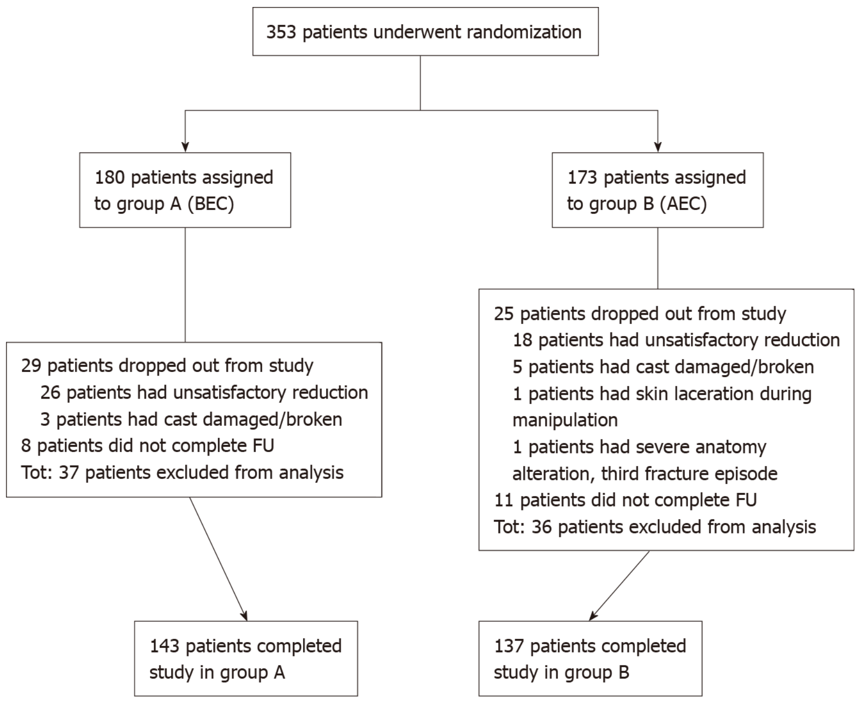

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Figure 2 Study flow chart. BEC: Below elbow cast; AEC: Above elbow cast.

observed (66% maintained in BEC *vs* 74% in AEC for type 2, 61% maintained in BEC *vs* 62% in AEC for type 3, and 62% maintained in BEC *vs* 61% in AEC for type 4; Table 3). DASH score, SF-12 [physical component summary (PCS) and mental component summary (MCS)] scores, and elbow ROM were collected for 122 out of 280 patients: 55 (38%) patients in group A and 67 (49%) patients in group B. DASH score for BEC patients was 59 (95%CI: 53.8-64.2) and 59.9 (95%CI: 55.6-64.3) for AEC patients; the mean PCS and MCS scores were 34.9 (95%CI: 32.9-36.9) and 43.6 (95%CI: 40.5-46.8), respectively, for BEC patients and 36.6 (95%CI: 34.9-38.2) and 41.8 (95%CI: 39.1-44.5) for AEC patients. No difference was

Table 2 Radiographic parameter comparison between below-elbow cast and above-elbow cast at baseline (post reduction) and at final control

Parameter	Group A (BEC), mean (95%CI)	Group B (AEC), mean (95%CI)	*t*-test (*t*) comparing groups	*P* value
Baseline (post reduction)				
RL	11.31 mm (11.03; 11.60)	11.35 mm (11.05; 11.64)	*t* = -0.17	*P* = 0.86
RI	20.90° (20.41; 21.39)	21.08° (20.58; 21.59)	*t* = -0.50	*P* = 0.62
VT	-8.06° (-9.11; -7.01)	-6.55° (-7.56; -5.55)	*t* = -2.05	*P* = 0.04
Final control (35 d)				
RL	9.73 mm (9.33; 10.12)	9.72 mm (9.35; 10.09)	*t* = 0.02	*P* = 0.99
RI	18.07° (17.42; 18.72)	18.54° (17.88; 19.19)	*t* = -1.01	*P* = 0.31
VT	-3.95° (-5.61; -2.29)	-3.03° (-4,35; -1,71)	*t* = -0.86	*P* = 0.39
∆ final control–baseline				
Parameter				
RL	-1.59 mm (-1.88; -1.29)	-1.63 mm (-1.89; -1.36)	*t* = 0.2	*P* = 0.84
RI	-2.83° (-3.37; -2.29)	-2.54° (-3.05; -2.03)	*t* = -0.77	*P* = 0.44
VT	4.11° (2.61; 5.61)	3.53° (2.22; 4.83)	*t* = 0.58	*P* = 0.56
∆ of loss of radiographic parameters during treatment (BEC–AEC)				
Parameter	Group A-B, mean (95%CI)			
RL	0.04 mm (-0.36; 0.44)			
RI	-0.29° (-1.03; 0.45)			
VT	0.59° (-1.39; 2.57)			

BEC: Below elbow cast; AEC: Above elbow cast; RL: Radial length; RI: Radial inclination; VT: Volar tilt.

Table 3 Radiographic criteria for acceptability of reduction and percentage of maintenance of reduction comparison between below elbow cast and above elbow cast

	Type I (Graham)	Type II (Gliatis)	Type III (Aro and Koivunen)	Type IV (Fernandez)
Radiographic criterion/acceptable measurement				
RL shortening	< 5 mm	< 5 mm	< 3 mm	< 3 mm
RI	≥ 15°	≥ 15°	≥ 15°	≥ 15°
VT	Between 15° and 20°	Between 10° and 20°	Between 15° and 20°	Between 10° and 20°
Maintenance, *n* (%)				
Group A (BEC)	99 (69)	95 (66)	87 (61)	89 (62)
Group B (AEC)	106 (77)	101 (74)	87 (63)	83 (61)
Chi-squared test (χ^2)	χ^2 = 2.36	χ^2 = 1.77	χ^2 = 0.21	χ^2 = 0.09
P value	*P* = 0.12	*P* = 0.18	*P* = 0.65	*P* = 0.75

BEC: Below elbow cast; AEC: Above elbow cast; RL: Radial length; RI: Radial inclination; VT: Volar tilt.

observed between patient groups. Subgroup analysis for dominant side fracture did not change the result. Regarding elbow ROM, BEC patients exhibited a mean flexion of 123.6° (95%CI: 117.1-130.1), mean extension of 6.7° (95%CI: 2.5-10.8), mean pronation of 69.5° (95%CI: 63.8-75.3), and mean supination of 52.5° (95%CI: 45.6-59.3). AEC patients had similar ROM, with a mean flexion of 123.9° (95%CI: 118.9-128.9), mean extension of 5.5° (95%CI: 1.4-9.5), mean pronation of 72.1° (95%CI: 66.4-77.9), and mean supination of 52.9° (95%CI: 45.5-60.3). Again, no difference was observed between the groups.

DISCUSSION

Noninferiority tests are the most appropriate way to evaluate the hypothesis that BEC and AEC have similar efficacy. They are based on minimal clinically important thresholds that are established *a priori* by drawing on empirical assumptions. When observed between-treatment differences fall below these thresholds, treatments can be considered equivalent. Statistical superiority tests, for example, the percentage of fractures that maintain reduction *vs* the percentage of fractures that lose reduction, can be misleading since they tell us nothing about equivalence[12]. Therefore, in the current study, we analysed both dichotomic variables (*i.e.*, percentage of reduction maintenance) and continuous variables (*i.e.*, radiographic radial parameters) for which noninferiority thresholds could be predetermined. By employing a noninferiority design, the current study showed that the efficacy of BEC in maintaining the reduction of manipulated DRFs is similar to that of AEC. According to our model, when clinicians have to choose between using BEC or AEC to immobilize a DRF, the maximum predictable outcome difference between the two treatments does not exceed 2 mm in terms of RL loss and 3° in terms of RI and VT loss. Maintenance of reduction of DRFs is more likely to depend on factors other than length of cast used, for example, patient age and stability or type of fracture. SLA-VER has some limitations that warrant discussion. Quality of reduction was not assessed and could have potentially influenced the difference between BEC and AEC. Given that no computerized tomography was carried out, we may not have accurately measured every articular gap, and it is possible that its prevalence might be different between the study groups. However, our approach is consistent with general clinical practice. Furthermore, we limited our investigation to radiological outcomes only and did not include clinical outcome measures. SLA-VER aimed only at ascertaining whether the type of casting used affects the likelihood of fracture maintenance. A large amount of data about factors associated with loss of reduction risk and clinical outcome has already been published[16,27-39]. Only a small number of patients completed the DASH and SF-12 questionnaires and received elbow ROM measurements, even though this was a secondary study endpoint. Our data did not reveal a clear difference in patient comfort between BEC and AEC and this remained true even after subgroup analysis of dominant side fractures. Surprisingly, elbow range of motion was not affected by the type of cast as one would have expected. One explanation could be that the time of immobilization may have been too short to result in significant elbow stiffness or that the absence of elbow injury might have contributed to preserving joint mobility. This finding is also reported by Okamura *et al*[11]. Finally, it may be that DASH scores are not the most appropriate way to assess cast comfort. Bong *et al*[7] found better DASH scores in below-elbow splints, although to a lesser degree than expected, suggesting that DASH might not be able to specifically address the comfort level of the two constructs. Furthermore, Caruso *et al*[10] did not find any difference in DASH scores between BEC and AEC at the 4 wk follow-up but reported a significant difference in favour of BEC using the Mayo elbow score. Similarly, Park *et al*[8] did not find any difference in DASH score between BEC and AEC, although they found a correlation with the dominant side and a higher incidence of shoulder pain in the latter group. Nevertheless, BEC is broadly considered more comfortable and preferable than AEC[8].

CONCLUSION

Data from this trial lead us to conclude that BEC performs as well as AEC in maintaining reduction of a manipulated DRF. When clinicians have to choose between BEC and AEC, the maximum predictable difference does not exceed 2 mm in terms of RL loss and 3° in terms of RI and VT loss. We recommend BEC over AEC for its non-inferior performance and better tolerability.

ARTICLE HIGHLIGHTS

Research background

Distal radius fracture (DRF) treatment is a common challenge in orthopaedic trauma care. Uncertainty exists on how best to immobilize a DRF.

Research motivation

The necessity of blocking the elbow when immobilizing a DRF is still a matter of debate.

Research objectives

To test the hypothesis that blocking the elbow is not necessary and that a below arm cast (BEC) performs as well as an above elbow cast (AEC).

Research methods

A noninferiority randomized clinical trial was conducted on 280 patients diagnosed with a DRF managed nonsurgically. Loss of reduction was evaluated considering variation in radiographic parameters [radial length (RL), radial inclination (RI), and volar tilt (VT)].

Research results

Rates of loss of reduction were similar between BEC and AEC. Variation of radiographic parameters (RL, RI, and VT) was similar between BEC and AEC and fell within the predetermined noninferiority thresholds.

Research conclusions

BEC performs as well as AEC in maintaining reduction of a manipulated DRF.

Research perspectives

Further large population randomized controlled trials and meta-analyses are required to confirm the hypothesis that BEC should become the option of choice for DRF treatment.

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FOOTNOTES

Author contributions: Dib G and Cengarle M equally conceptualized and designated the research work; Maluta T contributed to organizing and performing the research; Marconato G performed the research and was actively involved together with Dib G and Cengarle M in reviewing patients' X-ray; Bernasconi A analyzed the data; Dib G drafted the manuscript; Magnan B and Corain M revised the manuscript.

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Clinical trial registration statement: This study was registered on ClinicalTrials.org (NCT03468023).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Observational Study

Revision anterior cruciate ligament reconstruction: Return to sports at a minimum 5-year follow-up

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Abstract

BACKGROUND

Between 43% and 75% of patients who undergo primary anterior cruciate ligament (ACL) surgery return to sport activity. However, after a revision ACL reconstruction (ACLR) the rate of return to sports is variable. A few publications have reported returns to sports incidence between 56% to 100% after revision ACLR.

AIM

To determine return to sports and functional outcomes after a single-stage revision ACLR with a 5-year minimum follow-up at a single institution.

METHODS

All patients operated between 2010 and 2016 with a minimum 5 years of follow-up were included. Type of sport, intensity, frequency, expectation, time to return to sport and failure rate were recorded. Lysholm, Tegner and International Knee Documentation Committee forms were evaluated prior to the first ACLR surgery, at 6 mo after primary surgery and after revision ACLR at 5 years minimum of follow-up. Objective stability was tested with the knee arthrometer test (KT-1000 knee arthrometer, Medmetric Corp).

RESULTS

A total of 41 patients who underwent revision ACLR during that period of time were contacted and available for follow-up. Median patient age at time of revision was 29 years old [interquartile range (IQR): 24.0-36.0], and 39 (95.0%) were male. The median time from revision procedure to follow-up was 70 mo (IQR: 58.0-81.0). Regarding return to sports, 16 (39.0%) were at the same level compared to preinjury period, and 25 patients (61.0%) returned at a lower level. Sixty-three percent categorized the sport as very important and 37.0% as important. One patient (2.4%) failed with a recurrent ACL torn. Mean preoperative Lysholm and subjective International Knee Documentation Committee scores were 58.8 [standard deviation (SD) 16] and 50 (SD 11), respectively. At follow-up, mean Lysholm and subjective International Knee Documentation Committee scores were 89 (SD 8) and 82 (SD 9) (P = 0.0001). Mean Tegner score prior to primary ACLR was 6.7 (SD 1.3), 5.1 (1.5 SD) prior to revision ACLR and 5.6 (1.6 SD) at follow-up (P = 0.0002). Overall, knee arthrometer test measurement showed an average of 6 mm (IQR: 4.0-6.0) side-to-side difference of displacement prior to revision ACLR and 3mm (IQR: 1.5-4.0) after revision.

CONCLUSION

Almost 40.0% of patients returned to preinjury sports level and 60.0% to a lower level. These may be useful when counseling a patient regarding sports expectations after a revision ACLR.

Key Words: Return to sport; Revision anterior cruciate ligament; Arthroscopy; Knee; Functional outcome

Core Tip: This was a retrospective case series with 41 patients seeking to evaluate return to sports and clinical outcomes after revision anterior cruciate ligament reconstruction at 5 years minimum of follow up. Retrospective analyzed data included physical examination, Tegner activity level, Lysholm, International Knee Documentation Committee, type of sport, intensity, frequency, expectation and time to return to sport. Objective stability was tested with the knee arthrometer test. All data were recorded at the base line and after a 5-year minimum follow-up.

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INTRODUCTION

Consequent to a substantial increase in the incidence of anterior cruciate ligament (ACL) ruptures, revision ACL reconstruction (ACLR) has also suffered an increase[1]. The ACL re-rupture rate is between 4% to 6%, with the event occurring in the first 2 years in more than half of the cases[2-4]. The rate of one-third of ACL ruptures is around 13% to 19% according to different publications[5-7]. In addition, these patients also present an increased risk of developing early arthritis[8].

Historically, return to sports (RTS) is defined as the return to the pre-injury activity in one or two seasons, at the same sporting level[9]. A recently published consensus described continuous RTS in three stages: return to participation, RTS and return to previous performance. Thus, return to participation refers to the return to training or to a lower sporting level than the one practiced by the patient previously. RTS refers to the return to the sport previously performed, although not at the desired level. Return to previous performance refers to the return to the same level or a higher level than before the injury[10].

Between 43% and 75% of patients who undergo primary ACL surgery RTS[11-15]. However, after a revision ACLR the reported rates of RTS are very variable[16]. Causes of non-RTS are multifactorial and include age, sex, psychological factors, type of sport, number of previous surgeries, time lapse between surgeries and graft choice[11-26]. Few publications report sports return rates after revision ACLR, both in the medium and long term, and they vary from 56% to 100%[27-31]. The purpose of this study was to evaluate the rate of RTS in patients with revision ACLR after 5 years of surgery. The secondary purpose was to report the functional outcomes.

MATERIALS AND METHODS

Study group

This study was approved by the Ethics Committee of our hospital. A retrospective study was performed including all patients who underwent a revision ACLR between 2010 and 2016. The inclusion criteria were patients with traumatic or atraumatic knee instability with a displacement equal to or larger than 5 mm anteroposterior compared to the contralateral knee measured with the KT-1000 arthrometer after primary ACL surgery and older than 18 years.

Patients with multiligament injuries (more than two ligaments injured at the same time), second ACL revision and patients with osteotomies at time of revision ACLR surgery were excluded (Table 1).

Surgical technique

A single stage revision ACLR was performed in the whole series. A diagnostic arthroscopy was performed in every case, and if necessary associated meniscal and cartilage lesions were treated. In 5 patients, allografts were used. The fixation technique was with 2 titanium screws for bone tendon bone, and in cases of hamstrings or anterior tibial allograft; fixation was performed with a cortical button in the femur and a biocomposite interferential screw in the tibia.

Postoperative rehabilitation

All patients entered the same rehabilitation protocol with rearrangements for individual needs. Partial loading was allowed for the first 3 wk. Passive flexion and extension range of motion were carried out. In special cases with complex meniscal sutures or cartilage treatment with mosaicoplasty, full loading was delayed until week 6. From the 4^{th} month onwards, low impact workout exercises and progressive muscle strengthening were started. RTS was allowed after 10 mo depending on the sport practiced prior to the revision ACLR and based on an evaluation by our rehabilitation team.

Evaluation

Assessment was performed by a single evaluator in this study. Age, sex, follow-up time, injury mechanism prior to revision ACLR, time between primary surgery and re-rupture, time between revision ACLR and RTS, technique used in both primary surgery and revision ACLR and associated procedures were recorded.

All patients were asked about the type and level of sport practiced, the motivation to RTS and the expectation of returning to sport in three instances: prior to the first ACL reconstruction surgery, after primary surgery and after revision ACLR and RTS. RTS activity was considered to be the return to their sport prior to the last injury at the same level or below the previous level. Motivation was classified as: very important, important, moderately important, minimally important or not important. The expectation regarding RTS was classified as: return to the same sport level, return to a lower level or not returning to the same sport. The number of sports practices per week before and after the revision ACLR was recorded.

Using the Tegner score, the type of sport was classified into high impact, moderate and low impact, according to the classification published in 2015 by the American Heart Association[32]; high impact was considered those with Tegner greater or equal to 7, moderate impact with Tegner between 4 to 6 and low impact with Tegner between 1 to 3. Lysholm and International Knee Documentation Committee Knee (IKDC) scores were used prior to the revision ACLR and at the last follow-up. For an objective assessment, the KT-1000 arthrometer (Medmetric Corp) was used at the last follow-up.

We defined failure of revision ACLR surgery as ACL re-rupture, whether traumatic or atraumatic, associated with positive pivot shift and a difference in arthrometry with KT-1000 greater than or equal to 5 mm requiring new surgery.

Statistical analysis

Due to the small sample of patients non-sample size calculations were conducted. Continuous variables were described as median and interquartile ranges. Categorical variables were reported as proportions with their absolute frequency. Stata 14 software was used for the analysis. Statistical significance was considered to be $P = 0.05$.

RESULTS

A total of 87 revision ACLR were performed in the study period: 16 were excluded because of multiligamentary lesions, 8 were second revisions, and 10 were associated with osteotomy. Of the 53 patients who met the inclusion criteria, 12 patients were lost during follow-up. The series consisted of 41 patients with a median follow-up of 70 mo (IQR: 58.0-81.0) (Figure 1). Thirty-nine patients were male with a median age of 29 years (IQR: 24.0-36.0). Table 1 shows the demographic data.

Surgical data

A total of 27 (65.8%) patients had concomitant meniscal lesions. The medial meniscus was more frequently injured (n = 26); 20 (77.0%) were treated with meniscectomy, 6 (19.0%) with repair and 1 (4.0%) with meniscal transplantation. Lateral meniscus was injured in 14 patients; all were treated with partial meniscectomy. Chondral lesions were found in 5 (12.0%) patients; 3 (60.0%) were treated with microfractures and 2 (40.0%) with chondroplasty (Table 2).

Table 1 Demographics

Demographics	Results (*N* = 41)
Yr, median (IQR)	29 (24-36)
Male, *n* (%)	39 (95)
Follow up (mo) (IQR)	70 (58-81)
Period (a)	2010-2016
Injury mechanism prior revision ACLR	
Traumatic	26 (63.4%)
Atraumatic	15 (36.6%)
Time between (mo)	
ACL Primary surgery and retear	22 (22-39)
Revision ACLR and return to sport	13 (11-15)
Failure	1 (2.4%)

IQR: Interquartile range; ACLR: Anterior cruciate ligament reconstruction; ACL: Anterior cruciate ligament.

Table 2 Surgical technique and concomitant lesions

Graft	*n* (%)	Surgical technique	*n* (%)	Augmentation	*n* (%)
Primary ACL					
Hamstring	29 (70.7)	Monotunnel	36 (87.0)	-	-
BPTB	11(26.8)	Anatomic	5 (12.0)	-	-
Allograft	1 (2.4)				
Revision ACLR					
Hamstring	10 (24.3)	Anatomic	41 (100)	Lemaire	15 (36.0)
BTB	29 (70.3)			Allograft	2 (4.8)
Allograft	5 (2.0)			No Augmentation	24 (58.0)
Concomitant lesions					
Both meniscus	9 of 41 (21.0)				
Medial meniscus	26 of 41 (66.0)				
Meniscectomy	20 (77.0)				
Meniscal suture	5 (19.0)				
Meniscal transplantation	1 (4.0)				
Lateral meniscus					
Meniscectomy	14 of 41 (34.0)				
Chondral lesions	5 (12.0)				

BTB: Bone tendon bone; ACL: Anterior cruciate ligament; ACLR: Anterior cruciate ligament reconstruction; BPTB: Bone patellar tendon bone.

RTS

Prior to the first injury, 35 (85.0%) patients practiced high impact activities, 5 (12.0%) moderate and 1 (3.0%) low impact. After the first ACL surgery, 26 (63.0%) patients practiced high impact, 12 (29.0%) moderate and 3 (8.0%) low impact; 5 years after ACL revision, 19 (46.0%) continued to perform high impact, 20 (49.0%) moderate and 2 (5.0%) low impact (Figure 2). Prior to revision ACLR the patients practiced: soccer (24, 59.0%), running (9, 22.0%), gym (3, 7.0%), rugby (2, 5.0%), tennis (1, 2.0%), cycling (1, 2.0%) and other (1, 2.0%) other.

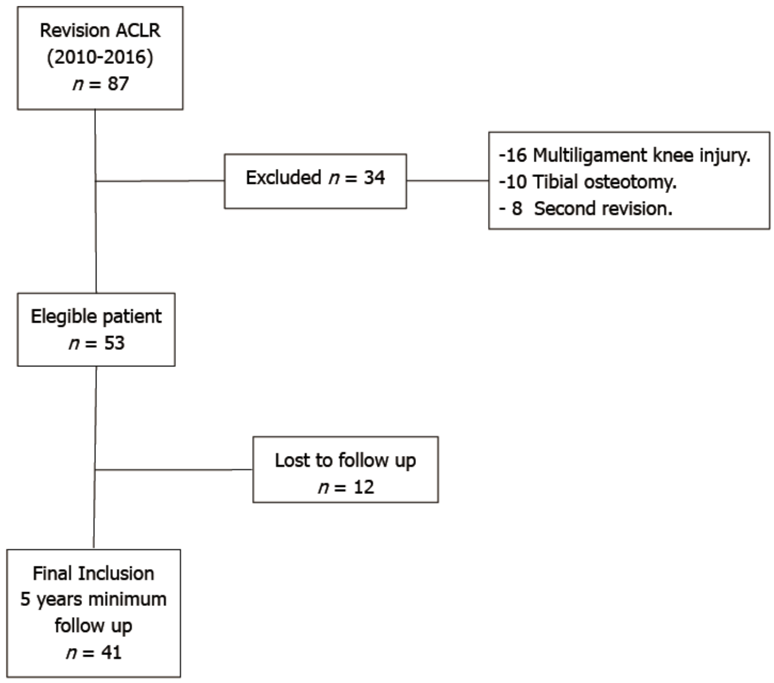

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Figure 1 Flowchart of patient inclusion. ACLR: Anterior cruciate ligament reconstruction.

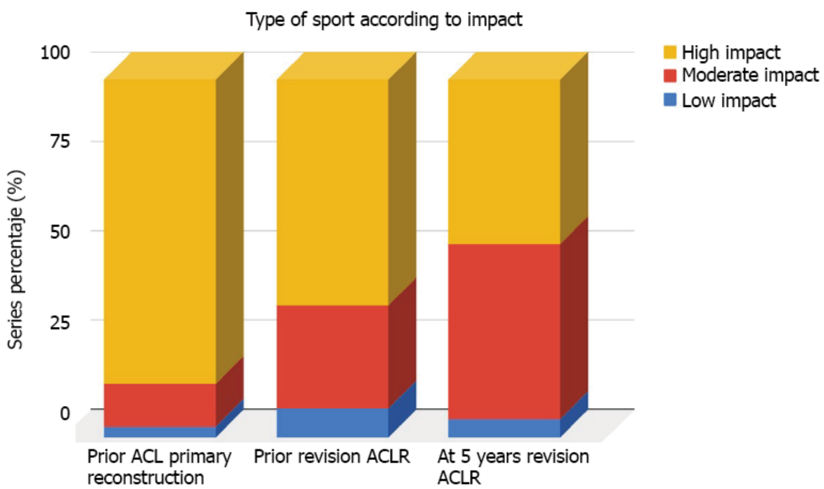

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Figure 2 Type of sports at time of return. Lower sports impacts increased before revision anterior cruciate ligament reconstruction at the final follow-up. ACL: Anterior cruciate ligament; ACLR: Anterior cruciate ligament reconstruction.

After primary ACL surgery, 13 (31.0%) returned to the same level of sport, 26 (64.0%) to a lower level and 2 (5.0%) did not RTS. The rate of RTS for revision ACLR was 16 (39.0%) returning to the same level of sport and 25 (61.0%) to a lower level (Table 3). The time to RTS for both post-primary surgery and revision ACLR was 13 mo (IQR 11.0-15.0) (Figure 3).

Eighty percent (12/15) of patients without associated procedures and 73.0% (19/26) of patients with associated procedures returned to the same sports level, with no statistically significant differences (P = 0.61). Similarly, we found no association (P > 0.44) between the associated procedures performed at the time of revision ACLR surgery and the type of sport.

Regarding impact activity after revision surgery, it is interesting to note that 13.0%[7] modified their sports practice. When classifying sports according to impact based on Tegner, we recorded a 40.0% decrease from high impact to moderate impact activity and a 2.2% decrease from moderate to low impact after 5 years of follow-up after revision ACLR (Table 4) (Figure 2). Of those who played soccer, 1 patient changed to tennis, 1 to functional training and 1 to running. Of those who performed running, 1 began to perform a pivoting activity (soccer) and the other 2 modified it to a low-impact activity (bicycle

Table 3 Return to sport rate after primary anterior cruciate ligament surgery and before revision anterior cruciate ligament reconstruction after a 5-yr minimum follow-up

	Return to sports rate	
	Primary ACLR, %	Revision ACLR, %
Total return	95.0	100
Same level	31.7	39.0
Lower level	63.4	61.0

ACLR: Anterior cruciate ligament reconstruction.

Table 4 Activity sports impact and time evolution

Impact sport and Tegner	Prior to primary ACLR, *n* (%)	At 5 yr revision ACLR, *n* (%)
Low	1 (2.4)	2 (4.8)
Moderate	5 (12.2)	20 (48.7)
High	35 (85.3)	19 (46.3)

ACLR: Anterior cruciate ligament reconstruction.

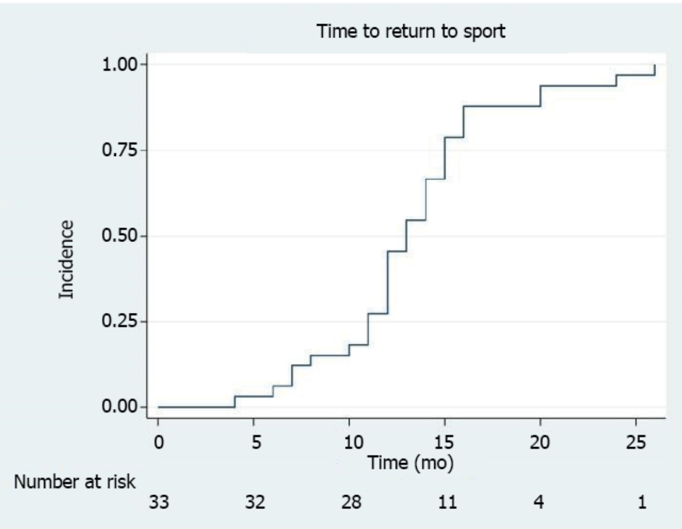

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Figure 3 Time to return to sports (Kaplan - Meier). Fifty percent of the population returned to sport at some level 13 mo after revision anterior cruciate ligament reconstruction.

and yoga). This result was not modified for patients older than 40 years, in contrast to what it may be thought that in older patients (older than 40 years) the chances of modifying or abandoning sport is higher. The frequency with which they practiced sports in a week before and after the revision ACLR was maintained over time, being an average of twice a week (range 1-3); 26 (63.0%) patients practiced activities twice a week before the revision ACLR and 21 (51.0%) post-surgery.

When assessing motivation, 26 (63.0%) classified it as very important and 15 (37.0%) as important. When the patients were asked about their expectations regarding the RTS after their primary ACL surgery, 33 (80.0%) patients described their intention to return to the same sports level and 8 (20.0%) to return to a lower level. Regarding their expectation after revision ACLR surgery, 16 (39.0%) patients intended to return to the same level and 25 (61.0%) to a lower level (Table 3).

Clinical evaluation

According to the American Heart Association's classification in relation to Tegner score, a 40.0% decrease in impact activities at 5 years postoperatively was registered. Tegner score prior to primary

ACL surgery showed that 80.5% performed recreational physical activity, 9.8% performed their usual light work and 9.8% performed competitive sports activity. After primary ACL surgery, 58.5% performed their usual work, 36.6% performed recreational physical activity and 4.9% performed competitive sports activity. Post revision ACLR, 53.7% performed recreational physical activity, 41.5% performed their usual work/task and 4.9% performed competitive sports activity.

Prior to revision ACLR surgery the Lysholm score was good in 1.9% of the series, 35.8% were fair, and 62.3% were poor. For postoperative revision ACLR the score was excellent in 31.7% of the series, good in 56.1%, fair in 7.3% fair and poor in 4.9%. The Tegner, Lysholm and IKDC scores are summarized in Table 5. With the differential KT-1000 arthrometer the median values prior to ACL revision were 5 mm (IQR: 4.0-6.0) and at last follow-up 3 mm (IQR: 1.5-4.0). Finally, 1 patient had a failure after ACL revision surgery (2.4%) at 72 mo postoperatively.

DISCUSSION

The main finding of this study was that all patients returned to their sports practice after revision ACLR, 61.0% at a lower level and 39.0% at the same level prior to revision ACLR surgery. The rate of return to full sport, according to a systematic review of 48 studies with 5770 patients, is 82% in patients with primary ACL surgery. Only 63% returned to the same pre-injury sport, but 44% were able to do so at a competitive level[19]. Although the literature is more limited for RTS in revision ACLR surgery, a systematic review of 23 studies with a total of 1090 patients indicated that 85% of patients returned to sport, 53% to their previous sport and 51% to a competitive level[16]. According to another systematic review, the rate of RTS in patients with revision ACLR surgery ranged from 56% to 100%[33], similar to our series.

There are several factors that influence RTS: social, psychological and demographic factors. Age and sex are important factors. Men have a 10% higher rate of return than women, and young people (< 25 years) have a rate higher than 30% compared to adult patients[19,20,31,33]. The longer the time between ACL re-rupture and revision surgery, the lower the rates of RTS as well as an increase in associated injuries as revision surgery is delayed[19]. In the same way, the graft choice could be a determining factor in the RTS; however, it has not been studied in depth[27].

In our series, the time to RTS was the same (13 mo) with no significant differences found when dividing the series into those older than 25 years and those younger than 25 years as well as when differentiating between sex. The median time between ACL re-rupture and revision ACLR was 21 mo (IQR: 3.0-24.0). For patients who took more than 1 year to undergo a revision ACLR, the RTS was also at 13 mo on average (7 to 26) with no significant differences with the overall rate of sports return (P = 0.64).

Focusing on the graft choice, according to a meta-analysis of 32 studies comparing hamstring and bone tendon bone for revision surgeries, an increase in the IKDC, Lysholm and Tegner scores and a decrease in complications and reoperations was observed in favor of hamstrings[40]. In contrast to this, the authors of the study recommended that the graft choice should be based on the circumstances of each patient, the technique preferred by each surgeon, the tunnel widening, the type of graft previously used and the possible availability of allografts and not on the rate of RTS according to the type of graft [40]. All patients in our series were treated with autografts with the exception of 5 patients where allografts were used. We did not find significant differences in the time to return in patients where an allograft was used, being 13 mo for both groups. The preference of the authors of this study is to use an autograft from the same injured knee. This is due to the fact that, according to literature, series of patients with revision surgeries in which an autograft was used showed faster rates of RTS in comparison with those in which allografts were used[38,39]. The use of contralateral hamstring tendons for revision ACLR surgeries presented similar subjective and objective rates at 5.2 years of follow-up compared to revision surgeries in which patellar or Achilles tendon allograft was used[39]. In our series we do not have patients operated with contralateral knee grafts.

Several authors recommend that when evaluating series to assess the RTS the Lysholm score should be used together with the Tegner score to be able to more effectively evaluate the sports activity[34]. In our series, Lysholm score after revision ACLR increased by 30.0% for excellent results considered as greater than 95 points (0% preoperative to 31% postoperative) and decreased by 50.0% for poor results (62% preoperative to 4.9% postoperative).

For the Tegner scale we observed a decrease of 1.7 points between preoperative primary ACL surgery and postoperative revision ACLR (P = 0.002) showing the decrease in impact activity between primary surgery and revision ACLR. When comparing our series with the literature for both the Lysholm, Tegner and IKDC scores we found results that are close to the mean (Table 6).

When evaluating the expectation of patients regarding their intention to RTS after primary ACL surgery, 80.0% of our series intended to return to the same sport level, while 39.0% reported this intention prior to revision surgery (Tables 7-10 case examples). This 40.0% decrease in the expectation of RTS is consistent with the literature as shown by a study of 675 patients with a return expectation after primary surgery at 1 year of 84% and 63% for revision ACLR surgeries (P < 0.001 and P = 0.08, respectively). A multivariate logistic regression showed two determinant factors for abandoning sports

Table 5 Tegner, Lysholm and subjective International Knee Documentation Committee scores prior to revision anterior cruciate ligament reconstruction and at the 5-yr follow-up

	Preoperative	SD	5 yr postoperative	SD	Delta	SD	95%CI	*P* value
Tegner	6.7	(1.3)	5.6	(1.6)	-1.170	(1.8)	-1.739 to -0.602	0.002
Lysholm	58.8	(16.0)	89.0	(8.0)	30.121	(17.0)	24.736 to 35.507	< 0.001
IKDC	50.0	(11.0)	82.0	(9.0)	31.475	(15.0)	26.649 to 36.300	< 0.001

$\chi 2$ test was used to estimate the *P* value. SD: Standard deviation; IKDC: International Knee Documentation Committee; CI: Confidence interval.

Table 6 Comparing our series with the literature for the Lysholm, Tegner and International Knee Documentation Committee scores

Ref.	*N*	Years	F-up in yr	RTS	IKDC	Lysholm	Tegner	KT-1000, mm ± SD	KOOS
Battaglia *et al*[28], 2007	63	31	6.1	42 (66%) same level	G/E 36%; P 17%; F 11%	-	-	< 3	-
Diamantopoulos *et al* [29], 2008	107	39	6	39 (36%) same level	G/E 57%; P 34%; F 7%	88.5 ± 12.4	6.3 ± 1.8	0.93 ± 1.15	-
Gifstad *et al*[30], 2013	56	26	7.5	7 (13%) same level	-	80 ± 15	6 ± 4	3.3 ± 2.7	70 ± 21
Shelbourne *et al*[31], 2014	259	22	7.2	178 (68%) same level	Subjective 76 ± 18.3	-	-	2.3 ± 1.7	-
Ortiz *et al*, 2022	41	29	5.8	61% same level & 39% lower level	G/E 43%; P 53%; F 4%	89 ± 8	5.6 ± 1.6	3 ± 1.2	-

N: Number of patients; F-up: Follow up; RTS: Return to sport; IKDC: International Knee Documentation Committee; G/E: Good to excellent; P: Poor; F: Fair; SD: Standard deviation; KOOS: Knee Injury and Osteoarthritis Outcome Score.

Table 7 Five representative cases

Case	Sex	Years	Time between in min				Graft choice		Augmentation at revision ACLR	Concomitant lesions
			Primary ACLR and retear	Revision ACLR and last evaluation, F-up	Return to sport		Primary	Revision		
					To Primary ACLR	To Revision ACLR	ACLR	ACLR		
1	Male	30	36	126	17	20	Hamstring	BPTB	Lemaire	Medial meniscus tear
2	Male	42	12	131	14	13	Hamstring	BPTB	Lemaire	Medial meniscus tear
3	Male	29	48	107	13	11	Hamstring	BPTB	Lemaire	Chondral lesions
4	Male	35	22	115	10	14	Hamstring	BPTB	-	Chondral lesions
5	Female	28	13	103	14	16	Hamstring	BPTB	-	Medial meniscus tear

ACLR: Anterior cruciate ligament reconstruction; BPTB: Bone patellar tendon bone; F-up: Follow-up.

practice, which were having suffered a revision ACLR (*P* < 0.0001) and being female (*P* = 0.02). In our series, all patients returned to sports, and we did not obtain representative casuistry to make a comparison between sexes[34].

The association between chondral and meniscal lesions showed poor functional results in patients with revision ACLR surgery; the association of chondral lesions at the time of revision surgery showed lower values according to the Lysholm score in comparison with patients who did not present it. In the same way, patients who presented this lesion modified their intensity in RTS[34-37]. Another study showed poor results in Marx, Knee Injury and Osteoarthritis Outcome Score-quality of life and IKDC

Table 8 Return to sport was considered to be the return to their sport prior to the last injury, at the same level or below the previous level

Case	Sex	Years	Return to sport After		Type of Sports			Training frequency Days per week	
			Primary ACLR	Revision ACLR	Prior ACLR	Prior revision ACLR	After revision ACLR	Prior revision ACLR	After revision ACLR
1	Male	30	Lower level	Lower level	Soccer	Running	Running	2	1
2	Male	42	Same level	Same level	Soccer	Soccer	Tennis	2	1
3	Male	29	Lower level	Same level	Soccer	Running	Soccer	2	2
4	Male	35	Lower level	Same level	Soccer	Soccer	Soccer	2	2
5	Female	28	Lower level	Same level	Martial arts	Tennis	Tennis	2	2

ACLR: Anterior cruciate ligament reconstruction.

Table 9 Motivation was classified as very important, important, moderately important, minimally important or not important and expectation was classified as return to the same sport level, return to a lower level or not returning to the same sport

Case	Sex	Year	Motivation	Expectation	
				After primary ACLR	After revision ACLR
1	Male	30	Important	Same level	Lower level
2	Male	42	Very important	Same level	Same level
3	Male	29	Very important	Same level	Lower level
4	Male	35	Very important	Same level	Lower level
5	Female	28	Very important	Same level	Same level

ACLR: Anterior cruciate ligament reconstruction.

Table 10 Knee function and sports activity level

Case	Sex	Year	Tegner		Lysholm		IKDC	
			Prior revision ACLR	At 5-yr F-up revision ACLR	Prior revision ACLR	At 5-yr F-up revision ACLR	Prior revision ACLR	At 5-yr F-up revision ACLR
1	Male	30	7	4	47	65	62	71
2	Male	42	7	7	61	84	49	89
3	Male	29	7	4	39	86	59	90
4	Male	35	7	4	80	95	37	97
5	Female	28	7	6	38	86	49	86

ACLR: Anterior cruciate ligament reconstruction; F-up: Follow-up; IKDC: International Knee Documentation Committee.

activity scores after revision ACLR surgery in patients with chondral lesions and low scores for the Marx and Knee Injury and Osteoarthritis Outcome Score-quality of life scores in patients with medial meniscus lesions[29]. The level of RTS practice was equal or lower in patients who had associated injuries *vs* patients who did not have associated injuries at the time of revision ACLR surgery. Twelve patients returned to the same level; 3 patients returned to a lower level out of a total of 15 patients who underwent an associated procedure. In our series, 80.0% (12/15) of the patients without associated procedures and 73.0% (19/26) of the patients with associated procedures returned to the same sports level, with no statistically significant differences (P = 0.61).

Limitations

Among the limitations of our retrospective study, there was no control group of patients with high sports performance nor a numerical scale detailing the level of RTS practice, being this a subjective response of patients. No pre- and postoperative strength or resistance test was performed to determine the "level of muscle strength at their return." The series was a heterogeneous group of patients in terms of age and type of sport performed. Although the size of the series is close to those reported in international literature, the number is small. The strength of the study is that it is a case series operated in a single institution with a 5-year follow-up after revision ACLR.

CONCLUSION

Five years after a revision ACLR, 39.0% of patients returned to the same level of sport as before revision ACLR surgery and 61.0% to a lower level. The 13.2% (n = 7) of the series who changed their sports practice was a 40.0% decrease of high impact activity at the time of return. These data could be used to advise patients on the level and timing of sports return.

ARTICLE HIGHLIGHTS

Research background

Between 43% and 75% of patients who undergo primary anterior cruciate ligament (ACL) surgery return to sport activity. However, after a revision ACL reconstruction (ACLR) rate of return to sport are variable. Few publications report return to sports incidence between 56% to 100% after revision ACLR. Five-year minimum follow-up after revision ACLR is a good mid/long-term period evaluation to report return to sport of a case series patients.

Research motivation

Return to sports is a frequent question from patients during the first consultation. We believe this research could help other knee surgeons answer these types of questions. Motivation and expectation must be asked by surgeons during the consultation so as to give the patient a more detailed and realistic response to that question.

Research objectives

The objective was to report functional clinical outcomes and return to sport at a mid/long-term period after revision ACLR.

Research methods

A retrospective and observational study was performed to describe return to sport of an amateur case series of patients. The entire cohort was asked about motivation, expectation, intensity, frequency and level of return to sport after a 5-year follow-up after revision ACLR.

Research results

Thirty-nine percent of the cohort returned at the same level compared to the pre-injury period. Sixty-one percent returned at a lower level. Sixty-three percent categorized the sport as very important and 37.0% as important. One patient (2.4%) failed with a recurrent torn ACL.

Research conclusions

Almost 40.0% of patients returned to their pre-injury sport level and 60.0% to a lower level after 5 years of follow-up after revision ACLR.

Research perspectives

The direction of future research must be to compare return to sport of professional elite patients against amateur patients.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Fragility of statistically significant findings from randomized clinical trials of surgical treatment of humeral shaft fractures: A systematic review

Stephen Craig Morris, Anirudh K Gowd, Avinesh Agarwalla, Wesley P Phipatanakul, Nirav H Amin, Joseph N Liu

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Abstract

BACKGROUND
Despite recent meta-analyses of randomized controlled trials (RCTs), there remains no consensus regarding the preferred surgical treatment for humeral shaft fractures. The fragility index (FI) is an emerging tool used to evaluate the robustness of RCTs by quantifying the number of participants in a study group that would need to switch outcomes in order to reverse the study conclusions.

AIM
To investigate the fragility index of randomized control trials assessing outcomes of operative fixation in proximal humerus fractures.

METHODS
We completed a systematic review of RCTs evaluating the surgical treatment of humeral shaft fractures. Inclusion criteria included: articles published in English; patients randomized and allotted in 1:1 ratio to 2 parallel arms; and dichotomous outcome variables. The FI was calculated for total complications, each

complication individually, and secondary surgeries using the Fisher exact test, as previously published.

RESULTS

Fifteen RCTs were included in the analysis comparing open reduction plate osteosynthesis with dynamic compression plate or locking compression plate, intramedullary nail, and minimally invasive plate osteosynthesis. The median FI was 0 for all parameters analyzed. Regarding individual outcomes, the FI was 0 for 81/91 (89%) of outcomes. The FI exceeded the number lost to follow up in only 2/91 (2%) outcomes.

CONCLUSION

The FI shows that data from RCTs regarding operative treatment of humeral shaft fractures are fragile and does not demonstrate superiority of any particular surgical technique.

Key Words: Humerus fracture; Open reduction internal fixation; Intramedullary nail; Fragility index; Complications; Fragility index

Core Tip: Humerus shaft fractures have been managed with intramedullary nail fixation and plate osteosynthesis. Multiple randomized control trials have been performed to compare outcomes, complications, reoperations, and union rates between both treatment modalities. Despite multiple randomized control trials, there remains a lack of consensus from the existing literature regarding surgical treatment of humeral shaft fractures. This manuscript aims to further assess the quality of the literature that guides treatment decisions by employing a new metric, the fragility index.

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INTRODUCTION

Humeral shaft fractures represent approximately 3% of all long-bone fractures[1] with an incidence around 13 per 100000 people per year[2]. While the vast majority may be managed nonoperatively[1-5], surgical treatment is generally indicated for open fractures, polytrauma patients, ipsilateral humeral shaft and forearm fractures (floating elbow), segmental fractures, and cases of failed treatment in functional brace[3]. However, it is important to note that there are currently no defined gold standards for the treatment of humeral shaft fractures[6,7]. Surgical treatment options include external fixation, open reduction and plate osteosynthesis (ORPO), minimally invasive plate osteosynthesis (MIPO), and intramedullary nail (IMN). Implant options for both ORPO and MIPO include dynamic compression plate (DCP) and locking compression plate (LCP). Numerous recent systematic reviews, meta-analysis, and network meta-analysis (NMA) review papers have been published aiming to determine the efficacy of these treatment options in order to provide reliable evidence to guide clinical decision making[6,8-13]. Based on the lack of consensus from the existing literature regarding surgical treatment of humeral shaft fractures, this manuscript aims to further assess the quality of the literature that guides treatment decisions by employing a new metric, the fragility index (FI). The FI has been introduced to further evaluate the robustness (or fragility) of randomized control trial (RCT) results[14,15].

The evaluation of RCTs *via* systematic review, meta-analysis, or NMA represents level I evidence; however, the fact remains that many RCTs in orthopaedics, despite demonstrating statistically significant effects, are limited by small sample sizes and few outcome events[16-19]. Clinical studies are classically evaluated for statistical significance in the form of P values, and 95% confidence intervals, which help determine how likely observed effects would occur based solely on chance[20-22]. The FI represents the required number of participants in the RCT whose outcome would have to change from nonevent to event in order to convert a statistically significant result to nonsignificant. The FI is calculated by sequentially calculating the P value using the Fisher exact test while changing an outcome from nonevent to event between cycles until the calculated P value is not significant, or $P > 0.05$. Basically, the FI quantifies how many patients would be required to switch outcomes in order to change the study conclusions. In the case where a study reports a statistically significant result, but the FI is calculated to be zero, this would indicate that the Fisher's exact test did not find a *P* value < 0.05, whereas the statistical method used in the paper did. In addition, the FI may be lower than the number of patients lost to follow-up, limiting the confidence one may have in the study conclusion[14]. The higher the FI the more confidence the reader can have that the result is robust. While there is no defined cut off for the FI value, if the FI is zero or less than the number of patients lost to follow up, then any statistically significant result should be considered fragile and interpreted with caution. By applying the FI metric to RCTs evaluating surgical outcomes in humeral shaft fractures we can determine how much confidence these studies should be given in guiding treatment decisions.

Due to this added value, the FI has been gaining traction in the literature with studies published across numerous medical specialties[15,23,32-35,24-31], in addition to orthopaedic subspecialties[25,36-40]. This valuable, new tool, the FI, can serve to increase our understanding of the literature regarding treatment of humeral shaft fractures, aiding in clinical decision making. Our primary objective was to determine the robustness of statistically significant findings in RCTs of the surgical treatment of humeral shaft fractures by systematically applying the FI. We sought to accomplish this objective by testing our hypothesis that the median FI in these RCTs would be less than the number lost to follow up and therefore would indicate fragile results.

MATERIALS AND METHODS

The systematic review was completed, and results reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines statement[41]. We began by evaluating all review articles about humeral shaft fractures published from 2000 to 2019[6,8-12] and extracting from those studies all included RCTs for analysis. We then performed a systematic review of the literature to identify randomized controlled trials dealing with surgical treatment of humeral shaft fractures that had been published since the most recent review articles. The Medline and EMBASE databases were searched for the dates of January 1, 2016 to April 1, 2019 using the following Medical Subject Headings terms: "humeral fractures". The Reference Citation Analysis (RCA) was also used to ensure high quality studies were included in the analysis. These dates were selected to identify new RCTs that would not have been included in prior systematic review articles. Titles and abstracts were screened, and full text manuscripts reviewed. Inclusion criteria included the following: patients randomized to 2 parallel arms, articles published in English, patient allocated to treatment and control arms in 1:1 ratio, reported statistical significance for dichotomous variables. Exclusion criteria included: published abstract only; studies without available full text, (non-English manuscripts; studies reporting patient data published previously; retrospective studies; and prospective studies that were not randomized.

Data was extracted from the included studies by individual review of each study by the primary author. Accuracy of data extraction was confirmed by independent review by the remaining authors separately, with any discrepancy resolved by group consensus. An electronic data form was developed and the following data were extracted for each included study: First author, journal, publication year, comparison groups, randomization parameters, initial sample size, total patients lost to follow up, final sample size, patients in study group 1, patients in study group 2, patients lost to follow up in group 1, patients lost to follow up in group 2, presence of power analysis, as well as the number of events for each outcome in each group and reported p-value for dichotomous outcomes (delayed union/nonunion, iatrogenic radial nerve palsy, infection, malunion, shoulder impingement, elbow stiffness, secondary surgeries). For our study lost to follow up included any patients initially enrolled in the study but not included in final analysis for any reason. The total number of events for all complications was defined as the sum of delayed union/nonunion, iatrogenic radial nerve palsy, infection, malunion, shoulder impingement, and elbow stiffness. The total number of events for all complications was calculated for each study group within each included study.

For each study the FI was then calculated for all complications, secondary surgeries, as well as each complication individually. The FI was calculated *via* the method described previously by Walsh *et al*[14] using a publicly available calculator found at http://clincalc.com/Stats/FragilityIndex.aspx. After inputting the total number of patients in the control group, experimental group, control group with primary endpoint, and experimental group with primary endpoint, this tool calculates the *P* value using the Fisher exact test. If the *P* value is significant (< 0.05), the tool incrementally converts 1 outcome from nonevent to event and recalculates the *P* value until the *P* value increases above 0.05 and the result becomes insignificant. The methodological quality of each RCT was also assessed by calculating the Jadad scale[42], also known as the Oxford Quality Scoring System, for each trial.

RESULTS

Our review of RCTs from recent review articles as well as systemic search strategy produced 415 records screened and 28 full text articles assessed (Figure 1). Of these, 15 studies met inclusion criteria (Table 1)[43-57]. The primary outcome was only defined in two studies, shoulder function defined by

Table 1 Included randomized controlled trials with characteristics

First author (last name)	Journal	Year	Comparison	Patients enrolled	Patients lost to follow up	Final study, *n*	JADAD score	Power analysis
Kim	*J Orthop Trauma*	2015	ORPO (LCP) *vs* MIPO	72	4	68	3	Yes
Esmailiejah	*Trauma Mon*	2015	ORPO (DCP) *vs* MIPO	68	3	65	3	No
Fan	*Orthopedics*	2015	ORPO (LCP) *vs* IMN	60	0	60	2	Yes
Hadhoud	*Menoufia Medical Journal*	2015	ORPO (LCP) *vs* MIPO	30	0	30	2	No
Wali	*Strategies Trauma Limb Reconstr*	2014	ORPO (DCP) *vs* IMN	50	0	50	2	No
Benegas	*J Shoulder Elbow Surg*	2014	MIPO *vs* IMN	41	1	40	3	Yes
Lian	*Orthopedics*	2013	MIPO *vs* IMN	56	9	47	3	No
Li	*J Shoulder Elbow Surg*	2011	ORPO (LCP) *vs* IMN	50	5	45	3	Yes
Iqbal	*Annals of King Edward Medical University*	2011	ORPO (DCP) *vs* IMN	40	0	40	3	No
Singisetti	*Int Orthop*	2010	ORPO (DCP) *vs* IMN	45	9	36	1	No
Putti	*J Orthop Surg (Hong Kong)*	2009	ORPO (DCP) *vs* IMN	34	0	34	2	No
Changulani	*Int Orthop*	2007	ORPO (DCP) *vs* IMN	47	2	45	3	No
Kesemenli	*Acta Orthop Traumatol Turc*	2003	ORPO (DCP) *vs* IMN	60	0	60	2	No
McCormack	*J Bone Joint Surg (Br)*	2000	ORPO (DCP) *vs* IMN	44	3	41	2	No
Chapman	*J Orthop Trauma*	2000	ORPO (DCP) *vs* IMN	89	5	84	3	No

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

University of California, Los Angeles (UCLA) scoring system in one study[43] and shoulder function defined by the American Shoulder and Elbow Surgeons (ASES) score in the other[56]. Table 2 contains summary characteristics for these trials. The mean initial sample size was 52.4 (range 30-89), mean lost to follow up of 2.7 (range 0-9), while the mean final sample size was 49.7 (range 30-84). The mean Jadad scale score was 2.5 (range 1-3). Power analysis was only reported in 4 studies (26.7%).

The most common comparison was between ORPO with DCP and IMN, found in 8 studies (53.3%). ORPO with LCP *vs* IMN, MIPO *vs* IMN, and ORPO with DCP *vs* IMN were the comparison groups of 2 studies each (13.3% each), and 1 study (6.7%) compared ORPO with DCP and MIPO. All 15 studies evaluated both the outcomes of delayed union/nonunion and iatrogenic radial nerve palsy. The majority of studies also reported incidence for infection (14 studies, 93.3%), secondary surgeries (11 studies, 73.3%), and shoulder impingement (10 studies, 66.7%). Malunion was a reported outcome in 7 studies (46.7%), while only 4 studies (26.7%) reported the outcome of elbow stiffness.

The cumulative FI values for each outcome within each study are listed in Table 3 and presented graphically (Figure 2). The FI was found to be 0 for all individual outcomes except for iatrogenic nerve palsy in 1 out of 14 studies (higher rate with DCP compared with IMN), malunion in 1 of 7 studies (higher rate in IMN compared with LCP), shoulder impingement in 4 of 10 studies (higher rate in IMN compared with MIPO or DCP), elbow stiffness in 1 of 4 studies (higher rate in DCP compared with IMN), and secondary surgeries in 1 of 11 studies (higher rate with IMN compared with DCP). When totaling all complications for each study, the FI was >0 in 2 out of the 15 studies, with higher complication rates in IMN compared with MIPO or DCP. Overall, the FI was greater than 0 in only 9.8% (9/91) and was greater than the number lost to follow up in 2% (2/91) of outcomes studied.

The relationship between enrolled initial sample size and FI for all complications (Figure 3) was calculated using the Spearman correlation coefficient and was found to not be significant with a P value of 0.830. The majority of included RCTs reported continuous variable outcomes such as operative time,

Table 2 Summary characteristics of included randomized controlled trials

Characteristic	No.	% or range
Initial sample size, mean No.	52.4	(30-89)
Lost to follow up, mean No.	2.7	(0-9)
Final sample size, mean No.	49.7	(30-84)
Power analysis	4	26.7%
Comparison groups		
ORPO (DCP) *vs* IMN	8	53.3%
ORPO (LCP) *vs* IMN	2	13.3%
MIPO *vs* IMN	2	13.3%
ORPO (LCP) *vs* MIPO	2	13.3%
ORPO (DCP) *vs* MIPO	1	6.7%
Outcome assessed		
Delayed union/nonunion	15	100.0%
Iatrogenic radial nerve palsy	15	100.0%
Infection	14	93.3%
Secondary surgeries	11	73.3%
Shoulder impingement	10	66.7%
Malunion	7	46.7%
Elbow stiffness	4	26.7%

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

radiation exposure time, operative blood loss, length of hospital stay, time to union, and functional outcome scores such as the UCLA scoring system, Mayo elbow performance index, and the ASES score. The outcomes with reported differences between groups are summarized in Table 4.

DISCUSSION

Our systemic review looked at randomized control trials (RCTs) of the surgical treatment of humeral shaft fractures and discovered that the median FI for all outcomes was 0. In the studies with data leading to FI > 0, the FI exceeded the number lost to follow up in only two instances (2%): (1) Lower incidence of iatrogenic radial nerve palsy with IMN compared with ORPO[45]; and (2) Lower rate of overall total complication with ORPO compared with IMN[56]. Therefore, all evaluated outcomes (nonunion, radial nerve palsy, infections, malunion, malrotation, shoulder impingement, elbow stiffness, secondary surgeries, and overall complications) were extremely fragile and did not demonstrate superiority of one intervention (ORPO, MIPO, IMN) over another.

In analyzing all outcomes individually for humeral shaft fractures, the median FI was 0, and remained so when calculating median FI for all outcomes combined. This result is not surprising given the median FI ≤ 3 reported in the orthopaedic literature previously[36-40]. A recent study used FI to explore the literature on the treatment of clavicular fractures and found the median FI to be 2, with 46.7% of trials reporting the number of patients lost to follow-up exceeded the FI[40]. Sample sizes in an operative population are inherently lower. In addition, the cost, time, and resources required to complete RCTs with sufficiently large sample sizes often pose a significant challenge in orthopaedics, where the incidence of desired exposures and events can be low[18,58]. Simply increasing sample size alone, however, is not sufficient to guarantee increased FI values, as even very large sample size studies can still have fragile results if the between-group difference is very small[14].

While the FI was found to be > 0 in 9 outcomes total, the fact that the number lost to follow up exceeded the FI in 89/91 (98%) instances further confirms that those outcomes are quite fragile, and the significance of those conclusions should be called into question. When the number lost to follow up exceeds the FI this indicates that inclusion of the patients lost to follow up alone could have resulted in a nonsignificant *P* value. Kesemenli *et al*[45] reported significantly higher rate of iatrogenic radial nerve

Table 3 Fragility index values for each outcome for included randomized controlled trials

First author (last name)	Comparison	Delayed union/ Nonunion	Iatrogenic radial nerve palsy	Infection	Malunion	Shoulder Impingement	Elbow Stiffness	All complications	Secondary surgeries
Kim	ORPO (LCP) *vs* MIPO	0	0	0	0	NA	NA	0	0
Esmailiejah	ORPO (DCP) *vs* MIPO	0	0	0	0	NA	NA	0	0
Fan	ORPO (LCP) *vs* IMN	0	0	NA	NA	NA	NA	0	NA
Hadhoud	ORPO (LCP) *vs* MIPO	0	0	0	NA	NA	NA	0	NA
Wali	ORPO (DCP) *vs* IMN	0	0	0	NA	0	0	0	0
Benegas	MIPO *vs* IMN	0	0	0	0	0	NA	0	0
Lian	MIPO *vs* IMN	0	0	0	0	1	0	4	NA
Li	ORPO (LCP) *vs* IMN	0	0	0	2	NA	NA	0	NA
Iqbal	ORPO (DCP) *vs* IMN	0	0	0	NA	0	NA	0	0
Singisetti	ORPO (DCP) *vs* IMN	0	0	0	NA	0	0	0	0
Putti	ORPO (DCP) *vs* IMN	0	0	0	NA	0	NA	0	0
Changulani	ORPO (DCP) *vs* IMN	0	0	0	NA	1	NA	0	0
Kesemenli	ORPO (DCP) *vs* IMN	0	1	0	NA	0	NA	0	0
McCormack	ORPO (DCP) *vs* IMN	0	0	0	0	2	NA	6	1
Chapman	ORPO (DCP) *vs* IMN	0	0	0	0	2	1	0	0

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.

palsy among the DCP group compared with the IMN group. Of note, this study reported no patients lost to follow up. While this suggests a robust outcome, the fact remains that the other 14/15 studies showed no difference among treatment groups regarding iatrogenic radial nerve palsy. Regarding all complications combined, two studies[55,56] resulted in FI > 0, but the FI exceeded the number lost to follow up in only one[56].

The difference between treatment options may possibly be captured only by continuous variables, and not by dichotomous variables. There is precedence for this in the orthopaedic literature, as Bhandari *et al*[58] recommended that when orthopaedic surgeons anticipate small sample sizes they can optimize their study's statistical power by choosing a continuous outcome variable. In reviewing 76 orthopaedic RCTs, these authors found significantly greater study power in RCTs reporting continuous variables compared with studies reporting dichotomous variables (P = 0.042), despite similar mean sample size in each group (P > 0.05). The difference in treatment options for humeral shaft fractures, however, has been reported and analyzed by continuous variables previously. As summarized in this review in Table 4, the majority of included RCTs reported on continuous variable outcomes. The FI is not designed to evaluate continuous variables, and therefore all these continuous outcomes fell outside the scope of our review. As such, application of the FI does not add to the commentary favoring any one treatment over the others on the basis of these continuous variables.

Our study has potential weaknesses, with some inherent to the requirements of the FI. In order to calculate an FI, a study must compare 2 treatment arms, randomize patients to those arms in 1:1 ratio, and report dichotomous outcomes. These inclusion criteria limit both the number of studies that can be included for analysis, as well as the number of outcomes or results that can be analyzed from the included studies. Another requirement of the FI is that a study must be a prospective, randomized trial.

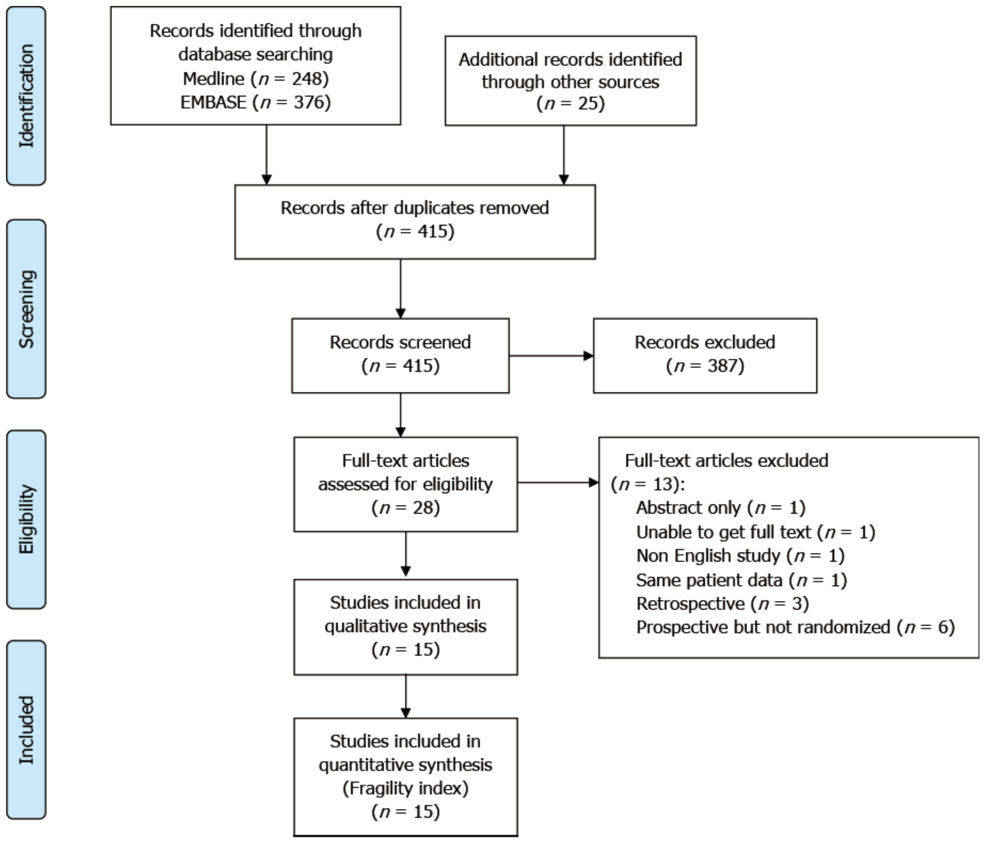

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Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of included studies.

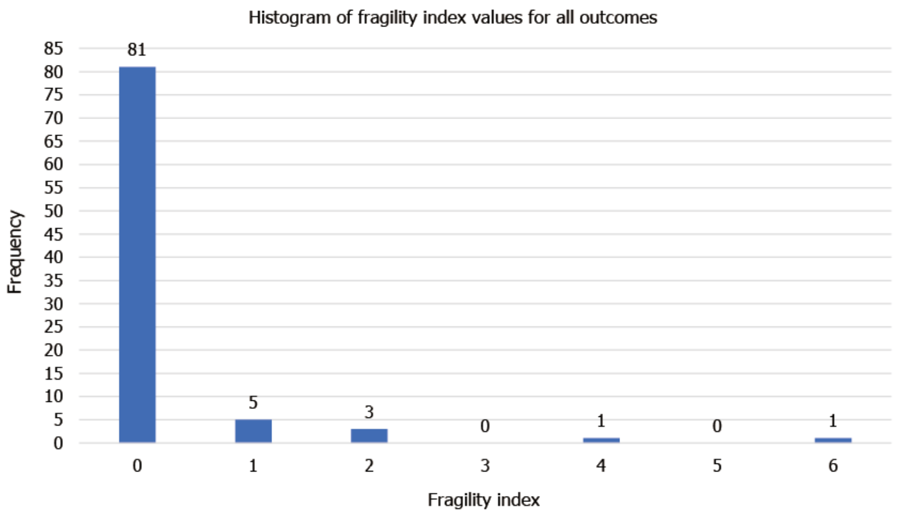

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Figure 2 Distribution of fragility indices from all studies and for all outcomes.

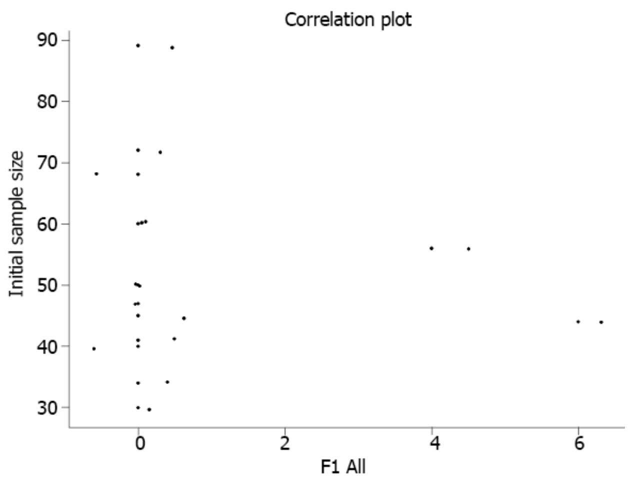
Due to this requirement, we excluded 3 retrospective studies and another 9 prospective studies that were not randomized. While this represents a loss in the number of included studies, and associated decrease in number of included patient outcomes, we do not feel this represents a significant loss as it means that the included studies represent the highest level of data availability.

Another potential weakness relates to the FI itself, which is not without inherent weakness or controversy. RCTs with small samples and in which the event of interest is rare, are common in orthopaedics and tend to be inherently fragile. The FI revolves around the statistical threshold of using $P < 0.05$ as a strict criterion of correct inference. While this cutoff is necessary for making statistical determinations, the actual judging of the quality of inference is a complex activity with more nuance

Table 4 Summary of outcomes with reported differences between groups

Continuous variable	Superior treatment	Inferior treatment	First author (last name)
Time to union	IMN	ORPO	Changulani
Time to union	IMN	ORPO	Fan
Operative time	IMN	ORPO	Fan
Operative time	IMN	ORPO	Wali
Operative time	MIPO	IMN	Lian
Operative time	MIPO	ORPO	Hadhoud
Intraoperative blood loss	IMN	ORPO	Fan
Intraoperative blood loss	IMN	ORPO	Wali
Intraoperative blood loss	MIPO	IMN	Lian
Hospital stay	IMN	ORPO	Fan
Hospital stay	IMN	ORPO	Wali
Constant scores	MIPO	IMN	Li
Rodriguez-Merchan criteria	DCP	IMN	Singisetti
Shoulder ROM	MIPO	IMN	Li
Shoulder ROM	DCP	IMN	Chapman
Elbow ROM	IMN	DCP	Chapman

ORPO: Open reduction and plate osteosynthesis; DCP: Dynamic compression plate; LCP: Locking compression plate; IMN: Intramedullary nail; MIPO: Minimally invasive plate osteosynthesis.



DOI: 10.5312/wjo.v13.i9.825

Figure 3 Relationship between initial sample size and FI for all outcomes.

than is afforded in having a *P* value slightly greater of less than 0.05[59]. The misinterpretation of statistical tests extends beyond just the FI[60].

CONCLUSION

The FI represents a valuable tool that can aid in the interpretation of results from RCTs. Along with *P* value and confidence intervals, the FI provides a quantitative metric regarding the robustness of the reportedly significant results. In applying the FI to RCTs comparing surgical treatment options for humeral shaft fractures, this study has shown that there is a significant lack of robust data to recommend one treatment option over another on the basis of delayed union/nonunion, iatrogenic radial nerve palsy, infection, malunion, shoulder impingement, elbow stiffness, or secondary surgeries. The results published in the literature for treatment of humeral shaft fractures should be interpreted cautiously. This study, while limited in the analysis of functional outcome, suggests no clear benefit of one surgical technique over another with respect to dichotomous outcomes. Plate and nail techniques should both be considered as options for surgical treatment of humeral shaft fractures.

ARTICLE HIGHLIGHTS

Research background

Humeral shaft fractures are a common injury which could be managed non-operatively or operatively. There is a lack of clear evidence to support open reduction internal fixation *vs* intramedullary nail fixation.

Research motivation

Identify the fragility index, which identifies the number of patients have a change in outcome from a significant to non-significant. This is important as higher level studies guide management in orthopedics.

Research objectives

Applying the fragility index to humeral shaft fractures will aid in clinical decision making on treatment of humeral shaft fractures.

Research methods

A systematic review of randomized controlled trials (RCTs) evaluating the surgical treatment of humeral shaft fractures was conducted. The fragility index (FI) was calculated for total complications, each complication individually, and secondary surgeries using the Fisher exact test, as previously published.

Research results

Fifteen RCTs were included in the analysis comparing open reduction plate osteosynthesis with dynamic compression plate or locking compression plate, intramedullary nail, and minimally invasive plate osteosynthesis. The median FI was 0 for all parameters analyzed. Regarding individual outcomes, the FI was 0 for 81/91 (89%) of outcomes. The FI exceeded the number lost to follow up in only 2/91 (2%) outcomes.

Research conclusions

The FI shows that data from RCTs regarding operative treatment of humeral shaft fractures are fragile and does not demonstrate superiority of any particular surgical technique.

Research perspectives

Further research is needed to delineate whether open reduction internal fixation or intramedullary nail fixation is superior in the management of humeral shaft fractures.

FOOTNOTES

Author contributions: Morris SC is responsible for the data collection; Morris SC and Gowd AK analyze the data; Phipatanakul WP, Liu JN and Amin NH are responsible for the study conception; all authors participate in the manuscript preparation.

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SYSTEMATIC REVIEWS

Return to work following shoulder arthroplasty: A systematic review

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Abstract

BACKGROUND

Many patients prioritize the ability to return to work (RTW) after shoulder replacement surgeries such as total shoulder arthroplasty (TSA), reverse TSA (rTSA), and shoulder hemiarthroplasty (HA). Due to satisfactory clinical and functional long-term outcomes, the number of shoulder replacements performed will continue to rise into this next decade. With younger individuals who compose a significant amount of the workforce receiving shoulder replacements, patients will begin to place a higher priority on their ability to RTW following shoulder arthroplasty.

AIM

To summarize RTW outcomes following TSA, rTSA, and HA, and analyze the effects of workers' compensation status on RTW rates and ability.

METHODS

This systematic review and analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A literature search regarding RTW following shoulder arthroplasty was performed using four databases (PubMed, Scopus, Embase, and Cochrane Library), and the *Reference Citation Analysis* (https://www.referencecitationanalysis.com/). All studies in English relevant to shoulder arthroplasty and RTW through January 2021 that had a level of evidence I to IV were included. Nonclinical studies, literature reviews, case reports, and those not reporting on RTW after shoulder arthroplasty were excluded.

RESULTS

The majority of patients undergoing TSA, rTSA, or HA were able to RTW between one to four months, depending on work demand stratification. While sedentary or light demand jobs generally have higher rates of RTW, moderate or heavy demand jobs tend to have poorer rates of return. The rates of RTW following TSA (71%-93%) were consistently higher than those reported for HA (69%-82%) and rTSA (56%-65%). Furthermore, workers' compensation status negatively influenced clinical outcomes following shoulder arthroplasty. Through a pooled means analysis, we proposed guidelines for the average time to RTW after TSA, rTSA, and HA. For TSA, rTSA, and HA, the average time to RTW regardless of work demand stratification was 1.93 ± 3.74 mo, 2.3 ± 2.4 mo, and 2.29 ± 3.66 mo, respectively.

CONCLUSION

The majority of patients are able to RTW following shoulder arthroplasty. Understanding outcomes for rates of RTW following shoulder arthroplasty would assist in managing expectations in clinical practice.

Key Words: Shoulder replacement; Total shoulder arthroplasty; Reverse total shoulder arthroplasty; Hemiarthroplasty; Return to work

Core Tip: Many patients prioritize the ability to return to work after shoulder replacement surgeries such as total shoulder arthroplasty, reverse total shoulder arthroplasty, and shoulder hemiarthroplasty. While rates of return to work have been studied in the literature following shoulder arthroplasty, a consensus on which is the most effective treatment is still controversial. Information about the ability to return to work following any type of shoulder arthroplasty would assist patients and surgeons in managing expectations and put into place evidence-based guidelines. This systematic review examines how return to work following shoulder arthroplasty has been studied and reported in the literature.

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INTRODUCTION

Over the last two decades, the number of shoulder arthroplasties, including total shoulder arthroplasty (TSA), reverse TSA (rTSA), and shoulder hemiarthroplasty (HA), has increased at exponential rates[1-4]. TSA has typically been indicated for end-stage shoulder conditions in individuals with intact rotator cuff and sufficient glenoid bone stock to allow for stable glenoid component implantation[1-4]. The TSA procedure involves replacing the humeral head and glenoid with similarly shaped prosthetic components. rTSA, on the other hand, was historically indicated for patients with massive rotator cuff tears and involves using a convex glenoid hemispheric ball and a concave humerus articulating cup to reconstruct the glenohumeral joint. HA has traditionally been indicated in patients with glenohumeral arthritis where the glenoid bone stock is inadequate for TSA[1-4]. This procedure involves removing the humeral articular surface and replacing it with a stemmed humeral component.

Due to satisfactory clinical and functional long-term outcomes, the number of shoulder replacements performed will continue to rise into this next decade, with models predicting between 174810 and 350558 procedures by 2025[2,5,6]. Historically, shoulder replacements have been performed in elderly patients for degenerative shoulder conditions; however, these procedures are becoming more prevalent in younger and more active populations[5-8]. Furthermore, individuals born between 1981 and 1996 make up the largest generation of workers in the U.S. Labor Force[9]. With younger individuals who compose a significant amount of the workforce receiving shoulder replacements, patients will begin to place a higher priority on their ability to return to work (RTW) following shoulder arthroplasty.

Prior studies have shown varying levels of RTW after shoulder arthroplasty based on arthroplasty type, diagnosis, and work intensity[10-12]. While informative, a compilation comparing various demographics, arthroplasty types, diagnoses, and work intensities has not been performed in recent years. The purpose of this systematic literature review and analysis is to summarize outcomes of RTW following TSA, rTSA, and HA as well as analyze the effects of workers' compensation (WC) status on rates and ability to RTW.

MATERIALS AND METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic review and analysis was performed[13,14]. The PubMed, Scopus, Embase, and Cochrane Library databases was queried using the search terms "shoulder arthroplasty", "shoulder replacement", "shoulder hemiarthroplasty", or "humeral resurfacing" combined with "return to work". The *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) software was also used to identify any additional studies. The final search was performed on January 8, 2021. Additionally, the references of each study were manually assessed as well for potential inclusion in this investigation. The flow diagram summarizes the progression of the literature review with 12 total references meeting the inclusion criteria (Figure 1).

Clinical studies were evaluated and included if they were in English, had level of evidence I to IV, and reported on RTW after shoulder arthroplasty. Nonclinical studies, literature reviews, case reports, and those not reporting on RTW after shoulder arthroplasty were excluded. Title and abstract reviews were performed by two of the study authors (Lalehzarian SP and Liu JN). The full texts of articles meeting inclusion criteria based on title and abstract were then reviewed by two of the study authors (Lalehzarian SP and Agarwalla A) for final inclusion in the study. As referenced in Figure 1, 23 references were initially identified by the keyword search terms described above. After the title review, 8 references were excluded as 7 were irrelevant to the topic of discussion and 1 was a case report. One reference was excluded after abstract review as it was a review article and two references were excluded after full text review as they did not include RTW data. Following the review process, there were 12 references left and all were included in this review.

Included studies were evaluated using the Methodological Index for Non-Randomized Studies (MINORS) checklist[15]. Studies were evaluated on 8 items to 12 items, with each scored 0 (not reported), 1 (reported but poorly or inadequately done), or 2 (reported, well done and adequate), with a maximum score of 16 and 24 for noncomparative and comparative studies, respectively. Articles were scored by one of the study authors (Lalehzarian SP) and confirmed by two of the study authors (Agarwalla A and Liu JN). An analysis of the 12 total articles is shown in Tables 1-3.

RESULTS

RTW after TSA

TSA has shown to be a highly effective treatment for degenerative shoulder disease with adequate long-term outcomes, low revision rates, and high implant survivorship[7,16]. The number of anatomic total shoulder arthroplasties has increased from 29414 in 2011 to 40750 in 2017 partly due to an increased demand from younger populations and expanded indications[2,17-20]. With this increase in demand and volume, RTW following anatomic TSA is an important metric for many employed patients.

In a study by Bülhoff *et al*[10], 57 TSA patients were analyzed after meeting inclusion criteria. At the most recent follow-up, 22 total patients (39%) returned to work. It is important to note that 6 patients (11%) cited their inability to pursue work at the time of most recent follow-up due to shoulder problems. While the authors concluded that approximately 61% of their patients did not retire or cease their vocation because of TSA, a large number of patients who were not working at final follow-up had retired from work[10]. This major limitation could be responsible for a low rate of RTW.

Liu *et al*[12] reported on 52 patients (54 shoulders), who were 55 years or younger at the time of surgery, worked in the 3 years leading up to surgery, and were available for a minimum follow-up of 2 years. Forty-eight patients (92%) were able to RTW postoperatively at an average of 2.1 mo after surgery. In addition to calculating the rate of RTW, the authors stratified patients by intensity of work: sedentary, light, moderate, or heavy. Forty one of 41 (100%) patients who had sedentary, light, or moderate work preoperatively were able to return to the same level of work. However, only 7 of 11 (64%) patients who had heavy-intensity work preoperatively were able to RTW. Of the 4 patients who did not RTW, only one patient cited shoulder pain and limited range of motion as the reason[12]. Additionally, the intensity of work was positively correlated with time to RTW. The authors found a statistically greater time to RTW when comparing heavy intensity (4.2 mo) to sedentary, light, and moderate intensity, respectively.

Cvetanovich *et al*[21] analyzed 27 shoulders (24 patients) that underwent anatomic TSA with an inlay glenoid component and stemless ovoid humeral head component. Twenty five (93%) of 27 patients were able to RTW with an average duration of 3.7 mo following surgery. Of the 2 patients who were not able to return, one patient cited reasons unrelated to the shoulder and the other patient cited back issues. When stratified by job intensity preoperatively, the rates of RTW were as follows: 5/5 for sedentary, 2/2 for light, 9/9 for moderate, and 9/11 for heavy. Furthermore, of the 25 patients who returned to work, 19 (76%) were able to return to their preoperative occupational demands. The 6 patients who returned to work at a lower intensity held heavy intensity occupations[21]. In addition to corroborating high rates of RTW for patients undergoing TSA, the authors found that patients with heavier demand jobs were less likely to RTW at the same occupational level postoperatively than patients in the other work

Table 1 Study characteristics

Ref.	Design	No. of groups	Level of evidence	Mean follow-up (range), yr	MINORS score
Bülhoff *et al*[10], 2015	Retrospective	1	IV	6.2 (2.6-12.6)	7/16
Jawa *et al*[56], 2015	Retrospective	2	III	3.9 (2.0-5.6)	17/24
Morris *et al*[55], 2015	Retrospective	2	III	3.5 (2-8)	20/24
Garcia *et al*[28], 2016	Retrospective	1	IV	2.6 (1-4.7)	10/16
Garcia *et al*[36], 2016	Retrospective	1	IV	5.1 (1-7.5)	10/16
Hurwit *et al*[11], 2017	Retrospective	2	III	HHA: 5.3 (1.1-7.5); rTSA[1]: 2.7 (1.0-4.9)	16/24
Liu *et al*[12], 2018	Retrospective	1	IV	5.4 (2.5-8.6)	10/16
Kurowicki *et al*[41], 2018	Retrospective	2	III	2.4 (0.5-7.6)	17/24
Gowd *et al*[48], 2019	Retrospective	2	III	Hemi RR: 5.7 (SD ± 2.0); aTSA: 5.8 (SD ± 2.2)	17/24
Cvetanovich *et al*[21], 2020	Retrospective	1	IV	3.4 (1.9-5.0)	9/16
Jayasekara *et al*[22], 2020[2]	Retrospective	3	IV	NR	NA
Liu *et al*[49], 2020	Retrospective	2	III	HHA: 5.2 (2.0-7.5); aTSA: 5.18 (2.0-7.49)	16/24

[1]Represents duplicate data from Garcia *et al*[28]; not included in meta-analysis.
[2]Numbers are relevant to groups who underwent total shoulder arthroplasty, reverse total shoulder arthroplasty, and hemiarthroplasty.
MINORS: Methodological Index for Non-Randomized Studies; HHA: Humeral hemiarthroplasty; rTSA: Reverse total shoulder arthroplasty; NR: Not reported; NA: Not available; Hemi RR: Hemiarthroplasty with ream-and-run resurfacing; aTSA: Anatomic total shoulder arthroplasty.

demand classes.

In a large clinical series by Jayasekara *et al*[22], 1773 patients were examined. TSA was one of the twelve surgeries analyzed with a total number of 38 patients. At the six month follow-up, 27 (71%) patients were able to return to some type of work: 14 (37%) patients returned with full duty, 13 (34%) patients returned with lighter duty, and 11 (29%) patients were unable to RTW. Of the twelve surgeries analyzed, TSA at 71% was shown to have a lower rate of RTW compared to surgeries such as HA and rTSA which had 82% and 56%, respectively[22]. This lower rate of RTW may have been due to a higher average age of patients who underwent TSA compared to those in previous studies; therefore, the age of the patients may have negatively influenced their desire and ability to RTW[22].

In summary, the majority of studies cited a rate of RTW between 71% and 93% with an average duration of 1 mo to 4 mo following TSA[12,21]. Furthermore, most patients who undergo TSA are able to RTW at the same preoperative intensity level with the exception of those patients in heavy intensity jobs who are less likely to RTW after TSA.

RTW after rTSA

In 2003, the United States Food and Drug Administration approved the use of rTSA for rotator cuff arthropathy[1,23]. Since that time, the volume of rTSA has drastically increased, from 21916 in 2011 to 63845 in 2017, in part due to its encouraging results and expanded indications to cover proximal humerus fracture and previous failures of arthroplasty[24-27]. When comparing the number of rTSA to the total number of shoulder replacements from 2011 and 2017, the percentage has increased from 33% to 58%[2]. Due to the exponential increase in rTSA use, a clinical review outlining the rate of RTW after rTSA will assist orthopedic surgeons in treating future patients with shoulder conditions.

Garcia *et al*[28] conducted a study on 40 patients who had undergone rTSA. Of the 40 patients analyzed, 26 (65%) of them were able to RTW with an average time of 2.3 mo. From the 14 patients who did not RTW, only two of them retired due to shoulder reasons while the other 12 retired due to nonorthopedic causes. When stratified into intensity level, rates were comparable to the overall rate of RTW with 17 (68%) of 25 patients returning in the sedentary class and 9 (60%) of 15 returning in the light class. Additionally, patients with sedentary jobs returned to work more quickly than those with light work (1.4 mo *vs* 4.0 mo).

Jayasekara *et al*[22] evaluated 34 rTSA patients, with 19 (56%) of them able to return to some type of work at the 6 mo follow-up. Eight of the 19 patients who returned to work were able to RTW with full duties and the other eleven returned to work with lighter duties. From the twelve surgeries included in the study, rTSA was associated with the lowest rate of RTW at 56%. Jayasekara *et al*[22] concluded that this percentage is consistent with prior studies which cited a 65% rate of RTW[11,28].

Table 2 Characteristics of the patients

Ref.	No. of shoulders	Mean age (range), yr	Gender (M/F), *n*	Dominant/nondominant, *n*	BMI, kg/m^2 (range)	WC/NWC	RTW (%)	Work intensity
Bülhoff *et al*[10], 2015	154	72 (33-88)	35/119	103/51	NR	NR	22/57 (38.6)[1]	NR
Jawa *et al*[56], 2015	13	55.9 (39-74)	13/0	NR	NR	13/0	4/13 (30.8)	1 light, 12 heavy
Morris *et al*[55], 2015	28	WC: 58.8 (49-69); NWC: 63.4 (50-72)	20/8	19/9	WC: 32.0 (SD ± 8.4); NWC: 27.1 (SD ± 5.3)	14/14	WC: 2/14 (14.3); NWC: 5/11 (45.5)[1]	WC: 8 sedentary/light, 6 heavy/strenuous; NWC: 3 retired, 7 sedentary/light, 4 heavy/strenuous
Garcia *et al*[28], 2016 (rTSA)	40	74.7 (56-82)	16/24	26/14	28.8 (14.8-46.2)	0/40	26/40 (65)	25 sedentary, 15 light
Garcia *et al*[36], 2016 (HHA)	79	69 (27.6-97.1)	24/55	62/17	28.3 (19.8-49.3)	0/79	34/49 (69.4)[1]	20 sedentary, 25 light, 4 moderate
Hurwit *et al*[11], 2017	81	HHA: 60.8 (40-88); rTSA: 68.6 (41-48)	33/48	52/29	HHA: 28.9; rTSA: 29.5	NR	55/81 (84.6)	44 sedentary, 33 light, 4 heavy
Liu *et al*[12], 2018	52	67.2 (56-96)	38/14	24/28	28.0 (18.1-52.9)	5/47	48/52 (92)	10 sedentary, 14 light, 17 moderate, 11 heavy
Kurowicki *et al* [41], 2018[2]	265	aTSA: 69; rTSA: 75	NR	NR	NR	NR	21% higher difference in ability to RTW following aTSA than rTSA	115 retired, 72 housework, 49 desk job, 16 prolonged standing, 11 yard work, 9 creative jobs, 5 requires lifting, 4 carpenter/construction, 5 cook/food prep
Gowd *et al*[48], 2019	53	Hemi RR: 52.8 ± 7.7; aTSA: 53.3 ± 9.2	48/5	28/25	Hemi RR: 28.5 ± 3.5; aTSA: 31.1 ± 5.7	4/49	50/53 (94.3)	17 sedentary, 12 light, 13 moderate, 11 heavy
Cvetanovich *et al* [21], 2020	27	52.1 ± 6 (42-63)	25/2	NR	NR	3/24	25/27 (92.6)	5 sedentary, 2 light, 9 moderate, 11 heavy
Jayasekara *et al* [22], 2020[3]	83	TSA: 65 ± 1.6 (48-86); rTSA: 72 ± 1.6 (54-91); Hemi: 72 ± 2.7 (57-84)	42/41	NR	NR	3/83	55/83 (66.3)	28 full duty, 27 lighter duty
Liu *et al*[49], 2020	49	HHA: 62.4 (42.7-87.7); aTSA: 61.7 (47.7-75.6)	22/27	30/19	HHA: 29.8 ± 7.1; aTSA: 29.2 ± 6.5	NR	36/49 (73.5)	20 sedentary, 21 light, 6 heavy

[1]Excluding those who were retired preoperatively, retired due to medical concerns, or retired due to non-specified reasons.

[2]Only includes individuals who responded to question 10 of the ASES questionnaire in regards to work.

[3]Numbers are relevant to groups who underwent total shoulder arthroplasty, reverse total shoulder arthroplasty, and hemiarthroplasty.

M: Male; F: Female; BMI: Body mass index; WC: Workers' compensation; NWC: Non-workers' compensation; RTW: Return to work; NR: Not reported; aTSA: Anatomic total shoulder arthroplasty; rTSA: Reverse total shoulder arthroplasty; HHA: Humeral hemiarthroplasty.

Table 3 Diagnosis and surgical characteristics

Ref.	Diagnosis	Surgery	Mean time out of work (range), mo	Complications
Bülhoff *et al* [10], 2015	Primary OA, 154 (100%)	aTSA	NR	NR
Jawa *et al*[56], 2015	OA, 11 (84.6%); capsulorrhaphy arthropathy, 2 (15.4%)	aTSA	4.2 (2.9-6.0)	NR
Morris *et al* [55], 2015	CTA, 14; massive RCT, 8; post-traumatic malunion, 4; failed prior arthroplasty, 2	rTSA	NR	WC (4): postoperative anterior dislocation (2), intraoperative humeral shaft fracture, postoperative periprosthetic infection; NWC (2): postoperative anterior dislocation
Garcia *et al*[28], 2016 (rTSA)	CTA, 21 (53.5%); OA, 10 (25%); PHFx, 7 (17.5%); RA, 2 (5%)	rTSA	2.3 (0.5-11)	NR
Garcia *et al*[36], 2016 (HHA)	OA, 40 (50.6%); PHFx, 17 (21.5%); AVN, 11 (13.9%); CTA, 8 (10.1%); RA, 3 (3.8%)	HHA	1.4 (0.25-24)	8 complications: 4 revision HHA (2 for dislocation, 2 for periprosthetic fracture after fall); 3 HHA revised to TSA; 1 HHA revised to rTSA for continued pain/glenoid wear
Hurwit *et al* [11], 2017	CTA, 63 (77.8%); RA, 14 (17.2%); PHFx, 2 (2.5%)	rTSA; HHA	rTSA: 3.1; HHA: 2.3	rTSA: 20 chronic pain and stiffness/limited mobility; 1 returned to OR; HHA: 4 chronic pain and stiffness/limited mobility; 5 returned to OR
Liu *et al*[12], 2018	OA, 42 (81%); failed prior arthroplasty, 7 (13%); AVN, 2 (4%); RA, 1 (2%)	aTSA	2.1 (SD: 1.7)	22 complications: 17 postoperative stiffness, 6 chronic pain, 3 instability, 4 returned to OR
Kurowicki *et al* [41], 2018	NR	aTSA; rTSA	NR	NR
Gowd *et al*[48], 2019	End-stage glenohumeral OA, 53 (100%)	Hemi RR; aTSA	Hemi RR: 2.5 ± 4.8; aTSA: 1.98 ± 2.6	Hemi RR: 3 chronic pain, 1 felt unstable, 5 postoperative stiffness, 1 nagging soreness, 1 acute pain, 2 conversion to aTSA, 1 received arthroscopic debridement; aTSA: 1 chronic pain, 2 weakness, 6 postoperative stiffness, 1 subscapularis repair, 1 revision with glenoid explantation due to loosening
Cvetanovich *et al*[21], 2020	Glenohumeral OA, 23 (85.1%); post-traumatic OA, 4 (14.9%)	aTSA	3.7 ± 5.2	1 hematoma, 1 pulmonary embolism
Jayasekara *et al* [22], 2020[1]	NR	aTSA; rTSA; HHA	NR	NR
Liu *et al*[49], 2020	End-stage glenohumeral OA, 49 (100%)	HHA; aTSA	HHA: 1.9 ± 2.3; aTSA: 1.3 ± 1.0	HHA: 15 chronic pain, 8 postoperative stiffness, 2 conversion to aTSA, 2 conversion to rTSA; aTSA: 3 postoperative stiffness

[1]Numbers are relevant to groups who underwent total shoulder arthroplasty, reverse total shoulder arthroplasty, and hemiarthroplasty.
OA: Osteoarthritis; CTA: Cuff tear arthropathy; RCT: Rotator cuff tear; PHFx: Proximal humerus fracture; RA: Rheumatoid arthritis; AVN: Avascular necrosis; aTSA: Anatomic total shoulder arthroplasty; rTSA: Reverse total shoulder arthroplasty; HHA: Humeral hemiarthroplasty; TSA: Total shoulder arthroplasty; NR: Not reported; WC: Workers' compensation; NWC: Non-workers compensation; OR: Operating room.

The available data suggests that the majority of patients who undergo rTSA are able to RTW at rates between 56% and 65%. Despite this low percentage, the volume of rTSA continues to rise due to expanding indications[2].

RTW after HA

Traditionally, HA was considered a safer option compared to TSA or rTSA for patients who wished to remain active following surgery due to its low failure rate and utilization of an intact glenoid[29]. Despite exponential rises in TSA and RTSA, the rate of HA procedures has steadily declined from 15860 in 2011 to 6150 in 2017[2]. This is in part due to the increase in rTSA for shoulder replacement. Since the indications for rTSA have been expanded to include fractures, the rate of HA for fracture use has decreased by nearly 30%[30-32]. Additionally, recent studies have shown that clinical outcomes from HA are significantly inferior to that of TSA and that patients undergoing HA had statistically significantly worse functional scores[11,33-35]. With this steady decline over the last decade, there is much necessity for a clinical review that examines all available literature regarding the rates of RTW for HA.

Garcia *et al*[36] examined 49 patients who worked preoperatively and underwent HA. Thirty-four (69.4%) patients were able to return to previous employment at an average duration of 1.4 mo. Preoper-

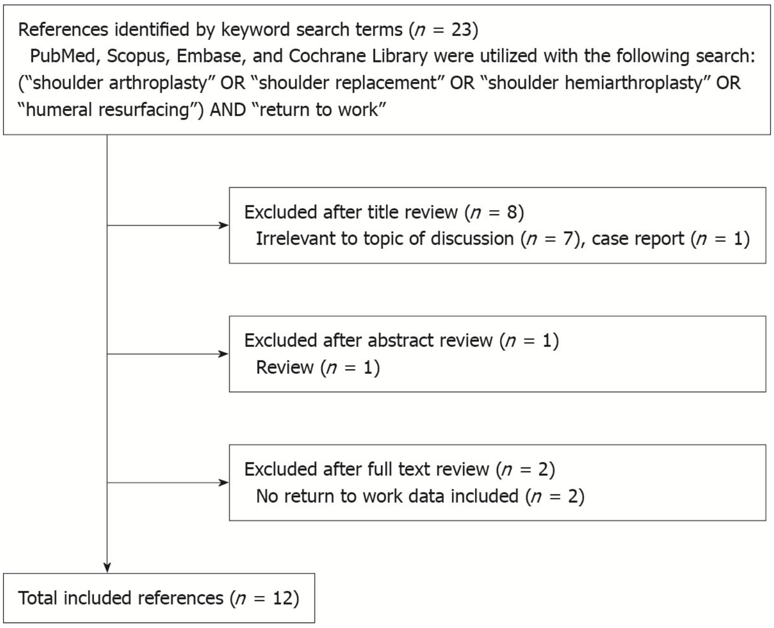

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Figure 1 Flow diagram illustrating systematic literature review process.

atively, 20 (41%) patients classified their jobs as sedentary, 25 (51%) patients as light physical work, and 4 (8%) patients as moderate physical work. Following HA, 15 of 20 (75%) patients returned as sedentary, 17 of 25 (68%) patients as light physical work, and 2 of 4 (50%) patients as moderate physical work. While no patients changed job demand level postoperatively, the average time to return to employment varied: 1.9 mo for sedentary, 2.6 mo for light, and 13.1 mo for moderate. As one of the first studies to analyze the rates of RTW following HA, Garcia *et al*[36] was able to quantify evidence that aided physicians in managing expectations of patients undergoing shoulder HA.

Jayasekara *et al*[22] included 11 patients who underwent shoulder HA. Nine (82%) patients were able to return to some type of work at 6 mo follow-up with 6 (55%) patients able to return to full duties, 3 (27%) able to return to lighter duties, and 2 (18%) unable to RTW. While the reason for not returning to work was not cited, it may be due to the fact that the average age of patients undergoing HA in this cohort was 72 years of age. Although a limitation of this study was a smaller size, Jayasekara *et al*[22] found higher rates of RTW despite an average age much higher than previous studies[11,36].

Recent literature has shown rates of RTW for shoulder HA between 69% and 82% compared to both TSA and rTSA[22,36]. Despite higher rates of RTW for HA compared to rTSA, the number of HA cases continues to decline with poor functional outcomes at long-term follow-up[11,37].

Comparison of RTW between TSA and rTSA

In patients with end-stage glenohumeral arthritis and an intact rotator cuff, TSA has shown to be a highly effective treatment with high rates of functional recovery[5]. While the original indication for rTSA was rotator cuff arthropathy, the indications for rTSA have expanded to include conditions such as TSA and HA implant failures, complex proximal humerus fractures, asymmetric glenoid wear, posterior humeral head subluxation in patients with intact rotator cuffs, and irreparable rotator cuff tears in the absence of arthritis[38-40]. Similarly, the indications for TSA have also expanded to now include a more diverse and active patient population[41]. As younger patients undergo shoulder replacements, many patients cite their ability to work as instrumental in their decision to have surgery. With increased indications for both surgeries, assessing the ability of patients to RTW following TSA and rTSA is imperative to educate future patients and manage expectations.

In one recent study, Kurowicki *et al*[41], evaluated 159 patients undergoing TSA (average age 69) and 106 patients undergoing rTSA (average age 75). Authors used the American Shoulder and Elbow Surgeons (ASES) Assessment Form as a way to track patients' ability to RTW. Among usually reported work, it is important to note that 43% of patients cited retirement as their work, with housework (27%) and desk jobs (18%) as the second and third most cited, respectively. Kurowicki *et al*[41] reported a 21% higher difference in overall ability to work for patients following TSA compared to those patients who underwent rTSA. In particular, statistically significant differences were found between TSA and rTSA amongst patients who cited their work as housework or gardening.

Kurowicki *et al*[41] is the only study that compares the ability of TSA patients to RTW to rTSA patients. Based on this study, authors concluded that returning to work after TSA is more favorable than rTSA in fields of work that require low-demand activities such as housework and gardening[41]. This study was limited by its reporting bias from survey-based studies, small sample size within work subgroups, and population representation differences particularly in age. Regardless, comparisons among these groups hold importance in defining patient and surgeon expectations after surgery.

Comparison of RTW between TSA and HA

If non-operative treatment for glenohumeral osteoarthritis with intact rotator cuff integrity fails, patients are often told to consider HA or TSA. While the optimal surgical treatment remains controversial, there are benefits to both procedures. Multiple studies have shown that patients with glenohumeral arthritis who undergo TSA have improved pain relief, higher functional scores, and more range of motion compared to those who undergo HA[35,36,42-44]. However, TSA also has an increased operative time, more blood loss, more technical difficulty, and incurs the risk of glenoid loosening[45]. On the other hand, while HA has the benefits of decreased operative time, decreased blood loss, and less technical difficulty, there is some concern regarding the progression of arthritic changes especially with bone loss and the need for future revision surgeries such as conversion to TSA[45,46]. Furthermore, many patients have lifting restrictions after TSA, which may limit their ability to RTW[47].

Gowd *et al*[48] analyzed 53 total patients with glenohumeral arthritis. Twenty five patients (average age of 52.8 years) received HA with ream-and-run resurfacing and 28 patients (average age of 53.3 years) received TSA. Of the 25 patients undergoing HA, all 25 (100%) were able to RTW at an average duration of 1.98 mo. On the other hand, 25 (89%) of 28 patients receiving TSA were able to RTW with an average time of 2.5 mo following surgery. When HA patients were stratified preoperatively into work demand level, 7 patients were categorized as sedentary, 7 were light, 4 were moderate, and 7 were heavy. For TSA, 10 patients were categorized as sedentary, 5 were light, 9 were moderate, and 4 were heavy. Postoperatively, all HA patients (100%) in sedentary, light, and moderate were able to RTW. For TSA, 9 (90%) of 10 returned to sedentary work, while all (100%) light and moderate duty patients returned to work. For the heavy category, 7 (100%) of 7 HA patients were able to return compared to 2 (50%) of 4 TSA patients demonstrating that heavy duty workers undergoing HA had a significantly higher rate of RTW[48]. Of the 2 TSA heavy duty patients who were unable to RTW, only one reported permanent restriction with overhead lifting. Despite this difference, authors concluded near equivalent rates of RTW between HA and TSA.

Liu *et al*[49] evaluated 49 total patients with end-stage glenohumeral osteoarthritis. Twenty-six patients underwent HA (average age of 62.4 years) and 23 patients underwent TSA (average age 61.7). Sixteen (62%) of 26 HA patients were able to RTW at an average duration of 1.88 mo following surgery. Of the patients undergoing TSA, 20 (87%) were able to RTW at an average time of 1.29 mo following surgery. From the 10 HA patients who did not RTW, only one had retired postoperatively due to shoulder issues. The other nine patients retired preoperatively due to the shoulder, other medical reasons, or postoperatively due to non-specified reasons. Of the three TSA patients who did not RTW, zero had retired postoperatively due to the shoulder. Patients either retired preoperatively due to the shoulder, other medical concerns, or non-specified reasons. For patients who underwent TSA, 7 (100%) of 7 returned to a sedentary work demand level, 9 (82%) of 11 returned to a light work demand level, and 3 (100%) of 3 returned to a heavy work demand level (Table 4). For patients who underwent HA, 8 (62%) of 13 returned to a sedentary work demand level, 7 (70%) of 10 returned to a light work demand level, and 1 (33%) of 3 returned to a heavy work demand level (Table 4). (68%) of 25 returned to a sedentary work level and 9 (60%) of 15 returned to a light work demand level (Table 4). Liu *et al*[49] concluded that patients with osteoarthritis undergoing TSA have higher rates of RTW and function compared to those undergoing HA.

From these two studies, there is still a discrepancy in terms of ability to RTW between HA and TSA. The mixed results could potentially be due to the limitations of each study. For example, in Gowd *et al*[48], surgeons counseled their TSA patients that they would have permanent overhead lifting restrictions, whereas those who underwent HA would not receive these restrictions. Comparatively, in Liu *et al*[49], surgeons placed no postoperative work restrictions on either group. Furthermore, the average age of individuals in Gowd *et al*[48] (52.8 and 53.3 years of age) was significantly lower than the average of individuals in Liu *et al*[49] (62.4 and 61.7 years of age) possibly indicating that older patients either hold more sedentary, less demanding occupations or may benefit more in their ability to RTW following TSA compared to HA[48,49].

Comparison of RTW between HA and rTSA

When TSA is contraindicated, in cases such as rotator cuff or deltoid dysfunction, deficiencies in glenoid bone stock, or proximal humerus fractures, patients must be educated on the benefits and drawbacks of HA *vs* rTSA[50]. Many studies over the last decade have shown more predictable and superior outcomes for rTSA compared to HA[51-53]. Yet, in the younger population, especially those who want to remain employed following surgery, surgeons often feel more comfortable recommending HA given the theoretical risk of glenoid component loosening or failure in rTSA[54]. Furthermore, surgeons tend to place more activity restrictions on patients who undergo rTSA, which could significantly limit their ability to RTW.

Table 4 Return to work after total shoulder arthroplasty *vs* hemiarthroplasty[49]

Occupation intensity	RTW after TSA (%)	RTW after HA (%)
Sedentary	7/7 (100)	8/13 (62)
Light	9/11 (82)	7/10 (70)
Heavy	3/3 (100)	1/3 (33)
Total	20/23 (87)	16/26 (62)

RTW: Return to work; TSA: Total shoulder arthroplasty; HA: Hemiarthroplasty.

Hurwit *et al*[11] compared 40 rTSA patients (average age of 68.6 years) to 41 HA patients (average age of 60.8 years) all of whom had end-stage glenohumeral arthritis with rotator cuff dysfunction, deficiencies in glenoid bone stock that prohibited the insertion of an anatomic glenoid component, or proximal humerus fracture. Of the patients who underwent rTSA, 26 (65%) of them were able to RTW at an average duration of 2.3 mo following surgery. Only two patients who were unable to RTW cited their main reason as issues with the shoulder following surgery, while the other twelve either retired preoperatively due to medical reasons or non-specified reasons. Twenty-nine (71%) of the 41 HA patients were able to RTW at an average time of 3.1 mo after surgery. In this cohort, only one patient retired postoperatively due to shoulder issues. The other eleven had retired preoperatively due to the shoulder, medical reasons, or non-specified reasons. For patients who underwent HA, 14 (74%) of 19 were able to return to a sedentary work demand level, 13 (72%) of 18 returned to a light demand level, and 2 (50%) of 4 returned to work at a heavy work level (Table 5). For patients who underwent rTSA, 17 (68%) of 25 returned to a sedentary work level and 9 (60%) of 15 returned to a light work demand level (Table 5). Hurwit *et al*[11] concluded no significant difference between the two groups in terms of return to low- and moderate-intensity work, despite an older age for patients undergoing rTSA.

Despite a higher rate of RTW for HA patients, no significant differences were found by Hurwit *et al* [11]. A potential limitation with this study was the significant difference in average age of each cohort (68.6 years for rTSA patients and 60.8 years for HA patients), even though this did not affect RTW rates [11]. Furthermore, this study only had sufficient sample sizes for sedentary and light duty workers. Due to the lack of heavy duty workers, especially in rTSA, it is possible to hypothesize that heavy laborers may have experienced more difficulty in returning to work.

Comparison of RTW between WC and non-WC

Work-related injuries are a common cause of disability in the United States and have significant implications for workers, employers, insurers, and physicians[18,55,56]. WC status has shown to have a detrimental effect on clinical outcomes following orthopedic surgery[57,58]. The impact of WC status on postoperative outcomes is an important consideration for patients undergoing shoulder arthroplasty.

Morris *et al*[55] compared 14 WC patients who underwent rTSA to a matched cohort of 14 patients without WC status who also underwent rTSA. From the patients with WC claims, only 2 (14%) of 14 were able to RTW. Of the 12 patients who were not able to RTW, one was unemployed and seeking employment at the time of follow-up, five were disabled, and six had retired following rTSA. In the matched cohort of non-WC patients, only 11 patients had worked prior to the surgery. From these 11 patients, 5 (46%) were able to RTW, one was disabled, and five had retired after rTSA. No patients, WC or non-WC, were able to return to heavy/strenuous work demands after rTSA. Despite significant improvement from preoperative to final follow-up outcomes, WC patients had significantly worse Constant scores, ASES scores, Western Ontario Osteoarthritis of the Shoulder Index scores, and less external rotation compared with the matched cohort group. Morris *et al*[55] reported that while WC patients had significant improvements following rTSA, they achieved significantly worse outcomes compared to non-WC patients after rTSA.

In Jawa *et al*[56], a cohort of 13 WC patients (average age of 55.9 years) who underwent TSA were compared to a control group of 63 patients (average age of 63.2 years) who also underwent TSA. While RTW rates were not cited for the control group, only 4 (31%) of the 13 WC patients were able to RTW following TSA. Of the four patients who returned, one returned to the same job with lifting restrictions and the other three changed jobs to those that require less lifting. From the nine patients who did not return, 7 did not return due to functional restrictions after the surgery and 2 had retired. Additionally, Jawa *et al*[56] found the ASES score to be significantly lower in the WC cohort compared to the control group. From this study, authors concluded no WC patients were able to return to full duty work at their current job and that WC patients receiving TSA had poorer outcomes compared to non-WC patients.

Despite the lack of difference in RTW rates following shoulder arthroplasty for patients with or without WC claims, many studies in orthopedic literature have found poorer outcomes, lower satisfaction rates, and more pain in patients with WC status after shoulder arthroplasty[55,56,59,60]. Similar findings exist in the shoulder literature outside of shoulder arthroplasty. For example, in

Table 5 Return to work after hemiarthroplasty vs reverse total shoulder arthroplasty[11]

Occupation intensity	RTW after HA (%)	RTW after rTSA (%)
Sedentary	14/19 (74)	17/25 (68)
Light	13/18 (72)	9/15 (60)
Heavy[1]	2/4 (50)	-
Total	29/41 (71)	26/40 (65)

[1]No reverse total shoulder arthroplasty patients were classified into the heavy work category.
RTW: Return to work; rTSA: Reverse total shoulder arthroplasty; HA: Hemiarthroplasty.

numerous rotator cuff studies, patients with WC status have been found to be significantly less compliant with postoperative protocols and have less improvement in functional outcomes and pain after controlling for confounding factors such as age, marital status, education level, preoperative expectations, work demands, smoking, comorbidities, duration of symptoms, size of tear, and repair technique[61-64]. Furthermore, other similar results have been found in WC cohorts undergoing acromioplasty, superior labral anterior-posterior tear, and biceps tenodesis for failed superior labral anterior-posterior repair[65-68]. Regardless of procedure type, the differences in pain and outcomes persist, suggesting that WC status may play a crucial role in inferior outcomes.

DISCUSSION

RTW guidelines

While the decision to RTW depends on a variety of factors, all physicians have the goal of returning patients to maximal function in the shortest period of time with the least residual disability[69,70]. Based on the available literature, guidelines can be proposed for average time to RTW for each work demand level within each type of shoulder arthroplasty (Table 6). We determined these averages through a pooled analysis[71].

Throughout the rehabilitation process, physicians must assess patients, especially those with WC status, in terms of work restrictions and limitations. Given the little published evidence for guidelines regarding physical restrictions after shoulder arthroplasty, the work restrictions are commonly based on the physician's clinical judgment[69]. On the other hand, work limitations are easier to define as they are based on the patient's ability to perform a certain task[69].

Particularly for WC patients who undergo shoulder replacement and rehabilitation and have still failed to RTW at their desired work demand level, work conditioning or work hardening therapy regimens can be prescribed[69,72]. Work conditioning, a task simulation program lasting two to four hours per day for three to five days per week, is meant to develop a patient's ability to tolerate specific tasks they would typically encounter at work. Work hardening has the same goal in mind with a higher intensity lasting up to eight hours per day for five days per week[69].

When recovery from shoulder arthroplasty has reached a therapeutic plateau for either non-WC or WC patients, a physician must rate the residual permanent impairment and individually assess how long each injured patient should remain on this plateau before considering them at maximum medical improvement (MMI)[69]. MMI is established when no further treatment will significantly change the patient's outcome; at this point, a patient can be recovered completely without any residual impairment or have some permanent impairment[69,73]. Specifically for TSA, Cabarcas *et al*[74] established MMI at twelve months postoperatively. While Puzzitiello *et al*[75] established MMI for rTSA at twelve months following surgery, Matar *et al*[76] found patients undergoing rTSA may reach MMI as early as six months after surgery. If a patient has reached MMI, but has failed to achieve their pre-injury or prior level of work status, then a physician can utilize a functional capacity evaluation to determine the patient's ability and impose final work restrictions[69]. Although the results of the FCE are often used to set work limitations, some studies have questioned its utility as FCE does not take biopsychosocial factors into account and possibly measures a patient's tolerance to an activity as opposed to the patient's true ability[69,77,78].

After MMI has been reached, there are two outcomes: (1) The patient is able to RTW with or without permanent restrictions at the same job; or (2) The patient finds a new job because the employer cannot accommodate the patient's work limitations[69]. Using evidence-based guidelines to determine MMI for TSA, rTSA, and HA is important not only for counseling patients, but also modifying their expectations prior to surgery.

Table 6 Time to return to work (mo)

	Intensity[1]				
	Sedentary	Light	Moderate	Heavy	Overall
TSA					
Gowd *et al*[48], 2019	2.1 ± 3.8	1.3 ± 1.2	2.1 ± 2.0	3.0 ± 2.8	2.0 ± 2.6
Liu *et al*[12], 2018	1.3 ± 1.2	1.6 ± 1.3	2 ± 1.7	4.2 ± 2.0	2.1 ± 1.7
Liu *et al*[49], 2020	1.04 ± 0.87	1.06 ± 0.73	-	1.83 ± 1.04	1.29 ± 0.96
Cvetanovich *et al*[21], 2020	-	-	-	-	3.7 ± 5.2
Average[2]	1.19 ± 1.24	1.25 ± 0.99	2.03 ± 1.79	2.96 ± 3.23	1.93 ± 3.74
rTSA					
Garcia et al[28], 2016/ Hurwit *et al*[11], 2017[3]	1.38 ± 0.93	4 ± 3.4	-	-	2.3 ± 2.4
HA					
Hurwit *et al*[11], 2017/Garcia *et al*[24], 2015[4]	1.96 ± 3.0	2.72 ± 2.6	-	13.13 ± 15.4	3.1 ± 4.9
Gowd *et al*[48], 2019	0.9 ± 1.1	1.0 ± 1.7	6.8 ± 11.5	3.1 ± 2.3	2.5 ± 4.8
Liu *et al*[49], 2020	1.06 ± 0.98	2.76 ± 3.27	-	2.25[5]	1.88 ± 2.34
Average[2]	1.09 ± 1.36	2.00 ± 3.36	6.8 ± 11.5	3.16 ± 2.74	2.29 ± 3.66

[1]Intensity as based on US Department of Labor[56].
[2]Pooled means using meta analysis[57].
[3]Both studies used the same reverse total shoulder arthroplasty population.
[4]Both studies used the same hemiarthroplasty population.
[5]Only one patient in the heavy group, so no standard deviation available.
TSA: Total shoulder arthroplasty; rTSA: Reverse total shoulder arthroplasty; HA: Hemiarthroplasty.

Limitations and future research directions

Our narrative systematic review and analysis has several limitations. First, identification and inclusion of references utilized for this review relied on the previously described search strategy in 4 different databases. We searched 4 different databases in order to limit the possibility of overlooking studies related to shoulder arthroplasty and RTW. Second, our data relied on the data reported in the included studies. Therefore, we are limited by the clarity of the results reported as well as the study design and level of evidence. As a result, we utilized the MINORS score to evaluate the quality of the 12 included studies and any potential publication bias. We found that the 12 studies were of acceptable quality and determined no findings suggestive of publication bias. Additionally, our data shows a high level of heterogeneity which may lead to treatment bias effect. Similarly, with regard to work intensity, our study is limited by what was reported and those studies may exclude important nuances that could have led to functional consequences. Furthermore, the heterogeneity of our data is reflective of the reality of clinical practice and often most accurately represents what orthopedic surgeons encounter in the clinical setting[79-81]. Despite these limitations, the findings in our study provide important data that help orthopedic surgeons manage patient expectations about RTW following TSA, rTSA, or HA.

In the future, systematic reviews and analyses regarding shoulder arthroplasty and RTW will hopefully have access to references that are more homogenous with higher levels of evidence. Although the reality that a high level of heterogeneity may be inevitable in the clinical research setting, additional research should be conducted that compares short- and long-term outcomes following TSA, rTSA, and HA and a patients' ability to RTW. Furthermore, revision arthroplasty and ability to RTW may be a topic worth exploring as the average age of patients undergoing shoulder replacement is decreasing.

CONCLUSION

The majority of patients are able to RTW following TSA, rTSA, and shoulder HA. The rates of RTW following TSA (71%-93%) seem to be consistently higher than those reported for HA (69%-82%) and rTSA (56%-65%), although this may reflect demographic differences such as age in patient populations. Sedentary, light demand jobs generally have higher rates of RTW than moderate or heavy demand jobs. On average, most patients who underwent TSA, rTSA, or HA were able to RTW at an average duration between 1 mo to 4 mo depending on work demand level. Furthermore, WC status negatively influenced clinical outcomes following shoulder arthroplasty.

ARTICLE HIGHLIGHTS

Research background

Over the last two decades, the number of shoulder arthroplasties, including total shoulder arthroplasty (TSA), reverse TSA (rTSA), and shoulder hemiarthroplasty (HA), has increased at exponential rates. Due to satisfactory clinical and functional long-term outcomes, the number of shoulder replacements performed will continue to rise into this next decade. Additionally, these procedures are becoming more prevalent in younger and more active populations. With younger individuals who compose a significant amount of the workforce receiving shoulder replacements, patients will begin to place a higher priority on their ability to return to work following shoulder arthroplasty.

Research motivation

Prior studies have shown varying levels of return to work after shoulder arthroplasty based on arthroplasty type, diagnosis, and work intensity. While informative, a compilation comparing various demographics, arthroplasty types, diagnoses, and work intensities has not been performed in recent years.

Research objectives

The aim of the review article was to summarize return to work outcomes following TSA, rTSA, and HA, and analyze the effects of workers' compensation status on return to work rates and ability.

Research methods

This systematic review and analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A literature search regarding return to work following shoulder arthroplasty was performed using four databases through January 2021. All studies included in this review were analyzed by at least two authors. Included studies were then evaluated using the Methodological Index for Non-Randomized Studies checklist.

Research results

The majority of patients undergoing TSA, rTSA, or HA were able to return to work between one to four months, depending on work demand stratification. While sedentary or light demand jobs generally have higher rates of return to work, moderate or heavy demand jobs tend to have poorer rates of return. Furthermore, workers' compensation status negatively influenced clinical outcomes following shoulder arthroplasty. Through a pooled means analysis, we proposed guidelines for the average time to return to work following TSA, rTSA, and HA.

Research conclusions

The majority of patients were able to return to work following TSA, rTSA, or HA. Understanding outcomes for rates of return to work following shoulder arthroplasty should assist surgeons and patients in managing expectations in clinical practice.

Research perspectives

Further research and analyses comparing short- and long-term outcomes following TSA, rTSA, and HA and a patients' ability to return to work would provide tremendous benefit. Additionally, revision arthroplasty and ability to return to work may be a topic worth exploring as the average age of patients undergoing shoulder replacement is decreasing.

FOOTNOTES

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Abstract

BACKGROUND

Spine surgery is evolving and in the due course of its evolution, it is useful to have a comprehensive summary of the process to have a greater understanding to refine our future directives. With the multiple domains of research in the spine, it has become difficult for a surgeon to find the potential hotspots in research or identify the emerging research frontiers.

AIM

To analyze RCTs (1990–2019) for potential research domains along with their research networks and identify the hot topics for future research.

METHODS

A comprehensive and systematic analysis of all the RCTs published on spinal surgery from 1990 to 2019 retrieved from the Web of Science Core Collection database. Scientometric and visual analysis of their characteristics, cooperation networks, keywords, and citations were made using CiteSpace software. Journal and article impact index were retrieved from *Reference Citation Analysis* (*RCA*) Database.

RESULTS

A total of 696 RCTs were published on spinal surgery from 1990 to 2019; of which, the United States (*n* = 263) and China (*n* = 71) made a significant contribution. Thomas Jefferson University (*n* = 16) was the leading contributor to RCTs on spinal surgery. Weinstein JN was the most cited author in the field followed by Deyo RA. *Spine* (*n* = 559) remained the top-cited journal for RCTs on spinal surgery. On literature co-citation analysis, spinal stenosis, anterior cervical discectomy and fusion, degenerative disc disease, and minimally invasive decompression were identified as the hotspots and potential research frontiers.

CONCLUSION

The identified hotspots that extending the frontiers in the management of degenerative disorders of the spine through further research holds the potential for advancement in spinal care.

Key Words: Randomized controlled trials; Scientometrics; Spine surgery

Core Tip: The evolutionary process of a field is analyzed through various parameters like citation metrics, keywords and author networks in Scientometrics. With advances in the field of spinal surgery, surgeons find it difficult to identify the potential hotspots for their prospective research. We noted that research cooperation among the developed and developing nations remains crucial and needs to be strengthened. On literature co-citation analysis, spinal stenosis, anterior cervical discectomy and fusion, degenerative disc disease, and minimally invasive decompression were identified as the hotspots and potential research frontiers in the field of spinal surgery.

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INTRODUCTION

The safety and efficacy of the evolving treatment methods in clinical practice are assessed by randomized controlled trials (RCTs), are is considered the gold standard research method on the top of the evidence pyramid[1]. With the ongoing drive of the evidence-based approach in spinal surgery, RCTs are used to generate clinically important findings with valid conclusions on the prognosis and diagnosis of varied clinical conditions and effectiveness of their treatment methods[2]. Hence, by analyzing the research trend of RCTs in spinal surgery one could determine the evolution of evidence in the field.

With the rapid evolution in the advancements in spinal surgery, in order to have a better understanding of the advancements for streamlining our future directives, we need to have a comprehensive summary of the evolutionary process. Research with regards to spinal surgery has expanded to various domains and surgeons find it difficult to identify the potential hotspots in its advancement to direct their prospective research. Visualization of the evolutionary process in a field is possible with the current technological developments like information analytics, graphic drawing and data mining, combined with computational statistics. The evolutionary process in a field is analyzed through various parameters like citation metrics, keyword and author networks in scientometrics[3]. Using knowledge maps in scientometrics, one can visualize this panorama of information to explore hotspots in research [4]. This methodology has been established to study the evolution of fields such as orthopedics[5], public health[6], and artificial intelligence[7].

With a newer perspective, scientometric tools including text mining, co-word analysis, word frequency analysis, co-citation analysis, cluster analysis, and network analysis were used to do a systematic and comprehensive review to assess the potential research domains and research trend of RCTs published on spinal surgery for the past three decades (1990–2019) apart from analyzing their research networks to identify the hot topics for future research.

MATERIALS AND METHODS

Data sources

Various databases such as PubMed, Scopus, Google Scholar and Web of Science (WoS) were used by the researchers. Each has its own merits and demerits. While Google Scholar has wider literature coverage, it is limited by the quality of results and duplication[8]. PubMed is rich in medical literature but lacks wider coverage in other subject areas[9]. Scopus and WoS are considered complementary databases without many differences. However, it was noted that for visual analysis and knowledge mapping with software such as CiteSpace, WoS was considered to be better[9,10]. Hence, WoS was used as the source for data retrieval. Among the WoS databases, WoS Core Collection with indexes SCI-EXPANDED, SSCI, and A&HCI were used for data extraction. The detailed data retrieval strategy is given in Figure 1. Preliminary data were standardized with deduplication and merge functions in CiteSpace. The literature search date was August 24, 2020. The resultant core dataset on the subject is subjected to natural language processing, network analyses using CiteSpace and thematic cluster knowledge maps were developed and individual clusters are analyzed using semantic network of author keywords and their hierarchy and key results are synthesized. Journal and article impact index was retrieved from *RCA* database[11].

Data visualization and analysis

Scientometric and visualization analysis was performed with CiteSpace (5.7.R1). CiteSpace was used to visualize the structure, regularity, and distribution of research domains in spinal surgery and analyze the article co-citation data to mine the knowledge clustering and citation space distribution. The co-occurrence between the additional research units such as cooperation among various authors, institutions, and countries in the field of spinal surgery was also analyzed. Consolidating the results of the analysis, a comprehensive knowledge map elaborating on the emerging research trend with the potential research domain from RCTs published in spinal surgery was built.

The scientometric analysis results are depicted as knowledge maps with the key parameters detailed as follows. The knowledge map depicts the time interval between its components with warm and cold colors. With time close to 2019, the components are depicted in warm colors and time close to 1990 in cold colors. The size of the nodes in the knowledge graphs indicates the frequency of authors, institutions and countries, while the connection between them indicates that they are from the same article[12]. When two or more authors or institutions or countries are noted in the same article, it is considered a scientific cooperative relationship between the group of authors or institutions or countries [13].

The scientometric analysis uses certain parameters for evaluation. H-index is used to quantify the academic output from researchers and institutions where h indicates the number of papers of the author/institution having $\geq h$ citations of all the papers published by the author/institution[14]. The degree indicates the total connection between the authors, institution, or country in the analyses of their co-occurrences. A high value denotes strong cooperation and communication among the group of authors, institutions or countries. The importance of nodes in the research cooperation network is indicated by the degree, whereas the half-life represents the continuum of institutional research on a timeline[15].

RESULTS

The database search recovered 696 RCTs published on spinal surgery from the global literature from 24 256 articles that included 20 458 non-RCTs, 2206 reviews, 583 proceedings papers, and 313 meeting abstracts from 1990 to 2019. Figure 2 shows the output of the RCTs published in the field of spinal surgery. The first two decades (1990–2009) had an average of three RCTs published per year, which later increased to 51 RCTs per year in the last decade (2010–2019). There was an overall rising trend in the scientific output on spinal surgery (Figure 2). This increasing trend in publication of RCTs shows the increased attention paid in the field of spinal surgery by surgeons and researchers to improve the standard of care. It is also evident from Figure 2 that the other types of research communication documents such as original articles, reviews and proceedings papers, and meeting abstracts also had a proportionate growing trend.

Journal analysis

The number of citations that the RCTs published in a journal receive reflects the importance and influence of a journal in the field. CiteSpace was used to analyze the list of journals where the retrieved RCTs were published and generated a map of journals that cited them (Figure 3). The journal citation network had 52 nodes and 358 links among them. Based on the citation frequency, the top 10 journals were selected and tabulated (Table 1). With due consideration to the impact factor, H-index, centrality, and citation frequency of the journals, the top five journals in spinal surgery were *Spine* (IF: 2.646, H-index: 243), *European Spine J* (IF: 2.458, H-index:128), *J Bone Joint Surg Am* (IF: 4.578, H-index: 322), *Spine J* (IF: 3.191, H-index: 102), *J Neurosurg-Spine* (IF: 3.011, H-index: 205). As shown in Figure 3, the node circles of *Spine*, *European Spine J*, *J Bone Joint Surg Am*, *Spine J*, *J Neurosurg-Spine* were larger and there were cool-tone areas within them. However, node circles of *J Spinal Disord Tech*, *Neurosurgery*, *New Engl J Med*, and *JAMA* were mostly depicted in warm colors. Early critical RCTs in spinal surgery were

Table 1 Top 10 journals in spinal surgery based on the co-citation network frequency

Rank	Source	Cited frequency	Impact factor	H-index	Degree	Centrality	2022 JAII
1	*Spine*	559	2.646	243	42	0.53	44.770
2	*Eur Spine J*	371	2.458	128	24	0.05	-
3	*J Bone Joint Surg Am*	322	4.578	249	33	0.24	55.199
4	*Spine J*	269	3.191	102	13	0.01	16.013
5	*J Neurosurg-Spine*	205	3.011	93	13	0	18.692
6	*Clin Orthop Relat R*	198	4.329	197	23	0.05	25.424
7	*J Spinal Disord Tech*	156	1.594	79	11	0	4.831
8	*Neurosurgery*	143	4.853	192	23	0.04	23.060
9	*New Engl J Med*	137	74.699	987	17	0.08	110.705
10	*J-J Am Med Assoc*	120	45.540	654	19	0.04	38.773

JAII: Journal Article Influence Index.

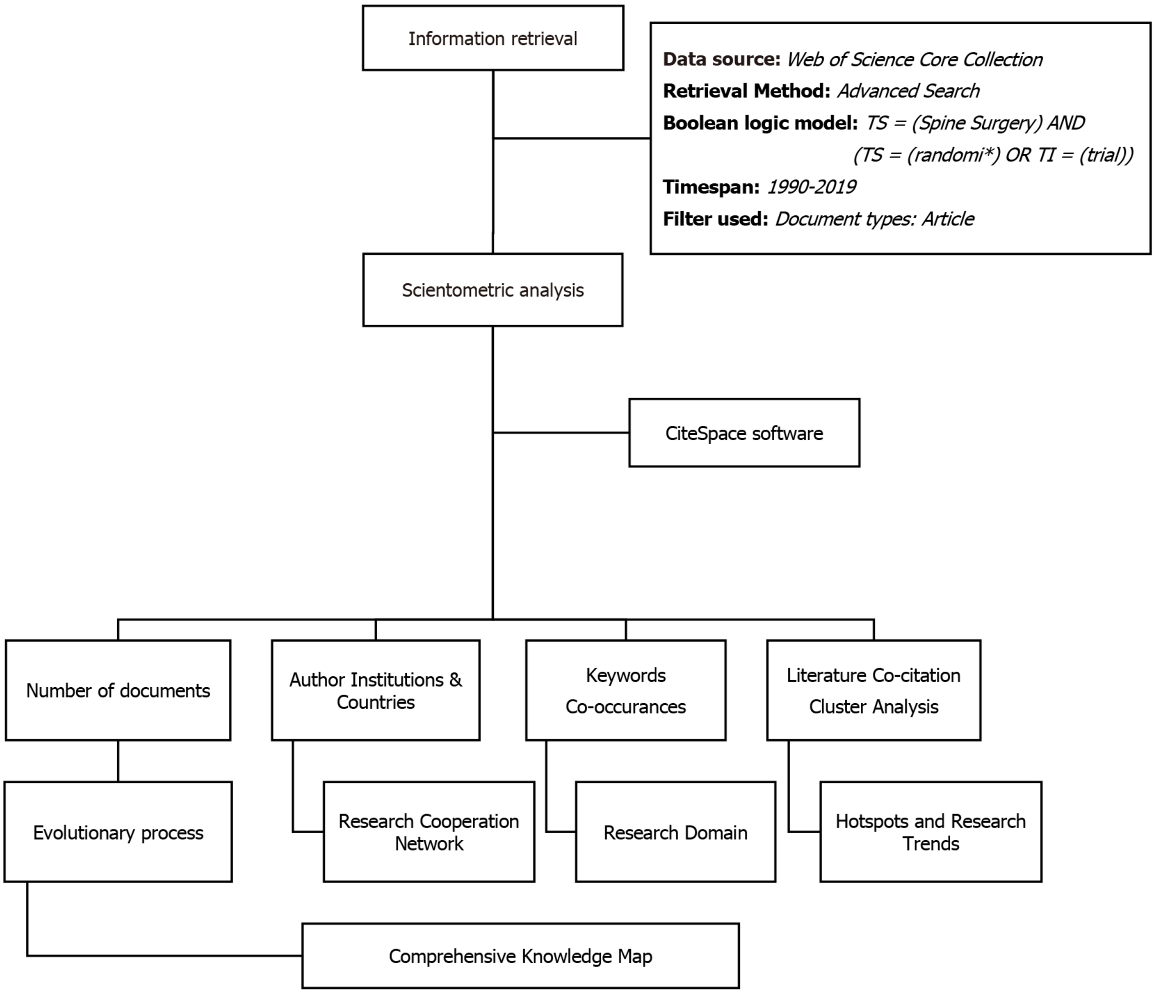

Figure 1 Scientometric analysis framework.

published in *Spine, European Spine J, J Bone Joint Surg Am, Spine J* and *J Neurosurg-Spine*. It is also worth noting that the top five journals on spinal surgery came from the United States (*Spine, J Bone Joint Surg Am, Spine J, J Neurosurg-Spine)* and Germany (*European Spine J*).

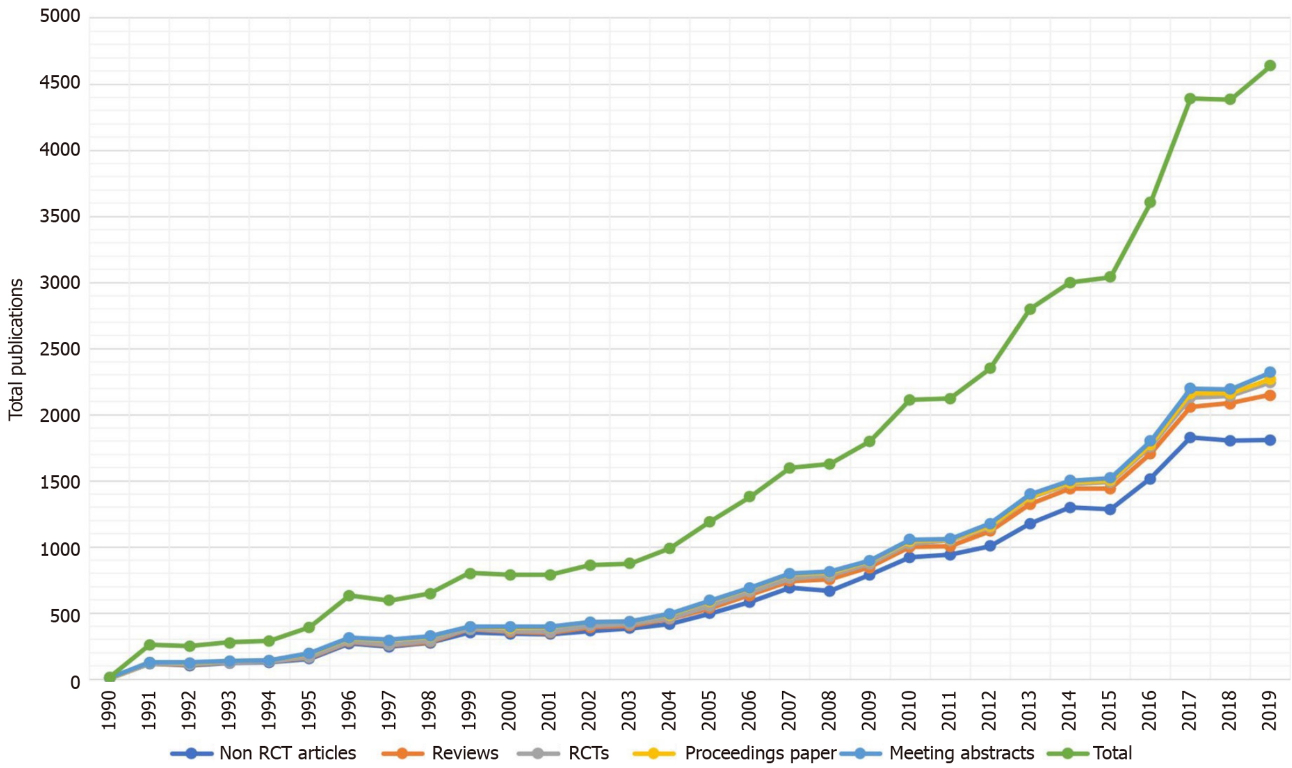

Figure 2 Scientific output in stem cell therapy for diabetes from 1990–2019. RCT: Randomized controlled trials.

Scientific cooperation network analysis

Coauthor analysis: The author co-occurrence network map had 245 nodes, and 1128 connections with a network density of 0.0377 (Figure 4). On the whole, the authors in the network map had a fair connection strength among each other; however, there were some poorly connected islands of author groups that need global strengthening (Figure 4).

The research cooperation group with the closest communication was from Weinstein JN, Deyo RA, Atlas SJ, Ware JE and Fairbank JCT. The details of the top 10 authors who published RCTs on spinal surgery are shown in Table 2. Weinstein JN published the highest number of RCTs in spinal surgery, with a degree value of 35 and H-index of 68. His research spanned several areas in spinal surgery. Weinstein JN was principal investigator in various outcome trials involving disc herniation, spinal stenosis and degenerative spondylolisthesis, and investigated the role of surgery and conservative therapy in these conditions. He also did a lot of work on pain and first developed the lumbar radiculopathy model. Deyo RA (degree: 55; H-index: 116), being a member of the Cochrane Review Group on Back Disorders, conducted trials mostly on clinical intervention and patient aids for spinal surgery. Atlas SJ concentrated on sciatica and spinal stenosis in spinal surgery. The other two authors in the top five were Ware JE and Fairbank JCT, who did pioneering works on quality of life measures in spinal surgery and Oswestry Disability Index, respectively.

Co-institutional analysis: The co-institutional network is presented in Figure 5, and consisted of 95 nodes and 118 links with a network density of 0.0264. There was weak collaboration among the institutions globally, but the network of domestic institutions seemed closer. The top 10 list of institutions that published maximum RCTs are listed in Table 3. Thomas Jefferson University (16 RCTs), Seoul National University (11 RCTs), University of California San Francisco (10 RCTs), Dartmouth Medical School (8 RCTs), and Dartmouth Institute of Health Policy & Clinical Practice (8 RCTs) were the predominant institutions with major contributions. These institutions made a central contribution to the RCTs in spinal surgery. Six of the top 10 institutions were from the United States (3 universities, 2 institutes, and 1 School), Sweden came second with two institutions (1 university and 1 institute). The contribution of United States and Sweden in the field of spinal surgery has been shown to be exceptional in this analysis.

Co-country analysis: In the co-country map depicted in Figure 6, 25 nodes and 64 links were noted with a network density of 0.2133. From a global standpoint, the density of the network as depicted in Figure 6 was weak with few connections between the countries in terms of conducting RCTs in spinal surgery. Further global cooperation is needed for research in spinal surgery. With the rising demand for advancement in the management of spinal ailments, countries must try to solve the problem by coordinating their efforts together for conducting RCTs. Table 4 shows the top 10 countries publishing

Table 2 Top 10 authors in spinal surgery based on the co-citation network frequency

Rank	Author	Cited frequency	H-index	Degree	Centrality
1	Weinstein JN	94	68	35	0.06
2	Deyo RA	83	116	55	0.21
3	Atlas SJ	57	43	37	0.08
4	Ware JE	55	78	47	0.27
5	Fairbank JCT	37	38	28	0.04
6	Fritzell P	35	15	38	0.18
7	Akbarnia BA	26	42	10	0
8	Carragee EJ	24	50	18	0.06
9	Zdeblick TA	22	41	38	0.21
10	Cloward RB	22	23	37	0.06

Table 3 Co-institution collaboration network map in spinal surgery

Rank	Institutions	Publications	Degree	Centrality	Half-life
1	Thomas Jefferson Univ	16	8	0.02	1.5
2	Seoul National Univ	11	4	0	0.5
3	Univ California San Francisco	10	5	0.02	6.5
4	Dartmouth Med School	8	10	0.05	3.5
5	Dartmouth Inst Health Policy & Clinical Practice	8	5	0	0.5
6	Rush Univ	8	5	0.02	2.5
7	Linkoping Univ	8	10	0.01	3.5
8	Dartmouth Hitchcock Med Cen	8	5	0.01	0.5
9	Karolinska Inst	8	9	0	3.5
10	Leiden Univ	8	2	0	7.5

Table 4 Co-country collaboration network map in spinal surgery

Rank	Country	Publications	Percent	Degree	Burst	Half-life
1	United States	263	37.8	15	5.11	16.5
2	China	71	10.2	5	-	8.5
3	Germany	59	8.5	9	4.18	13.5
4	South Korea	36	5.2	1	-	5.5
5	Sweden	35	5	10	4.71	14.5
6	England	27	3.9	12	5.72	7.5
7	Netherlands	23	3.3	4	-	8.5
8	Canada	20	2.9	5	-	5.5
9	Japan	15	2.2	0	-	2.5
10	Denmark	13	1.9	7	-	9.5

RCTs in spinal surgery. The United States has contributed most to the field of spinal surgery, with 263 RCTs, accounting for 37.8% of the global contribution. Other countries contributing to the publication of RCTs in spinal surgery included China (71 RCTs, 10.2%), Germany (59 RCTs, 8.5%), South Korea (36 RCTs, 5.2%), and Sweden (35 RCTs, 5%). Developed nations like the United States had a cold tone in

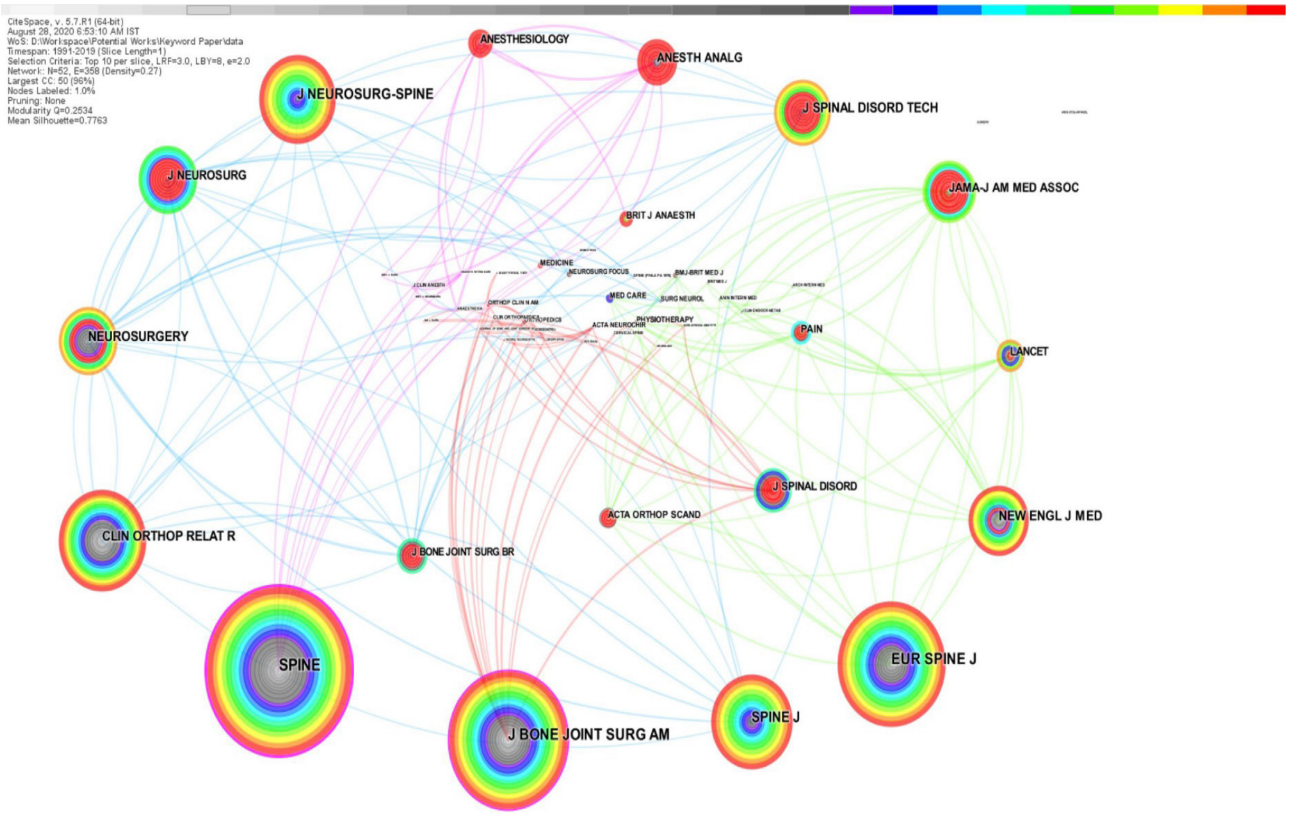

Figure 3 Journal citation network on stem cell therapy for diabetes. Journals with more than 750 co-citations were labelled.

their node circle whereas China, as a developing country, which conducted RCTs later than the developed nations, had a warm tone in their nodes (Figure 6). Despite having 71 RCTs published by China, none of their authors or institutions were in the top 10 list of contributors. It indicates that despite the late start of research in the field in China, it has developed at a rapid rate to achieve the current number of published RCTs.

Keyword analysis

We analyzed the co-occurrence network of the key words used in the field and their summary and classification based on research direction and frequency is given in Table 5. The keywords were manually sorted into five major topics. The first topic included localizing keywords such as "spine (133)", "lumbar spine (42)" and "cervical spine (7)". It focused mainly on the region of the spine involved in RCTs. Topic 2 included keywords related to disease pathology involved in RCTs such as "spondylolisthesis (11)", "disease (9)", "spinal disease (7)", degenerative spondylolisthesis (5)", *etc.* The third topic of keywords involved symptomatology such as "low back pain (104)", "pain (36)", "radiculopathy (10)" and "sciatica (7)". The fourth topic involved keywords related to management methods such as "surgery (208)", "fusion (91)", "spinal surgery (87)", "outcome (79)", "management (62)", "complications (59)", *etc.* The fifth topic was concerned with the outcome measure keywords such as "efficacy (40)", "reliability (9)", "risk (6)", "safety (6)", *etc.*

Co-citation analysis

It is a common practice for the researchers to cite the evidences from the results of RCTs in their research work as references. Scientific development is made through such mutual citations of scholarly works in the field.[16] The citation network of RCTs published in the 1990s looks relatively sparse while the network of RCTs published around the 2000s and 2010s look denser (Figure 7). It is also noted that highly cited RCTs are from the middle and late periods. Based on Figure 7, the top 10 RCTs cited by frequency are presented in Table 6. The frequency of citation of these RCTs was limited to the mutual citations between the 696 included RCTs, which was different from the citation frequency available in WoS. The article "Surgical *vs* nonoperative treatment for lumbar disk herniation – The Spine Patient Outcomes Research Trial (SPORT) observational cohort" by Weinstein JN is the most frequently cited RCT in spinal surgery. This pioneering work established the equivalence in the effectiveness of surgical and conservative treatment for lumbar disc herniation. The burst value in the table shows that these articles had been the focus of research for a period of time. The highest burst value was noted for the same article mentioned above by Weinstein JN. It is also noted from the table that *JAMA*, *Spine* and *New*

Table 5 Keyword analysis in spinal surgery

Topic	Keyword	Frequency	Centrality	Degree	Burst
1	Spine	133	0.27	22	-
	Lumbar spine	42	0.1	14	3.53
	Cervical spine	7	0.03	5	3.84
2	Spondylolisthesis	11	0.09	6	-
	Disease	9	0	5	4.7
	Spinal stenosis	7	0.01	6	-
	Stenosis	6	0	4	3.73
	Degenerative spondylolisthesis	5	0	4	-
	Herniation	5	0.01	6	-
	Intervertebral disc	5	0	2	-
	Scoliosis	5	0	2	-
3	Low back pain	104	0.2	21	-
	Pain	36	0.14	13	3.67
	Radiculopathy	10	0	4	4.35
	Sciatica	7	0.05	6	3.94
4	Surgery	208	0.2	18	-
	Fusion	91	0.3	24	-
	Spine surgery	87	0.09	14	-
	Outcome	79	0.09	16	-
	Management	62	0.16	16	7.22
	Complication	59	0.2	18	-
	Follow-up	42	0.16	19	5.11
	Diskectomy	32	0.19	19	5.65
	Spinal fusion	20	0.03	8	3.58
	Decompression	20	0.09	11	4.05
	Arthrodesis	19	0.16	14	3.48
	Interbody fusion	15	0.05	7	-
	Nonoperative treatment	14	0.02	9	7.77
	Postoperative pain	12	0	5	-
	Analgesia	8	0	2	-
	Discectomy	7	0.02	8	3.47
	Instrumentation	7	0.01	4	4.36
	Nonsurgical management	7	0.01	7	-
	Tranexamic acid	6	0	5	-
	Rehabilitation	6	0	2	-
	Bone graft	5	0	4	-
	Laminectomy	5	0	3	-
	Arthroplasty	5	0	2	-
	Total disc replacement	5	0.01	3	-
5	Efficacy	40	0.07	15	-
	Reliability	9	0.07	8	-

Randomized controlled trial	8	0	2	-
Risk	6	0.01	4	-
Safety	6	0	5	-
Children	5	0	2	-

Table 6 Top 10 cited literature in spinal surgery

Rank	Frequency	Author	Journal	Year	Burst	Half-life	Impact index
1	24	Weinstein JN	*JAMA*	2006	8.79	4.5	44.9
2	24	Heller JG	*Spine*	2009	5.39	3.5	26.9
3	22	Weinstein JN	*JAMA*	2006	7.75	3.5	31.1
4	21	Murrey D	*Spine J*	2009	5.66	4.5	26.3
5	20	Akbarnia BA	*Spine*	2013	7.3	3.5	16.3
6	19	Cheung KMC	*Lancet*	2012	7.6	4.5	19.1
7	19	Weinstein JN	*New Engl J Med*	2008	4.66	2.5	48.2
8	19	Weinstein JN	*New Engl J Med*	2007	5.37	3.5	37.2
9	16	Bess S	*J Bone Joint Surg Am*	2010	7.67	6.5	29.1
10	16	Dannawi Z	*Bone Joint J*	2013	7.67	3.5	13.3

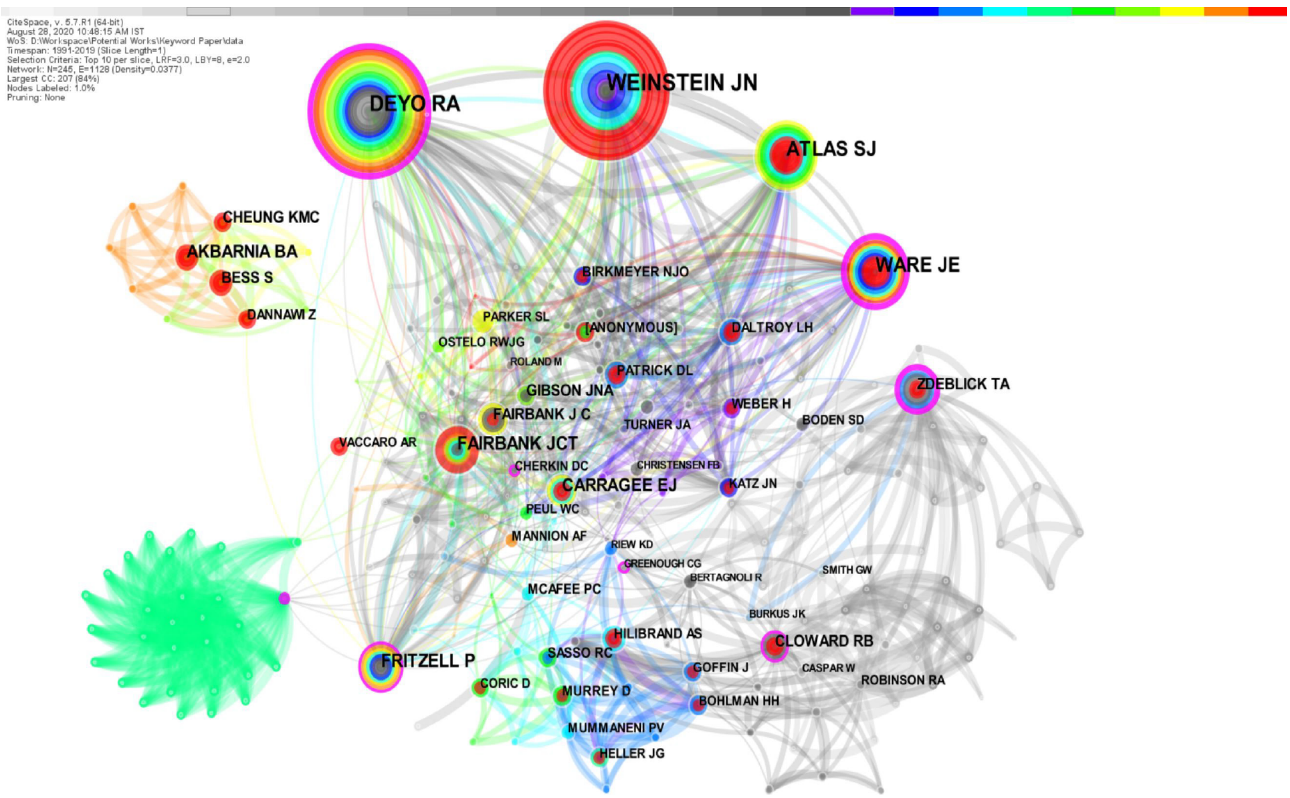

Figure 4 Coauthor collaboration network in spinal surgery.

Engl J Med each contributed two articles to the top 10 list. Of the top 10 articles, three RCTs compared surgical and conservative treatment for lumbar disc disease, three RCTs evaluated the role of growth rods in early-onset scoliosis, and three RCTs compared the results of fusion and arthroplasty for cervical disc disease.

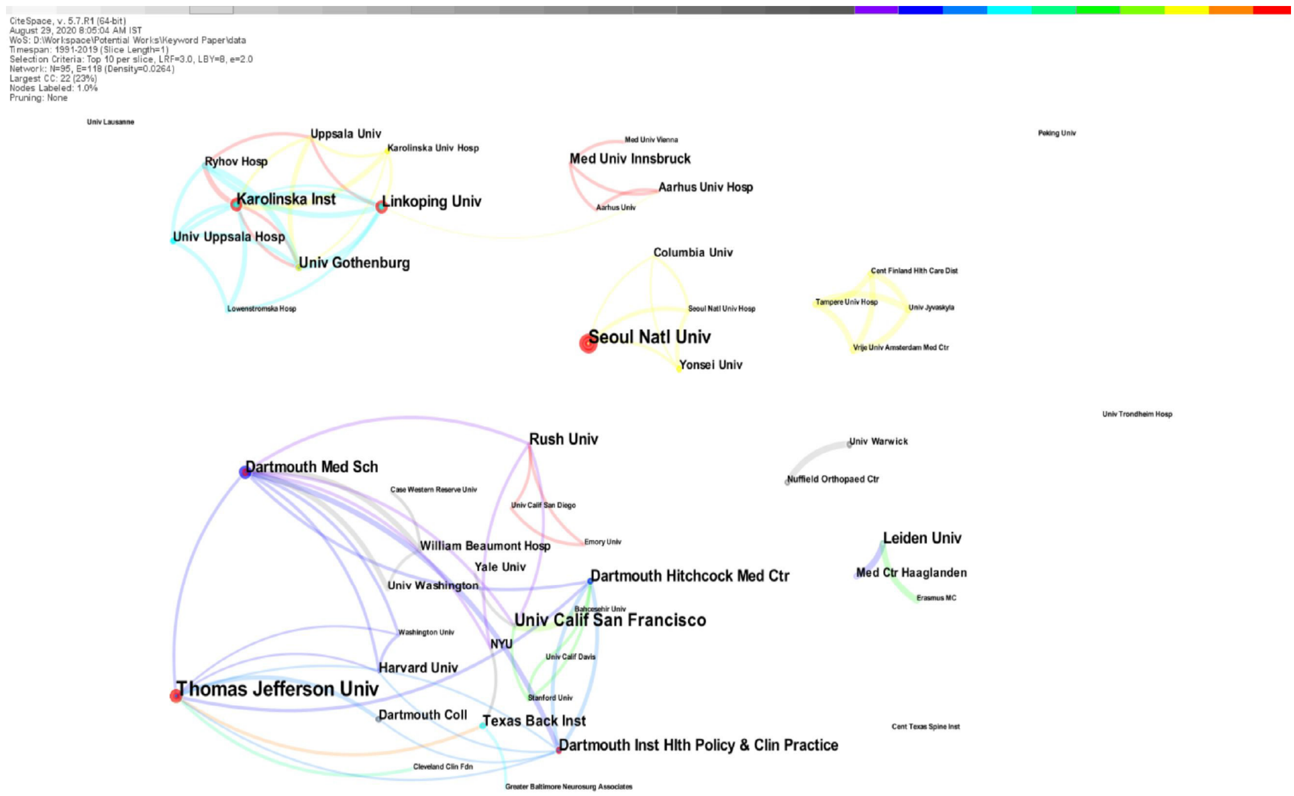

Figure 5 Co-institution collaboration network in spinal surgery.

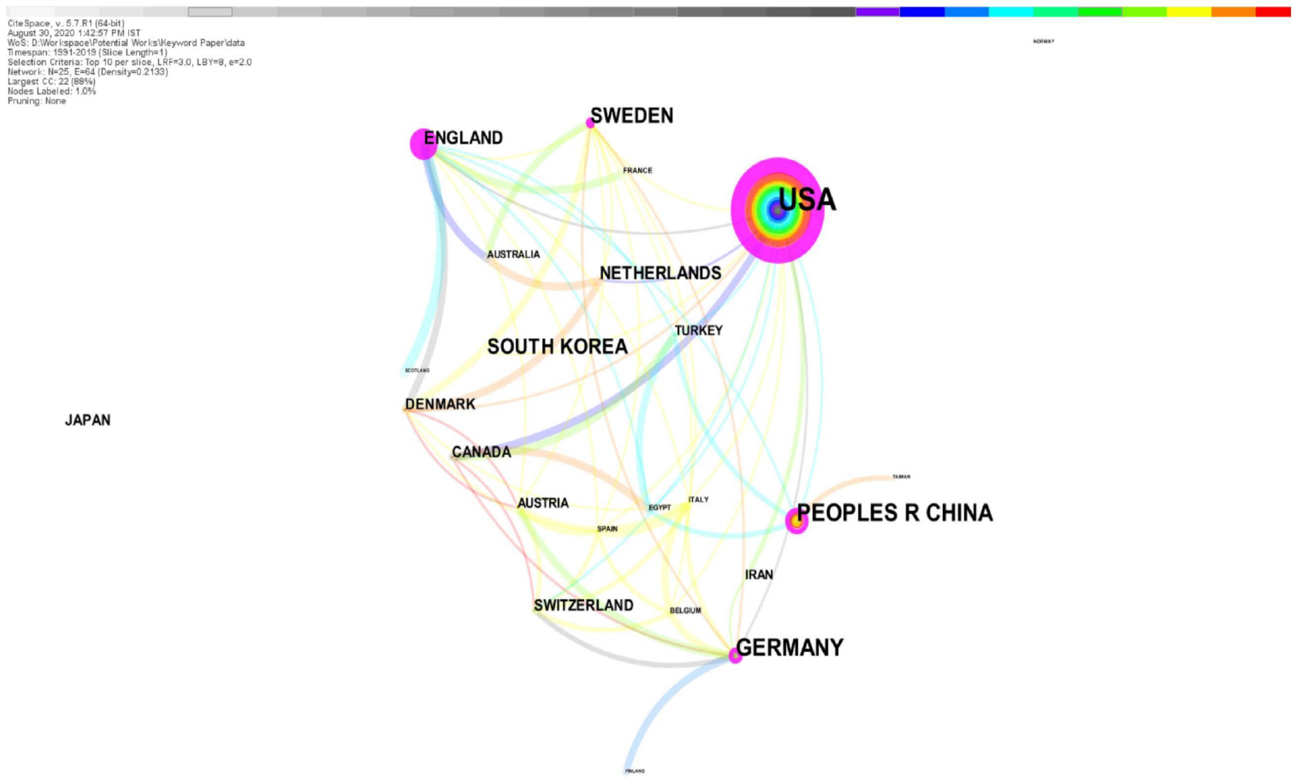

Figure 6 Co-country collaboration network in spinal surgery.

Cluster analysis of co-citation network

Using exploratory data mining techniques, analysis of the data clusters enables the identification of important topics, and their evolutionary trends. A comprehensive clustering of the RCTs published in a given theme is done in cluster analysis and an objective projection of the principle content is visualized

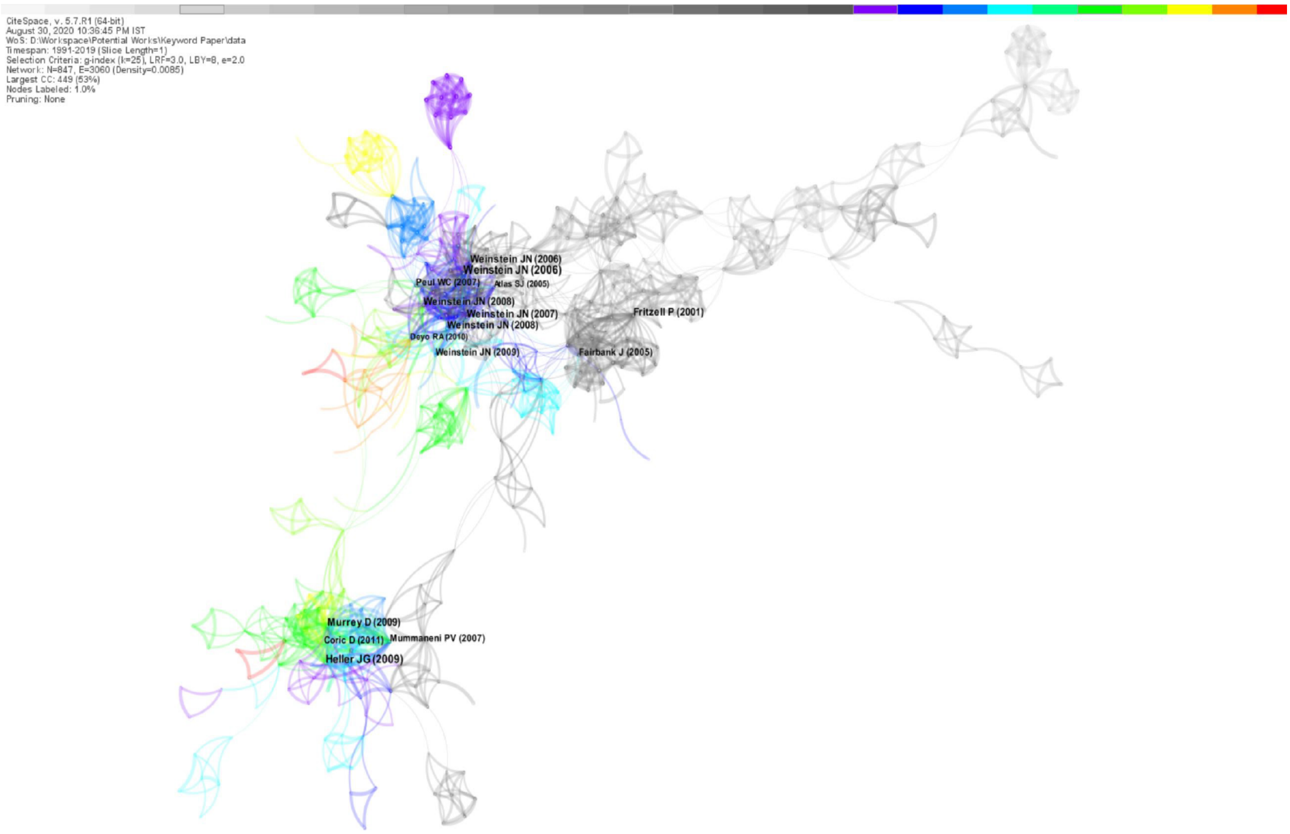

Figure 7 Co-citation network in spinal surgery. The studies depicted in the network are the top 50 per slice and labeled with a threshold frequency of 10 citations and the largest citation subnetwork is displayed.

[17]. The RCT cluster map on spinal surgery is depicted in Figure 8. The time needed for clustering from far to near is depicted as the color of the clusters from cold to warm. The articles with high burst values are presented as cluster blocks with red nodes. The higher the presence of red nodes in a cluster it denotes that the clustered topic is a research frontier and hot spot in the field. We summarized the information of the clusters in Table 7. Considering the cluster analysis from Figure 8 and Table 7, "spinal stenosis", "anterior cervical discectomy and fusion", "degenerative disc disease" and "minimally invasive decompression" were the hotspots in the field of spinal surgery and considered as the potential research frontiers that need further research.

Category co-occurrence analysis

Based on the category co-occurrence analysis, one can intuitively understand the main subjects of research in the field of concern[18]. The categories used for classification were taken from the WoS core collection database. As shown in Figure 9, the highlighted circle on the nodes indicate that it has high–intermediate values of centrality. Table 8 gives the list of top 10 categories in spinal surgery with high co-occurrence frequency. From Figure 9 and Table 8 it is evident that the research categories involve multiple disciplines and fields. The comprehensive knowledge map in spine surgery research from 1990 to 2019 is depicted in Figure 10.

DISCUSSION

We noted a rising trend in the number of published studies on spinal surgery based on the research outputs analyzed. We also noted an increase in the academic activities in the field of spinal surgery through a proportionate increase in the number of proceeding papers and meeting abstracts. This denoted an increase in international attention for innovation in the field of spinal surgery and improvisation of the existing standards of care. With the advances in technology, we noted an increase in survival period and proportionate increase in the aging population[19], which raises a concern to increase our focus on degenerative disorders of the spine.

Some of the landmark papers in spinal surgery research were published in *JAMA* and *New Engl J Med* , which were in the publishing field for more than a century with a high academic reputation. They have laid a foundation for spinal surgery research and paved the way for the field-specific journals to cater to the subsequent research in spinal surgery. Among the specific journals recognized in the field, *Spine, Eur*

Table 7 Cluster summary of co-citation network

Cluster ID	Size	Silhouette	Mean (Year)	Label (LLR)
0	69	0.925	2006	Spinal stenosis, sciatica
1	63	0.982	2009	Anterior cervical discectomy and fusion, clinical outcome
3	57	0.952	2002	Chronic low back pain, degenerative disc disease
5	22	0.968	2003	Cloward, nerve injury
6	21	0.991	2011	Spine Patient Outcomes Research Trial (SPORT), National Surgical Quality Improvement Project (NSQIP)
9	13	0.963	2010	Minimally invasive decompression, multicenter study
11	11	1	2005	Discogenic, Prospective randomized multicenter clinical study
14	6	0.995	2008	Biologics, extreme lateral interbody fusion

Silhouette is a parameter in CiteSpace software to analyze the clustering effect in terms of homogeneity of the network. A value closer to 1 means higher homogeneity and results more than 0.7 has high reliability.

Table 8 Top 10 subject categories in spinal surgery

Rank	Category	Frequency	Centrality	Burst
1	Neurosciences and neurology	390	0.03	7.18
2	Clinical neurology	389	0.03	7.23
3	Orthopedics	367	0.04	11.42
4	Surgery	151	0.06	-
5	Anesthesiology	67	0.05	-
6	General and internal medicine	53	0.03	-
7	Research and experimental medicine	26	0.01	-
8	Rheumatology	14	0.02	-
9	Rehabilitation	13	0.01	-
10	Pharmacology and pharmacy	5	0.00	-

Spine J, *J Bone Joint Surg Am*, and *Spine J* were affiliated with various regional, national, international societies and associations and have been in publication for > 40 years and have contributed to progress in the field of spinal surgery. Most of the hotspots in spinal surgery arose from RCTs published in these high-impact journals. Researchers interested in spinal surgery should closely follow the high-quality trials published by these journals in real time.

Our revies explored the research cooperation in spinal surgery from three perspectives, namely, small-author cooperation network, intermediate-institutional cooperation network, and large-national cooperation network. We noted academic cooperation mostly among the predominant institutions in a particular country and prominent authors in an institution. In the publication of RCTs, developed nations like the United States and Germany were leading the way, while in developing countries like China, although they had more publications, they were not from prominent institutions or authors. Hence, increased research collaboration with the developing countries will be conducive to advancement of spinal surgery.

The potential research topics and emerging trends have been revealed by analyzing the keyword co-occurrences and literature co-citations in spinal surgery. Keywords are one of the research data that gives an idea about the main themes of research in a particular article. With the advanced scientometric techniques such as text mining and keyword co-occurrence analysis, we can visualize the research trends in a field and identify the hotspots of research[20]. From the result of such analysis, the five main research topics in spinal surgery include regional localization such as cervical and lumbar surgery; disease pathology like spondylolisthesis, stenosis, intervertebral disc, and scoliosis; surgical treatment methods like fusion surgery, decompression surgery, instrumentation surgery, and arthroplasty; outcome measures like efficacy, risks, safety and reliability of the treatment methods.

Literature co-citation analysis noted that spinal stenosis, anterior cervical discectomy and fusion, degenerative disc disease, and minimally invasive decompression are the current hotspots and research

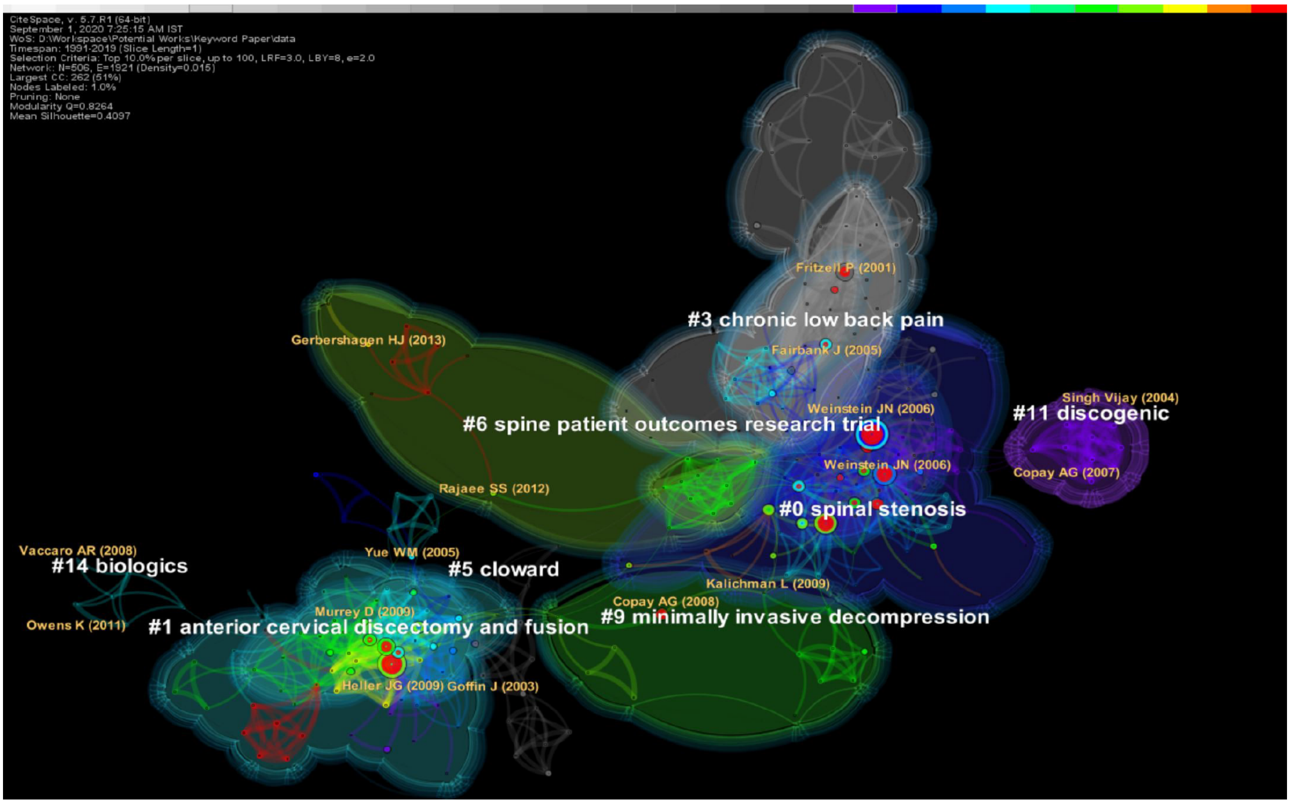

Figure 8 Cluster map of literature in spinal surgery. The clusters are named in CiteSpace based on the keywords used in articles along with a log-likelihood algorithm.

frontiers. With the global aging population > 60 years expected to outnumber children younger than 5 years by 2020[19], spinal stenosis and its fusion procedures have become one of the major research frontiers. With the drive for minimally invasive surgical procedures considering their lower morbidity with minimal hospitalization period[21], much of the research efforts are being directed towards making such surgical procedures safer for these aging patients and simpler for surgeons.

Spinal surgery has made technological advancements in recent years in terms of intraoperative imaging, 3D navigated operations, materials with nanoscale architecture, *etc.*[22-25]. Material science research has brought about a revolution in the instrumentation options involved in spinal surgery. The development of materials with high biocompatibility and biomechanical characteristics comparable to those of the native has resulted in a faster and more physiological ossification when used in spinal fusion[26]. Hence, topics such as discogenic pain, nerve injury, clinical outcome, biologics and extreme lateral interbody fusion (XLIF) have been the important research topics directing the progress of spinal surgery.

Our study had a few limitations. The core data used for analysis were from the WoS Core Collection database and *RCA* database. We had an English language restriction for the published RCTs. We did not consider the grey literature such as unpublished conference documents, scientific reports, dissertations, scientific archives, *etc.*, for analysis of the research trend. From a visual analysis perspective, all the available information was not incorporated into the knowledge map.

Our analysis revealed the key areas of ongoing research in spinal surgery to advance the management of spinal diseases like spinal cord injury, spondylolisthesis, spinal stenosis, intervertebral disc disease, and scoliosis. Since arthroplasty is a sought-after field of research in the orthopedic forum, the spine is no exception. However, recent trials are being conducted on surgical treatment methods like fusion surgery, decompression surgery, instrumentation surgery, and arthroplasty. With the current abundance of evidence on novel treatment methods using regenerative principles and mesenchymal stromal cells and their derivatives to combat various inflammatory and degenerative disorders, we except more upcoming trials investigating their role in spinal surgery too. The current research hotspots are presented in the PICO format as Table 9.

CONCLUSION

Spinal surgery research was extensive with multidisciplinary methods and technologies and its development needs the involvement of researchers from various fields. We recommend strengthening

Table 9 Research hotspots in spinal surgery

Category	Hotspot
Patient	Spinal cord injury
	Spondylolisthesis
	Spinal stenosis
	Intervertebral disc disease
	Scoliosis
Intervention	Arthroplasty
	Fusion surgery
	Decompression surgery
	Instrumentation surgery
	Biological therapy
Comparator	Conventional treatment methods
Outcome	Clinical outcome
	Patient reported outcome measures

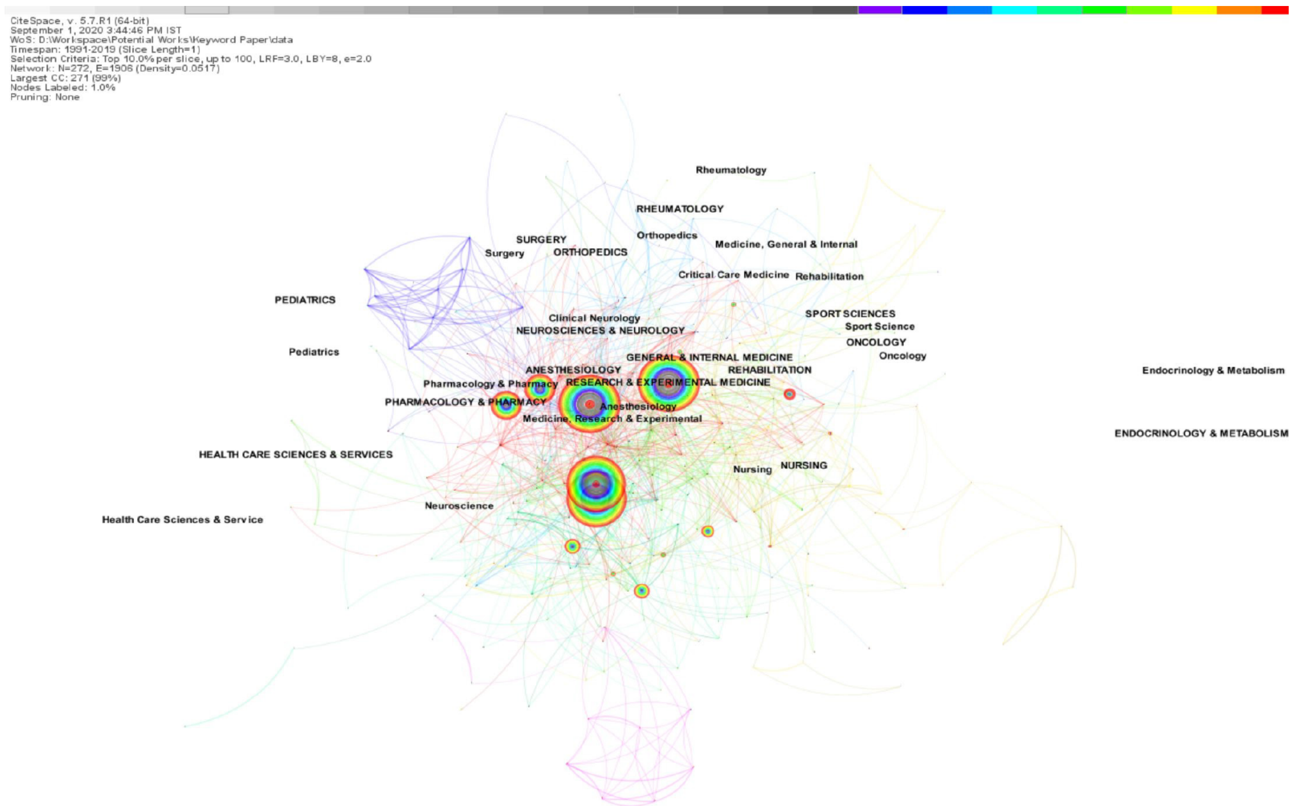

Figure 9 Co-occurrence network of research categories in spinal surgery.

research cooperation among the developed and developing nations. This study provides an overview of research fields in spinal surgery through a systematic and comprehensive scientometric analysis of published RCTs and identified the emerging trends and research hotspots. It was evident from the identified hotspots that degenerative disorders remain the potential frontier in spinal surgery that holds the promise for future advancements.

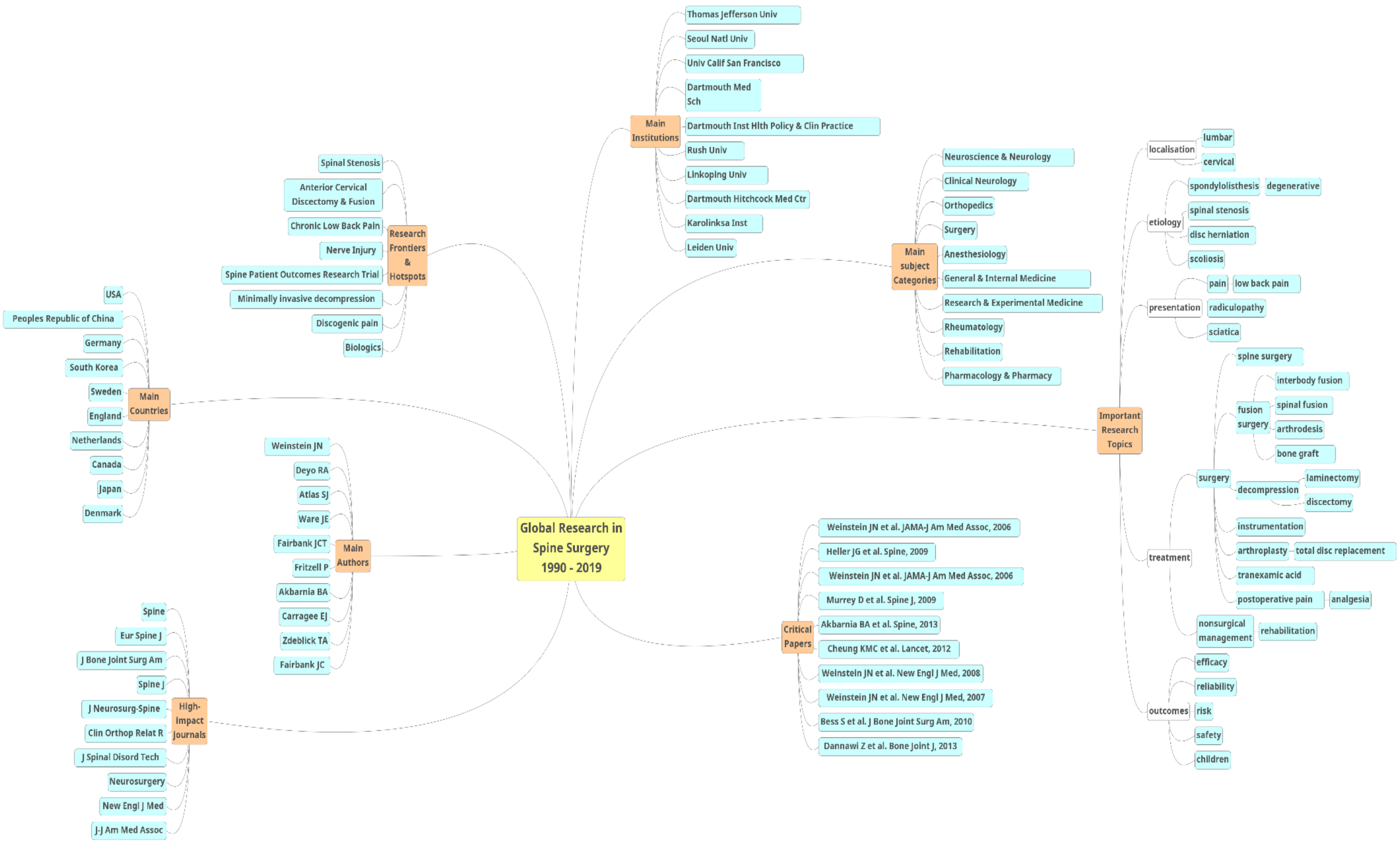

Figure 10 Comprehensive knowledge map in spinal surgery research: 1990–2019.

ARTICLE HIGHLIGHTS

Research background

Spinal surgery is evolving and in the due course of its evolution, it is useful to have a comprehensive summary of the process to have a greater understanding to refine our future directives.

Research motivation

With the multiple domains of research on the spine, it has become difficult for surgeons to find the potential hotspots in research or identify the emerging research frontiers.

Research objectives

To assess the potential research domains of randomized controlled trials (RCTs) for the past three decades (1990–2019), along with their research networks, and to identify the hot topics for future research.

Research methods

A comprehensive and systematic analysis of all the RCTs published on spinal surgery from 1990 to 2019 retrieved from the Web of Science Core Collection database. Scientometric and visual analysis of their characteristics, cooperation networks, keywords, and citations were made using CiteSpace software.

Research results

A total of 696 RCTs were published on spinal surgery from 1990 to 2019; of which, the United States (n = 263) and China (n = 71) made a significant contribution. Thomas Jefferson University (n = 16) was the leading contributor to RCTs. Weinstein JN was the most cited author in the field followed by Deyo RA. *Spine* (n = 559) remained the top-cited journal for RCTs on spinal surgery. On literature co-citation analysis, spinal stenosis, anterior cervical discectomy and fusion, degenerative disc disease, and minimally invasive decompression were identified as the hotspots and potential research frontiers.

Research conclusions

Research cooperation among developed and developing nations remains crucial and needs to be strengthened. It was evident from the identified hotspots that extending the frontiers in the management of degenerative disorders of the spine through further research holds the potential for advancement in spinal care.

Research perspectives

Our analysis revealed the key areas of ongoing research in spinal surgery to advance the management of spinal diseases like spinal cord injury, spondylolisthesis, spinal stenosis, intervertebral disc disease, and scoliosis. Since arthroplasty is a sought-after field of research in the orthopedic forum, the spine is no exception. However, recent trial are being conducted on surgical treatment methods like fusion surgery, decompression surgery, instrumentation surgery, and arthroplasty. With the current abundance of evidence on novel treatment methods using regenerative principles and mesenchymal stromal cells and their derivatives to combat various inflammatory and degenerative disorders, we except more upcoming trials investigating their role in spinal surgery.

FOOTNOTES

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CASE REPORT

Calcium pyrophosphate dihydrate crystals in a 9-year-old with osteomyelitis of the knee: A case report

William Pavlis, David S Constantinescu, Rajan Murgai, Spencer Barnhill, Brian Black

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Abstract

BACKGROUND

Calcium pyrophosphate dihydrate deposition disease (CPPD), or pseudogout, is an inflammatory arthritis common among elderly patients, but rarely seen in patients under the age of 40. In the rare cases presented of young patients with CPPD, genetic predisposition or related metabolic conditions were almost always identified.

CASE SUMMARY

The authors report the case of a 9-year-old boy with no past medical history who presented with acute knee pain and swelling after a cat scratch injury 5 d prior. Synovial fluid analysis identified calcium pyrophosphate dihydrate crystals. Further MRI analysis identified osteomyelitis and a small soft tissue abscess.

CONCLUSION

This case presents the extremely rare diagnostic finding of calcium pyrophosphate dihydrate crystals in a previously healthy pediatric patient. The presence of osteomyelitis presents a unique insight into the pathogenesis of these crystals in pediatric patients. More research needs to be done on the role of CPPD in pediatric arthritis and joint infection.

Key Words: Calcium pyrophosphate; Pseudogout; Pediatrics; Crystals; Osteomyelitis; Case report

Core Tip: Calcium pyrophosphate dihydrate deposition disease (CPPD) is rarely seen in patients under the age of 40. This case represents a rare diagnostic finding of CPP crystals in a 9-year-old patient. Previously, the youngest patients ever described in case reports were 16 years old. In the rare cases presented of young patients with CPPD, genetic predisposition or related metabolic conditions were almost always identified. In this case, the presence of osteomyelitis presents a unique insight into the pathogenesis of these crystals in pediatric patients. This case highlights the need for more research on the pathogenesis of these crystals and their role in pediatric arthritis and joint infection.

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INTRODUCTION

Calcium pyrophosphate dihydrate deposition disease (CPPD), formerly known as pseudogout, is a common inflammatory arthritis that may asymptomatically present as chondrocalcinosis or as episodes of acute calcium pyrophosphate (CPP) crystal arthritis. Increasing age is one of the strongest risk factors for the condition, with the condition rarely seen before the age of 40 and common in patients over 80[1]. In cases where the condition has been identified in patients under 40, risk factors such as genetic predisposition or metabolic disorders are almost always present[2]. In this report, we present the case of a 9-year-old male with no past medical history developing CPP crystals in the synovial fluid of the knee during an episode of osteomyelitis caused by cat scratch injury. The patient's mother consented to the publication of this case report and accompanying images.

CASE PRESENTATION

Chief complaints

A 9-year-old, African American male presented to the emergency room accompanied by his mother with right knee pain of 5 d duration.

History of present illness

The patient stated that the pain began after he was scratched by a cat 5 d prior to presentation. His mother noticed her son was not bearing weight on the right lower extremity 2 d after the incident. He described the pain as constant and worsening and aggravated by both passive movement of the knee and weight bearing of the extremity. The patient and his mother denied any history of fever or drainage from the wound but did report antecedent upper respiratory infection symptoms one week prior. He had not trialed NSAIDs or acetaminophen for the injury. The patient was in the 2nd grade and lived with both parents. The orthopedics service was consulted to rule septic arthritis of the right knee.

History of past illness

The patient had no past medical history.

Personal and family history

The patient had no relevant family history, including no history of metabolic disorders such as hereditary hemochromatosis or hyperparathyroidism.

Physical examination

Focused examination of the right lower extremity demonstrated warmth and swelling across the knee. Superficial scratches were noted across the anterolateral leg. One punctate wound on the lateral knee was noted without erythema or drainage. Thigh and leg compartments were soft and compressible. Significant pain was reproduced with both axial loading and passive range of motion of the knee from 0°-40°. Sensation and motor function were intact in all nerve distributions with palpable distal pulses and brisk capillary refill in all toes.

Laboratory examinations

Initial laboratory studies showed a white blood cell count of 8.9, C-reactive protein of 1.1, and erythrocyte sedimentation rate of 39. The patient had a calcium level of 9.7 and alkaline phosphatase of

209. Due to the clinical concern for septic arthritis, joint aspiration was performed. Aspiration yielded 10 mL of cloudy, viscous, yellow fluid. Follow-up cell counts of the synovial fluid yielded a glucose of 99, protein of 4.9, and a WBC of 7,345 with 59% polymorphic neutrophils. Positively birefringent, rhomboid shaped crystals were present and identified as calcium pyrophosphate dihydrate crystals. Bacterial and fungal cultures of the fluid were both negative for any growth. This synovial fluid analysis was suggestive of an inflammatory origin and a preliminary diagnosis of CPP arthritis was made.

Imaging examinations

Radiographs of the right knee demonstrated a joint effusion within the suprapatellar recess and trace effusion within Hoffa's fat pad (Figure 1). No chondrocalcinosis was observed. Follow-up ultrasound of the right knee was performed for comparison, which showed a simple fluid collection in the knee joint.

The patient was placed in an ace wrap for compressive dressing, started on oral ibuprofen, intravenous (IV) ceftriaxone and clindamycin, and admitted for additional work-up. Pediatric infectious disease was consulted and elected to continue ongoing antibiotic management and perform Bartonella titers, which were negative. On the third day of admission, MRI with IV contrast was performed and significant for a focal, intra-synovial area of enhancing, 6 mm cortical defect at the lateral border of the lateral femoral condyle (Figure 2). Additionally, a small joint effusion and subcutaneous soft tissue edema overlying the proximal tibia, rim enhancement suggestive of synovitis, and a collection within the inflammatory changes of the vastus lateralis with rim enhancement suggesting small abscess formation were also found.

FINAL DIAGNOSIS

A diagnosis of osteomyelitis was made with a rare, incidental finding of calcium pyrophosphate dihydrate crystals in synovial fluid analysis of the knee.

TREATMENT

Antibiotic management was changed to IV ampicillin-sulbactam due to concern for Pasteurella secondary to cat scratch. A diagnosis of CPPD was considered very unlikely due to the patient's young age, lack of previous episodes or family history of CPPD, and absence of other medical issues considered risk factors for CPPD, such as hyperparathyroidism, hereditary hemochromatosis, chronic kidney disease, or loop diuretic use.

Debridement of the osteomyelitis and needle aspiration of the soft-tissue abscess were not performed due to the small size of the deformities and marked clinical improvement in the patient. Due to this, no cultures or drug sensitives of the abscess or bone were performed. By the fourth day of admission, the patient had remained afebrile, his CRP had decreased to less than 0.5, his right knee had become significantly less edematous, and he no longer endorsed pain or reduced range of motion. After final discussion with the infectious disease team, the decision was made to discharge the patient with a 4-wk supply of oral amoxicillin-clavulanate. The patient did not require physical therapy and was discharged without a walker. The patient was referred for follow-up in the infectious disease to ensure resolution of symptoms and monitor for side effects of antibiotic treatment. The mother was agreeable with the nonoperative management of her son and counseled to return to the emergency room if symptoms recurred.

OUTCOME AND FOLLOW-UP

At 6-wk follow-up, the patient was asymptomatic, had completed his course of oral antibiotics, and had returned to prior function. The patient's mother reported no ongoing noticeable disability or changes in her child. She reported overall satisfaction with the treatment of her child and the quality of care she received from the physician, nursing, and physical therapy staff during her son's hospitalization.

DISCUSSION

In this case, we present the rare finding of CPP crystals in the synovial fluid of a healthy 9-year old child with osteomyelitis and a soft-tissue abscess following minor knee trauma. CPPD is a common inflammatory arthritis with a strong association with increasing age. A community prevalence study in the United Kingdom found the mean age of individuals with the condition to be 63.7, with prevalence increasing from 3.7% in those aged 55-59 to 17.5% in those aged 80-84[3]. Cases are very rarely identified

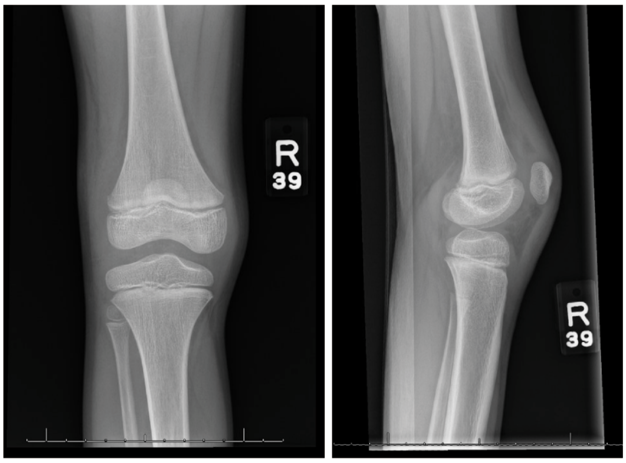

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Figure 1 Anteroposterior (left) and lateral (right) radiographs of the right knee demonstrating evidence of a joint effusion within the suprapatellar recess and Hoffa's fat pad.

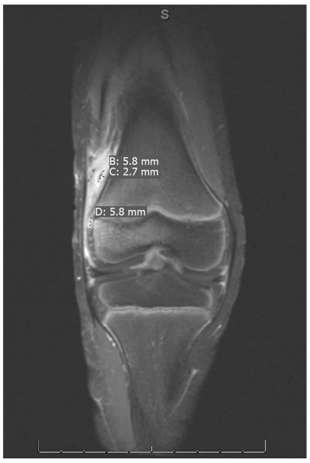

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Figure 2 Magnetic resonance imaging with intravenous contrast of the right knee demonstrating a small enhancing cortical defect along the lateral border of the lateral femoral condyle, measuring approximately 6 mm, suggestive of osteomyelitis. There is a collection within the inflammatory changes of the vastus lateralis demonstrating rim enhancement measuring approximately 0.6 cm × 0.2 cm representing tiny abscess formation.

in patients under the age of 40. In a study of a region encompassing one million people in Sweden, only 6 of 706 cases were identified in individuals under the age of 34, with the youngest patient being 20[4].

In the literature, few reports of CPPD in younger patients have been published, with most being associated with significant relevant co-morbidities[5-9]. The youngest cases of CPPD disease identified from the literature were two 16 year old patients in Germany[9]. The condition's occurrence in those younger than 55 has been linked to familial hereditary predisposition and metabolic conditions such as hyperparathyroidism, hemochromatosis, Wilson's disease, hypophosphatasia, and hypomagnesemia [2]. In two prior cases, patients presented with CPPD disease at age 24 and 31 despite no relevant co-morbidities or similar familial occurrence[6,7]. The patient in this case similarly demonstrated no metabolic or genetic abnormalities and lacked any similar family history. Acute attacks of CPPD are often found in the setting of acute joint trauma or illness, making this patients concomitant trauma and osteomyelitis a likely inciting factor[2]. However, the pathogenesis of this condition is still not fully understood, and this case highlights the need for more research on the role of join trauma and inflammation on the development of CPPD.

CPPD is frequently asymptomatic and believed to be severely underdiagnosed. One study found that CPP crystals were present in the synovial fluid of 30% of patients undergoing knee arthroplasty for osteoarthritis[10]. Diagnosis rates are dependent on methods of diagnosis. The identification of articular chondrocalcinosis on radiographs is a common means of diagnosis; however, studies of prevalence of the condition using this method vary widely based on the type and number of joints examined[1]. The most accurate form of diagnosis remains the identification of positively birefringent, rhomboid-shaped crystals in synovial fluid from the affected joint. In this study, no chondrocalcinosis was observed despite the identification of CPP crystals in synovial fluid.

This study is limited by the short follow-up period. Further follow-up will be required to evaluate the significance of this finding in the setting of this young patient's acute injury. Additionally, this patient was not formally screened for several metabolic conditions associated with early-onset CPPD, such as hereditary hemochromatosis and hyperparathyroidism. Observation for repeat episodes of acute joint pain or the development of chondrocalcinosis will require further investigation for underlying causes of CPPD. However, this case report successfully presents findings of CPP crystals in a pediatric patient younger than any other previous reported in the literature. Further research could generate key findings on the pathogenesis of these crystals in the setting of trauma and infection in pediatric patients.

CONCLUSION

CPPD is a common form of arthritis with still relatively little known about its pathogenesis and prevalence. The condition is rarely identified in those under the age of 40. In this study, we present the rare case of a 9-year-old with CPP crystals in the synovial fluid of the knee during an episode of osteomyelitis. This rare finding presents further questions regarding the pathogenesis of the condition and its role in pediatric joint infection and arthritis. Future diagnostic studies among pediatric populations may identify additional cases of CPP crystals in children and shed new insights on the mechanisms of CPP deposition.

FOOTNOTES

Author contributions: Pavlis W is responsible for the data curation and write original draft; Constantinescu D is responsible for methodology; Pavlis W, Constantinescu D, Murgai R and Barnhill S participate in the investigation; Pavlis W and Constantinescu D are responsible for the project administration; Black B is responsible for supervision; all authors participate in the manuscript conceptualization, review and editing.

Informed consent statement: The patient's mother provided informed consent for the publication of this case report and accompanying images.

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