Use of Different Devices for Surgical Treatment of Proximal Humerus Fractures in Adults: A Systematic Review

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Abstract

Background: Proximal humeral fracture is one of the most common osteoporotic fractures in elderly people. The proper treatment choice is controversial. Open reduction and internal fixation (ORIF) with plate and screws is currently the most common treatment for the majority of displaced proximal humeral fractures. The aim of this systematic review is to investigate the surgical treatment outcomes of PHFs, focusing on main used devices and surgical approaches.

Methods: From the earliest record up to 21 July 2020, two independent authors conducted a systematic review of two medical electronic database (PubMed and Science Direct). To achieve the maximum sensitivity of the search strategy, the following terms were combined: “(proximal NOT shaft NOT distal) AND humeral AND fracture AND (plate OR locking plate OR osteosynthesis NOT nail NOT arthroplasty)” as either key words or MeSH terms. The risk of bias of the included studies was assessed, agreeing to the Cochrane Handbook guidelines.

Results: Thirty-four articles were initially noticed after the term string research in the two electronic databases. Finally, after full-text reading and analyzing the reference list, 8 studies were selected. The mean age recorded was 69.5 years (Range 67-72). All the studies included two-, three-, four-fragments fracture. Seven studies investigated PHILOS (Synthes, Bettlach, Switzerland) implants results, while one investigated CFR-PEEK plate (PEEK Power Humeral Fracture Plate; Arthrex, Naples, Florida, USA) outcomes or other plates. Deltopectoral and Transdeltoid approaches were the more common used.

Conclusions: Both deltopectoral and transdeltoid approaches are valid approach in plating after proximal humerus fractures, for these reasons, the surgeon experience is crucial in the choice. The more valid implant is still unclear. The develop of prospective randomized comparative studies is strongly encourages.

Background

Proximal humeral fracture (PHF) is one of the most common osteoporotic fractures in elderly people, accounting for about 4% to 5% of all human fractures. Its incidence increased by 13.7%, maybe due to the increased risk of osteoporosis in ageing population [1]. Minor trauma may cause fractures in cases of reduced bone quality, which explains why more than 76% of all humeral fractures are observed in patients over 60 years [2]. The most used classification is by Neer [3], that describes the fracture pattern in two, three and four parts fracture, according to the anatomical segments of the proximal humerus: humeral head, greater and lesser tubercles and shaft. Another classification system frequently used is the AO [4], that divides proximal humeral fractures into three groups, A, B and C; each with subgroups, placing more emphasis on the blood supply to the articular surface; if either the lesser or greater tuberosity remain attached to the articular segment, blood supply is probably adequate to avoid avascular necrosis [3,5]. Most of fractures are undisplaced or minimally displaced and could be nonoperatively treated [6]. Thirteen to 16% of all PHFs are three- and four-parts and comminuted displaced. Operative treatment of these fractures in younger patients is not controversial [7]. The main debate involves elderly patients with varying degrees of osteoporosis and severe displacement, secondary to a low-energy trauma [7].

Open reduction and internal fixation (ORIF) still represent the most common option for most displaced proximal humeral fractures [8]; locking plates and intramedullary nails are used for stable fixation of PHFs [8]; the minimally invasive plate osteosynthesis (MIPO) has been developed as a potential solution to ameliorate the weak points of open plating in terms of soft tissue preservation in PHFs [9]; the Proximal Humerus Internal Locking System (PHILOS) is an interlocking anatomically recontoured plate, that is proximally broader than distally. Good functional outcomes have been reported after fixation with the PHILOS plate [1].

However, some postoperative complications have been reported, including poor shoulder joint function, reduction loss, failure of the internal fixation, impingement syndrome, malunion or nonunion of the fracture, and humeral head osteonecrosis [1]. To avoid the problem of osteoporotic bone and to achieve fracture stability, NCB (non-contact-bridging) plate is a fixed angle device, that allows both open and minimally invasive indication [10]. The plates materials are often titanium, stainless steel and, rarely, carbon fiber reinforced polyetheretherketone. Intramedullary nails have become an attractive alternative treatment, due to their superior biomechanical advantages, including significant stiffness and higher load to failure. However, intramedullary nails do not contribute to satisfactory fracture reduction and the damage to rotator cuff may compromise the shoulder function [8].
Conservative treatment is also an alternative solution for PHFs in the elderly. Although conservative treatment does not achieve stable fracture fixation, better radiographic outcomes and early mobilization were reported, leading to a satisfactory shoulder function and lower complication rate [8]. For surgically treated displaced fractures, the traditional deltopectoral approach is the most common for plate fixation of PHFs. However, some authors considered that this approach requires extensive soft tissue dissection and muscle retraction, to gain adequate exposure to the lateral aspect of the humerus [8]. As an alternative, a less invasive, deltoid-split approach has been described with the goal of minimizing local soft tissue trauma [11].

The aim of this systematic review is to analyze the surgical treatment outcomes of PHFs, focusing on main used devices and surgical approaches.

**Methods**

**Study selection**

From the earliest record up to 21 July 2020, two independent authors (AV and RD) conducted a systematic review of two medical electronic database (PubMed and Science Direct) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [12]. The following terms were combined in order to achieve the maximum sensitivity of the search strategy: “(proximal NOT shaft NOT distal) AND humeral AND fracture AND (plate OR locking plate OR osteosynthesis NOT nail NOT arthroplasty)”. From all chosen article, a standard records admission form was used to find: sample size, mean age at treatment, sex ratio, fracture classification, fixation type, materials, surgical approach, clinical score, radiological assessment, complications and year of the study. To maximize the comprehensiveness of the search, the lists of sources used in all relevant articles found in the above search were manually reviewed. The quality studies estimation was performed by two independent authors (AV and GT). Records conflicts were resolved by dialogue with a senior author (VP).

**Inclusion and exclusion criteria**

Articles were initially screened by title and abstract. Articles unclear from title or abstract were reviewed according the selection criteria trough full text. Initially, the studies were screened by title and abstract. Undefined titles or abstracts were reviewed, according to selection criteria through full text. Two authors (RD and DC) independently extracted data from the studies that met the inclusion criteria and they were blinded to each other's. The exclusion criteria were studies without sufficient data, duplicate articles, research works without a clear methodology, respective studies, case series, case report, and review articles, and follow-up of less than 12 months.

**Definition of outcomes**

The pain severity and functional status of the shoulder were considered as outcome assessment. The visual analog scale (VAS) results were extracted to evaluate the shoulder pain. The shoulder pain and disability index (SPADI), Disabilities of the Arm, Shoulder and Hand score (DASH), the Constant-Murley score (CMS), The Oxford Shoulder Score (OSS), Simple Shoulder Test (SST), Neer scoring system (NSS), and UCLA Scoring System were utilized to assess the functional outcome.

**Risk of bias assessment**

The risk of bias of the included studies was assessed agreeing with to the Cochrane Handbook guidelines [13]. Three authors (AV, RD, and GT) performed the evaluation. The disagreements were debated with the senior investigator (VP) for the final decision. All the raters agreed the results of each stage of the assessment.

**Results**

**Included studies**
Thirty-four articles were initially noticed after the term string research in the two electronic database 3 studies were excluded due to duplication. After the initial assessment, 21 studies were appropriate for full-text reading. Meta-analyses or systematic reviews were excluded. Finally, after full-text reading and analyzing the reference list, 8 studies were selected. A PRISMA [12] flowchart of the selection procedure was presented in Fig. 1. The studies results are summered in Table 1.
| Author               | Sample (Mean Age) | Fracture types | Plate              | Approach | Outcome measures | Results (Mean (Standard deviation)) | Complication                  | Limits of the study                        |
|---------------------|-------------------|----------------|--------------------|----------|------------------|-------------------------------------|---------------------------------|--------------------------------------------|
| Olerud P, (2011).   | 30 (72.9)         | Neer 3 fragments | PHILOS DP          | CMS, DASH| 24 months:       | CMS 61.0 (19.2) DASH 26.4 (25.2)    | ISP: 5 GTSD: 4 AVN: 3 Additional surgery: 9 | Selection bias risk, No pre-injure assessment. Recall bias risk |
| Hoon-Sang Sohna,    | 45 (62.6)         | Neer 2, 3, 4 fragments | PHILOS DP          | CMS, UCLA, VAS | 24 months: | CMS 79.7 (11.9) UCLA 30.0 (3.4) VAS 1.7 (1.4) | ISP 3 SL 1 PI 3 Varus collapse 2 GTSD 2 Avn 1 Stiff shoulder 6 | Small size Sample. Short follow-up period Multicenter design |
| Hoon-Sang Sohna,    | 45 (61.0)         | Neer 3 fragments | PHILOS TD          | CMS, UCLA, VAS | 24 months: | CMS 80.7 (13.99) UCLA 29.0 (4.7) VAS 1.8 (0.9 0) | ISP 2 SL 2 PI 3 Varus collapse 3 GTSD 2 AVN 0 Stiff shoulder 4 | Small size Sample. Short follow-up period Multicenter design |
| Ziegler, P., (2019).| 32 (61.8)         | Neer 2, 3, 4 fragments | CFR-PEEK DP        | DASH, SST, OSS | 6 months: | OSS 37.7 (8.8) SST 62.5 (22.3) DASH 27.5(20.5) | NA | Short follow-up Selection bias risk |

ORIF: Open reduction and internal fixation; MIPO: minimally invasive plate osteosynthesis; PHILOS: Proximal Humerus Internal Locking; CFR-PEEK: plate PEEK Power Humeral Fracture Plate; NCB-PH: non-contact bridging plate; AUG: augmentation with MIIG X3 Hivisc; DP: Deltoidpectoral approach; TD: Transdeltoid approach; VAS: visual analog scale; SPADI: Shoulder pain and disability index; DASH: Disabilities of the Arm; Shoulder and Hand score; CMS: Constant-Murley score; OSS: Oxford Shoulder Score; SST: Simple Shoulder Test; NSS: Neer scoring system; ISP: Intra-articular screw penetration; GTSD: Secondary displacement of the greater tubercle; SL: Screw loosening; PI: Plate impingement; AVN: Avascular necrosis.
| Author          | Sample (Mean Age) | Fracture types | Plate           | Approach | Outcome measures | Results Mean (Standard deviation) | Complication | Limits of the study |
|-----------------|-------------------|----------------|-----------------|----------|-----------------|-----------------------------------|--------------|---------------------|
| Ziegler, P.     | 31(60.9)          | Neer 2, 3, 4 fragments | PHILOS          | DP       | DASH, SST, OSS  | 6 months: OSS 38.6 (6.8) SST 65.0 (20.1) DASH 28.5 (17.9) | NA           | Short follow-up     |
| Liu, Z. Z.      | 21(69.7)          | Neer 3, 4 fragments | PHILOS          | TD       | NSS             | NSS 75.5                          | Varus collapse 1 GTSD 2 ISP 2 | Small size sample. |
| Liu, Z. Z.      | 21(69.7)          | Neer 3, 4 fragments | PHILOS + AUG    | TD       | NSS             | NSS 83.7                          | AVN 1        | Small size sample.  |
| Voigt, C.       | 28(72.0)          | Neer 3, 4 fragments | HSP             | DP       | SST, DASH       | 12 months: SST 9.7 (1.8) DASH 15.7 (11.8) | Implant malposition 1 ISP 7 Varus collapse 4 GTSD 1 AVN 2 | Short follow-up |
| Voigt, C.       | 20(75.5)          | Neer 3, 4 fragments | PHILOS          | DP       | SST, DASH       | 12 months: SST 8.6 (3.2) DASH 17.8 (16.2) | Implant malposition 0 ISP 6 Varus collapse 1 GTSD 2 AVN 3 | Short follow-up |
| Fjalestad, T.   | 25(72.2)          | Neer 3, 4 fragments | Nonspecific LCT | DP       | CMS             | 12 months: CMS 52.3 (20.9) | AVN 8 osteoarthritis: 4 | No anatomic reduction in severely displaced fractures |

ORIF: Open reduction and internal fixation; MIPO: minimally invasive plate osteosynthesis; PHILOS: Proximal Humerus Internal Locking; CFR-PEEK: plate PEEK Power Humeral Fracture Plate; NCB-PH: non-contact bridging plate; AUG: augmentation with MIIG X3 Hivisc; DP: Deltoidpectoral approach; TD: Transdeltoid approach; VAS: visual analog scale; SPADI: Shoulder pain and disability index; DASH: Disabilities of the Arm; Shoulder and Hand score; CMS: Constant-Murley score; OSS: Oxford Shoulder Score; SST: Simple Shoulder Test; NSS: Neer scoring system; ISP: Intra-articular screw penetration; GTSD: Secondary displacement of the greater tubercle; SL: Screw loosening; PI: Plate impingement; AVN: Avascular necrosis.
| Author       | Sample (Mean Age) | Fracture types | Plate         | Approach      | Outcome measures | Results Mean (Standard deviation) | Complication | Limits of the study |
|--------------|-------------------|----------------|---------------|---------------|------------------|----------------------------------|--------------|---------------------|
| Zhao, L.,   | 17(64.3)          | Neer 2, 3      | ITS (MIPO)    | DP            | CMS, NSS, VAS    | 48 months: CMS 88.8 (1.0) NSS 87.4 (1.2) | Incision infection = 1 pneumonia = 1 | Small sample size |
| (2017).     | 19(63.6)          | fragments      |               |               |                  |                                  |              |                     |
|             |                   | Neer 2, 3      | ITS (ORIF)    | DP            | CMS, NSS, VAS    | 48 months: CMS 86.9 (2.1) NSS 85.7 (2.6) VAS 3.1 (1.3) | Incision infection = 2 decubitus = 1 | Small sample size |
|             |                   | fragments      |               |               |                  |                                  |              |                     |
| Zhao, L.,   | 15(67)            | Neer 2         | NCB-PH        | TD            | CMS, VAS         | 4, 5 years: CMS 68.0 (24) VAS 3.4 (3.5) ISP SL GTSD Wound infection | Lack of objective measurements. Loss of follow-up |              |
| (2015).     |                   | fragments      |               |               |                  |                                  |              |                     |
|             | 56(67)            | Neer 3, 4      | NCB-PH        | TD            | CMS, VAS         | 4, 5 years: CMS 68.0 (24) VAS 3.2 (2.9) ISP SL GTSD Wound infection | Lack of objective measurements. Loss of follow-up |              |
|             |                   | fragments      |               |               |                  |                                  |              |                     |

ORIF: Open reduction and internal fixation; MIPO: minimally invasive plate osteosynthesis; PHILOS: Proximal Humerus Internal Locking; CFR-PEEK: plate PEEK Power Humeral Fracture Plate; NCB-PH: non-contact bridging plate; AUG: augmentation with MIIG X3 Hivisc; DP: Deltoidpectoral approach; TD: Transdeltoid approach; VAS: visual analog scale; SPADI: Shoulder pain and disability index; DASH: Disabilities of the Arm; Shoulder and Hand score; CMS: Constant-Murley score; OSS: Oxford Shoulder Score; SST: Simple Shoulder Test; NSS: Neer scoring system; ISP: Intra-articular screw penetration; GTSD: Secondary displacement of the greater tubercle; SL: Screw loosening; PI: Plate impingement; AVN: Avascular necrosis.

**Mean Age and Fragment Fracture patterns**

According to our results, the mean age recorded was 69.5 years with a range varying between 67 and 72 years old. All the studies included two-, three-, four-fragments fracture. except three articles, in these cases were selected only more than 3-fragments fracture.
Implants

Seven studies investigated PHILOS (Synthes, Bettlach, Switzerland) implants results [6, 9, 14–18], while the CFR-PEEK plate (PEEK Power Humeral Fracture Plate; Arthrex, Naples, Florida, USA) [14], a nonspecific LCT plate (Synthes, Bettlach, Switzerland) [17], humeral suture plate (HSP) (Arthrex, Naples, FL) [16], ITS proximal humeral locking plate (GE medical, USA) [18], and the non-contact bridging plate (NCB-PH; Zimmer, Warsaw, IN, USA) [19] were explored one time in different studies.

Shoulder Pain

Deltopectoral approach. Li Zhao et al. [18] evaluated 36 patients divided in two groups, the MIPO, composed of 17 patients mean aged of 64.3 years, and the ORIF, composed of 19 subjects mean aged of 63.6 years. The authors in the MIPO group noted a mean VAS 3.1 ± 1.3 and in the ORIF cohort of 3.2 ± 1.3 at 2 years follow-up. Hoon-Sang Sohna et al [9] investigated 45 patients with a mean age of 62.6 years and found at 24 months follow-up a VAS of 1.7 ± 1.4.

Transdeltoid approach. Bockmann et al. [19] investigated the mid-term results of a less-invasive locking plate fixation method in 2 groups according to the fracture pattern. In the study included 15 2-fragment fractures, and 56 3- and 4-part fractures. The 2-fragment group recorded a 4 years VAS 3.4 ± 3.5, while the 3 and 4-fragments fracture recorded a mean VAS of 3.2 ± 2.9. Hoon-Sang Sohna et al [9] reported a mean VAS value of 1.8 ± 0.90.

Functional Outcome

Deltopectoral approach. Ziegler et al. [14] evaluated two different cohorts, comparing two implants (CFR-PEEK plate and PHILOS plate). The authors noted for the CFR-PEEK plate a mean OSS of 37.7 ± 8.8, a mean SST 62.5 ± 22.3 at 6 months follow-up. On the other hand, in the PHILOS Group a mean OSS of 38.6 ± 6.8, a mean SST 65.0 ± 20.1 at the same time. The mean DASH of 27.5 ± 20.5 and 25.8 ± 17.9 for the CFR-PEEK and PHILOS plate, respectively at half year follow-up. Fjalestad et al. [17] assessed 25 elderly patients (72.2 years) and observed a CMS of 52.3 ± 20.9 after 1 years from the surgery. Hoon-Sang Sohna et al. [9] found a CMS mean of 79.7 ± 11.9 and an UCLA score mean of 30.0 ± 3.4. Voight et al. [16] compared the humeral suture plate (HSP) and PHILOS plate in elderly. The HSP group included 20 subjects while the PHILOS group was composed of 28 patients. The researchers recorded the significant difference (p < 0.001) in both the group between the preoperative and at 12 months after surgery DASH mean results. Moreover, the authors reported a mean SST score of 8.6 ± 3.2 in HSP group and 9.7 ± 1.8 in PHILOS group. Li Zhao et al. [18] recorded a mean CMS of 88.8 ± 1.0 and 86.9 ± 2.1, in the MIPO and ORIF cohorts respectively at 24 months follow-up. Olerud et al. [6] recorded a CMS of 61.0 ± 19.2 and a DASH of 26.4 ± 25.2.

Transdeltoid approach. Hoon-Sang Sohna et al. [9] reported a CMS mean of 80.7 ± 13.99 and an UCLA score mean of 29.0 ± 4.7. Bockmann et al. [19] found a CMS of 68 ± 24 in 2-fragments cohort and 71 ± 20 in 3- and 4-fragments group. Zi-zhang Liu study [15] reported the result of two the MIPO cohorts, the first one with injectable graft (AUG), and the second group without (NAUG). At 12 months postoperatively, according to the NSS, the mean in AUG group was 75.5 with an excellent-to-good rate of 76.2%. The NAUG recorded a NSS mean score of 83.7 with the excellent-to-good rate of 82.8%. No statistical differences were founded (p > 0.05).

Discussion

According to our results, all the patients treated with plating for more than two-fragments PHFs reported good functional outcome and a reduced pain. Deltopectoral and transdeltoid approaches are commonly performed for the implant. The most common investigated plate is the PHILOS.

There is no common consensus among the orthopedic surgeons, and several treatment algorithms for the proximal humerus fractures have been proposed [14]; moreover, numerous articles reported dissonant results in the mid-term functional outcome, when compared surgical and nonsurgical treatments [21–23], but higher complication rates after surgical procedures have been shown [2, 6, 14].

The surgical approach is still debated: the most commons are the deltopectoral and the transdeltoid. The proximal humerus has a rich, but vulnerable blood supply, which must be carefully protected during open reduction. Avascular necrosis of the humeral head represents a complication, due to vascular traumatic damage [24].
In each included study, both approaches were found valid for shoulder pain and functional outcomes. Bockmann et al. [19] analyzed and compared the approaches and found similar score values and complication rate. At the same time, the sample had a small size, a short follow-up and number of patients lost to follow-up. Most cases of complications in the deltopectoral group were represented loosening of the plate in the shaft [19, 25]. On the other hand, in the deltopectoral approach, the substantial soft tissue dissection, including the deltoid muscle partial release and retraction, the humeral manipulation to access the lateral aspect of the humerus and vascular damage during plating and dissection, represent the main literature controversies [14, 25], despite anatomic exposure is performed under the intact deltoid muscles as a functional unit [9]. In the MIPO technique, the deltoid splitting approach provides a direct access to the lateral aspect of the proximal humerus; therefore, the plate could be placed more easily than with the deltopectoral approach [9].

Similarly, the most proper implant type is not already defined, and the use of locking or non-locking screws is widely debated. Locking screws have threaded heads, that lock into the plate's screw holes to create an angular stable fixation. While the conventional non-locking screws rely on the bone-plate interface for stability, locking screws are reliant on the bone-screw interface instead, resulting in theoretically lower friction [26]. The two types of screws failure modes are different. Toggling, loosening or the pulling out are the more common causes of failure for the non-locking plates, while the pullout or failing of all screws are common in of locking plates [27]. Locking plates advantages including excellent elastic stiffness and good fatigue behaviour under axial compression and larger stiffness than blade plates in the cyclic external rotation [28]. Non-locking plates constructs in 20° of abduction have been proven greater stiffness than locking plate [28, 29]. In order to assess the result of Polyaxial and monoaxial locking screws, Philos and NCB plates were compared in three studies [30–32]: it has been proven that Philos plate needed more numerous, but thinner screws to report similar NCB plate performances under axial compression [28]. At the same time, the use of monoaxial screws could cause a significant number of complications, due to the perforation of screws through the humeral head [28].

The overall rate for complications after internal fixation of PHFs is documented in the recent literature as between 10% and 34% [26]. In osteoporotic bone several implants have been developed, to enhance the clinical outcome and avoid complications [19, 25]. According to biomechanical studies, fixation with CFR-PEEK plates was documented similar or superior in screws and plate connection stability. The plate has been proved to allow more minimal movements at the fracture site than fixation with titanium plates. In addition, CFR-PEEK is a radiolucent material, offering the advantage of easier intraoperative and postoperative radiographic assessment of the fracture situation [14]. Ziegler et al. [14] in their study evidenced several CFR-PEEK plates benefits, including intraoperative fluoroscopic visibility of the fracture fragments and the absence of screw-to-plate cold fusion, associated to easier plate removal [14]. In addition, the polyaxial locking self-tapping screws allow for correct screw placement in the parts of the humeral head with high bone mineral density [14]. On another hand, Röderer G et al. [10] highlighted that NCB system in an osteoporotic PHF model, providing higher survival rate when exposed to cyclic torsional loading and more strength in this anatomical region.

Another common complication is the loss of reduction, often caused by the high stiffness of the locking plate or the underestimation of the regional bone density differences [32]. Posterior and superior region of the humeral head purchase significantly better bone quality compared to the anterior aspect of the humeral head, suggesting that the best screw fixation might be achieved in the cranio-central and posterior-medial aspect of the humeral head [32]. Secondary displacement, screw cut-out and osteonecrosis were observed more frequently if not at least one screw was purchased in the superoposterior region [18, 32]. For these reasons, as suggested by Zi-zhang Liu and colleagues, the augmentation of minimally invasive injectable calcium sulfate implant (MIIG) can enhance the healing rate and decrease the incidence of fixation loosening, delayed fracture healing and fracture displacement. It has minor disadvantages than iliac grafts, polymethacrylic acid bone cement and calcium phosphate cements [15].

Main limits of this study were the heterogenous of the scores considered to assess the patient functional outcome and the paucity of prospective randomized comparative studies, in comparison to studies results. We extensively searched and identified all relevant plating in PHFs articles. Therefore, risk of bias assessment showed moderate overall risk which could influence our analysis.

**Conclusions**

Both deltopectoral and transdeltoid approaches are valid approach in plating after proximal humerus fractures, for these reasons, the surgeon experience is crucial in the choice. The more valid implant is still unclear. The develop of prospective randomized
comparative studies is strongly encouraged.

Declarations

Ethics approval and consent to participate.
Not applicable

Consent for publication.
Not applicable

Availability of data and materials.
The datasets generated and/or analysed during the current study are available at the following link:
https://docs.google.com/forms/d/1SP-7zeVakqKVTxDXyo-1Qhhv4io_DV12L1LfTjs0FFo/edit#responses.

Competing interests.
Authors declare that they have no competing interests. GT declare to be the Associate Editor of BMC Musculoskeletal Disorders

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Authors' contributions.
VP: Study idea, Study design, Manuscript review, Final approval of manuscript. AV: Study idea, Study design, Data analysis, Manuscript preparation and review, Final approval of manuscript. RD: Data collection, Data analysis, Final approval of manuscript. DC: Data collection, Final approval of manuscript. VFC: Data collection, Final approval of manuscript. GC: Data collection, Final approval of manuscript. GS: Final approval of manuscript. GT: Study idea, Study design, Manuscript review. All authors have read and approved the manuscript.

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**Figures**
Figure 1

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart of the systematic literature review