Meta-analysis

Platelet-Rich Plasma Injection Can Be a Viable Alternative to Corticosteroid Injection for Conservative Treatment of Rotator Cuff Disease: A Meta-analysis of Randomized Controlled Trials

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Purpose: To explore whether platelet-rich plasma (PRP) injection can be a viable alternative to corticosteroid (CS) injection for conservative treatment of rotator cuff disease. **Methods:** This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. PubMed, EMBASE, The Cochrane Library, and Web of Science were searched from January 1, 1990, to March 20, 2022, for English-language randomized controlled trials that compared PRP and CS injections for patients with rotator cuff disease. Two evaluators independently screened the literature, extracted data, and assessed the level of evidence and methodologic quality of the enrolled studies. The meta-analysis was conducted using RevMan software (version 5.3.3). **Results:** Thirteen nonsurgical randomized controlled trials with 725 patients were included. Compared with CS, PRP provided statistically worse short-term (<2 months) changes in American Shoulder and Elbow Surgeons (ASES) assessment scores, Simple Shoulder Test scores, and Disabilities of the Arm, Shoulder and Hand questionnaire scores but provided better medium-term (2-6 months) changes in Disabilities of the Arm, Shoulder and Hand scores, as well as long-term (≥6 months) changes in Constant-Murley scores, ASES scores, and Simple Shoulder Test scores. No statistically significant differences regarding pain reduction were found between the 2 groups. PRP injections led to worse short-term changes in forward flexion and internal rotation but better medium-term changes in forward flexion and external rotation. PRP showed significantly lower rates of post-injection failure (requests for subsequent injections or surgical intervention prior to 12 months) than CS. No outcome reached the minimal clinically important difference. After sensitivity analyses excluding studies with substantial clinical and/or methodologic heterogeneity, PRP showed better medium-term changes in ASES scores and visual analog scale scores and long-term changes in visual analog scale scores that reached the minimal clinically important difference. **Conclusions:** Without the drawbacks of CS injection, PRP injection is not worse than CS injection in terms of pain relief and function recovery at any time point during follow-up. PRP injection may reduce rates of subsequent injection or surgery, and it might provide better improvements in pain and function in the medium to long term. PRP injection can be a viable alternative to CS injection for conservative treatment of rotator cuff disease. **Level of Evidence:** Meta-analysis of Level I and II studies.

Rotator cuff disease accounts for up to 70% of shoulder pain cases.[1,2] Characterized by chronic degeneration or inflammation, rotator cuff disease includes rotator cuff tendinopathy, subacromial impingement syndrome, partial rotator cuff tears, and tendinitis, which may develop into full-thickness tears.

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Pain during overhead activities and at night and decreased range of motion (ROM) are the most frequent complaints of patients with rotator cuff disease.[3] It is commonly age dependent, with 30% of the population older than 60 years and 62% of the population older than 80 years affected, imposing a heavy socioeconomic burden.[4]

At present, conservative options, including activity modification, anti-inflammatory medicine, and physiotherapy, have been suggested as initial treatments for a broad spectrum of rotator cuff disease.[5,6] If these treatments do not work well, subacromial injections are often clinically effective at reducing symptoms.[7] Corticosteroid (CS) injection into the subacromial space is the most widely used and recognized option because a single injection can reduce pain and improve motion in many cases. However, recent studies have revealed that CS injections are only effective in the short term (3-8 weeks) and might exert adverse effects such as degeneration of the humeral head cartilage, supraspinatus tendon atrophy or even spontaneous rupture, decreased quality of tissue available for further surgery, and an increased risk of infection during subsequent surgery.[8-13]

Owing to its potential to provide growth factors and cellular mediators—and possibly accelerate the healing process—platelet-rich plasma (PRP) has been considered for the treatment of pathologic conditions of tendons, which have limited intrinsic capacity for regeneration and spontaneous healing.[14-16] Some studies have reported favorable outcomes of PRP in treating tendinopathies such as lateral epicondylitis and patellar tendon tendinitis.[17-21] Regarding the rotator cuff tendons, previous systematic reviews have been conducted to compare PRP versus CS injections for conservative treatment of rotator cuff disease. With 21 studies included, a network meta-analysis found that CS injection played a role in the short term (3-6 weeks) rather than in the long term (>24 weeks) whereas PRP injection yielded better outcomes in the long term.[10] Another systematic review that included 9 studies indicated that PRP injection led to better long-term (>24 weeks) function recovery and superior pain reduction from short-term (2-6 weeks) to long-term follow-up compared with CS injection.[22] However, the 2 aforementioned systematic reviews only included 1 study and 3 studies that directly compared PRP versus CS injections. A recent systematic review and meta-analysis included 6 studies comparing CS and PRP injections.[23] The authors concluded that CS injection resulted in significantly better improvements in short-term (3-6 weeks) function and pain, whereas no difference between PRP and CS injections could be observed at medium-term (8-12 weeks) to long-term (>12 weeks) follow-up. The main limitations of these reviews were relatively small sample sizes, the low methodologic quality of the eligible studies, and the failure to report the minimal clinically important difference (MCID). Therefore, controversy exists regarding whether PRP injection is able to be an alternative to CS injection for conservative treatment of rotator cuff disease.

The purpose of this study was to explore whether PRP injection can be a viable alternative to CS injection for conservative treatment of rotator cuff disease. It was hypothesized that without the drawbacks of CS injection, PRP injection would at least not be worse than CS injection in terms of clinical outcomes at any time point during follow-up.

Methods

Search Strategy

This study was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[24] PubMed, EMBASE, The Cochrane Library, and Web of Science were independently searched by 2 authors (L.P. and Y.X.) on March 20, 2022, to identify potentially eligible literature from January 1, 1990, to March 20, 2022, using the following search items: (Platelet-rich plasma OR PRP OR Plasma, platelet-rich OR Platelet rich plasma) AND (Corticosteroids OR Corticosteroid OR Corticoids OR Corticoid OR Steroids OR Steroid) AND (Shoulder OR Rotator cuff OR Supraspinatus OR Infraspinatus OR Subscapularis OR Teres minor OR Impingement OR Tendinopathy OR Tendinitis). All possibly eligible studies were manually retrieved to identify possibly relevant publications.

Study Selection

The titles and abstracts of the studies identified were screened by 2 authors (L.P. and Y.X.) independently. The full texts of potentially relevant articles were acquired for subsequent assessment. Any disagreement was resolved by a third opinion (X.T.). The flow diagram of literature retrieval is presented in Figure 1.

Inclusion and Exclusion Criteria

Studies meeting the following criteria were included: (1) randomized controlled trials (RCTs); (2) studies focusing on participants aged 18 years or older with previously untreated rotator cuff disease; (3) studies in which patients in the intervention group and comparator group received PRP and CS injections, respectively; and (4) studies with a minimum 2-month follow-up period. The following exclusion criteria were applied: (1) letters, editorial materials, reviews, case reports, conference abstracts, and animal experiments; (2) studies including patients who underwent previous injections or surgical procedures; (3) studies not written in English; and (4) studies lacking pain or function

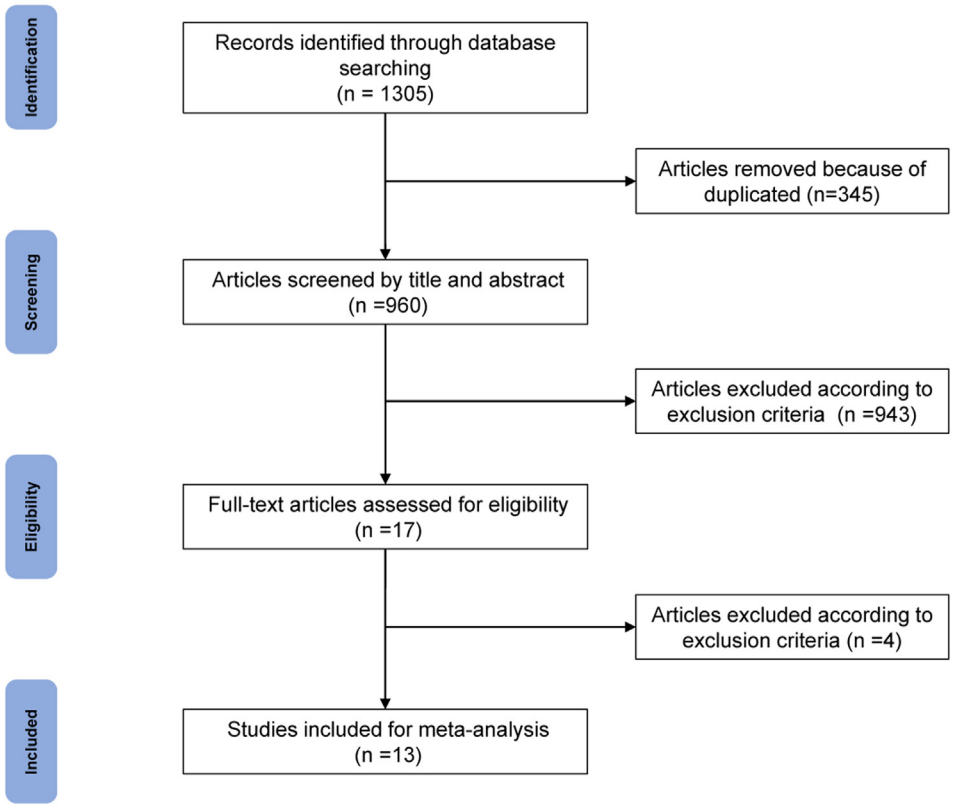

Fig 1. Flowchart of literature retrieval.

score results. Two independent evaluators (L.P. and Y.X.) determined study eligibility. Disagreements were resolved by a third author (X.T.).

Data Collection and Management

Data collection was independently accomplished by 2 evaluators (L.P. and Y.X.), and a consensus was reached after further discussion of any disagreement. The extracted and summarized data included the title, first author, trial design, level of evidence, patient characteristics, sample size, details of the intervention, and follow-up period. The main research outcomes were changes in function scores, pain scores, and ROM after injection. Function scores included the Constant-Murley score (CMS); American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form score; Simple Shoulder Test (SST) score; Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire score; University of California—Los Angeles (UCLA) shoulder rating scale score; and Western Ontario Rotator Cuff Index (WORC) score. Pain was assessed using the visual analog scale (VAS) score. These outcome measures have been validated by previous studies.[25-27] On the basis of the previous literature,[28] we defined short term as within 2 months after injection, medium term as 2 to 6 months after injection, and long term as 6 months or more after injection. The MCID was set as at least a 10-point change in the CMS,[29,30] a 12-point change in the ASES score,[31] a 2-point change in the SST score,[31] a 10-point change in the DASH score,[29,30] a 3.5-point change in the UCLA score,[32,33] a 5-point change in the WORC score,[26] a 1.4-cm change (on a 10-cm scale) in the VAS score,[34] and a 10° change in ROM.[29]

Risk of Bias

The risk of bias of enrolled trials was assessed with a domain-based evaluation using the Cochrane risk-of-bias tool to determine the methodologic quality of eligible studies.[35] Sequence generation and concealment of allocation (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), lack of selective reporting (reporting bias), incomplete outcome data addressed (attrition bias), and other sources of bias were evaluated as unclear, high, or low risk by 2 separate reviewers (L.P. and Y.X.). Inter-rater agreement was calculated using the κ statistic ($\kappa < 0$, less than chance agreement; $\kappa = 0.01$-0.20, slight agreement; $\kappa = 0.21$-0.40, fair agreement; $\kappa = 0.41$-0.60, moderate agreement; $\kappa = 0.61$-0.80, substantial agreement; and $\kappa = 0.81$-0.99, almost perfect agreement).[36] Any disagreements were settled by further discussion.

Statistical Analysis

Statistical analyses were performed with Review Manager (RevMan) software (version 5.3.3; The Cochrane Collaboration, Oxford, England). We analyzed the outcomes by calculating the weighted mean difference (WMD) and pooled odds ratio with corresponding 95% confidence interval. $P < .05$ was considered statistically significant. We evaluated and characterized the heterogeneity of each eligible study with the Cochran Q statistic and the I^2 statistic. A random-effects model was applied to synthesize data with inevitable heterogeneity. In case of any substantial heterogeneity ($I^2 > 50\%$), the following methods might be applied to explain the sources of heterogeneity: (1) sensitivity analysis and (2) subgroup analysis or meta-regression. Sensitivity analyses were conducted to confirm the robustness of pooled outcomes by excluding studies with substantial clinical or methodologic heterogeneity. Furthermore, we constructed funnel plots and used the Begg test to evaluate publication bias.

Results

Characteristics of Included Studies

The researchers (L.P. and Y.X.) searched PubMed, EMBASE, The Cochrane Library, and Web of Science, and 1,305 studies were retrieved. A total of 345 duplicated studies were excluded, and 943 of the remaining studies were excluded after a review of the title and abstract. A total of 17 full-text articles were assessed for eligibility by 2 researchers (L.P. and Y.X.), and 4 articles were excluded according to the exclusion criteria. Two studies were excluded because they enrolled patients with adhesive capsulitis of the shoulder.[37,38] One RCT was excluded because it focused on patients with greater trochanteric pain syndrome.[39] Another study compared PRP and CS injections for rotator cuff tendinopathy, but it was a retrospective comparative study.[40] Finally, 13 RCTs with 725 patients were included after assessment of the full text[41-53] (Fig 1). Table 1 shows the detailed characteristics of the included studies.

Risk of Bias Across Included Studies

Two independent reviewers (L.P. and Y.X.) assessed the risk of bias across the included studies. Inter-rater agreement of the 2 independent reviewers was fair for detection bias ($\kappa = 0.36$); moderate for random sequence generation ($\kappa = 0.60$), allocation concealment ($\kappa = 0.42$), and performance bias ($\kappa = 0.54$); and good for the remaining domains (κ values ranging from 0.78 to 0.90). Random sequence generation, attrition bias, reporting bias, and other bias were the domains in which the included studies were consistently at low risk. However, at least half of the studies were assessed at unclear risk in the domains of allocation concealment, performance bias, and detection bias. Allocation concealment and blinding of outcome assessment were the domains that had the most variability in terms of risk of bias. Figure 2 shows the summarized risk of bias of the eligible studies.

Outcomes of Changes in Function Scores After Injection

At short-term follow-up, PRP resulted in statistically worse functional improvement as evaluated by changes in the ASES, SST, and DASH scores but was not statistically better or worse than CS when measured by the CMS, UCLA score, or WORC score (Table 2). At medium-term follow-up, PRP provided statistically better changes in the DASH score but comparable improvement in changes in the CMS, ASES score, SST score, UCLA score, and WORC score when compared with CS (Table 2). At long-term follow-up, PRP led to statistically better changes in the CMS, ASES score, and SST score but similar improvement in changes in the DASH score and the UCLA score when compared with CS (Table 2). No difference in any function score between the 2 groups at any time point reached the MCID.

Outcomes of Changes in VAS Scores After Injection

A total of 8 studies,[41,45-50,53] 5 studies,[47-50,52] and 5 studies[41,47,48,50,53] focused on short-term, medium-term, and long-term changes in VAS scores, respectively, and no statistically significant difference in pain relief was found for all 3 periods (Table 2).

Outcomes of Changes in ROM After Injection

Four studies reported short-term changes in ROM. Compared with the PRP group, statistically greater improvements in the CS group were observed in changes in forward flexion and changes in internal rotation.[41,45,47,49] However, no significant differences in changes in abduction or changes in external rotation were observed between the 2 groups (Table 2).

Four studies reported medium-term changes in ROM,[41,47,49,52] but the data from only 3 studies were pooled[41,47,49] because 1 study reported the number of patients with limitations in ROM.[52] PRP yielded superior outcomes in changes in forward flexion and changes in external rotation but similar improvements in changes in abduction and changes in internal rotation (Table 2). Sabaah and Nassif[52] reported no significant improvements in ROM in either the PRP group ($P = .529$) or CS group ($P = .121$) at 3 months after injection. No difference in ROM between the 2 groups at any time point reached the MCID.

Safety and Failures

No treatment-related local or systemic complications were reported in any enrolled trials. Only 1 trial

Table 1. Characteristics of Included Studies

Authors	Year	Country	LOE	Sample Size, n		Age, Mean ± SD, yr		Sex: M/F, n		Symptom Duration, Mean ± SD, mo		Follow-up, mo	Details of Injection Procedure		Details of Rotator Cuff Disease
				PRP	CS	PRP	CS	PRP	CS	PRP	CS		PRP	CS	
Say et al.[41]	2016	Turkey	II	30	30	49.2 ± 7	50.2 ± 2.7	10/20	12/18	>3	>3	0, 0.75, 6	Single injection into subacromial space 2.5 mL of autologous pure PRP APC: 4× platelet count of whole blood ALC: NA	Single injection into subacromial space 1 mL of methyl-prednisolone (40 mg) + 8 mL of prilocaine	SIS patients who had not responded to conservative treatment with NSAIDs and exercise for >3 mo: rotator cuff tendinosis (n = 42) or partial tendon tear (n = 18) Shape of acromion was flat (n = 38), curved (n = 18), or hooked (n = 4)
Shams et al.[42]	2016	Egypt	II	20	20	52 ± 12	50 ± 10	10/10	11/9	>3	>3	0, 0.75, 3, 6	Blind single injection into subacromial space 2-2.5 mL of autologous pure PRP APC: NA ALC: NA	Blind single injection into subacromial space 5 mL of triamcinolone acetonide (40 mg)	Patients who complained of persistent pain in 1 shoulder for ≥3 mo with MRI evidence of partial supraspinatus tear
Von Wehren et al.[43]	2016	Germany	II	25	25	53 ± 14	55 ± 10	12/13	14/11	>2	>2	0, 0.75, 3, 6	3 sequential injections in 7-d intervals into subacromial space 5 mL of autologous conditioned plasma APC: NA ALC: NA	Single injection into subacromial space 5 mL of triamcinolone acetonide (40 mg)	Adults who experienced persistent continual pain in 1 shoulder for ≥2 mo and had MRI evidence of partial supraspinatus tear

(continued)

Table 1. Continued

Authors	Year	Country	LOE	Sample Size, n		Age, Mean ± SD, yr		Sex: M/F, n		Symptom Duration, Mean ± SD, mo		Follow-up, mo	Details of Injection Procedure		Details of Rotator Cuff Disease
				PRP	CS	PRP	CS	PRP	CS	PRP	CS		PRP	CS	
Barreto et al.[44]	2019	Brazil	II	26	25	53.2 ± 9.4	53 ± 11	11/15	17/8	NA	NA	0, 1, 3, 6	Single blind injection into subacromial space 3 mL of autologous pure PRP APC: NA ALC: NA	Single blind injection into subacromial space 1 mL of beta-methasone dipropionate + 2 mL of lidocaine (1%)	SIS patients aged 18-70 yr with positive Neer test results
Ibrahim et al.[45]	2019	Egypt	II	15	15	46.8 ± 10.4	41.5 ± 12.5	6/9	7/8	2.12	1.21	0, 2	Single US-guided injection into subacromial space 2 mL of autologous pure PRP APC: NA ALC: NA	Single US-guided injection into subacromial space 1 mL of methyl-prednisolone acetate + 1 mL of lidocaine	Patients with rotator cuff tendinopathy: tendinitis/bursitis (n = 17), partial tear (n = 16), calcification (n = 7), effusion (n = 9), and full-thickness tear (n = 1)
Pasin et al.[46]	2019	Turkey	II	30	30	49.4 ± 9.1	47.73 ± 9.552	NA	NA	>3	>3	0, 0.75, 2	Single injection into subacromial space 4 mL of autologous pure PRP APC: NA ALC: NA	Single injection into subacromial space 1 mL of triamcinolone acetonide (40 mg/mL) + 3 mL of lidocaine (2%)	Stage 2 SIS patients with diagnosis based on clinical and MRI evidence who presented with symptoms of shoulder pain for ≥3 mo without major trauma

(continued)

Table 1. Continued

Authors	Year	Country	LOE	Sample Size, n		Age, Mean ± SD, yr		Sex: M/F, n		Symptom Duration, Mean ± SD, mo		Follow-up, mo	Details of Injection Procedure		Details of Rotator Cuff Disease
				PRP	CS	PRP	CS	PRP	CS	PRP	CS		PRP	CS	
Sari and Eroglu[48]	2020	Turkey	II	33	33	NA	NA	NA	NA	>3	>3	0, 3, 12, 24	Single US-guided injection into subacromial space 5 mL of autologous pure PRP APC: 5× platelet count of whole blood ALC: NA	Single US-guided injection into subacromial space 2 mL of triamcinolone acetonide (40 mg) + 2 mL of lidocaine (1%) + 1 mL of saline solution	Patients aged 18-75 yr who had experienced shoulder pain for ≥3 mo with rotator cuff pathology (bursitis, tendinosis, or grade I partial tear) confirmed by physical examination and MRI findings
Sabaah and Nassif,[52]	2020	Egypt	I	20	20	41.85 ± 10.21	41.85 ± 10.21	6/14	6/14	>3	>3	0, 3	2 US-guided injections, 2 wk apart, into subacromial space 5 mL of autologous pure PRP APC: 6.7× platelet count of whole blood ALC: NA	2 US-guided injections, 2 wk apart, into subacromial space 3 mL of beta-methasone + 2 mL of lidocaine	Patients in whom unilateral rotator cuff tendinopathy was diagnosed clinically with symptoms for ≥3 mo after failed conservative treatment in form of physical modalities and therapeutic exercises for ≥4 wk
Jo et al.[47]	2020	Republic of Korea	I	30	30	55.3 ± 10.3	52.5 ± 11.2	11/19	9/21	11.6 ±11.4	13.1 ±15.6	0, 1 ,3, 6	Single US-guided injection into subacromial space 4 mL of allogeneic pure PRP APC: 988.67 × 10^9/L ALC: 0.01 × 10^9/L	Single US-guided injection into subacromial space 1 mL of triamcinolone acetonide (40 mg/mL) + 3 mL of lidocaine (2%)	Adult patients who had unilateral shoulder pain for ≥3 mo Participants had to present with either Neer or Hawkins impingement sign Participants were required to have either painful arc or positive result on Jobe test

(continued)

Table 1. Continued

Authors	Year	Country	LOE	Sample Size, n		Age, Mean ± SD, yr		Sex: M/F, n		Symptom Duration, Mean ± SD, mo		Follow-up, mo	Details of Injection Procedure		Details of Rotator Cuff Disease
				PRP	CS	PRP	CS	PRP	CS	PRP	CS		PRP	CS	
Dadgostar et al.[49]	2021	Iran	I	30	28	57.33 ± 9.80	53.60 ± 7.24	5/25	6/22	>3	>3	0, 0.25, 1, 3	Single US-guided injection into affected tendon and subacromial space 6 mL of autologous pure PRP APC: NA ALC: NA	Single US-guided injection into subacromial space 1 mL of Depo-Medrol (Pfizer; 40 mg) + 1 mL of lidocaine (2%)	Patients aged > 40 yr who had tendinitis or incomplete tear of rotator cuff tendon, which was confirmed with MRI; had pain for >3 mo; and had positive results for 3 of following 5 tests: Neer, Speed, full can, empty can, and Hawkins
Kwong et al.[50]	2021	Canada	I	47	52	49.94 ± 9.70	49.08 ± 9.54	16/31	19/33	>3	>3	0, 1.5, 3, 12	Single US-guided injection into affected tendon and subacromial space 3-5 mL of autologous leukocyte-poor PRP Filtration of red blood cells: 99.7% Filtration of white blood cells: 87%-89% Filtration of mononuclear cells: 70%-75% Filtration of granulocytes: 96.5%	Single US-guided injection into subacromial space 1 mL of triamcinolone (40 mg/mL) + 2 mL of bupivacaine (5 mg/mL)	Adults with MRI- or US-documented tendinopathy or partial-thickness rotator cuff tears: degenerative (n = 73) or traumatic (n = 25) Patients must have been symptomatic for minimum of 3 mo and exhausted adequate course of nonoperative treatment

(continued)

Table 1. Continued

Authors	Year	Country	LOE	Sample Size, n		Age, Mean ± SD, yr		Sex: M/F, n		Symptom Duration, Mean ± SD, mo		Follow-up, mo	Details of Injection Procedure		Details of Rotator Cuff Disease
				PRP	CS	PRP	CS	PRP	CS	PRP	CS		PRP	CS	
Oudelaar et al.[51]	2021	Netherlands	I	41	39	48.8 ± 5.8	48.5 ± 6.3	16/25	16/23	>6	>6	0, 1.5, 3, 6, 12, 24	Single US-guided injection into affected tendon 5.5 mL of autologous leukocyte-rich PRP APC: 1,133 × 10^9/L (enrichment factor, 4.8) ALC: 47 × 10^9/L (enrichment factor, 4.7)	Single US-guided injection into subacromial space 1 mL of triamcinolone acetonide (40 mg/mL) + 4 mL of bupivacaine (2.5 mg/mL)	Patients aged between 18 and 55 yr with clinical signs of calcific tendinitis defined as pain in deltoid region worsening with elevation of arm above shoulder level and/or at night for minimal duration of 6 mo Patients had to experience ≥2 unsuccessful types of nonoperative treatment
Thepsoparn et al.[53]	2021	Thailand	I	15	16	51.3 ± 10.8	52.4 ± 10.5	3/12	3/13	8.3 ± 11.6	13.5 ± 12.5	0, 1, 6	Single US-guided injection into affected tendon 5 mL of autologous leukocyte-poor PRP APC: NA ALC: NA	Single US-guided injection into subacromial space 1 mL of triamcinolone acetonide (40 mg/mL) + 4 mL of lidocaine (1%)	Patients aged between 18 and 80 yr with partial supraspinatus tendon tears confirmed by MRI Tendon tears should have been caused by repetitive trauma or overuse only Patients had to experience nonoperative treatment including physical therapy and oral medication for ≥3 mo

ALC, average leukocyte count; APC, average platelet count; CS, corticosteroid; F, female; LOE, level of evidence; M, male; MRI, magnetic resonance imaging; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; PRP, platelet-rich plasma; SD, standard deviation; SIS, subacromial impingement syndrome; US, ultrasound.

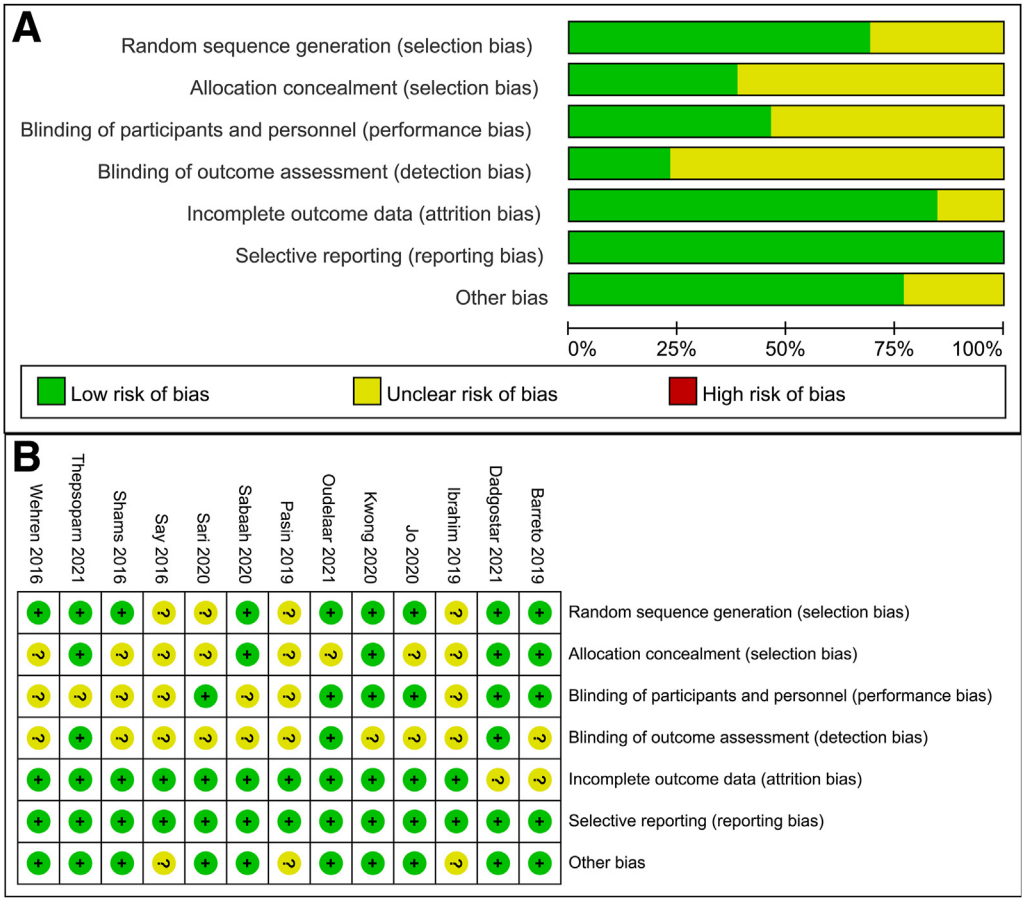

Fig 2. (A) Risk-of-bias summary. (B) Risk of bias of included studies.

described 6 adverse events, of which 5 were frozen shoulders in the PRP group and 1 was chemical bursitis in the CS group ($P = .11$).[51] All patients with frozen shoulders achieved full recovery using pain medication (2 patients), physical therapy (2 patients), and intra-articular CS injection (1 patient). In particular, the development of frozen shoulder after injection did not influence the outcome.

Failures were defined as requests for a subsequent injection or surgical intervention prior to 12 months. Three studies reported failures after injection, indicating that PRP showed significantly lower rates of post-injection failure (odds ratio, 0.49; 95% confidence interval, 0.25-0.96; $I^2 = 0\%$; $P = .04$) than CS.[43,50,51]

Post-injection Magnetic Resonance Imaging and Ultrasound Findings

Two studies used magnetic resonance imaging (MRI) to evaluate the grade of tendinopathy (grade 0, no tendinopathy; grade 1, mild tendinopathy; grade 2, moderate tendinopathy; grade 3, moderate tendinopathy with a partial-thickness tear present; grade 4, severe tendinopathy with or without a partial-thickness tear present; and grade 5, severe tendinopathy with a full-thickness tear present).[42,43] These 2 studies reported that MRI at the 6-month follow-up showed a slight but not statistically significant improvement in tendinopathy grades in both groups. The improvement in tendinopathy grades between the PRP and CS groups was similar.

Five studies reported ultrasound findings for the rotator cuff tendons.[45,49-52] Ibrahim et al.[45] found that PRP produced a significant reduction in the frequency of partial tears ($P = .0005$) and effusion ($P = .01$) whereas CS induced a significant reduction in the frequency of tendinitis ($P = .0008$) at 2 months after injection. In the study by Sabaah and Nassif,[52] a significant improvement in the grade of tendon lesions was observed in the PRP group ($P = .020$) but no improvement occurred in the CS group at the 3-month follow-up ($P = .470$). The study by Dadgostar et al.[49] revealed no differences in supraspinatus thickness at any follow-up time. In the study by Kwong et al.,[50] ultrasound findings revealed progression to a full-thickness rotator cuff tear in 1 patient in the PRP group and 2 patients in the CS group at 3 months after injection ($P > .05$), along with 2 patients in the PRP group and 3 patients in the CS group at 12 months after injection ($P > .05$). Oudelaar et al.[51] revealed a comparable incidence of partial-thickness and interstitial

Table 2. Summary of Changes in Function Scores, VAS Scores, and ROM

	No. of Patients (No. of Studies)	WMD	95% CI	I^2, %	*P* Value	In Favor of PRP or CS
Short-term follow-up						
Function						
CMS	337 (6)	−3.64	−7.74 to 0.45	84	.08	
ASES score	306 (5)	−7.24	−14.27 to −0.22	88	.04	In favor of CS
SST score	147 (3)	−1.58	−1.81 to −1.35	0	<.01	In favor of CS
DASH score	305 (5)	8.18	4.99 to 11.37	59	<.01	In favor of CS
UCLA score	168 (3)	−1.36	−5.20 to 2.48	97	.49	
WORC score	217 (3)	−3.07	−6.68 to 0.54	0	.10	
VAS score	455 (8)	0.39	−0.30 to 1.09	91	.27	
ROM (°)						
Forward flexion	205 (5)	−1.51	−2.70 to −0.32	0	.01	In favor of CS
Abduction	205 (5)	−0.76	−5.32 to 3.80	56	.75	
External rotation	205 (5)	−0.54	−4.65 to 3.56	56	.80	
Internal rotation	205 (5)	−0.21	−0.41 to −0.01	0	.04	In favor of CS
Medium-term follow-up						
Function						
CMS	270 (5)	3.62	−1.82 to 9.05	86	.19	
ASES score	300 (5)	6.33	−1.91 to 14.58	91	.13	
SST score	141 (3)	0.45	−1.24 to 2.14	84	.60	
DASH score	298 (5)	−1.76	−3.10 to −0.41	20	.01	In favor of PRP
WORC score	257 (4)	−0.90	−10.77 to 8.97	81	.86	
VAS score	308 (5)	−0.34	−1.28 to 0.60	90	.47	
ROM (°)						
Forward flexion	169 (3)	2.24	0.60 to 3.88	5	.008	In favor of PRP
Abduction	169 (3)	1.70	−3.66 to 6.77	53	.51	
External rotation	169 (3)	3.51	2.09 to 4.94	40	<.01	In favor of PRP
Internal rotation	169 (3)	−1.35	−4.56 to 1.86	50	.41	
Long-term follow-up						
Function						
CMS	328 (6)	4.84	0.14 to 9.54	80	.04	In favor of PRP
ASES score	240 (4)	3.57	1.78 to 5.36	0	<.01	In favor of PRP
SST score	141 (3)	1.13	0.81 to 1.45	8	<.01	In favor of PRP
DASH score	178 (3)	−3.83	−12.70 to 5.04	96	.40	
UCLA score	102 (2)	0.13	−0.33 to 0.59	44	.59	
VAS score	310 (5)	−0.46	−1.87 to 0.94	98	.52	

ASES, American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; CI, confidence interval; CMS, Constant-Murley score; CS, corticosteroid; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; PRP, platelet-rich plasma; ROM, range of motion; SST, Simple Shoulder Test; UCLA, University of California—Los Angeles shoulder rating scale; VAS, visual analog scale; WMD, weighted mean difference; WORC, Western Ontario Rotator Cuff Index.

rotator cuff tears between groups at the 1-year ($P = .78$) and 2-year ($P = .44$) follow-up assessments.

Sensitivity Analyses

Sensitivity analyses were conducted by removing studies that were significantly different from other studies in clinical or methodologic properties. After sensitivity analyses, the following outcomes changed significantly: short-term changes in the ASES score and SST score; medium-term changes in the CMS, ASES score, SST score, DASH score, and WORC score; long-term changes in the ASES score, SST score, and DASH score; short-term to long-term changes in the VAS score; short-term changes in forward flexion and internal rotation; and medium-term changes in forward flexion and external rotation (Figs 3-8; Appendix Table 1, available at www.arthroscopyjournal.org). The other outcomes remained steady. After sensitivity analyses, medium-term changes in the ASES score (WMD, 14.50) and VAS score (WMD, −1.84), as well as long-term changes in the VAS score (WMD, −1.87), reached the MCID (Appendix Table 1).

Discussion

The main findings of this meta-analysis were that the differences in function recovery, pain relief, and improvement in ROM when comparing PRP versus CS injections for conservative treatment of rotator cuff disease were not clinically significant (no difference in any outcome between the 2 groups reached the MCID) at any time point during follow-up and PRP injection might be related to a lower rate of requests for a subsequent injection or surgical intervention prior to 12 months. After sensitivity analyses, PRP showed clinically better medium-term changes in the ASES score

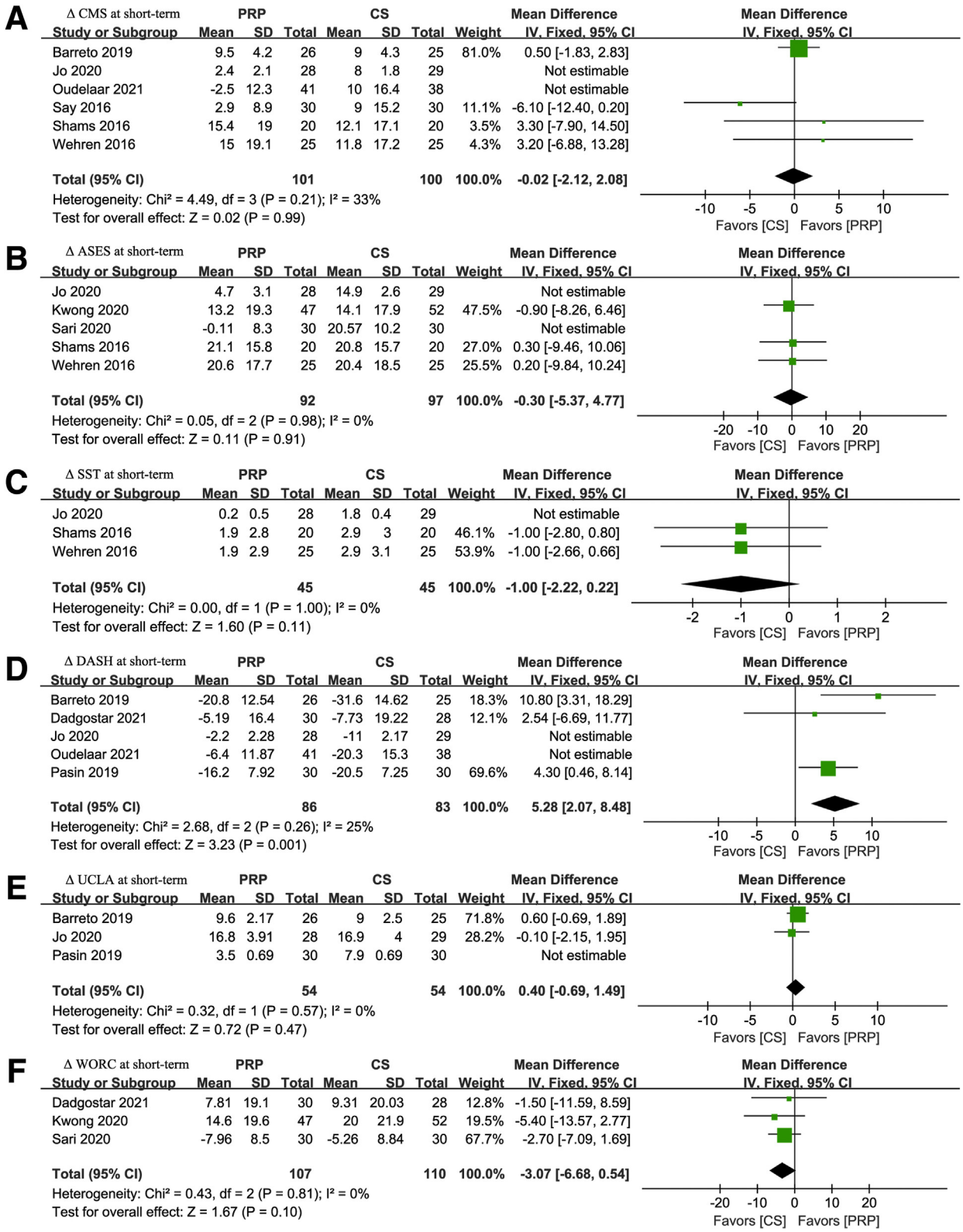

Fig 3. Meta-analysis of change in function scores at short-term follow-up after sensitivity analysis: change in Constant-Murley score (CMS) (A); change in American Shoulder and Elbow Surgeons (ASES) score (B); change in Simple Shoulder Test (SST) score (C); change in Disabilities of the Arm, Shoulder and Hand (DASH) score (D); change in University of California—Los Angeles (UCLA) score (E); and change in Western Ontario Rotator Cuff Index (WORC) score (F). (CI, confidence interval; CS, corticosteroid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation.)

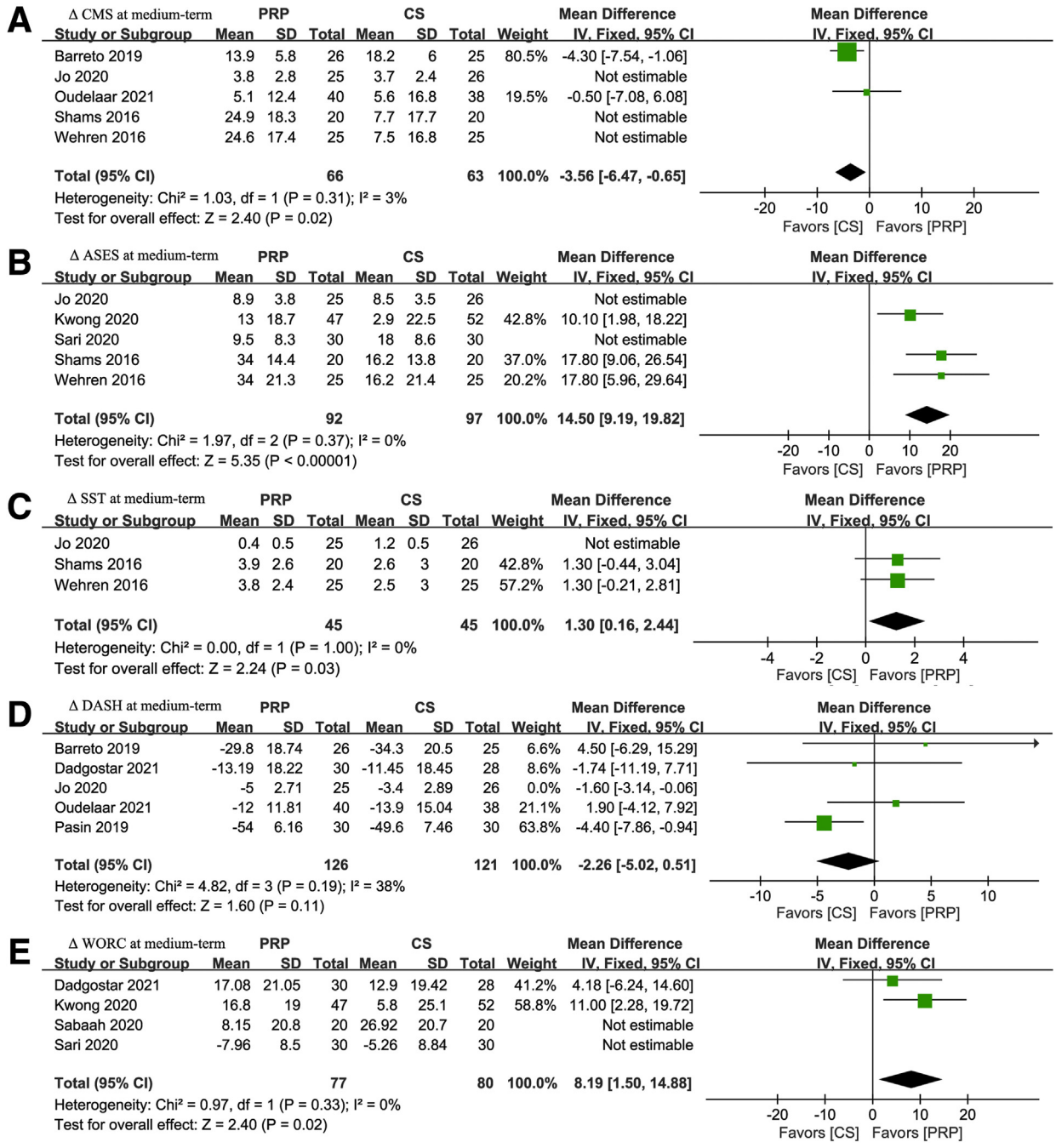

Fig 4. Meta-analysis of change in function scores at medium-term follow-up after sensitivity analysis: change in Constant-Murley score (CMS) (A); change in American Shoulder and Elbow Surgeons (ASES) score (B); change in Simple Shoulder Test (SST) score (C); change in Disabilities of the Arm, Shoulder and Hand (DASH) score (D); and change in Western Ontario Rotator Cuff Index (WORC) score (E). (CI, confidence interval; CS, corticosteroid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation.)

and VAS score and long-term changes in the VAS score that reached the MCID.

Several studies have compared PRP injection with CS injection as treatments for rotator cuff disease. A meta-analysis including 5 articles conducted by Hurley et al.[54] showed that PRP did not result in greater pain reduction or functional recovery than exercise therapy alone. However, the lack of PRP cytology and characteristic descriptions and the high risk of bias in published studies weakened the reliability of this conclusion. A network meta-analysis comparing diverse injections to treat rotator cuff disease included 21 studies and showed that CS helped in the short term (3-6 weeks) but PRP was significantly more beneficial in terms of pain relief and functional recovery in the long term (>24 weeks).[10] Notably, the meta-regression analysis was

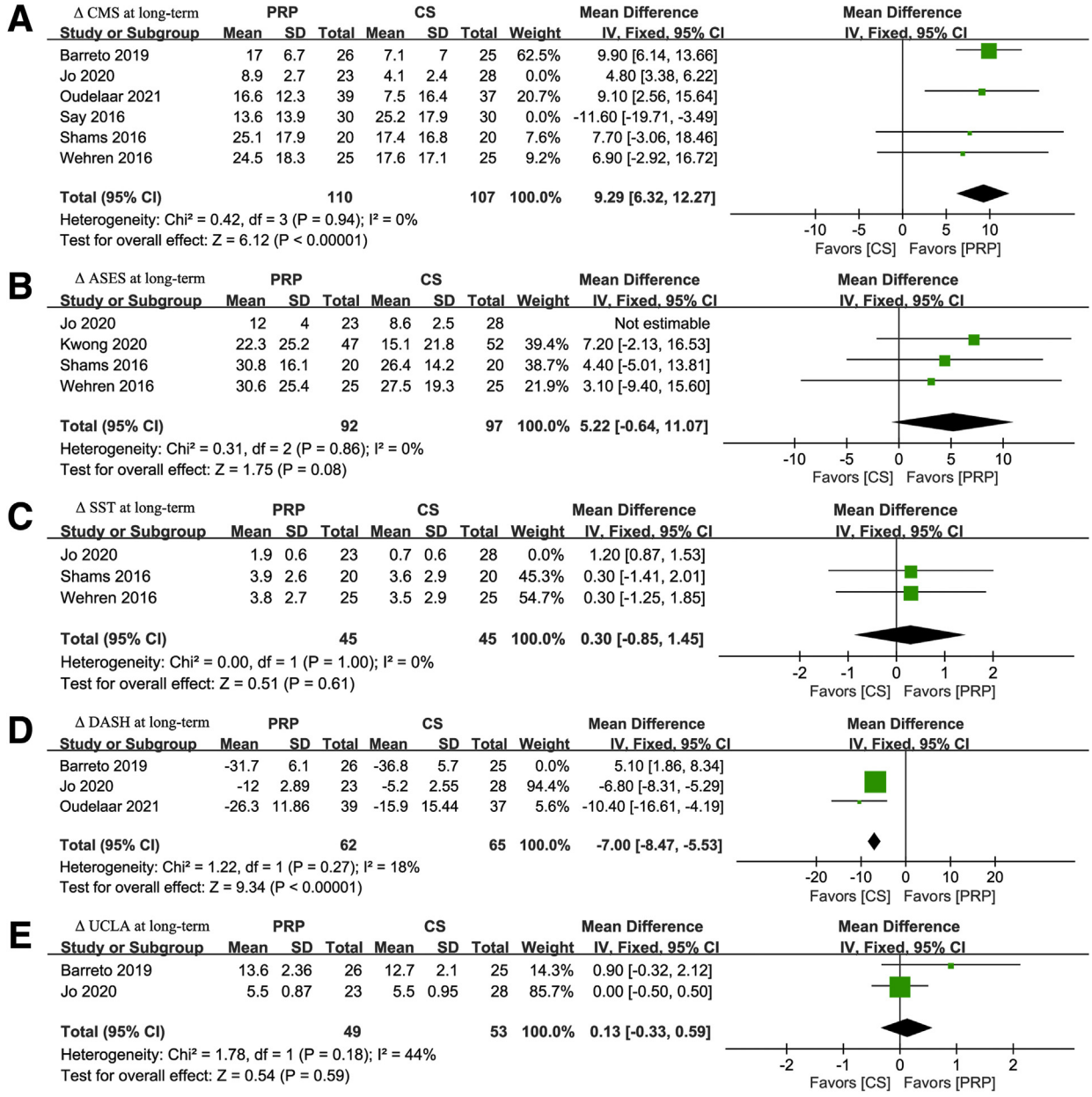

Fig 5. Meta-analysis of change in function scores at long-term follow-up after sensitivity analysis: change in Constant-Murley score (CMS) (A); change in American Shoulder and Elbow Surgeons (ASES) score (B); change in Simple Shoulder Test (SST) score (C); change in Disabilities of the Arm, Shoulder and Hand (DASH) score (D); and change in University of California—Los Angeles (UCLA) score (E). (CI, confidence interval; CS, corticosteroid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation.)

performed across trials and did not have the benefit of randomization. In another systematic review, Giovannetti de Sanctis et al.[22] found that PRP only produced better pain relief in the long term but was more advantageous at inducing functional recovery from the short term to the long term. Because the difference was below the MCID and a high risk of selection bias was present owing to a lack of description of randomization, the conclusions should be interpreted with caution. Wang et al.[23] conducted a meta-analysis of 6 studies. In patients with rotator cuff injury, CS injection resulted in greater functional recovery and pain relief in the short term (3-6 weeks). However, no significant differences in medium-term (8-12 weeks) or long-term (>12 weeks) functional or pain improvement were observed, nor were differences in improved ROM observed during the whole follow-up period (3-24 weeks). These results should be interpreted with caution owing to the limited number of trials and sample size, the relatively low methodologic quality, and lack of reporting of the MCID.

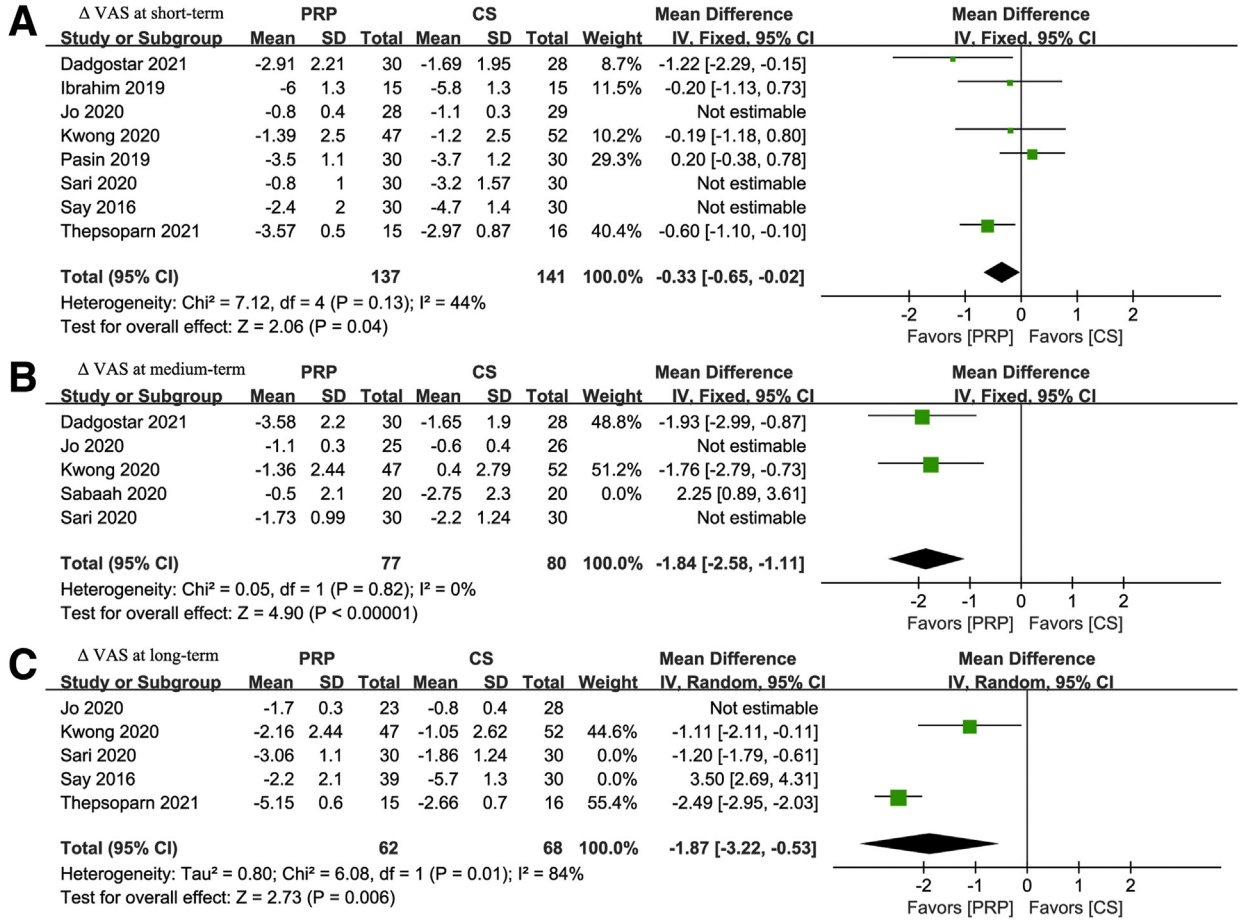

Fig 6. Meta-analysis of change in visual analog scale (VAS) scores after sensitivity analysis at short-term follow-up (A), medium-term follow-up (B), and long-term follow-up (C). (CI, confidence interval; CS, corticosteroid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation.)

The guidelines on rotator cuff disease issued by the American Academy of Orthopaedic Surgeons in the United States in 2020 indicated that a single injection of CS and local anesthesia can reduce pain and improve function in the short term but multiple injections of CS may damage the rotator cuff structure. The guidelines do not advocate the use of PRP as a routine treatment for partial rotator cuff injuries primarily because of insufficient evidence and high-quality RCTs.[55] Many basic scientific studies have found that PRP shortens the tendon repair time and increases cell proliferation, but some clinical studies have reported that PRP may increase the expression of apoptotic cells and potentially adversely affect tendon healing.[56-59] In this meta-analysis, the integrity of the rotator cuff tendons after injection was assessed using MRI in 2 trials[42,43] and using ultrasound examination in 5 other trials.[45,49-52] Ibrahim et al.[45] found that PRP significantly reduced the number of partial tears and cases of effusion whereas CS provided better relief of tendinitis at the 2-month follow-up. However, the findings of this study should be interpreted with caution as ultrasound evaluation of partial tears is subjective and prone to bias. In addition, this study was among the studies rated the poorest in terms of risk of bias. Sabaah and Nassif[52] reported a significant improvement in the grade of tendon lesions in the PRP group but no improvement in the CS group at the 3-month follow-up. According to the limited evidence mentioned earlier, we could not draw a definite conclusion regarding whether PRP injection is superior to CS injection in preserving the integrity of tendons.

Coombes et al.[60] provided strong evidence that CS injection is beneficial in the short term owing to its rapid and potent anti-inflammatory effect, but it was worse than conservative treatment in the medium and long term for the management of tendinopathy. Moreover, possible deleterious effects on rotator cuff tendons have been shown in animal models,[9,61,62] as well as human studies.[63,64] Conversely, PRP injection increases the local concentrations of growth factors and platelets, which release many pro- and anti-inflammatory mediators that activate cascades contributing to anti-inflammatory processes, immunomodulation, and

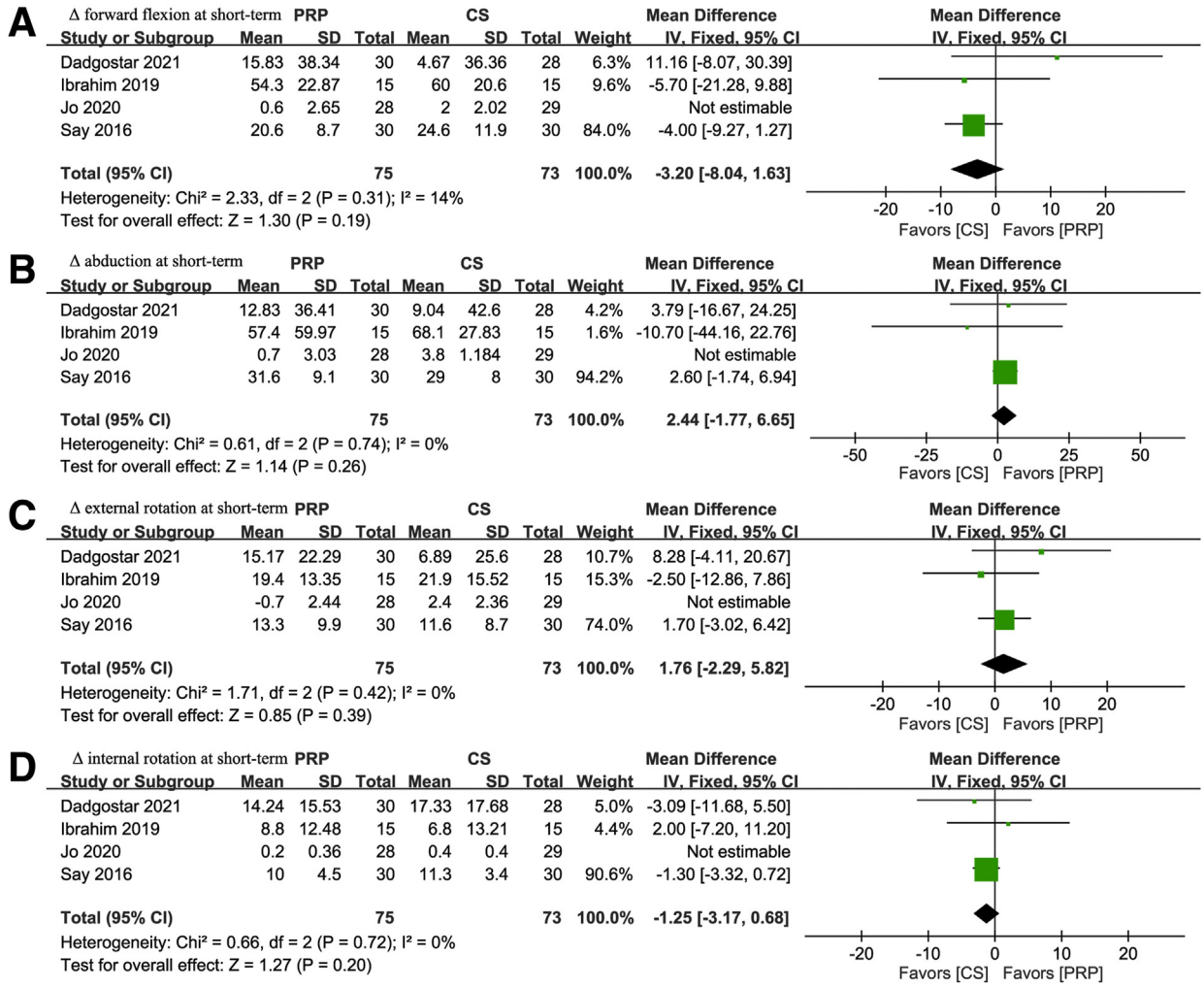

Fig 7. Meta-analysis of change in range of motion (in degrees) at short-term follow-up after sensitivity analysis: change in forward flexion (A), change in abduction (B), change in external rotation (C), and change in internal rotation (D). (CI, confidence interval; CS, corticosteroid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation.)

angiogenesis, which may reduce pain and promote tissue repair.[65] The effects of PRP injection might be slower but steadier than those of CS injection, which is supported by the outcomes of our study.

This research has several strengths. First, strict inclusion and exclusion criteria were applied. Second, a complete assessment of study quality was conducted. Third, with a relatively large sample size (725 patients), this is a comprehensive meta-analysis that analyzed function recovery, pain relief, ROM improvement, complications, failures, and MRI and ultrasound findings.

However, the potential long-term superiority of PRP over CS might be caused by the negative effects of CS. Thus, introducing a placebo control group in further strictly blinded RCTs would be a solution to this problem. To produce more reliable estimates on account of more clinically and methodologically consistent studies, future researchers should give detailed descriptions of the components of PRP injections (concentrations of platelets, leukocytes, and growth factors) and CS injections (type, concentration, and combined local anesthetics), as well as important clinical characteristics such as the age and activity level of the patients, cause and chronicity extent of rotator cuff disease, and method and site of injection.

Limitations

The main limitations of this study are the clinical heterogeneity across the included trials and the quality of the original studies. With 13 RCTs included, this is a meta-analysis of continuous and subjective outcomes, which tends to show high statistical heterogeneity.[66,67] Differences in race, mean age, sex proportion, cause and chronicity extent of rotator cuff disease, and method (blind or ultrasound-guided) and site (affected tendon and/or subacromial space) of injection were inevitable. In addition, the concentrations of platelets,

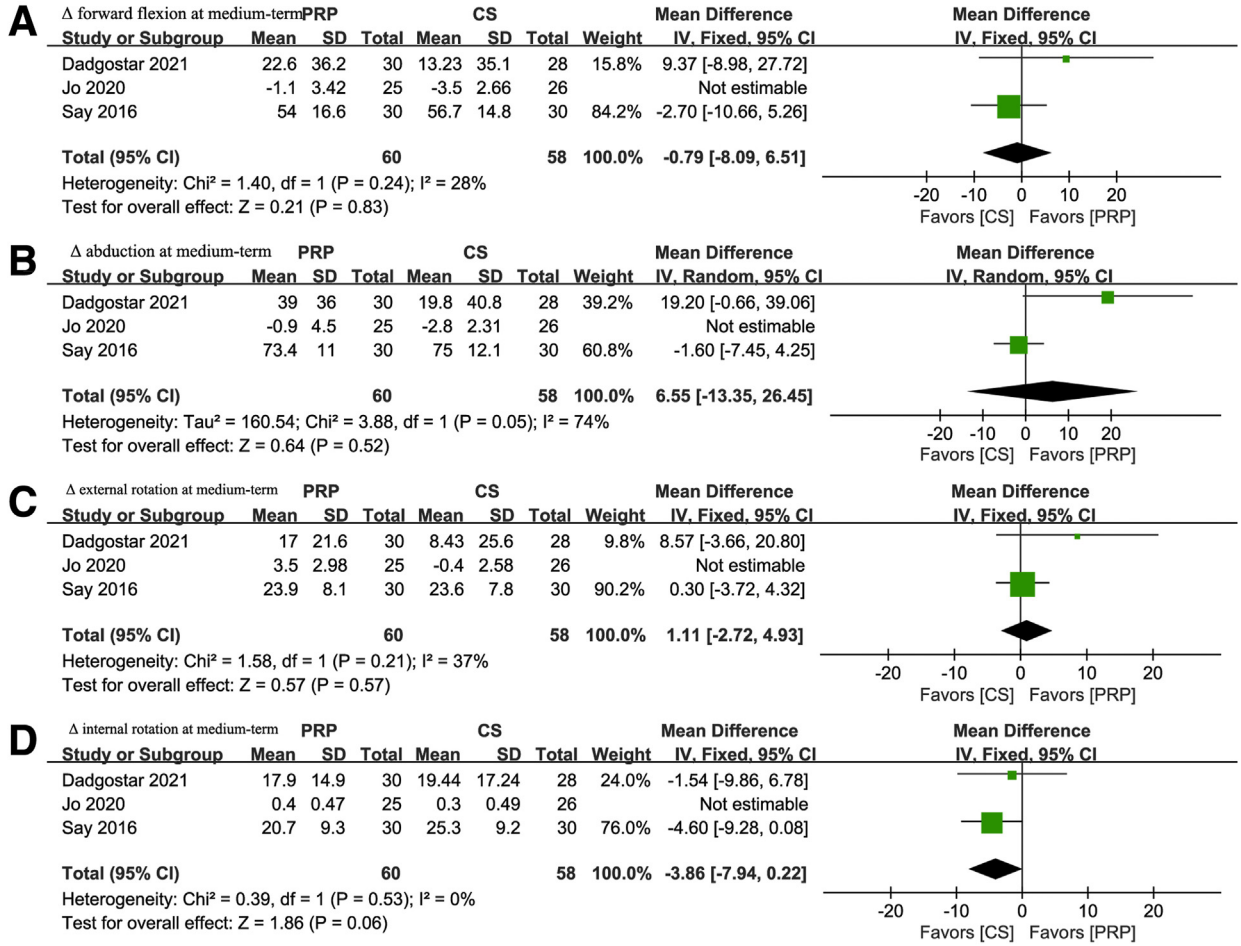

Fig 8. Meta-analysis of change in range of motion (in degrees) at medium-term follow-up after sensitivity analysis: change in forward flexion (A), change in abduction (B), change in external rotation (C), and change in internal rotation (D). (CI, confidence interval; CS, corticosteroid; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation.)

leukocytes (leukocyte-rich or leukocyte-poor PRP), and growth factors, as well as the centrifugation speed and time for the PRP products, were not homogeneous across these trials. Similarly, the CS injections varied regarding type, concentration, and combined local anesthetics. These might be the sources of clinical heterogeneity. Regarding the quality of the original trials, at least half were rated as having an unclear risk in the domains of allocation concealment and blinding, which are critical for highly subjective outcomes such as pain and self-reported function. This might be the source of methodologic heterogeneity. Last, this meta-analysis did not include non—English-language studies, which might provide more evidence to compare PRP and CS injections for conservative treatment of rotator cuff disease.

Conclusions

Without the drawbacks of CS injection, PRP injection is not worse than CS injection in terms of pain relief and function recovery at any time point during follow-up. PRP injection may reduce rates of subsequent injection or surgery, and it might provide better improvements in pain and function in the medium to long term. PRP injection can be a viable alternative to CS injection for conservative treatment of rotator cuff disease.

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Appendix Table 1. Summary of Changes in Function Scores, VAS Scores, and ROM After Sensitivity Analyses

	No. of Patients (No. of Studies)	WMD	95% CI	I^2, %	*P* Value	In Favor of PRP or CS
Short-term follow-up						
Function						
CMS	201 (4)	−0.02	−2.12 to 2.08	33	.99	
ASES score	189 (3)	−0.30	−5.37 to 4.77	0	.91	
SST score	90 (2)	−1.00	−2.22 to 0.22	0	.11	
DASH score	178 (3)	5.28	2.07 to 8.48	25	.001	In favor of CS
UCLA score	108 (2)	0.40	−0.69 to 1.49	0	.47	
WORC score	217 (3)	−3.07	−6.68 to 0.54	0	.10	
VAS score	278 (5)	−0.33	−0.65 to −0.02	44	.04	In favor of PRP
ROM (°)						
Forward flexion	148 (3)	−3.20	−8.04 to 1.63	14	.19	
Abduction	148 (3)	2.44	−1.77 to 6.65	0	.26	
External rotation	148 (3)	1.76	−2.29 to 5.82	0	.39	
Internal rotation	148 (3)	−1.25	−3.17 to 0.68	0	.20	
Medium-term follow-up						
Function						
CMS	129 (2)	−3.56	−6.47 to −0.65	3	.02	In favor of CS
ASES score	189 (3)	14.50	9.19 to 19.82	0	<.01	In favor of PRP
SST score	90 (2)	−1.00	−2.22 to 0.22	0	.03	In favor of PRP
DASH score	247 (4)	−2.26	−5.02 to 0.51	38	.11	
WORC score	157 (2)	8.19	1.50 to 14.88	0	.02	In favor of PRP
VAS score	157 (2)	−1.84	−2.58 to −1.11	0	<.01	In favor of PRP
ROM (°)						
Forward flexion	118 (2)	−0.79	−8.09 to 6.51	28	.83	
Abduction	118 (2)	6.55	−13.35 to 26.45	74	.52	
External rotation	118 (2)	1.11	−2.72 to 4.93	37	.57	
Internal rotation	118 (2)	−3.86	−7.94 to 0.22	0	.06	
Long-term follow-up						
Function						
CMS	217 (4)	9.29	6.32 to 12.27	0	<.01	In favor of PRP
ASES score	189 (3)	5.22	−0.64 to 11.07	0	.08	
SST score	90 (2)	0.30	−0.85 to 1.45	0	.61	
DASH score	127 (2)	−7.00	−8.47 to −5.53	18	<.01	In favor of PRP
UCLA score	102 (2)	0.13	−0.33 to 0.59	44	.59	
VAS score	130 (2)	−1.87	−3.22 to −0.53	84	.006	In favor of PRP

ASES, American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form; CI, confidence interval; CMS, Constant-Murley score; CS, corticosteroid; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; PRP, platelet-rich plasma; ROM, range of motion; SST, Simple Shoulder Test; UCLA, University of California—Los Angeles shoulder rating scale; VAS, visual analog scale; WMD, weighted mean difference; WORC, Western Ontario Rotator Cuff Index.