

Application of Platelet-Rich Plasma in Arthroscopic Rotator Cuff Repair

A Systematic Review and Meta-analysis

Wennan Xu,* PhD, and Qingyun Xue,*[†] PhD

Investigation performed at the Orthopaedics Department, Beijing Hospital, Beijing, PR China

Background: It is unclear how and which factors affect the clinical efficacy of platelet-rich plasma (PRP) applied during arthroscopic rotator cuff repair.

Purpose: To evaluate the clinical efficacy of PRP for arthroscopic repair of full-thickness rotator cuff tear and investigate the factors that affect its clinical efficacy.

Study Design: Systematic review; Level of evidence, 1.

Methods: We searched Cochrane Library, EMBASE, MEDLINE, and OVID to identify randomized controlled trials (RCTs) of patients who received PRP treatment and arthroscopic rotator cuff repair (PRP group) versus controls (no-PRP group). The primary outcomes included retear rate, Constant-Murley score, University of California Los Angeles (UCLA) score, short-term American Shoulder and Elbow Surgeons (ASES) score, visual analog scale (VAS) score for pain, and adverse events.

Results: A total of 14 RCTs were included in this systematic review. Significant improvement in Constant-Murley, UCLA, and VAS pain scores were found in the PRP group during short-term, midterm, and long-term follow-up. The PRP group had a significantly decreased retear rate (risk ratio [RR], 0.57 [95% CI, 0.42 to 0.78]; $P = .0003$), especially for long-term follow-up (RR, 0.38 [95% CI, 0.17 to 0.83]; $P = .02$), large to massive tears (RR, 0.58 [95% CI, 0.42 to 0.80]; $P = .0008$), use of leukocyte-poor PRP (RR, 0.50 [95% CI, 0.33 to 0.76]; $P = .001$), and intraoperative application of PRP (RR, 0.57 [95% CI, 0.42 to 0.79]; $P = .0007$). No significant difference between the 2 groups was found in the incidence of adverse events (RR, 1.34 [95% CI, 0.83 to 2.15]; $P = .23$) or in ASES scores at short-term follow-up (weighted mean difference, 1.04 [95% CI, -3.10 to 5.19]; $P = .62$).

Conclusion: The results of this review indicated that arthroscopic rotator cuff repair with PRP significantly reduced the long-term retear rate and shoulder pain and provided improved long-term shoulder function in patients. Intraoperative application of PRP, use of leukocyte-poor plasma, and large to massive tear size contributed to a significantly decreased retear rate for rotator cuff repair combined with PRP.

Keywords: rotator cuff; arthroscopic; platelet-rich plasma; retear rate

[†]Address correspondence to Qingyun Xue, PhD, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, No. 1 DaHua Road, Dong Dan, Beijing 100730, P.R. China (email: xqybjhsp@163.com).

*Orthopaedics Department, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, PR China.

Final revision submitted January 6, 2021; accepted February 3, 2021.

The authors declared that there are no conflicts of interest in the authorship and publication of this contribution. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

The Orthopaedic Journal of Sports Medicine, 9(7), 23259671211016847

DOI: 10.1177/23259671211016847

© The Author(s) 2021

Rotator cuff injury is one of the most common causes of shoulder pain, with a prevalence of 2.5% to 62%; the prevalence increases with older age.^{16,32,37} Although arthroscopic rotator cuff repair can improve postoperative function and pain, the postoperative retear rate varies between 5% and 51%, with a higher retear rate in older patients.^{6,10,26} Therefore, more studies are being performed on biological therapies to assist the healing of rotator cuff tendon, such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF).^{4,13,14,17,22,29,30}

PRP is an autologous plasma produced using centrifugation and separation of whole blood, which is enriched with a higher platelet concentration than normal blood.³⁶ Dohan Ehrenfest et al⁷ classified different platelet concentrates into 4 categories according to the content of fibrin and leukocyte: pure platelet-rich plasma, leukocyte- and platelet-

This open-access article is published and distributed under the Creative Commons Attribution - NonCommercial - No Derivatives License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits the noncommercial use, distribution, and reproduction of the article in any medium, provided the original author and source are credited. You may not alter, transform, or build upon this article without the permission of the Author(s). For article reuse guidelines, please visit SAGE's website at <http://www.sagepub.com/journals-permissions>.

rich plasma, pure PRF, and leukocyte and PRF. Each technique for deriving platelet concentrates results in different biological characteristics, clinical efficacy, and applications.

Numerous studies have been published on the clinical efficacy of PRP in patients who received arthroscopic rotator cuff repair,^{1,3,9,30} but the conclusions have been inconsistent. Some studies found that PRP reduced the retear rate and improved shoulder function,^{5,18} whereas other studies came to a different conclusion.^{1,9} Controversies exist regarding the application time of PRP.^{8,30,34} In addition, differences in the number of participants, the methods used, and factors such as tear size, type of injured rotator cuff, time of PRP application, PRP type, and type of surgical procedure might affect the final conclusions.^{8,12,19,22} Sufficient knowledge is lacking about the role of these factors in patients who receive arthroscopic rotator cuff repair combined with PRP. In addition, research about the cost-effectiveness of PRP in the arthroscopic surgery of rotator cuff tear is limited.^{28,33}

To evaluate the efficacy of PRP and investigate the role of related factors, we performed a systematic review and meta-analysis. We hypothesized that arthroscopic rotator cuff repair combined with PRP would reduce the postoperative retear rate but would not improve postoperative shoulder function.

METHODS

Search Strategy

The study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²³ Electronic databases including Cochrane Library, EMBASE, MEDLINE, and OVID were searched between inception and June 20, 2020, for randomized controlled clinical trials (RCTs) on patients treated using arthroscopic rotator cuff repair combined with PRP; there were no language restrictions. We used the following search string: ((((((random*[Title/Abstract] OR prospect*[Title/Abstract] OR RCT*[Title/Abstract]))) OR "Random Allocation"[Medical Subject Headings (MeSH)])) AND (((PRP[Title/Abstract] OR "Platelet-Rich Plasma"[MeSH]) OR "platelet - rich plasma"[Title/Abstract]))) AND (((("Rotator Cuff Injuries"[MeSH] OR "Rotator Cuff Tear Arthropathy"[MeSH]) OR (((("Rotator Cuff"[MeSH] OR "Rotator Cuff Injuries"[MeSH] OR "Shoulder Impingement Syndrome"[MeSH]) OR subscapularis[Title/Abstract]) OR infraspinatus[Title/Abstract]) OR supraspinatus[Title/Abstract]) OR "rotator cuff"[Title/Abstract]))) to identify the relevant RCTs.

Eligibility Criteria

Articles were assessed by both authors (W.X. and Q.X.) independently using predesigned eligibility criteria, and any disagreements between researchers were settled via consensus. We also evaluated the reference lists of related comparative studies and reviews for additional relevant studies.

Studies were selected based on the following inclusion criteria: (1) participants: patients with arthroscopic rotator cuff repair; (2) intervention: PRP; (3) comparison: placebo group (saline solution); (4) outcome measures: reported at least 1 of the following outcomes: retear rate, Constant-Murley score, University of California Los Angeles (UCLA) score, American Shoulder and Elbow Surgeons (ASES) score, visual analog scale (VAS) score for pain, and adverse events; and (5) study design: RCT. Exclusion criteria were studies in which (1) PRF matrix or platelet-leukocyte membrane was involved, (2) none of the above major outcomes were reported, and (3) no detailed data were provided and (4) related studies including the same patients.

Data Extraction

Data that contained related information and major outcomes were independently extracted from the included studies by both authors. The recorded data included patient sex, tear size (small to massive), number of injured tendons, follow-up time (short term vs midterm vs long term), leukocyte concentration of PRP (leukocyte poor vs leukocyte rich), PRP volume, PRP type (gel vs liquid), time of PRP application (intraoperative vs postoperative), injection site, type of surgical procedure (single row vs double row), and postoperative rehabilitation. We considered retear rate to be the primary outcome measure, with patient-reported outcomes (Constant-Murley, UCLA, ASES, and VAS pain scores) and adverse events as secondary outcome measures.

Considering that most of the studies provided multiple results at different follow-up points, we pooled the outcomes that were reported in ≥ 4 studies at 3 months, 6 months, 12 months, and 24 months. In addition, we categorized follow-up time as short term (up to 6 months), midterm (≥ 12 months), and long term (≥ 24 months). Sugaya grades 4 and 5 were considered retear events.³¹ Adverse events included complications such as infection, excessive pain, local swelling, postoperative shoulder stiffness, and neurologic or vascular deficit.

Quality Assessment of Methodology

The methodological quality assessment for the included studies was based on the Cochrane risk-of-bias criteria. The 7 items used to evaluate bias in each trial included randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias; items were graded as *low risk*, *high risk*, or *unclear risk*. The included studies were independently assessed by both researchers, and any controversy was resolved by final consensus.

Statistical Analysis

Data from the included studies were analyzed using Stata 15 software. Dichotomous variables (retear rate and adverse events) were expressed using risk ratio (RR) and 95% confidence interval (CI), whereas weighted mean difference (WMD) was calculated for continuous data

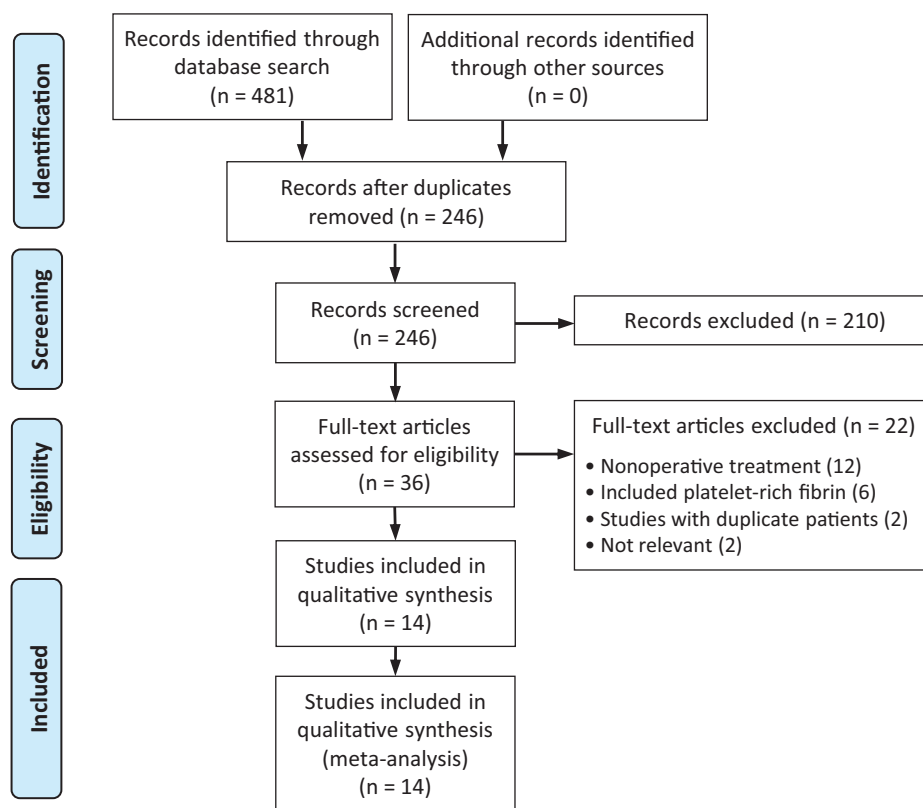


Figure 1. PRISMA (Preferred Reporting Items for Systematic Meta-Analyses) flow diagram of study selection.

(Constant-Murley, UCLA, and VAS pain scores). The Q and I^2 tests were used to estimate the heterogeneity among studies. The I^2 test was used to assess heterogeneity based on the thresholds reported in the Cochrane Handbook for Systematic Reviews of Interventions¹⁵: 0%-40%, not significant, 30%-60%, moderate heterogeneity; 50%-90%, substantial heterogeneity; and 75%-100%, considerable heterogeneity. When $I^2 < 50%$ or $P > .1$, a fixed-effects model was applied for the meta-analysis; otherwise, a random-effects model was used.

Subgroup analysis of retear rate was conducted according to the following factors: follow-up time (short term vs midterm vs long term), tear size (small to medium vs large to massive), number of injured tendons (1 or 2 [supraspinatus and/or infraspinatus] vs 3 [supraspinatus, infraspinatus, and subscapularis]), leukocyte concentration of PRP (leukocyte poor vs leukocyte rich), PRP type (gel vs liquid), surgical procedure (single row vs double row), and time of PRP application (intraoperative vs postoperative). For all outcome measures, forest plots were used to present the results of the individual studies and the pooled estimates of effect size.

RESULTS

Study Selection

A total of 481 potentially relevant citations were extracted from the 4 electronic databases. After removing duplicates

and reading the abstract and title, we screened the full-text of 36 studies for relevance. Of these, 14 RCTs[‡] with 923 patients were considered to meet the eligibility criteria and were included in the systematic review. All studies were published between 2011 and 2020. The process of selecting appropriate studies is shown in Figure 1.

Characteristics of Included Studies

Of the 923 patients with arthroscopic rotator cuff repair included in this systematic review and meta-analysis, 458 patients received PRP treatment (PRP group), and 465 patients did not receive PRP treatment (no-PRP group). All of the included studies reported patient sex, tear size, number of injured tendons, follow-up time, leukocyte concentration, PRP type, time of PRP application, injection site, surgical procedure, postoperative rehabilitation, and at least 1 major outcome. Detailed information of the studies is displayed in Table 1.

In all of the studies, the rotator cuff injuries were full-thickness tears, and the PRP group received saline solution injection as a placebo. The total number of participants ranged from 25 to 120, with 423 male patients and 500 female patients, and the age range was 54 to 63 years. The follow-up time ranged from 6 weeks to 51 months. We found that 9 studies[§] used leukocyte-poor PRP, whereas

[‡]References 5, 8, 9, 11, 12, 18, 19, 21, 24, 25, 27, 30, 34, 39.

[§]References 8, 9, 11, 18, 19, 21, 24, 27, 34.

TABLE 1
Characteristics of the Included Studies^a

Lead Author (Year)	Patients (PRP/no-PRP), n	Tear Size	Involved Tendons	Age, y, mean ± SD	Follow-up Time	LR vs LP PRP	PRP Type	Time of PRP Application	Surgical Procedure	Time Immobilized
Holtby (2016) ¹²	82 (41/41)	Small to medium	Supraspinatus and/or infraspinatus	59.0 ± 8.0	6 mo	LR	Gel	Intraoperative	Single or double row	4 wk
Hak (2015) ¹¹	25 (12/13)	Small to medium	Supraspinatus and/or infraspinatus	55.0 ± 6.4	6 wk	LP	Liquid	Intraoperative and 4 wk postoperative	Single row	NR
Pandey (2016) ²⁴	102 (52/50)	Medium to large	Supraspinatus and/or infraspinatus	54.5 ± 8.4	24 mo	LP	Liquid	Intraoperative	Single row	4 wk
Randelli (2011) ²⁵	53 (26/27)	Small to massive	Supraspinatus, infraspinatus, subscapularis	60.5 ± 9.6	24 mo	LR	Gel	Intraoperative	Single row	4 wk
Snow (2020) ³⁰	87 (40/47)	Small to large	Supraspinatus and/or infraspinatus	61.3	12 mo	LR	Liquid	10-14 d postoperative	Single or double row	6 wk
Ebert (2017) ⁸	55 (27/28)	Small to medium	Supraspinatus	59.6 ± 11.2	36-51 mo	LP	Liquid	7 and 14 d postoperative	Double row	6 wk
Flury (2016) ⁹	120 (60/60)	Small to massive	Supraspinatus, infraspinatus, subscapularis	58.4 ± 8.1	24 mo	LP	Liquid	Intraoperative	Double row	6 wk
Jo (2013) ¹⁸	48 (24/24)	Large to massive	Supraspinatus, infraspinatus, subscapularis	63.1 ± 7.3	16 mo	LP	Gel	Intraoperative	Double row	4-6 wk
Jo (2015) ¹⁹	74 (37/37)	Medium to large	Supraspinatus, infraspinatus, subscapularis	60.5 ± 6.2	12 mo	LP	Gel	Intraoperative	Double row	4 wk
Malavolta (2014) ²¹	54 (27/27)	Small to medium	Supraspinatus	54.7 ± 7.5	24 mo	LP	Liquid	Intraoperative	Single row	6 wk
Wang (2015) ³⁴	60 (30/30)	Medium	Supraspinatus	59.1	16 wk	LP	Liquid	7 and 14 d postoperative	Double row	6 wk
D'Ambrosi (2016) ⁵	40 (20/20)	Medium	Supraspinatus	60.0 ± 9.6	6 mo	LR	Gel	Intraoperative	Single row	4 wk
Ruiz-Moneo (2013) ²⁷	63 (32/31)	Medium to massive	Supraspinatus, infraspinatus, subscapularis	55.5	12 mo	LP	Liquid	Intraoperative	Double row	NR
Zhang (2016) ³⁹	60 (30/30)	Medium to massive	Supraspinatus and/or infraspinatus	57.1 ± 6.7	12 mo	LR	Liquid	Intraoperative	Double row	NR

^aLP, leukocyte poor; LR, leukocyte rich; NR, not reported; PRP, platelet-rich plasma.

5 studies^{5,12,25,30,39} used leukocyte-rich PRP. Liquid PRP was used in 9 studies,¹¹ and 5 studies^{5,12,18,19,25} used gel-type PRP. Except for 3 studies,^{8,30,34} the studies used PRP intraoperatively. Single-row repair and double-row repair were adopted in 5 studies^{5,11,21,24,25} and 7 studies,^{8,9,18,19,27,34,39} respectively.

Studies conducted by Ruiz-Moneo et al²⁷ and Zhang et al³⁹ did not provide detailed information about the volume of PRP. Only 2 studies^{5,24} used ultrasound to determine rotator cuff retear after surgery, whereas the rest used magnetic resonance imaging. A total of 8 studies^{5,9,18,21,24,27,30,34} did not report the number of patients undergoing revision surgery for retears; in the remaining 6 studies,^{8,11,12,19,25,39} the total revision rate was 18.1% (63/349). All but 2 studies^{5,39} reported detailed information regarding the use of subacromial decompression and acromioplasty.

Risk-of-Bias Assessment

Among the 14 included RCTs,[¶] 7 studies^{8,9,12,18,19,30,39} had an unclear risk of bias in random sequence generation, and 2 studies^{8,39} had a high risk of bias in the blinding of participants and personnel. All of the studies had a low risk of bias in allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. The risk-of-bias summary is shown in Figure 2.

Retear Rate

The overall retear rate was 15.7% (11.4% for the PRP group vs 20.0% for the no-PRP group). The retear rate was 5.2% in patients with small to medium tears and 21.6% in those

^{||}References 8, 9, 11, 21, 24, 27, 30, 34, 39.

[¶]References 5, 8, 9, 11, 12, 18, 19, 21, 24, 25, 27, 30, 34, 39.

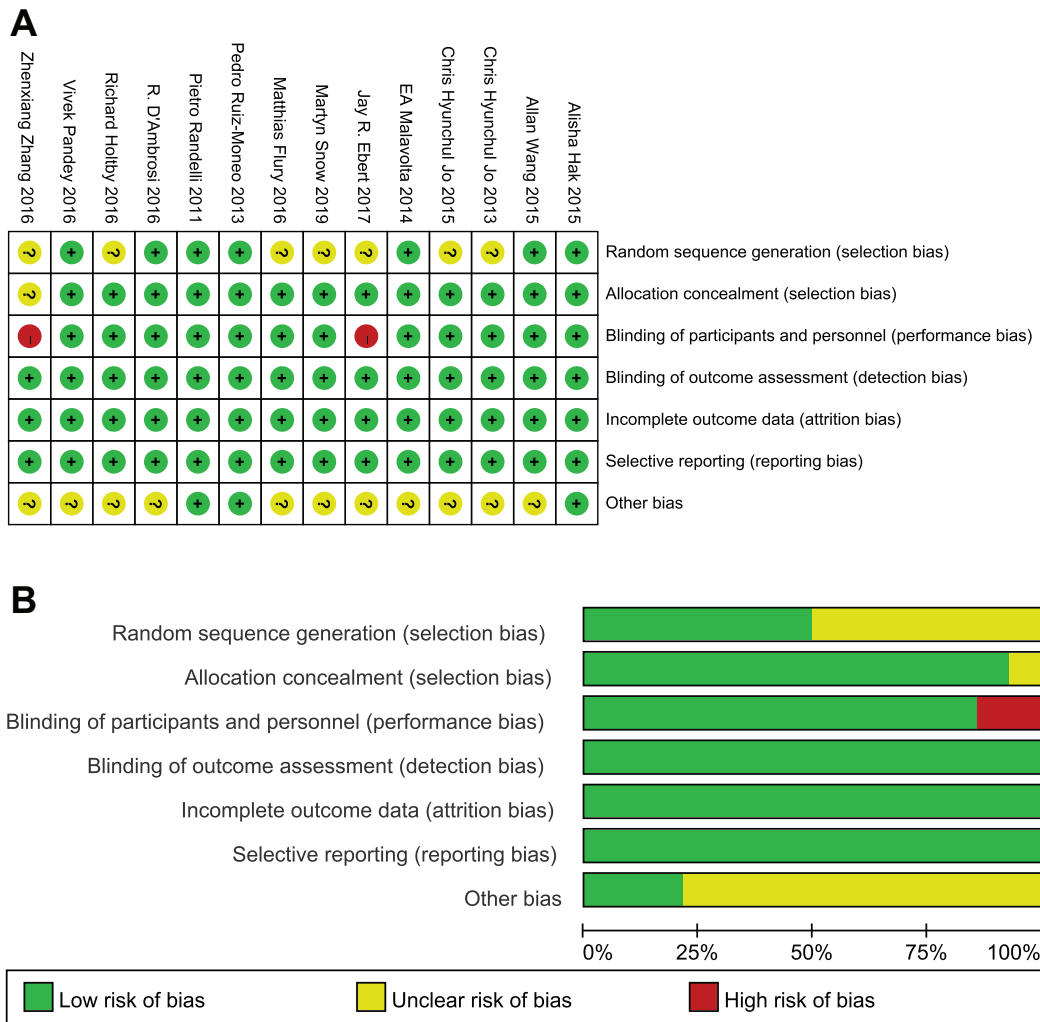


Figure 2. Summary of Cochrane risk-of-bias assessment for (A) individual studies and (B) overall.

with large to massive tears. The retear rate was 12.8% in patients receiving single-row fixation and 17% in patients receiving double-row fixation.

The overall effect of pooled outcomes indicated that patients in the PRP group had a significantly decreased retear rate compared with the no-PRP group (RR, 0.57 [95% CI, 0.42-0.78]; $P = .0003$; $I^2 = 5\%$) (Figure 3). Results of the subgroup analysis of retear rates are shown in Table 2. There were no significant differences between groups in retear rate for short-term follow-up (RR, 0.68 [95% CI, 0.25-1.83]; $P = .44$; $I^2 = 0$), midterm follow-up (RR, 0.76 [95% CI, 0.51-1.12]; $P = .17$; $I^2 = 6\%$), leukocyte-rich PRP (RR, 0.68 [95% CI, 0.44-1.06]; $P = .09$; $I^2 = 0$), small to medium tear size (RR, 0.54 [95% CI, 0.22-1.32]; $P = .18$; $I^2 = 0$), and postoperative use of PRP (RR, 0.57 [95% CI, 0.24-1.37]; $P = .21$; $I^2 = 0$). However, the PRP group had a significantly lower retear rate for long-term follow-up (RR, 0.38 [95% CI, 0.17-0.83]; $P = .02$; $I^2 = 0$), leukocyte-poor PRP (RR, 0.50 [95% CI, 0.33-0.76]; $P = .001$; $I^2 = 34\%$), and intraoperative use of PRP (RR, 0.57 [95% CI, 0.42-0.79]; $P = .0007$; $I^2 =$

25%) compared with the no-PRP group. A total of 8 studies[#] included patients with large or massive tears, and the pooled outcomes showed a significantly decreased retear rate for the PRP group (RR, 0.58 [95% CI, 0.42-0.80]; $P = .0008$; $I^2 = 33\%$), which indicated that PRP might be more suitable for large or massive rotator cuff injuries. PRP type (gel vs liquid; RR, 0.57 [95% CI, 0.42-0.78]; $P = .0003$; $I^2 = 5\%$), surgical procedure (single row vs double row; RR, 0.54 [95% CI, 0.39-0.75]; $P = .0003$; $I^2 = 22\%$), and number of torn tendons (RR, 0.57 [95% CI, 0.42-0.78]; $P = .0003$; $I^2 = 5\%$) did not affect the benefit of PRP in decreasing the retear rate.

Constant-Murley Score

A total of 11 studies^{**} containing 775 patients reported outcomes using the Constant-Murley score. Participants were

[#]References 9, 18, 19, 24, 25, 27, 30, 39.

^{**}References 5, 8, 9, 12, 18, 19, 21, 24, 25, 30, 39.

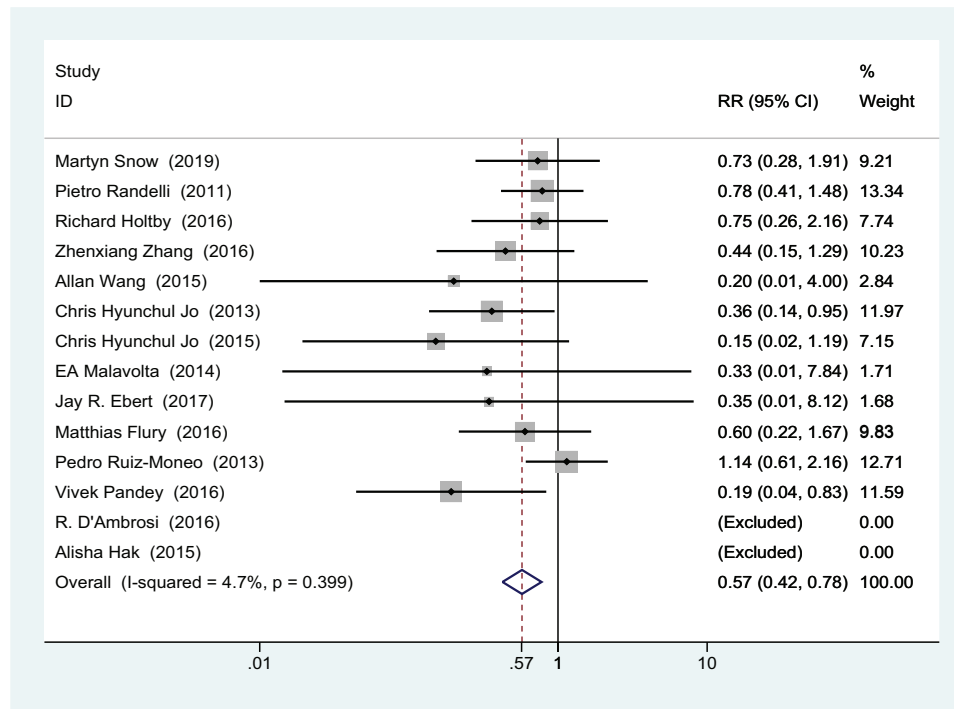


Figure 3. Forest plot of the overall effect of pooled outcomes in the retear rate. RR, risk ratio. ID, identification.

TABLE 2
Subgroup Analysis of Retear Rates^a

Variable	No. of Studies	No. of Patients	Risk Ratio (95% CI)	P Value
Follow-up time				
Short term (≤ 6 mo)	3	168	0.68 (0.25-1.83)	.44
Midterm (≥ 12 mo)	5	302	0.76 (0.51-1.12)	.17
Long term (≥ 24 mo)	3	259	0.38 (0.17-0.83)	.02
Tear size				
Small to medium	6	308	0.54 (0.22-1.32)	.18
Large to massive	8	550	0.58 (0.42-0.80)	.0008
No. of torn tendons				
1 or 2 (supraspinatus and/or infraspinatus)	9	547	0.47 (0.28-0.78)	.004
3 (supraspinatus, infraspinatus, and subscapularis)	5	311	0.66 (0.46-0.96)	.03
Leukocyte concentration of PRP				
Leukocyte poor	9	562	0.50 (0.33-0.76)	.001
Leukocyte rich	5	296	0.68 (0.44-1.06)	.09
PRP type				
Gel	5	260	0.54 (0.34-0.86)	.009
Liquid	9	598	0.60 (0.40-0.89)	.01
Surgical procedure				
Single row	5	266	0.50 (0.28-0.90)	.02
Double row	7	441	0.56 (0.37-0.84)	.005
Time of PRP application				
Intraoperative	10	641	0.57 (0.42-0.79)	.0007
Postoperative	3	192	0.57 (0.24-1.37)	.21

^aBolded P values indicate statistical significance ($P < .05$). PRP, platelet-rich plasma.

assessed at 3, 6, 12, and 24 months of follow-up. The results indicated statistically significant differences at 3 months (WMD, 3.82 [95% CI, 0.96-6.68]; $P = .009$; $I^2 = 23\%$), 6 months (WMD, 2.79 [95% CI, 0.93-4.65]; $P = .03$;

$I^2 = 0$), 12 months (WMD, 3.11 [95% CI, 1.47-4.75]; $P = .0002$; $I^2 = 0$), and 24 months (WMD, 3.10 [95% CI, 1.40-4.79]; $P = .0003$; $I^2 = 47\%$) (Figure 4). Patients in the PRP group had statistically better Constant-Murley scores

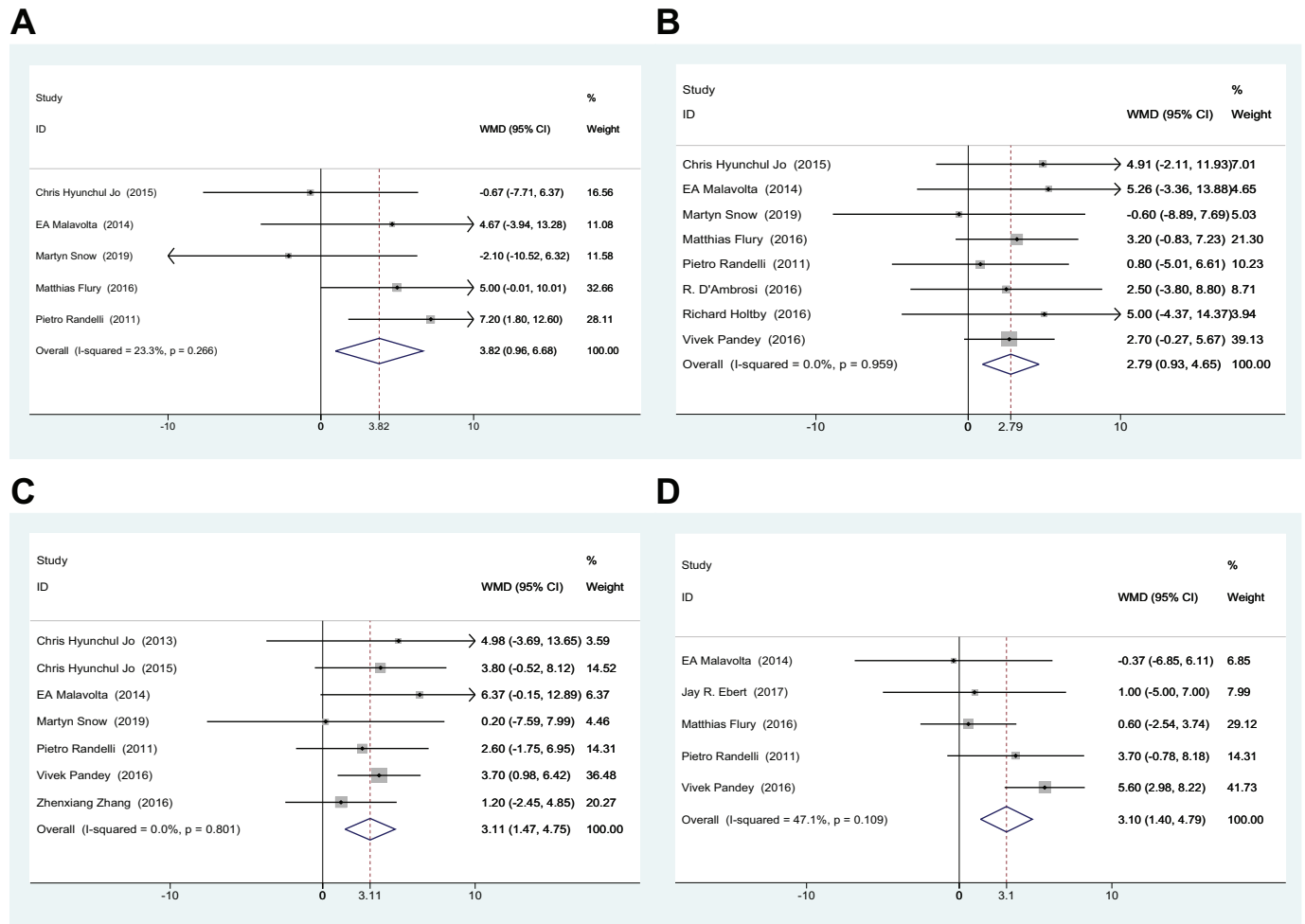


Figure 4. Forest plots of clinical outcomes according to Constant-Murley score at a follow-up of (A) 3 months, (B) 6 months, (C) 12 months, and (D) 24 months. ID, identification; WMD, weighted mean difference.

compared with patients in the no-PRP group in the short term, midterm, and long term.

UCLA Score

Outcomes reported using the UCLA score were offered by 6 studies^{18,19,21,24,25,27} with 394 patients. Participants were assessed at 3, 6, 12, and 24 months postoperatively. The results indicated statistical differences at 3 months (WMD, 2.43 [95% CI, 0.93-3.93]; $P = .002$; $I^2 = 0$), 6 months (WMD, 1.74 [95% CI, 0.86-2.62]; $P = .0001$; $I^2 = 0$), 12 months (WMD, 1.38 [95% CI, 0.62-2.14]; $P = .0004$; $I^2 = 0$), and 24 months (WMD, 1.64 [95% CI, 0.13-3.15]; $P = .03$; $I^2 = 63%$) (Figure 5). Patients in the PRP group had statistically better UCLA scores compared with those in the no-PRP group in the short term, midterm, and long term.

ASES Score

A total of 6 studies^{9,12,18,19,24,30} including 513 patients reported outcomes using the ASES score. We assessed

participants only at 6 months postoperatively. There was no significant difference in short-term follow-up (WMD, 1.04 [95% CI, -3.10 to 5.19]; $P = .62$; $I^2 = 52%$) between the 2 groups (Figure 6). Patients allocated to the PRP group did not have significantly better ASES scores than did those in the no-PRP group at 6-month follow-up.

VAS Pain Score

VAS pain scores were reported in 11 RCTs^{††} with 653 patients, and participants were evaluated at 1, 6, and >12 months postoperatively. Statistically significant differences in scores were found at 1 month (WMD, -0.81 [95% CI, -1.41 to -0.22]; $P = .008$; $I^2 = 88%$), 6 months (WMD, -0.61 [95% CI, -0.84 to -0.38]; $P < .00001$; $I^2 = 0$), and ≥ 12 months (WMD, -0.13 [95% CI, -0.20 to -0.06]; $P = .0006$; $I^2 = 4%$) (Figure 7), indicating that the PRP group had greater improvement in VAS pain scores compared with the no-PRP group up to 12 months postoperatively.

^{††}References 5, 8, 11, 12, 18, 19, 21, 24, 25, 34, 39.

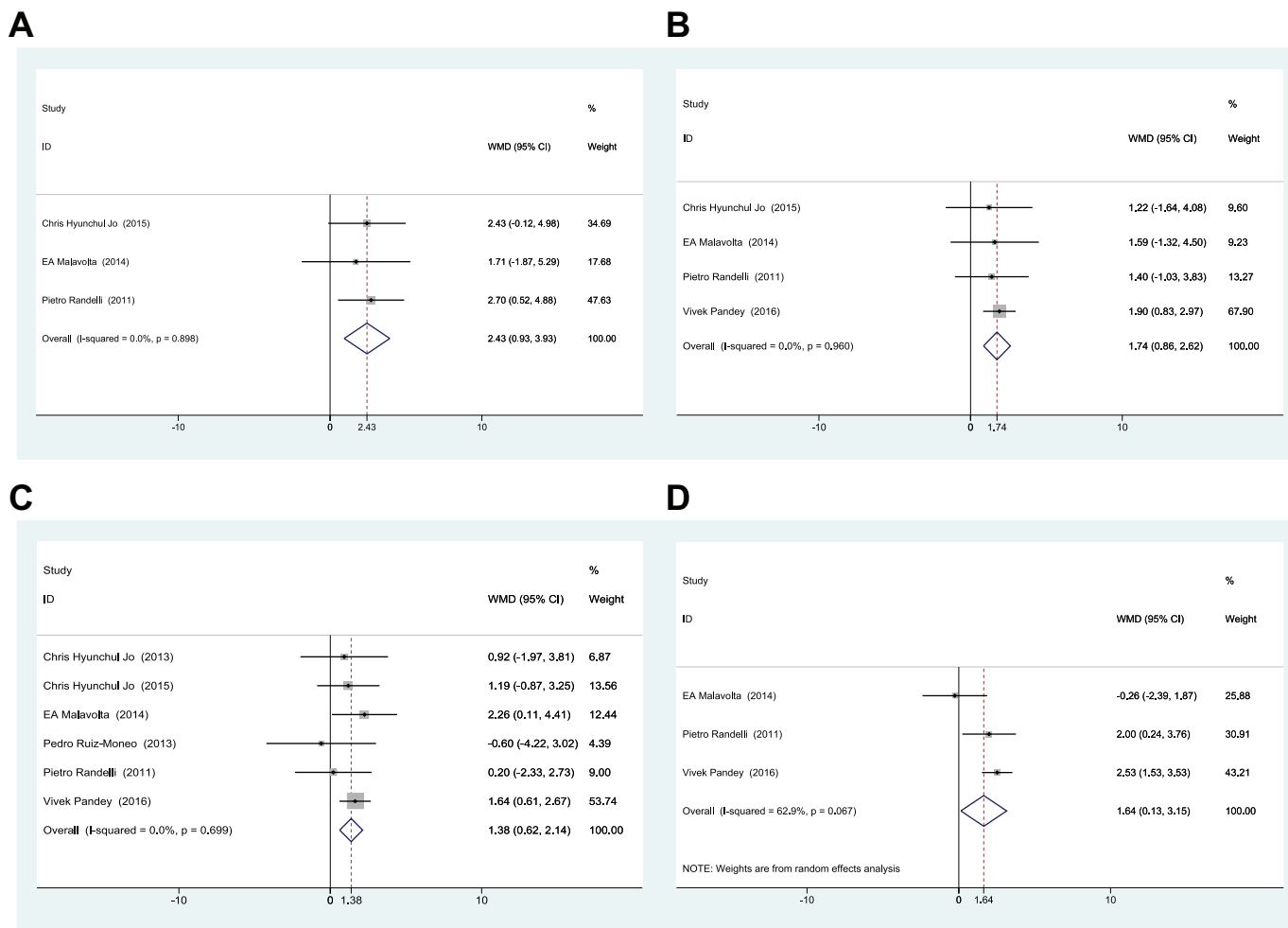


Figure 5. Forest plots of clinical outcomes according to the University of California Los Angeles score at a follow-up of (A) 3 months, (B) 6 months, (C) 12 months, and (D) 24 months. ID, identification; WMD, weighted mean difference.

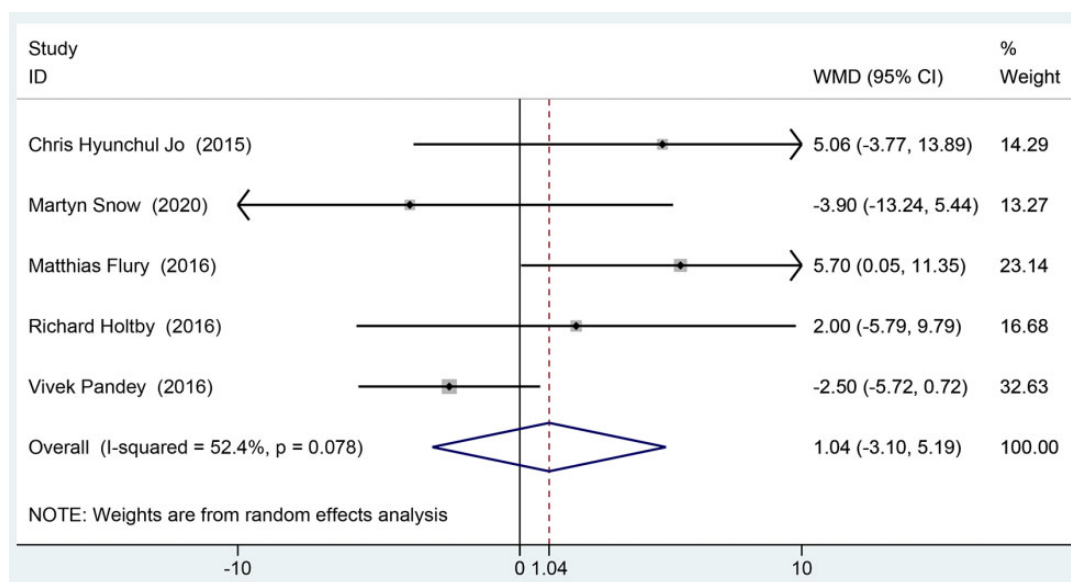


Figure 6. Forest plot of clinical outcomes according to American Shoulder and Elbow Surgeons score at 6-month follow-up. ID, identification; WMD, weighted mean difference.

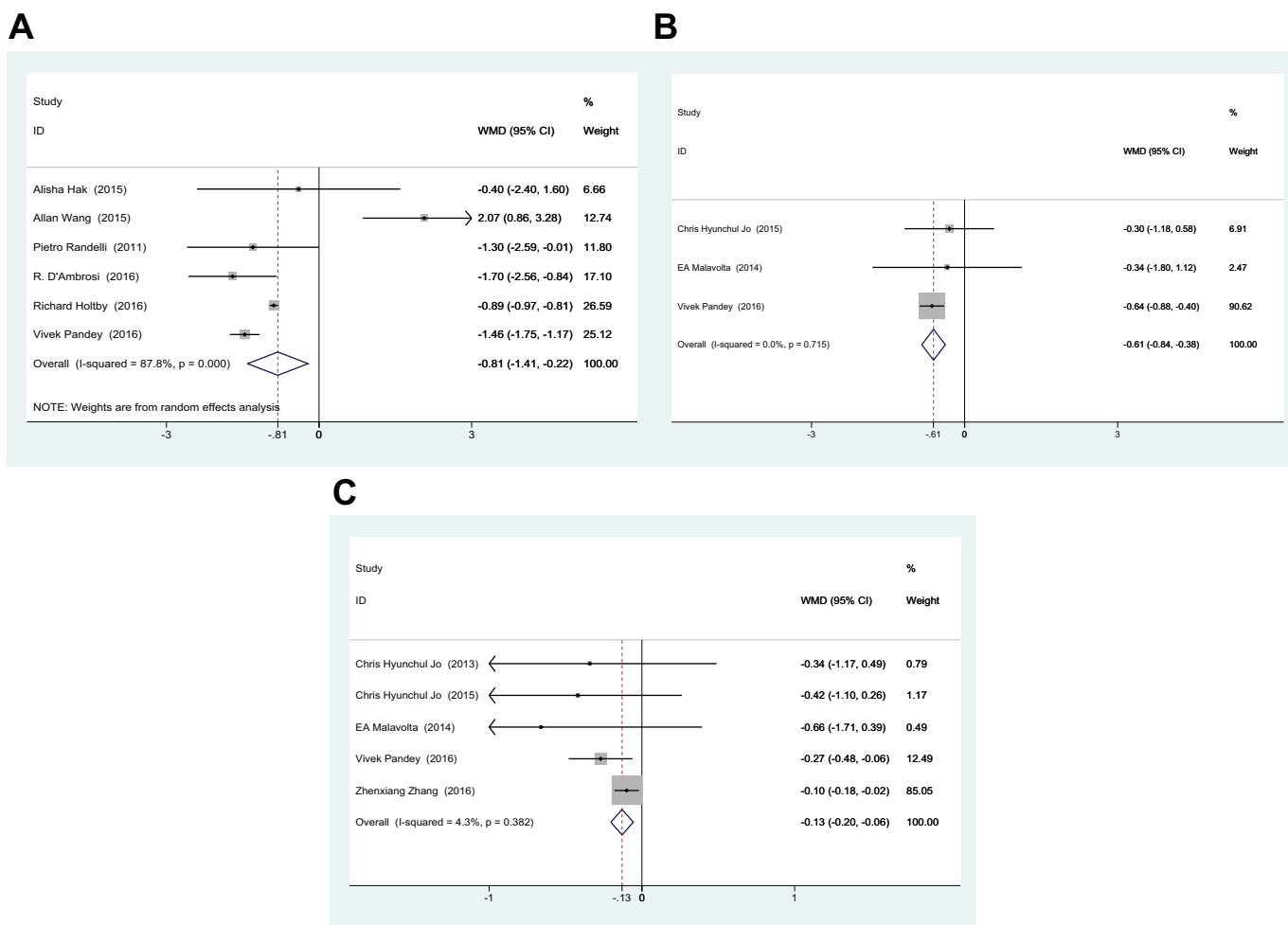


Figure 7. Forest plots of clinical outcomes according to visual analog scale pain scores at a follow-up of (A) 1 month, (B) 6 months, and (C) ≥ 12 months. ID, identification; WMD, weighted mean difference.

Adverse Events

Considering that 10 studies^{‡‡} with 659 patients reported adverse events, we performed a meta-analysis for adverse events using a fixed-effects model. We found no significant difference between the 2 groups in adverse events at the final follow-up (RR, 1.34 [95% CI, 0.83-2.15]; $P = .23$; $I^2 = 0$) (Figure 8). Patients in the PRP group had an increased incidence of adverse events compared with those in the no-PRP group.

DISCUSSION

In this study we evaluated the actual effect of PRP in patients who received arthroscopic rotator cuff repair, and we investigated the related factors that affected the utility of PRP in reducing the retear rate. Patients who underwent arthroscopic rotator cuff repair and received an intraoperative augmentation of PRP had significantly superior retear

rates and Constant-Murley, UCLA, and VAS pain scores without increased adverse events. Although some factors affected the efficacy of PRP in reducing the retear rate, significantly decreased retear rates were found in long-term follow-up, intraoperative use of PRP, application of leukocyte-poor PRP, and large to massive tear size. In addition, the PRP type (gel vs liquid), the surgical procedure (single row vs double row), and the number of torn tendons did not affect the efficacy of PRP in decreasing the retear rate. However, small to medium tear size, postoperative application of PRP, and application of leukocyte-rich plasma were not associated with decreased retear rate. Thus, this research did not support the adjuvant application of PRP in these 3 conditions during arthroscopic rotator cuff repair.

Chen et al³ found that PRP decreased long-term retear rate with a minimal clinically importance difference. They defined *long-term* as follow-up >12 months, which was equal to our midterm condition. However, their systematic review included patients who underwent arthroscopic rotator cuff repair and nonoperative treatment without subgroup analysis. Meanwhile, some studies about PRF were incorrectly taken for PRP studies and were included in

^{‡‡}References 5, 9, 11, 12, 21, 24, 25, 27, 34, 39.

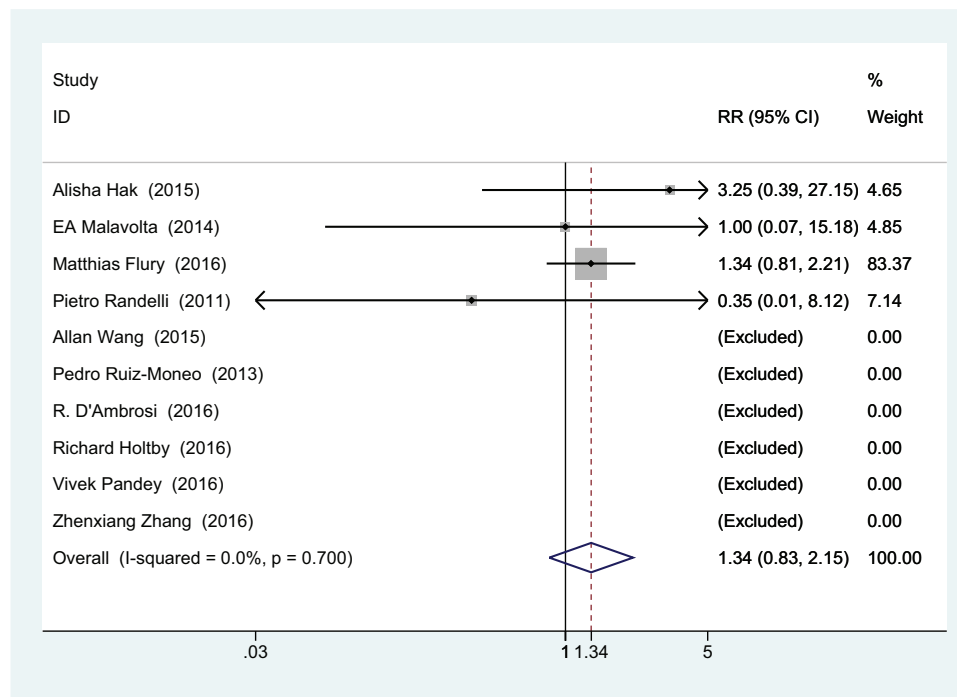


Figure 8. Forest plot of adverse events by study. ID, identification; RR, risk ratio.

their meta-analysis. Wang et al³⁵ evaluated the efficacy of PRP in arthroscopic repair of full-thickness rotator cuff tear. They suggested that PRP could effectively improve short-term outcomes and reduce the retear rate in arthroscopic rotator cuff repair. Moreover, Wang et al³⁵ recommended PRP injection as a supplementary therapy in single-row fixation in rotator cuff repair.

Although RCTs about PRP have been published, we found that the use of PRP differed among those studies. Some studies used liquid PRP,^{8,9,11,21,24,27,30,34} and others used gel PRP.^{5,12,18,19,25} Most studies used PRP intraoperatively, but in a few studies,^{8,30,34} the investigators injected PRP after arthroscopic shoulder surgery. Animal studies found that different types of growth factors were active at specific time points; some investigators²⁰ reported that platelet-derived growth factor had mild expression between 7 and 14 days, whereas others² suggested that platelet-derived growth factors had a more obvious effect on tendon healing at day 7. However, our study found that postoperative application of PRP was not associated with a significantly decreased retear rate. Moreover, the concentration of leukocyte was an important factor. Our review found that treatment using leukocyte-poor PRP in arthroscopic rotator cuff repair could decrease the retear rate, but there was no significant benefit associated with leukocyte-rich PRP.

Some studies suggested that the size of the rotator cuff tear could affect the efficacy of PRP.^{18,19,38} Our study indicated that PRP was not associated with a decreased retear rate in small to medium tears but had a potential benefit in large to massive tears. In addition, neither the single-row nor the double-row fixation technique affected the utility of PRP in reducing the retear rate in arthroscopic rotator cuff

repair. Vavken et al³³ found that PRP truly reduced the retear rate in arthroscopic rotator cuff repair, but this treatment was not cost-effective in small and medium-sized tears. Samuelson et al²⁸ indicated that if the cost of PRP were increased to \$1000, the retear rate would need to be decreased by at least 12.1% to achieve cost-effectiveness. All of these studies suggested that PRP cost-effectiveness needs to be taken into account as well as clinical outcomes.

Considering that the pooled outcomes of the meta-analysis might be affected by the above factors, we used strict eligibility criteria for the RCTs and performed subgroup analysis to assess the real utility of PRP. Although we have addressed the insufficiencies and confusion raised by previous studies, some limitations should be recognized. First, because different groups were separated according to the follow-up time, this may have resulted in insufficient studies or participants to analyze. Second, limited studies evaluated the cost-effectiveness of PRP during arthroscopic rotator cuff repair, and further related studies may be needed on this topic. Third, PRP technology and concentrations of PRP growth factors differed across studies, and we did not assess preoperative muscle quality on magnetic resonance imaging scans.

CONCLUSION

Our study suggests that intraoperative augmentation using PRP in patients who receive arthroscopic rotator cuff repair could improve long-term shoulder function and pain and significantly decrease the retear rate. However, this research did not show a reduction of the retear rate in patients who had small to medium-sized tears, in patients who received postoperative PRP, and when leukocyte-rich

plasma was used in performing arthroscopic rotator cuff repair with PRP.

REFERENCES

- Aurégan JC, Klouche S, Levy B, et al. Autologous conditioned plasma for tendon healing following arthroscopic rotator cuff repair: prospective comparative assessment with magnetic resonance arthrography at 6 months' follow-up. *Orthop Traumatol Surg Res.* 2019;105(2):245-249.
- Chan BP, Fu SC, Qin L, Rolf C, Chan KM. Supplementation-time dependence of growth factors in promoting tendon healing. *Clin Orthop Relat Res.* 2006;448:240-247.
- Chen X, Jones IA, Togashi R, Park C, Vangsness CT Jr. Use of platelet-rich plasma for the improvement of pain and function in rotator cuff tears: a systematic review and meta-analysis with bias assessment. *Am J Sports Med.* 2020;48(8):2028-2041.
- Chiu CH, Chen P, Yeh WL, et al. The gelling effect of platelet-rich fibrin matrix when exposed to human tenocytes from the rotator cuff in small-diameter culture wells and the design of a co-culture device to overcome this phenomenon. *Bone Joint Res.* 2019;8(5):216-223.
- D'Ambrosi R, Palumbo F, Paronzini A, Ragone V, Facchini RM. Platelet-rich plasma supplementation in arthroscopic repair of full-thickness rotator cuff tears: a randomized clinical trial. *Musculoskeletal Surg.* 2016;100(suppl 1):25-32.
- Diebold G, Lam P, Walton J, Murrell GAC. Relationship between age and rotator cuff retear: a study of 1,600 consecutive rotator cuff repairs. *J Bone Joint Surg Am.* 2017;99(14):1198-1205.
- Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol.* 2009;27(3):158-167.
- Ebert JR, Wang A, Smith A, et al. A midterm evaluation of postoperative platelet-rich plasma injections on arthroscopic supraspinatus repair: a randomized controlled trial. *Am J Sports Med.* 2017;45(13):2965-2974.
- Flury M, Rickenbacher D, Schwyzer HK, et al. Does pure platelet-rich plasma affect postoperative clinical outcomes after arthroscopic rotator cuff repair? A randomized controlled trial. *Am J Sports Med.* 2016;44(8):2136-2146.
- Gwark JY, Sung CM, Na JB, Park HB. Outcomes of arthroscopic rotator cuff repair in patients who are 70 years of age or older versus under 70 years of age: a sex- and tear size-matched case-control study. *Arthroscopy.* 2018;34(7):2045-2053.
- Hak A, Rajaratnam K, Ayeni OR, et al. A double-blinded placebo randomized controlled trial evaluating short-term efficacy of platelet-rich plasma in reducing postoperative pain after arthroscopic rotator cuff repair: a pilot study. *Sports Health.* 2015;7(1):58-66.
- Holtby R, Christakis M, Maman E, et al. Impact of platelet-rich plasma on arthroscopic repair of small- to medium-sized rotator cuff tears: a randomized controlled trial. *Orthop J Sports Med.* 2016;4(9):2325967116665595.
- Hurley ET, Hannon CP, Pauzenberger L, Fat DL, Moran CJ, Mullett H. Nonoperative treatment of rotator cuff disease with platelet-rich plasma: a systematic review of randomized controlled trials. *Arthroscopy.* 2019;35(5):1584-1591.
- Hurley ET, Lim Fat D, Moran CJ, Mullett H. The efficacy of platelet-rich plasma and platelet-rich fibrin in arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials. *Am J Sports Med.* 2019;47(3):753-761.
- Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions.* John Wiley & Sons; 2011.
- Jeong J, Shin DC, Kim TH, Kim K. Prevalence of asymptomatic rotator cuff tear and their related factors in the Korean population. *J Shoulder Elbow Surg.* 2017;26(1):30-35.
- Jo CH, Lee SY, Yoon KS, Oh S, Shin S. Allogenic pure platelet-rich plasma therapy for rotator cuff disease: a bench and bed study. *Am J Sports Med.* 2018;46(13):3142-3154.
- Jo CH, Shin JS, Lee YG, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: a randomized, single-blind, parallel-group trial. *Am J Sports Med.* 2013;41(10):2240-2248.
- Jo CH, Shin JS, Shin WH, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: a randomized controlled trial. *Am J Sports Med.* 2015;43(9):2102-2110.
- Kobayashi M, Itoi E, Minagawa H, et al. Expression of growth factors in the early phase of supraspinatus tendon healing in rabbits. *J Shoulder Elbow Surg.* 2006;15(3):371-377.
- Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assuncao JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: a prospective randomized study. *Am J Sports Med.* 2014;42(10):2446-2454.
- Malavolta EA, Gracitelli MEC, Assuncao JH, Ferreira Neto AA, Bordalo-Rodrigues M, de Camargo OP. Clinical and structural evaluations of rotator cuff repair with and without added platelet-rich plasma at 5-year follow-up: a prospective randomized study. *Am J Sports Med.* 2018;46(13):3134-3141.
- Moher D, Liberati A, Tetzlaff J, Altman DG; the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012.
- Pandey V, Bandi A, Madi S, et al. Does application of moderately concentrated platelet-rich plasma improve clinical and structural outcome after arthroscopic repair of medium-sized to large rotator cuff tear? A randomized controlled trial. *J Shoulder Elbow Surg.* 2016;25(8):1312-1322.
- Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg.* 2011;20(4):518-528.
- Rhee YG, Cho NS, Yoo JH. Clinical outcome and repair integrity after rotator cuff repair in patients older than 70 years versus patients younger than 70 years. *Arthroscopy.* 2014;30(5):546-554.
- Ruiz-Moneo P, Molano-Munoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: a randomized, double-blind, controlled clinical trial. *Arthroscopy.* 2013;29(1):2-9.
- Samuelson EM, Odum SM, Fleischli JE. The Cost-effectiveness of using platelet-rich plasma during rotator cuff repair: a Markov model analysis. *Arthroscopy.* 2016;32(7):1237-44.
- Slawson DC. Platelet-rich plasma injection not beneficial for nonoperative treatment of rotator cuff disease. *Am Fam Physician.* 2019;100(10):647-648.
- Snow M, Hussain F, Pagkalos J, et al. The effect of delayed injection of leukocyte-rich platelet-rich plasma following rotator cuff repair on patient function: a randomized double-blind controlled trial. *Arthroscopy.* 2020;36(3):648-657.
- Sugaya H, Maeda K, Matsuki K, Moriishi J. Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: single-row versus dual-row fixation. *Arthroscopy.* 2005;21(11):1307-1316.
- Teunis T, Lubberts B, Reilly BT, Ring D. A systematic review and pooled analysis of the prevalence of rotator cuff disease with increasing age. *J Shoulder Elbow Surg.* 2014;23(12):1913-1921.
- Vavken P, Sadoghi P, Palmer M, et al. Platelet-rich plasma reduces retear rates after arthroscopic repair of small- and medium-sized rotator cuff tears but is not cost-effective. *Am J Sports Med.* 2015;43(12):3071-3076.
- Wang A, McCann P, Colliver J, et al. Do postoperative platelet-rich plasma injections accelerate early tendon healing and functional recovery after arthroscopic supraspinatus repair? A randomized controlled trial. *Am J Sports Med.* 2015;43(6):1430-1437.
- Wang C, Xu M, Guo W, Wang Y, Zhao S, Zhong L. Clinical efficacy and safety of platelet-rich plasma in arthroscopic full-thickness rotator cuff repair: a meta-analysis. *PLoS One.* 2019;14(7):e0220392.
- Wu PI, Diaz R, Borg-Stein J. Platelet-rich plasma. *Phys Med Rehabil Clin North Am.* 2016;27(4):825-853.
- Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. *J Shoulder Elbow Surg.* 2010;19(1):116-120.
- Zhang Q, Ge H, Zhou J, Cheng B. Are platelet-rich products necessary during the arthroscopic repair of full-thickness rotator cuff tears: a meta-analysis. *PLoS One.* 2013;8(7):e69731.
- Zhang Z, Wang Y, Sun J. The effect of platelet-rich plasma on arthroscopic double-row rotator cuff repair: a clinical study with 12-month follow-up. *Acta Orthop Traumatol Turc.* 2016;50(2):191-197.