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REVIEW ARTICLES

The clinical efficacy of leukocyte-poor platelet-rich plasma in arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials

Di Zhao, MD[a], Yan-hong Han, MD[a], Jian-ke Pan, PhD[b], Wei-yi Yang, PhD[b], Ling-feng Zeng, PhD[b,c], Gui-hong Liang, MD[b,c], Jun Liu, PhD[b,c,*]

[a]*The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China*
[b]*Department of Orthopedics, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China*
[c]*Bone and Joint Research Team of Degeneration and Injury, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China*

Background: The efficacy of platelet-rich plasma (PRP) in the arthroscopic treatment of rotator cuff injury has been reported in the literature. However, conclusions have been inconsistent and more often related to differences in the types of PRP used. Therefore, to minimize these differences, we performed a meta-analysis of only studies investigating leukocyte-poor PRP to evaluate whether PRP promotes and improves the effects of arthroscopic rotator cuff repair.

Methods: A comprehensive search of the PubMed, Embase, and Cochrane Library databases was conducted to evaluate the efficacy of leukocyte-poor PRP in arthroscopic rotator cuff repair. The available data were extracted, and the methodologic quality of the included studies was evaluated by the Cochrane risk-of-bias assessment tool.

Results: In total, 10 randomized controlled trials involving 742 patients were included. The results of the meta-analysis showed that treatment with leukocyte-poor PRP performed better than the control treatment in relieving postoperative pain in the short-term (mean difference [MD], –0.57; 95% confidence interval [CI], –0.79 to –0.35; $P < .0001$) and medium- and long-term (MD, –0.18; 95% CI, –0.34 to –0.03; $P = .02$) follow-up groups. However, the changes in the MD in the visual analog scale score were below the minimal clinically important difference. Regarding the Constant shoulder (MD, 3.35; 95% CI, 1.68-5.02; $P < .0001$) and University of California, Los Angeles (MD, 1.73; 95% CI, 0.94-2.52; $P < .0001$) scores, statistically significant differences were found in favor of leukocyte-poor PRP over the control treatment. However, the changes in the MD in both the Constant and University of California, Los Angeles scores were below the minimal clinically important difference. Moreover, during medium- and long-term follow-up, the retear rate in the leukocyte-poor PRP group was lower than that in the control group regardless of the rotator cuff tear size (small and medium [<3 cm] [risk ratio (RR), 0.64; 95% CI, 0.43-0.97; $P = .03$] vs. medium and large [>3 cm] [RR, 0.51; 95% CI, 0.34-0.77; $P = .001$]) and surgical repair method (single-row repair [RR, 0.61; 95% CI, 0.43-0.87; $P = .007$] vs. double-row suture bridge repair [RR, 0.57; 95% CI, 0.38-0.84; $P = .005$]).

Conclusion: According to our study, leukocyte-poor PRP can significantly reduce the postoperative retear rate in the medium and long term regardless of the tear size and the method used for rotator cuff repair. However, the use of leukocyte-poor PRP failed to show clinically meaningful effects in terms of postoperative pain and patient-reported outcomes.

Institutional review board approval was not required for this meta-analysis.

*Reprint requests: Jun Liu, PhD, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 111 Dade Road, Guangzhou, China.

E-mail address: liujun3040@126.com (J. Liu).

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Level of evidence: Level II; Systematic Review and Meta-analysis
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Keywords: Rotator cuff repair; arthroscopic; leukocyte-poor platelet-rich plasma; clinical efficacy; rotator cuff; meta-analysis

Rotator cuff tears are common causes of pain and shoulder dysfunction. Arthroscopic rotator cuff repair can effectively relieve pain and improve function, and it has advantages over open operations, including less surgical trauma and a shorter recovery time. Thus, it has gradually become a major treatment approach. However, a higher postoperative retear rate after arthroscopic rotator cuff repair[2,32] substantially affects patient satisfaction and dramatically increases the probability of a second operation.[25,27] It has previously been demonstrated that the scar tissue formed at the tendon-bone interface is far inferior to the normal tissue of the anatomic fibrous cartilage-osseous tendon junction in terms of the dispersion and transfer of load stress.[34,38,49] Therefore, the formation of scar tissue may not be conducive to tendon-bone interface healing after arthroscopic rotator cuff repair. To improve the postoperative healing rate of the tendon-bone interface, the focus of current studies has shifted from mechanical repair alone to mechanical repair in conjunction with biological enhancement. Among the agents used in such approaches, platelet-rich plasma (PRP) contains a large number of active cells and growth factors, such as platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor, basic fibroblast growth factor, and transforming growth factor β.[1] These growth factors can promote cell proliferation and differentiation and matrix synthesis and deposition while stimulating angiogenesis and promoting vascularization; hence, PRP can biologically enhance the repair of rotator cuff injury.[7,21,22,41] Previously, some authors have reported on the healing effects of PRP in rotator cuff injury, but their conclusions have been inconsistent, potentially because of the different types of PRP used in the various studies.[11,15,20,33,35,37,50] To eliminate the influence of differences between leukocyte-rich PRP and platelet-rich fibrin (PRF) on the final results, our study only considered leukocyte-poor PRP. Studies have shown that leukocyte-poor PRP promotes the formation of normal collagen and reduces the synthesis of inflammatory factors[5] whereas leukocyte-rich PRP increases cell catabolism and the inflammatory response, which are not conducive to tendon healing.[4,8] For acute traumatic rotator cuff tears, the use of leukocyte-rich PRP may be particularly less conducive to postoperative rotator cuff healing.

Thus, to further clarify the clinical efficacy of leukocyte-poor PRP, we performed a meta-analysis of only studies investigating leukocyte-poor PRP to evaluate whether PRP improves the effects of arthroscopic rotator cuff repair. We hypothesized that leukocyte-poor PRP would play a positive role in improving the clinical outcomes of arthroscopic rotator cuff repair.

Methods

Search strategy

A comprehensive electronic search of the PubMed, Embase, and Cochrane Library databases was performed to retrieve articles published up to March 2020. The English-language search terms included "rotator cuff," "subscapularis," "infraspinatus," "supraspinatus," "platelet rich plasma," "leukocyte-poor platelet rich plasma," and "PRP." Moreover, the references in the relevant studies were searched and evaluated to ensure that the literature review was comprehensive.

Search selection

Two independent researchers excluded studies that did not meet the inclusion criteria by reading the titles and abstracts; the full text of potentially eligible studies was then read and screened. Studies that met the criteria were cross-checked and included. If there was a difference in opinion, it was up to the senior researcher to hold a discussion and make a decision.

Eligibility criteria

The inclusion criteria were as follows: (1) The participants received a diagnosis of a rotator cuff tear according to their imaging findings and underwent repair and suturing by routine arthroscopic surgery without revision surgery. (2) The study was a level I or II randomized controlled trial (RCT). (3) The trial group was treated with leukocyte-poor PRP. (4) The follow-up rate of the patients was >80%. (5) The postoperative outcome indicators included at least one of the following: the primary outcome, defined as the retear rate, and the secondary outcomes, comprising the visual analog scale (VAS) pain score, Constant shoulder score, University of California, Los Angeles (UCLA) shoulder score, American Shoulder and Elbow Surgeons (ASES) score, and Oxford shoulder score. The exclusion criteria were as follows: (1) level of evidence of III or IV; (2) treatment of the trial group with leukocyte-rich PRP, PRF, or another method; (3) surgical treatment not performed arthroscopically; and (4) incomplete data.

Data extraction

Two reviewers independently extracted the data from all available studies. The extracted data included the following: (1) the basic characteristics of the study; (2) the level of evidence included in

the literature; (3) the general condition of the subjects (eg, sex and age); and (4) the sample size, mode of surgical repair, follow-up time, and characteristics of the injection used in the trial group. We determined the final classification according to the number of white blood cells in the final PRP product. When the number of white blood cells in the PRP was lower than that of whole blood, the PRP was defined as leukocyte-poor PRP. When the specific white blood cell content was not specified in the studies, the relevant data from the PRP manufacturer and PRP kit were used to determine the leukocyte concentration.[36]

Quality and risk-of-bias assessment

The quality of the methodology included in each study was evaluated by 2 reviewers according to The Cochrane Collaboration risk-of-bias assessment tool.[14] The risk assessment mainly includes the following: (1) random sequence generation; (2) allocation concealment; (3) implementation bias, including blinding of participants; (4) measurement bias, including blinding of outcome assessors; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. The evaluation of each part was divided into low, unclear, and high risk to assess the risk of several biases that may occur in RCTs.

Statistical analysis

The statistical analyses were carried out using the statistical software Review Manager (RevMan, version 5.3; The Cochrane Collaboration, London, UK), as recommended by The Cochrane Collaboration network, to analyze the data extracted from the literature. According to the data type, corresponding indicators were used to analyze and describe the results. The risk ratio (RR) and 95% confidence interval (CI) were used in the statistical analysis of dichotomous variables. The mean difference (MD) and 95% CI were used in the statistical analysis of continuous variables. The χ^2 test was used to determine whether there was statistical heterogeneity among the studies. When the P value was $\geq$.10 and the I^2 value was $\leq$50%, the heterogeneity among the studies was considered not significant and a fixed-effects model was used for the meta-analysis. When the P value was $<$.10 and the I^2 value was $>$50%, the heterogeneity among the studies was considered significant and a random-effects model was used for the meta-analysis. The results were then subjected to subgroup analysis or sensitivity analysis to identify the sources of heterogeneity. To reduce the risk of bias, when $<$3 articles were included, the data were not merged. In the meta-analysis, $P < .05$ indicated that a statistically significant difference existed between the 2 groups. To evaluate the clinical effect, the outcome indicator needs to be compared with the minimal clinically important difference (MCID) value in patients with rotator cuff disease. According to previous reports, a change in the MD in the VAS score (0-10) of $\geq$2.4, a change in the MD in the Constant shoulder score of $\geq$6.7, a change in the MD in the ASES score of $\geq$6, and a change in the MD in the UCLA score of $\geq$3 were considered the MCIDs.[6,48,53] Regarding the retear rate, any increase or decrease in the rate of retear was considered clinically significant.

Results

Literature search

By searching the different databases, a total of 726 articles were retrieved, and 525 articles remained after duplicate studies were removed. After the titles and abstracts of the studies were read, 510 unrelated studies were excluded and 15 articles were screened for the first time. Then, the full text was further read in strict accordance with the inclusion and exclusion criteria, and a total of 11 articles were included. As 2 RCTs were based on data derived from the same trial but with different follow-up times, we selected the group with the longer follow-up time[29] for data extraction. The literature screening process and results are shown in Figure 1.

Study characteristics

A total of 10 RCTs with level I or II evidence were included, comprising 372 patients in the trial group and 370 patients in the control group. A blank control group was reported in 8 studies, whereas in the other 2 studies, the control group received treatment with saline solution or ropivacaine. The specific characteristics of the studies are shown in detail in Table I. Table II presents the characteristics of the leukocyte-poor PRP used in the trial group.

Risk-of-bias assessment of RCTs

The methodologic quality of the included studies was evaluated by the Cochrane risk-of-bias assessment tool. All 10 included articles applied randomized assignment using computer-generated random lists. Two studies had a high risk of performance bias.[15,24] One study showed selective reporting.[39] These findings are shown in Supplementary Figures S1 and S2.

Clinical outcomes

Retear rate

In total, 8 studies (including 538 patients) reported the retear rate at the final follow-up time.[9,10,15,23,24,29,34,51] To evaluate the outcomes, 5 of these studies used magnetic resonance imaging (MRI), 1 used MRI or ultrasound (US), 1 used MRI or computed tomography angiography, and 1 used US. The results of the heterogeneity test showed $P = .97$ and $I^2 = 0\%$, indicating good homogeneity among the studies, and a fixed-effects model was therefore used. The pooled analysis showed that using leukocyte-poor PRP reduced the retear rate compared with the control treatment (RR, 0.59; 95% CI, 0.45-0.77; $P = .0001$). The details are shown in Figure 2. To further clarify the effect of leukocyte-poor PRP on the postoperative retear rate at different follow-up time points, we conducted a subgroup analysis of patients with a

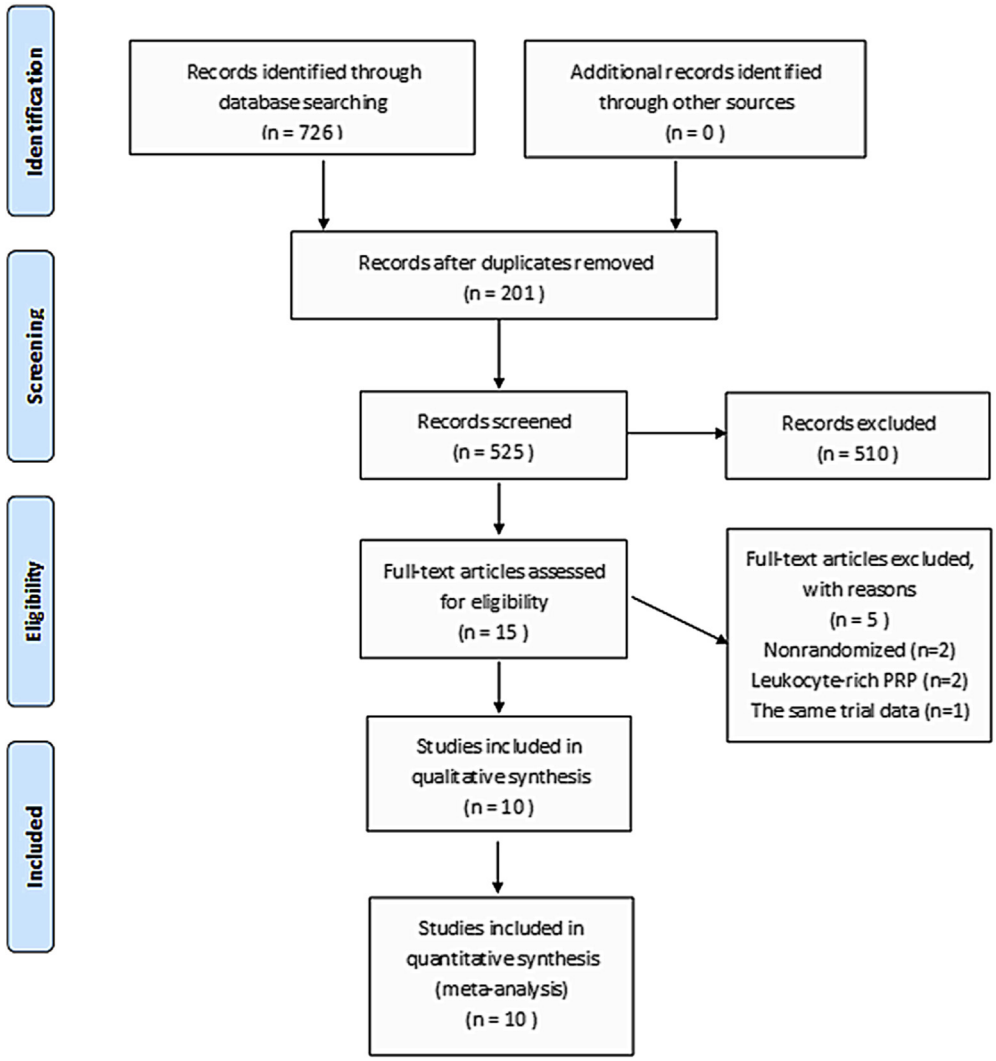

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) study selection flow diagram. *PRP*, platelet-rich plasma.

follow-up time $\leq$ 6 months (short-term follow-up) or a follow-up time $\geq$ 6 months (medium- and long-term follow-up). A total of 3 studies (including 188 patients) were included in the short-term follow-up group.[15,29,51] The results of the heterogeneity test showed $P = .76$ and $I^2 = 0\%$, indicating no heterogeneity between the 2 groups. After the data were pooled with a fixed-effects model, the pooled analysis showed no significant difference between the trial group (leukocyte-poor PRP) and the control group (RR, 0.67; 95% CI, 0.43-1.03; $P = .07$). A total of 7 articles (including 479 patients) were included in the medium- and long-term follow-up group.[9,10,15,23,24,29,34] The results of the heterogeneity test showed $P = .97$ and $I^2 = 0\%$, indicating no heterogeneity between the 2 groups. After the data were pooled with a fixed-effects model, the retear rate in the trial group (leukocyte-poor PRP) was significantly lower than that in the control group (RR, 0.57; 95% CI, 0.43-0.76; $P < .0001$).

In addition, differences in the size of the rotator cuff tears included in different studies may have had an impact on the postoperative retear rate. Therefore, in the medium- and long-term follow-up group, we analyzed subgroups consisting of small- and medium-sized rotator cuff tears (<3 cm) and medium- and large-sized rotator cuff tears (>3 cm). A total of 3 articles included patients with small- and medium-sized rotator cuff tears (including 173 patients).[9,15,29] The results of the heterogeneity test showed no heterogeneity between the 2 groups ($P = .94$, $I^2 = 0\%$). The pooled analysis showed that patients treated with leukocyte-poor PRP had a lower retear rate than those who received the control treatment (RR, 0.64; 95% CI, 0.43-0.97; $P = .03$). For medium- and large-sized rotator cuff tears (>3 cm), a total of 3 articles were included (including 213 patients).[23,24,34] The results of the heterogeneity test showed $P = .74$ and $I^2 = 0\%$, indicating no heterogeneity between the 2 groups. After the data were pooled with a fixed-effects model, patients treated with leukocyte-poor PRP had a lower retear rate than those who received the control treatment (RR, 0.51; 95% CI, 0.34-0.77; $P = .001$).

Table I Study characteristics and patient demographic characteristics of included randomized controlled trials

Author (year)	LOE	Tear size	Repair type	Follow-up, mo	Sample size		Male sex/total, n		Age, mean ± SD, yr	
					LP-PRP	Control	LP-PRP	Control	LP-PRP	Control
Hak et al[12] (2015)	II	<3 cm	Single row	1.5	12	13	9/12	10/13	55.0 ± 6.3	55.0 ± 6.4
Ebert et al[9] (2017)	I	<2 cm	Double row suture bridge	42	30	30	11/27	19/28	59.5 ± 11.0	59.7 ± 11.4
Malavolta et al[29] (2018)	II	<3 cm	Single row	60	27	27	8/26	9/25	55.4 ± 8.4	54.0 ± 6.5
Wang et al[51] (2015)	I	<2 cm	Double row suture bridge	4	30	30	11/30	17/30	59.8 ± 12.3	58.4 ± 9.5
Pandey et al[33] (2016)	I	1- to 5-cm full-thickness tear	Single row	24	52	50	38/52	36/50	54.8 ± 8.4	54.1 ± 8.3
Flury et al[10] (2016)	I	Not reported	Double row suture bridge	24	60	60	20/60	18/60	57.8 ± 8.0	58.9 ± 8.2
Ruiz-Moneo et al[39] (2013)	I	Not reported	Double row suture bridge	12	32	31	14/32	11/31	56.0 ± 8.8	55.0 ± 11.0
Jo et al[23] (2013)	I	>3 cm	Double row suture bridge	12	24	24	10/24	14/24	64.21 ± 6.09	61.92 ± 8.36
Jo et al[24] (2015)	I	1-5 cm	Double row suture bridge	12	37	37	8/37	9/37	60.08 ± 4.88	60.92 ± 7.34
Holtby et al[15] (2016)	I	<3-cm full-thickness tear or partial-thickness tear	Single row	6	41	41	21/41	20/41	59.0 ± 8.0	59.0 ± 8.0

LOE, level of evidence; *SD*, standard deviation; *LP-PRP*, leukocyte-poor platelet-rich plasma.

We also performed a subgroup analysis of the different surgical repair methods. In the medium- and long-term follow-up group, in total, 3 articles (including 220 patients) used single-row repair.[15,29,34] The results of the heterogeneity test showed no heterogeneity between the 2 groups ($P = .87$, $I^2 = 0\%$). The pooled analysis showed that the retear rate in the trial group (leukocyte-poor PRP) was significantly lower than that in the control group (RR, 0.61; 95% CI, 0.43-0.87; $P = .007$). In total, 4 articles (including 319 patients) reported the use of double-row suture bridge repair.[9,10,23,24] The results of the heterogeneity test showed $P = .84$ and $I^2 = 0\%$, indicating no heterogeneity between the 2 groups. After the data were pooled with a fixed-effects model, the retear rate in the trial group (leukocyte-poor PRP) was significantly lower than that in the control group (RR, 0.57; 95% CI, 0.38-0.84; $P = .005$). The aforementioned data are detailed in Table III.

VAS score

The VAS scores at short-term follow-up and medium- and long-term follow-up were reported by 5 studies (including 314 patients)[12,24,29,34,51] and 5 studies (including 330 patients),[9,23,24,29,34] respectively. A subgroup meta-analysis was performed to compare VAS scores based on the follow-up duration. Superior postoperative pain relief was observed in patients treated with leukocyte-poor PRP compared with those who received the control treatment at both short-term follow-up (MD, –0.57; 95% CI, –0.79 to –0.35; $P < .0001$; $I^2 = 0\%$) and medium- and long-term follow-up (MD, –0.18; 95% CI, –0.34 to –0.03, $P = .02$; $I^2 = 0\%$). However, the changes in the mean VAS score difference were below the MCID (2.4). These data are detailed in Figure 3.

Constant score

In total, 7 studies (including 509 patients) reported Constant shoulder scores at the final follow-up.[9,10,15,23,29,34] The results of the heterogeneity test showed $P = .28$ and $I^2 = 19\%$, indicating good homogeneity among the studies. Therefore, a fixed-effects model was adopted. The pooled analysis showed better Constant scores with leukocyte-poor PRP than with the control treatment (MD, 3.35; 95% CI, 1.68-5.02; $P < .0001$). However, the change in the mean difference in the Constant scores was below the MCID (6.7). These data are detailed in Supplementary Figure S3.

UCLA score

In total, 5 studies (including 338 patients) reported UCLA scores at the final follow-up.[23,24,29,34,39] The results of the heterogeneity test showed $P = .1$ and $I^2 = 49\%$, indicating

Table II Platelet-rich therapy injection characteristics

Author (year)	Platelet concentration, $\times 10^3$	Volume	Activating agent	Applied site	Preparation kit
Hak et al[12] (2015)	Not reported	6-9 mL	Not reported	Bone-tendon interface	ACP (Arthrex, Naples, FL, USA)
Ebert et al[9] (2017)	470	4-6 mL	Calcium chloride	Bone-tendon interface	ACP (Arthrex)
Malavolta et al[29] (2018)	1185.166 ± 404.472	24.6 mL	Calcium chloride	Bone-tendon interface	MCS1 (Haemonetics, Braintree, MA, USA)
Wang et al[51] (2015)	470	4-6 mL × 2	Calcium chloride	Bone-tendon interface	ACP (Arthrex)
Pandey et al[33] (2016)	474 ± 30	8 mL	Calcium chloride	Bone-tendon interface	Heraeus Cryofuge (Thermo Scientific, Waltham, MA, USA)
Flury et al[10] (2016)	Not reported	4 mL	Not reported	Bone-tendon interface	ACP (Arthrex)
Ruiz-Moneo et al[39] (2013)	600	Not reported	Calcium chloride	Bone-tendon interface and intratendon	PRGF System1 (B.T.I., Vitoria-Gasteiz, Spain)
Jo et al[23] (2013)	1096.48 ± 255.40	3 mL × 3	Calcium gluconate	Bone-tendon interface	COBE Spectra LRS Turbo (Caridian BCT, Lakewood, Colorado, USA)
Jo et al[24] (2015)	1218.40 ± 334.69	3 mL × 3	Calcium gluconate	Bone-tendon interface	COBE Spectra LRS Turbo
Holtby et al[15] (2016)	Not reported	9.5 mL	Not reported	Bone-tendon interface	SmartPrep 2 (Harvest Technologies, Plymouth, MA, USA)

no significant heterogeneity among the studies. Therefore, a fixed-effects model was adopted. The pooled analysis showed that leukocyte-poor PRP resulted in better UCLA scores than the control treatment (MD, 1.73; 95% CI, 0.94-2.52; $P < .0001$). However, the changes in the mean difference in the UCLA scores were below the MCID (3). These data are detailed in Supplementary Figure S4.

ASES score

In total, 5 studies (including 403 patients) reported ASES scores at the final follow-up.[10,15,23,24,34] The results of the heterogeneity test showed $P = .8$ and $I^2 = 0\%$, indicating good homogeneity among the studies; a fixed-effects model was therefore used. The pooled analysis showed no significant differences in the ASES scores between the trial group (leukocyte-poor PRP) and the control group (MD, 1.75; 95% CI, –0.13 to 3.63; $P = .07$). However, the changes in the mean difference in the ASES scores were below the MCID (6). These data are detailed in Supplementary Figure S5.

Oxford shoulder score

A total of 3 studies (including 219 patients) reported Oxford shoulder scores at the last follow-up.[9,10,51] The results of the heterogeneity test showed $P = .03$ and $I^2 = 73\%$, indicating the presence of heterogeneity among the studies; thus, a random-effects model was used. The pooled analysis showed no significant difference in the Oxford shoulder score between the trial group (leukocyte-poor PRP) and the control group (MD, –1.20; 95% CI, –4.21 to 1.82; $P = .44$). These data are detailed in Supplementary Figure S6.

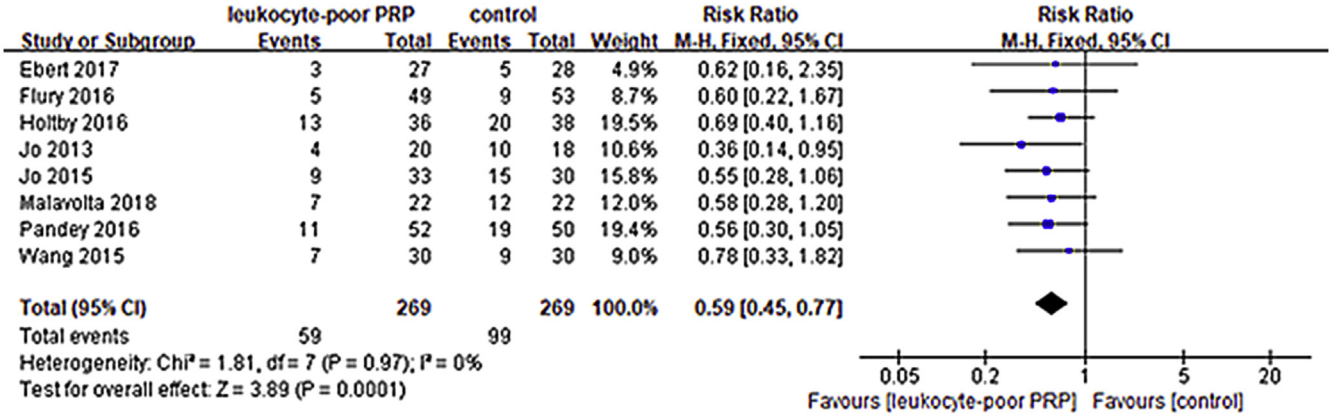

Figure 2 Forest plot of retear rates for patients who received and did not receive leukocyte-poor platelet-rich plasma *(PRP)*. *M-H*, Mantel-Haenszel; *CI*, confidence interval.

Table III Subgroup analysis of retear rate

Results	No. of cases (LP-PRP/ control)	Outcome (LP-PRP/ control), %	Heterogeneity	RR	95% CI	*P* value for effect size	Treatment favored
Follow-up time $\leq$ 6 mo	93/95	23.7/35.8	$P = 0.76$, $I^2 = 0\%$	0.67	0.43-1.03	.07	None
Follow-up time $\geq$ 6 mo	239/240	22.2/38.3	$P = 0.97$, $I^2 = 0\%$	0.57	0.43-0.76	<.0001	LP-PRP
Small and medium-sized rotator cuff tear (<3 cm): follow-up time $\geq$ 6 mo	85/88	27.1/42.0	$P = 0.94$, $I^2 = 0\%$	0.64	0.43-0.97	.03	LP-PRP
Medium- and large-sized rotator cuff tear (>3 cm): follow-up time $\geq$ 6 mo	105/98	22.9/44.9	$P = 0.74$, $I^2 = 0\%$	0.51	0.34-0.77	.001	LP-PRP
Single-row repair: follow-up time $\geq$ 6 mo	110/110	28.2/46.4	$P = 0.87$, $I^2 = 0\%$	0.61	0.43-0.87	.007	LP-PRP
Double-row suture bridge repair: follow-up time $\geq$ 6 mo	159/160	18.2/31.3	$P = 0.84$, $I^2 = 0\%$	0.57	0.38-0.84	.005	LP-PRP

LP-PRP, leukocyte-poor platelet-rich plasma; *RR*, risk ratio; *CI*, confidence interval.

Discussion

This meta-analysis found that compared with the control treatment, leukocyte-poor PRP could not only improve postoperative pain but also reduce the postoperative retear rate and improve postoperative shoulder function scores, including the Constant shoulder score and UCLA shoulder score. However, these results were only based on statistical differences, and reporting only these results might be misleading in terms of clinical decision making. Therefore, we carried out a specific analysis based on the MCID values.

In recent years, many studies have reported the efficacy of PRP for arthroscopic rotator cuff repair. However, controversy remains. In a systematic review of meta-analyses, Saltzman et al[42] found that the use of PRP in arthroscopic rotator cuff repair did not generally decrease the retear rate or affect the clinical outcome scores. In a critical analysis review, it was also reported that the general use of PRP had no significant clinical benefit in arthroscopic rotator cuff

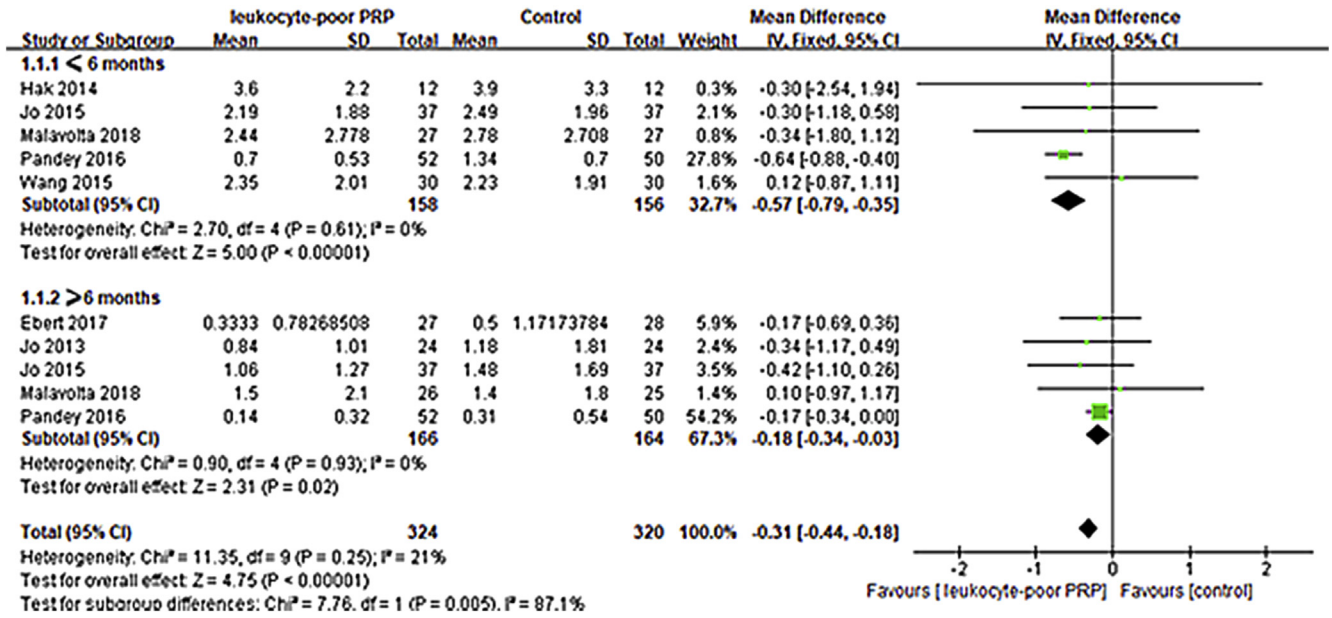

Figure 3 Forest plot of visual analog scale scores for patients who received and did not receive leukocyte-poor platelet-rich plasma *(PRP)*. *SD*, standard deviation; *IV*, inverse variance; *CI*, confidence interval.

repair.[45] Similarly, Le et al[28] suggested that PRP was insufficient to enhance rotator cuff repair. However, in another systematic review of meta-analyses, the authors found that the adjuvant use of PRP could reduce the postoperative retear rate.[17] Han et al[13] and Wang et al[52] also stated in their meta-analyses that PRP could improve not only the postoperative retear rate but also postoperative function. The disagreements in the final results are likely due to the use of different types of PRP in the analyses of the different studies.

PRP contains various cell growth factors that may exert beneficial biological effects during tendon healing.[1] Clinical trials have also shown that PRP can accelerate tendon repair and injured blood vessel remodeling.[22,41] However, differences in the PRP products available on the market, such as differences in the content of growth factors, leukocytes, and platelets, as well as differences between PRP and PRF, may lead to many differences in the healing of rotator cuff injuries.[47] Currently, the PRP products available on the market are mainly classified according to their leukocyte and fibrin contents. Cross et al[5] found that catabolic factors produced by high concentrations of leukocytes in PRP may antagonize the constructive metabolic factors produced by platelets. For moderately degenerative rotator cuff tendons, leukocyte-poor PRP can promote the production of a normal collagen matrix and reduce both the degradation of the matrix and the production of inflammation-related cytokines to a greater extent than leukocyte-rich PRP. Some scholars have found that leukocyte-rich PRP can increase levels of catabolic factors, trigger inflammation, and cause tissue matrix degradation.[47] Through animal experiments, Dragoo et al[8] showed that leukocyte-rich PRP causes more acute inflammation than leukocyte-poor PRP. A recent RCT found that leukocyte-rich PRP did not improve the retear rate and function, as measured by patient-reported outcome measures, after arthroscopic rotator cuff repair.[46] Regarding PRF, many clinical studies have shown that PRF is not beneficial for improving postoperative shoulder function and rotator cuff healing.[16,30,50] Therefore, Smith et al[45] and Le et al[28] suggested in their studies that PRP had no clinical effect when used in arthroscopic rotator cuff repair with combined leukocyte-poor PRP, leukocyte-rich PRP, and PRF.

We only investigated the use of leukocyte-poor PRP and made every effort to exclude the impact of other types of PRP on the final results. Currently, subgroup analyses of leukocyte-poor PRP have been reported in the literature, but the conclusions have varied. Smith et al[45] provided limited evidence suggesting that leukocyte-poor PRP improved the retear rate and clinical outcome scores after arthroscopic rotator cuff repair at >6 months' follow-up. However, this article combined leukocyte-poor PRP and leukocyte-poor PRF in the analysis. A study by Hurley et al[16] suggested that the use of leukocyte-poor PRP in rotator cuff repair could reduce pain levels and improve the healing rate and functional outcomes. However, this study only reported the statistical differences and ignored the worthwhile evaluation of the MCID. Thus, we conducted our meta-analysis of level I and II studies based on MCID values to comprehensively assess the clinical efficacy of leukocyte-poor PRP for arthroscopic rotator cuff repair.

The retear rate is one of the most important reference indexes used to evaluate the effect of a technique on rotator cuff tear healing, and it is an important factor affecting the final level of patient satisfaction. The diagnostic criteria for retears include partial-thickness retears and full-thickness retears shown on imaging including US. Therefore, to improve the understanding of the effect of leukocyte-poor PRP on the postoperative rotator cuff retear rate, we carried out several subgroup analyses of this index and found that in the short-term follow-up group, the use of leukocyte-poor PRP had no significant effect compared with the control treatment. However, in the medium- and long-term follow-up group, the postoperative retear rate was significantly lower in the leukocyte-poor PRP group than in the control group. Regarding the timing of retears after arthroscopic rotator cuff repair, different studies have reported different values: Iannotti et al[18] found that recurrent tears appear to occur more frequently between 6 and 26 weeks after arthroscopic rotator cuff repair. Miller et al[31] found that retears primarily occur within the first 3 months. Chona et al[3] conducted a meta-analysis and found that the retear rates generally increase until at least 10-15 months after arthroscopic rotator cuff repair, after which they likely level off. Additionally, research conducted by Kim et al[26] revealed that tendons that show good healing within the first 3 postoperative months rarely exhibit retears during the late postoperative period (after 3 months). Therefore, controversy regarding the occurrence time of retears after arthroscopic rotator cuff repair exists. In our study, although the results indicated that the retear rate showed no statistically significant difference in the short-term follow-up group, the use of leukocyte-poor PRP still reduced the retear rate during the early postoperative period to a certain extent (23.7% vs. 35.8%) and showed a maximum effect during the late postoperative period (medium- and long-term follow-up) ($P < .0001$).

Moreover, in the medium- and long-term follow-up group, we analyzed subgroups consisting of rotator cuff tears of different sizes and found that regardless of the rotator cuff tear size (small and medium [<3 cm] vs. medium and large [>3 cm]), the use of leukocyte-poor PRP significantly reduced the postoperative retear rate compared with the control treatment. Especially for medium and large rotator cuff tears, arthroscopic treatment combined with an injection of leukocyte-poor PRP can minimize the possibility of rotator cuff retears; this approach may also be helpful for improving the high postoperative retear rate of medium and large rotator cuff tears. At the same time, owing to the lack of a unified standard method of surgical repair, some of the included studies used single-row repair

whereas others used double-row suture bridge repair. Although double-row suture bridge repair theoretically increases the contact area between the tendon and bone, which is more conducive to tendon-bone healing, some studies have shown that there is no significant difference in the healing effect between the 2 techniques.[19,43,54,55] Therefore, there is some dispute regarding the use of the 2 repair methods. In our meta-analysis, we found that when combined with the use of leukocyte-poor PRP, both single-row repair and double-row suture bridge repair could reduce the postoperative retear rate.

Regarding the VAS scores, on the basis of the MCID value, no significant clinical benefits were observed in either the short-term follow-up group or medium- and long-term follow-up group. Similarly, the evaluation of postoperative function did not show a clinically significant difference. However, VAS scores and patient-reported outcomes may not be the best outcome measures for assessing PRP as these measures do not reflect the state of healing after rotator cuff repair. A systematic review indicated that some important differences in clinical outcomes likely exist between patients with healed and unhealed rotator cuff repairs.[44] However, owing to the mixed results and low-quality studies (level IV) included in the research, the results of the systematic review could not definitively show that the results of healed rotator cuff repairs are better based on any clinical outcomes. Russell et al[40] conducted a meta-analysis of level I and II studies and found that patients who underwent rotator cuff repair had no clinically important differences in validated functional outcome scores or pain levels regardless of the structural integrity of the repair. Therefore, although the clinical effect of leukocyte-poor PRP on postoperative pain and functional improvement is not significant, leukocyte-poor PRP can significantly improve the occurrence of postoperative retears, which is more beneficial for the postoperative recovery of patients.

Limitations

Some limitations in this study should be noted. As this is a meta-analysis, the limitations of all the included studies are present in this study. In this meta-analysis, although we included only studies of leukocyte-poor PRP to minimize the effects of leukocyte concentrations and PRF on our results, factors such as the number of platelets and the levels of growth factors and other cytokines can also affect the outcome of treatment with PRP. Because of the underreporting of these variables among the studies, it is impossible to completely clarify all of the factors that could affect the outcomes. These differences are key points that should be addressed in future studies. Despite these limitations, our results show homogeneity, with heterogeneity observed only in the Oxford shoulder score. However, we consider this heterogeneity to have been caused by differences in the intervention measure and in the size of the rotator cuff tears included in one of the studies.[10]

Conclusion

According to our study, leukocyte-poor PRP can significantly reduce the postoperative retear rate in the medium and long term regardless of the tear size and the method used for rotator cuff repair. However, the use of leukocyte-poor PRP failed to show clinically meaningful effects in terms of postoperative pain and patient-reported outcomes.

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Supplementary data

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