Meta-analysis

Clinical and Structural Outcomes After Arthroscopic Repair of Full-Thickness Rotator Cuff Tears With and Without Platelet-Rich Product Supplementation: A Meta-analysis and Meta-regression

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Purpose: The purpose of this study was to perform a systematic review, meta-analysis, and meta-regression of all Level I and Level II studies comparing the clinical or structural outcomes, or both, after rotator cuff repair with and without platelet-rich product (PRP) supplementation. **Methods:** A literature search of the PubMed and EMBASE databases was performed to identify all Level I or II studies comparing the clinical or structural outcomes, or both, after arthroscopic repair of full-thickness rotator cuff tears with (PRP+ group) and without (PRP− group) PRP supplementation. Data included outcome scores (American Shoulder and Elbow Surgeons [ASES], University of California Los Angeles [UCLA], Constant, Simple Shoulder Test [SST] and visual analog scale [VAS] scores) and retears diagnosed with imaging studies. Meta-analyses compared preoperative, postoperative, and gain in outcome scores and relative risk ratios for retears. Meta-regression compared the effect of PRP treatment on outcome scores and retear rates according to 6 covariates. Minimum effect sizes that were detectable with 80% power were also calculated for each study. **Results:** Eleven studies were included in this review and a maximum of 8 studies were used for meta-analyses according to data availability. There were no statistically significant differences between the PRP+ and PRP− groups for overall outcome scores or retear rates ($P > .05$). Overall gain in the Constant score was decreased when liquid PRP was injected over the tendon surface compared with PRP application at the tendon-bone interface (−6.88 points *v* +0.78 points, respectively; $P = .046$); however, this difference did not reach the previously reported minimum clinically important difference (MCID) for Constant scores. When the initial tear size was greater than 3 cm in anterior-posterior length, the PRP+ group exhibited decreased retear rates after double-row repairs when compared with the PRP− group (25.9% *v* 57.1%, respectively; $P = .046$). Sensitivity power analyses revealed that most included studies were only powered to detect large differences in outcome scores between groups. **Conclusions:** There were no statistically significant differences in overall gain in outcome scores or retear rates between treatment groups. Gain in Constant scores was significantly increased when PRPs were applied at the tendon-bone interface when compared with application over the top of the repaired tendon. Retear rates were significantly decreased when PRPs were used for the treatment of tears greater than 3 cm in anterior-posterior length using a double-row technique. Most of the included studies were only powered to detect large differences in outcome scores between treatment groups. In addition, an increased risk for selection, performance, and attrition biases was found. **Level of Evidence:** Level II, meta-analysis of Level I and Level II studies.

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Over the past decade, research has focused on enhancing the biomechanical properties of various rotator cuff repair constructs in an effort to improve the potential for tendon-footprint healing. Despite these improvements, retear rates have been persistently high regardless of the repair technique.[1-3] Given the high rate of structural failure at the tendon-bone interface,[4-7] successful rotator cuff repair is more likely to be reliant on the biological characteristics of healed tissues rather than the biomechanical strength of the repair construct.

After rotator cuff repair, it has been shown that the fibrovascular scar tissue deposited at the tendon-bone interface is inferior in quality to that of the native enthesis.[8,9] This factor may partially explain the high rate of observed retears at the tendon-bone interface after rotator cuff repair and the subsequent decline in clinical outcomes.[10-15] As a result, recent research has focused on the development of biological materials designed to enhance the strength and quality of repaired tissue at the tendon footprint.

Although many investigators have identified and studied the various biochemical signaling cascades involved in rotator cuff healing, an important study by Rodeo et al.[16] showed that isolated osteoinductive growth factors, specifically recombinant human bone morphogenic protein 12, could be used to improve the tissue quality at the site of rotator cuff repair in sheep. Others have shown that fibroblastic growth factor 2 may accelerate the remodeling process while also helping with the formation of granulation tissue.[17,18] Because many other growth factors are also released from the alpha granules of activated platelets in physiological concentrations, it is theorized that the application of a biological material rich in platelets may help stimulate the development of normal-appearing histologic tissue characteristics at the repair site, decrease retear rates, and improve clinical outcomes after rotator cuff repair.

Several prospective comparative studies have examined the clinical or structural outcomes after the integration of various platelet-rich products (PRPs) with rotator cuff repairs; however, the results have been conflicting to date. As a result, controversy exists regarding the clinical efficacy of PRP supplementation during arthroscopic rotator cuff repair. Therefore, the purpose of this study was to perform a systematic review, meta-analysis, and meta-regression of all the Level I and Level II studies comparing the clinical or structural outcomes, or both, after rotator cuff repair with and without PRP supplementation. We hypothesized that there would be no statistically significant differences in clinical or structural outcomes between treatment groups.

Methods

Study Design

This study was performed in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[19] and the research protocol designed by Wright et al.[20] in 2007. A systematic review, meta-analysis, and meta-regression were performed in which only prospective Level I or II clinical trials in any language with full-length articles that compared the clinical or structural outcomes, or both, after rotator cuff repair with and without PRP supplementation were included. Abstracts, meeting presentations, and all other studies that did not fit these strict criteria were excluded.

Literature Search

Two reviewers independently searched the PubMed and EMBASE databases along with major orthopaedic journals using the search terms "platelet rich plasma AND rotator cuff," "PRP AND rotator cuff," and "fibrin matrix AND rotator cuff" in September 2013. All the resulting titles and abstracts were screened for possible inclusion. After this initial search, the reference lists of included articles were carefully examined to locate further studies. Authors were also contacted to obtain information regarding completed but unpublished study results. The literature search was repeated in December 2013 to identify any new research that had become available between the time of the initial search and study completion.

Data Extraction

Two reviewers independently extracted article data. Data included study characteristics, patient demographics, surgical techniques, clinical and imaging follow-up intervals, and complications, along with clinical outcome scores and retears diagnosed by imaging studies. Whenever possible, extracted data were grouped into one of 2 categories depending on whether rotator cuff repair was performed with (PRP+ group) or without (PRP− group) concomitant PRP treatment. PRPs were defined as substances derived from standard platelet-rich plasma preparation protocols, including injectable liquid-based preparations or suturable products such as precoagulated gels or fibrin matrices.

Clinical outcome measures that were pooled and compared between PRP+ and PRP− groups included preoperative and minimum 12-month postoperative American Shoulder and Elbow Surgeons (ASES) scores, Constant-Murley (Constant) scores, University of California Los Angeles (UCLA) scores, Simple Shoulder Test (SST) scores, and visual analog scale (VAS) pain scores. Interval outcomes evaluations were also included when appropriate. To provide meaningful comparisons, clinical outcomes data were included in the meta-analysis only when 3 or more studies reported their results using the same validated outcomes measure with comparable follow-up intervals. For each included study, only preoperative and postoperative outcome scores (along with their ranges, standard deviations, or confidence intervals) were documented in an effort to obtain only those data points that had not been further manipulated by statistical methods. Therefore, any representations of "gain" or "change" in outcome scores were ignored. This strategy was chosen to ensure

identical treatment of all extracted data by avoiding the introduction of additional layers of potential variability in our results resulting from differing statistical methods that may have been used across each study.

Structural outcomes data obtained at least 9 months postoperatively from magnetic resonance imaging (MRI), magnetic resonance arthrography (MRA), computed tomographic arthrography (CTA) or ultrasonography (US) were included in the meta-analyses. In this study, a retear was defined as any recurrent or residual defect on postoperative imaging studies that was diagnosed as either a "retear" or a "lack of healing" in the study from which the data was obtained. Retears were grouped according to whether the initial tear size was less than 3 cm in anterior-posterior length or greater than 3 cm in anterior-posterior length. However, in one included study, Randelli et al.[21] reported tear sizes according to their medial-lateral length as classified by Patte.[22] In this case, stage 1 and 2 tears were considered to be less than 3 cm in anterior-posterior length, whereas stage 3 and 4 tears were considered to be greater than 3 cm in anterior-posterior length.

Quality Appraisal

A thorough risk-of-bias assessment was undertaken to identify factors that may have altered the results of this analysis. Two reviewers independently evaluated each included study and documented their potential for selection bias, performance bias, detection bias, attrition bias, and reporting bias using the Cochrane tool for assessing risk of bias in randomized trials.[23] Funnel plots were constructed to visually detect the presence of publication bias for both Constant scores and retear rates and are presented in Appendix A (available at www.arthroscopyjournal.org).

Synthesis of Results

Clinical Outcomes. Meta-analyses were performed to statistically compare the PRP+ and PRP− treatment groups regarding pre- and postoperative clinical outcome scores.[24] The weighted mean pre- to postoperative change in outcome scores was also calculated and compared between the PRP+ and PRP− treatment groups. The relative gain in outcome scores (θ) was defined as the pre- to postoperative change in the PRP+ group minus the pre- to postoperative change in the PRP− group. A positive number indicated that the PRP+ group had a greater pre- to postoperative change in the outcomes score, whereas a negative number indicated that the PRP− group had a greater pre- to postoperative change in the outcomes score.

Subgroup meta-analyses were performed to compare the overall effect of PRP treatment on preoperative, postoperative, and gain in Constant scores according to the following 6 covariates: levels of evidence (Level I *v* Level II), initial tear size (<3 cm *v* >3 cm), repair type (single row *v* double row), PRP preparation system (manual *v* commercial), PRP application procedure (injection at the tendon-bone interface *v* injection over the repaired tendon), and PRP types (platelet-rich fibrin

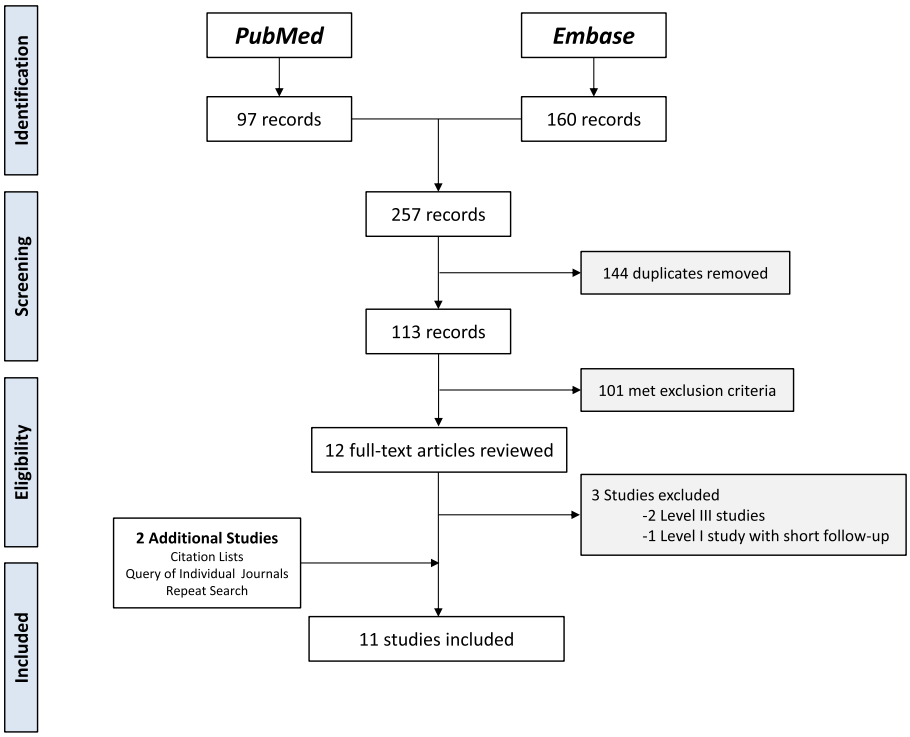


Fig 1. Flow diagram outlining the process of study selection.

matrix [PRFM] *v* liquid-based PRPs). Subgroup meta-analyses were performed using Constant scores only, because this measure was most consistently reported (8 studies).[21,25-31]

The concept of statistical power was explored using global variability estimates of Constant, ASES, and SST scores and sample sizes specific to each included study.[32,33] A minimum effect size able to be detected with 80% power was calculated for the observed sample size (sensitivity power analysis) and placed in the context of published minimum clinically important difference (MCID) estimates[32-35] and the small, medium, and large effect size guidelines described by Cohen.[36]

Structural Outcomes. Meta-analyses were performed to statistically compare the PRP+ and PRP− treatment groups regarding the overall relative risk ratio of a retear developing.[24] Subgroup meta-analyses were also performed to compare the overall effect of PRP treatment on the relative risk of sustaining a retear using the same 6 covariates as outlined earlier. A relative risk ratio of greater than 1.0 indicated an increased risk of sustaining a retear in the PRP+ group, whereas a relative risk ratio of less than 1.0 indicated an increased risk of sustaining a retear in the PRP− group.

Statistical Analyses

A random effects model, estimated using the DerSimonian-Laird method,[37] was chosen to combine the treatment effects of PRPs on clinical outcome scores and retear rates from each study. Leave-one-out analyses were performed to assess the sensitivity of results to each individual study. Meta-regression was performed to evaluate the effect of various characteristics of the included studies and their methods, including level of evidence, initial tear size, repair technique, PRP preparation, PRP application, and PRP consistency. Estimates of homogeneity quantities τ^2, Q, and I^2 are provided along with heterogeneity *P* values,[38] although these estimates were not used to direct our modeling decisions. Power calculations were performed using G*Power 3,[39] and all quantitative synthesis calculations were performed using the software OpenMeta[Analyst] for Windows.[40] Heterogeneity of $P < .10$ was considered statistically significant. In all other cases, statistical significance was defined for $P \leq .05$.

Results

Study Selection

A flow diagram outlining the process for study selection is presented in Figure 1. A literature search of the PubMed and EMBASE databases revealed a total of 113 unique records after the removal of duplicates. After the screening of titles and abstracts, 101 records were eliminated, leaving a total of 12 full-text articles

Table 1. Summary of Individual Study Characteristics

			Individual Study Characteristics								
Authors	Year	Level of Evidence	Shoulders Analyzed (PRP+/PRP−)	Male Sex, n (PRP+/PRP−)	Mean Age (PRP+/PRP−)	Minimum Clinical Follow-up, mo	Minimum Imaging Follow-up, mo	Repair Type	Imaging Modality	Tears <3 cm, n (PRP+/PRP−)	Tears >3 cm, n (PRP+/PRP−)
Castricini et al.[26]	2011	I	88 (43/45)	40 (17/23)	(55.5/55.2)	16	16	Double row	MRI	88 (43/45)	0
Randelli et al.[21]	2011	I	45 (22/23)	21 (8/13)	(61.3/59.5)	12	12	Single row	MRI/MRA/US	29 (14/15)	16 (8/8)
Gumina et al.[27]	2012	I	76 (39/37)	41 (20/21)	61 (60/63)	12	12	Single row	MRI	0	76 (39/37)
Weber et al.[43]	2012	I	59 (29/30)	36 (20/16)	(59.7/64.5)	12	12	Single row	MRI	56 (28/28)	3 (1/2)
Antuña et al.[25]	2013	I	28 (14/14)	6 (3/3)	65 (NR/NR)	12	12	Single row	MRA	0	28 (14/14)
Jo et al.[29]	2013	I	47 (24/23)	24 (10/14)	(64.2/61.9)	12	9	Double row	MRI/CTA	0	47 (24/23)
Ruiz-Moneo et al.[42]	2013	I	63 (32/31)	25 (14/11)	(56/55)	12	12	Double row	MRA	36 (18/18)	27 (14/13)
Malavolta et al.[30]	2014	I	54 (27/27)	17 (8/9)	(55.3/54.1)	12	12	Single row	MRI	54 (27/27)	0
Sánchez Márquez et al.[31]	2011	II	28 (14/14)	8 (NR/NR)	65 (NR/NR)	12	12	Single row	MRA	28 (14/14)	0
Jo et al.[28]	2011	II	42 (19/23)	15 (6/9)	(61.8/59.8)	16	9	Double row	MRI	22 (8/14)*	10 (7/3)*
Rodeo et al.[41]	2012	II	67 (35/32)	44 (23/21)	(58.9/57.2)	12	3	Double row	US	59 (30/29)	20 (10/10)
		Overall	597 (298/299)	269 (129/140)	(59.2/58.9)†	Mean 14.9	Mean 11.0	–	–	365 (181/184)	227 (117/110)

CTA, computed tomographic arthrography; MRA, magnetic resonance arthrography; MRI, magnetic resonance imaging; NR, not reported; PRP, platelet-rich product; US, ultrasonography.
*Includes only those who were available for imaging follow-up.
†Does not include data from Sánchez Márquez et al.[31] or Antuña et al.[25]

Table 2. Summary of Distinctive Study Characteristics and Relevant Findings

Distinctive Study Characteristics			
Authors	Population Differences	Outcomes Measured	Relevant Findings
Castricini et al.[26]	Included any full-thickness tear	Subjective: Constant Imaging: MRI at 16 mo	No difference in Constant scores between groups No difference in retear rates between groups
Randelli et al.[21]	Included any full-thickness tear Excluded smokers, steroid injections	Subjective: Constant, UCLA, SST Imaging: MRI/MRA/US at 12 mo	Significant improvement in Constant, UCLA, and SST in PRP+ group at 3 mo postoperatively No difference in outcomes at final follow-up
Gumina et al.[27]	Included only large tears Excluded partial tears, massive tears, traumatic tears, subscapularis tears, osteoarthritis	Subjective: Constant, SST Imaging: MRI at 12 mo	Significantly increased Constant score in PRP+ group, but no difference in change from pre- to postoperatively
Weber et al.[43]	Included any arthroscopic rotator cuff repair	Subjective: ASES, UCLA, SST, VAS Imaging: MRI at 12 mo ROM	No difference in outcome scores or ROM between groups No difference in retear rates between groups
Antuña et al.[25]	Included only repairable large tears (>5 cm)	Subjective: Constant, DASH, VAS Imaging: MRA at 12 mo	No difference in outcome scores 4 patients in PRP+ group had worsened outcomes between 12- and 24 mo follow-up
Jo et al.[29]	Included only large tears (>3 cm sagittal length) Included 4 partial repairs	Subjective: ASES, UCLA, Constant, SST, DASH, SPADI Imaging: MRI or CTA at 9 mo	PRP+ group had significantly decreased retear rates No difference in satisfaction between groups No difference in outcome scores between groups
Ruiz-Moneo et al.[42]	Included tendon retraction and fatty infiltration, smokers	Subjective: UCLA Imaging: MRA at 12 mo	No difference in UCLA scores between groups No difference in retear rates between groups
Malavolta et al.[30]	Included only tears < 3 cm in sagittal length	Subjective: Constant, UCLA Imaging: MRI at 3, 6, and 12 mo	No differences in Constant or UCLA scores between groups No difference in retear rates between groups
Sánchez Márquez et al.[31]	Included only repairable large tears (>5 cm) Excluded subscapularis tears	Subjective: Constant Imaging: MRA at 12 mo	No difference in Constant scores between groups No difference in retear rates between groups
Jo et al.[28]	Included all repairable full-thickness tears	Subjective: ASES, UCLA, Constant, SST, DASH, SPADI Imaging: MRI at 9 mo	ASES, Constant, and SPADI scores significantly increased in PRP− group 3 mo postoperatively No difference in clinical outcomes at final follow-up
Rodeo et al.[41]	Included full-thickness tears, age > 40 yr	Subjective: ASES, L'Insalata Imaging: US at 12 wk	No difference in outcome scores between groups No difference in retear rates between groups

ASES, American Shoulder and Elbow Surgeons; CTA, computed tomographic arthrography; DASH, Disabilities of the Arm, Shoulder, and Hand; MRA, magnetic resonance arthrography; MRI, magnetic resonance imaging; ROM, range of motion; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; UCLA, University of California Los Angeles; US, ultrasonography; VAS, visual analog scale.

that were reviewed. Three of these studies were excluded, leaving a total of 9 included studies.[21,25-29,41-43] Manual text and reference list searches revealed 2 additional studies that were also included.[30,31] Therefore, a total of 11 studies were included in this review, and a maximum of 8 studies were used for each meta-analysis according to data availability. Query of major orthopaedic journals and a repeated search at the end of the study period did not produce any other relevant studies.

Study Characteristics

Table 1 summarizes the individual study characteristics. Table 2 highlights the distinctive characteristics of each study, including their relevant findings. Table 3 outlines the methods of PRP preparation, rotator cuff repair techniques, and rehabilitation protocols used in each study. Regarding complications and treatment failures, Randelli et al.[21] reported that one patient in the PRP− group underwent revision rotator cuff repair 26 months after the index surgery. Castricini et al.[26] reported 3 cases of shoulder stiffness (2 in the PRP+ group, 1 in the PRP− group) that resolved with subsequent physical therapy. In addition, Malavolta et al.[30] reported 2 cases of shoulder stiffness (one in the PRP+ group and one in the PRP− group) that were treated nonoperatively. Six of the 11 studies reported no complications or treatment failures,[27,28,31,41-43] whereas 2 of the 11 studies did not report rates of complications or treatment failures.[25,29]

Risk of Bias Assessment

Figure 2 summarizes the results of the risk of bias evaluation for each study. The risk of bias was found to be high for 5 of 11 studies (45.5%) regarding randomization procedures (selection bias)[26-28,41,43] and for 7 of 11 (63.6%) studies regarding performance bias.[21,25,27-29,31] In 6 of 11 studies (54.5%), the completeness of the

Table 3. Summary of PRP Preparation Protocols, Surgical Techniques, and Rehabilitation Procedures

	Surgical Treatment and Rehabilitation Protocols		
	PRP Preparation Protocol	Rotator Cuff Repair Technique	Rehabilitation Protocol
Castricini et al.[26]	9 mL blood drawn, mixed with anticoagulant and separator gel, centrifuged for 6 min at 1,100 rpm Supernatant mixed with calcium chloride in Wheaton bottle, centrifuged again at 4,500 RCF for 25 min PRFM formed at bottom of container PRFM inserted between tendon and footprint	Double-row repair using 1 metal anchor medially (mattress configuration with nonsliding knot) and 2 anchors laterally tied using sliding knot with 3 alternating half-hitches	Shoulders immobilized in abduction for 3 wk Pendulum exercises allowed immediately postoperatively Passive ROM and active-assisted ROM for FF and ER at 3 wk Rotator cuff and periscapular strengthening at 6 wk Return to light activity at 3 mo, full activity at 6 mo
Randelli et al.[21]	54 mL of blood drawn, mixed with 6 mL anticoagulant and centrifuged for 15 min at 3,200 rpm PRP isolated from floating buoy PRP mixed with concentrated fibrinogen and thrombin that was obtained using other procedures PRP injected into dry subacromial space between the repaired tendon and footprint	Single-row repair using 5.0- and 6.5-mm absorbable anchors Acromioplasty performed in all cases	Continuous sling use for 10 d Passive-assisted ROM begun after 10 d Active-assisted ROM at 30 d Strengthening exercises begun at 2 mo
Gumina et al.[27]	10 mL blood drawn and centrifuged at 20 g for 10 min Supernatant mixed with calcium gluconate and an anticoagulant and centrifuged at >1,500 g for 20-30 min PRFM inserted at tendon-bone interface (one gel per anchor)	Single-row technique using preloaded 5.0-mm titanium anchors	Internal rotation sling Passive range of motion for first wk Sling removed at 4 wk, active-assisted ROM begun Full active motion allowed at 6-8 wk Strengthening at 15 wk
Weber et al.[43]	Used commercially available PRP preparation system PRFM inserted at tendon-bone interface	Standard single-row repair with suture anchors in all patients	Protocol not specified
Antuña et al.[25]	Used commercially available PRP preparation system 120 mL blood drawn 6 mL of resulting PRP applied directly over "repair site"	Single-row technique in all patients	Shoulder immobilized in abduction for 6 wk "Standard" rehabilitation program thereafter
Jo et al.[29]	Used platelet pheresis system with leukoreduction set Used 90-min double-needle procedure for blood collection PRP collection occurred 1 d before surgery Calcium gluconate was added to the PRP 1 hr before surgery to form a gel that could be easily implanted PRP interposed between tendon and bone (3 gels per shoulder)	Double-row repair using suture bridge technique Acromioplasty rarely performed Used tendon mobilization procedures: CH ligament release, superior capsulotomy, tendon medialization	Shoulders immobilized in abduction for 4-6 wk Passive ROM and Active assisted ROM begun after 4-6 wk Strengthening at 3 mo Return to sports between 6 and 9 mo

(continued)

Table 3. Continued

	Surgical Treatment and Rehabilitation Protocols		
	PRP Preparation Protocol	Rotator Cuff Repair Technique	Rehabilitation Protocol
Ruiz-Moneo et al.[42]	18-27 mL blood drawn, mixed with citrate, and centrifuged at 460 g for 8 min Leukoreduction with supernatant collected and mixed with calcium chloride PRP injected into tendon after repair and, after fluid evacuation from subacromial space, "spread widely" over the top of the repaired tendon	Double-row suture bridge technique using 5.5-mm anchors Acromioplasty performed when considered necessary	Protocol not specified
Malavolta et al.[30]	Used commercially available PRP preparation system 400 mL of blood was drawn to obtain approximately 30 mL of PRP Autologous thrombin used for platelet activation PRP injected percutaneously at tendon-bone interface between anterior and lateral portals	Single-row technique in all patients Acromioplasty performed in all patients Biceps tenodesis incorporated into rotator cuff repair constructs	Sling immobilization for 6 wk Passive ROM began after 3 wk Active and active-assisted ROM begun after 6 wk Strengthening begun after approximately 12 wk
Sánchez Márquez et al.[31]	Used commercially available PRP preparation system 120 mL blood drawn 7 mL of resulting PRP applied directly over "repair site"	Single-row technique using a mean of 3 double-loaded suture anchors (range, 2-5)	Immobilization in standard sling for 6 wk Strengthening delayed until 12 wk
Jo et al.[28]	Used platelet pheresis system with leukoreduction set Used 90-min double-needle procedure for blood collection PRP collection occurred 1 d before surgery Calcium gluconate was added to the PRP 1 hr before surgery to form a gel that could be easily implanted PRP interposed between tendon and bone	Double-row repair Acromioplasty rarely performed	Shoulders immobilized in abduction for 4-6 wk Passive ROM and active-assisted ROM begun after 4-6 wk Strengthening at 3 mo Return to sports between 6 and 9 mo
Rodeo et al.[41]	9 mL of blood drawn, used commercially available PRP preparation system Details not specified	Single-row, double-row, and transosseous equivalent repairs (reported no difference in construct type between PRP+ and PRP− groups) Acromioplasty routinely performed	Sling not specified, passive motion only until 6 wk postoperatively Active-assisted ROM within the plane of the scapula for 6 wk progressing to active elevation Rotator cuff and periscapular strengthening at 12 wk Home exercise program begun between 16 and 20 wk

CH, ■■■; ER, external rotation; FF, forward flexion; PRFM, platelet-rich fibrin matrix; RCF, relative centrifugal force; ROM, range of motion.

Investigators	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias		Other Biases
	Randomization	Allocation Concealment	Participant/Investigator Blinding	Assessor Blinding	Incomplete Data	Selective Reporting	Conflicts of Interest	
Castricini et al[26]	−	+	+	+	+	+	+	+
Randelli et al[21]	?	+	−	?	?	+	+	+
Gumina et al[27]	−	?	−	+	?	+	+	+
Weber et al[43]	−	−	+	+	?	+	+	?
Antuña et al[25]	?	+	−	+	?	+	+	+
Jo et al[29]	+	+	−	+	−	−	+	+
Ruiz-Moneo et al[42]	?	?	+	+	?	−	+	+
Malavolta et al[30]	?	+	?	+	+	+	+	+
Sánchez Márquez et al[31]	?	?	−	?	?	+	+	+
Jo et al[28]	−	−	−	?	−	+	+	+
Rodeo et al[41]	−	?	−	+	−	+	+	+

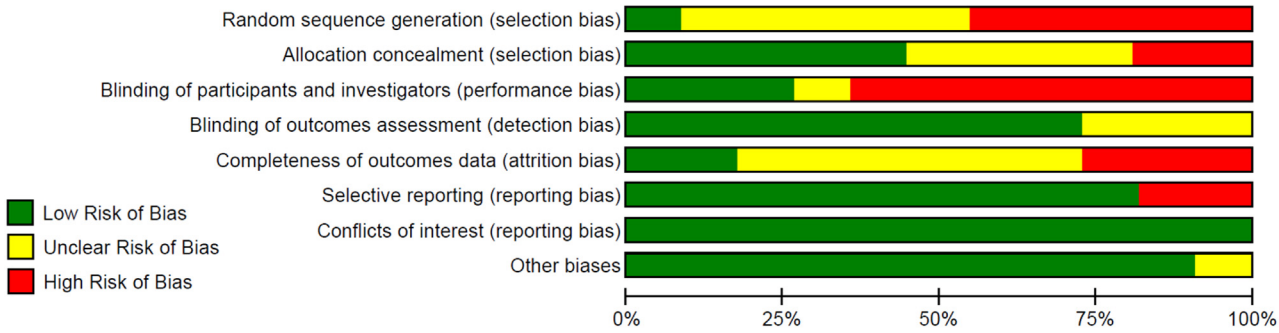


Fig 2. Results of risk of bias evaluation for each study according to the recommendations of the Cochrane Collaboration.[23]

reported data was unclear because of the lack of either a Consolidated Standards of Reporting Trials statement or intention-to-treat analysis.[21,25,27,31,42,43] The likelihood of publication bias was found to be low for Constant scores and high for retear rates based on visual examination of funnel plots (Appendix A, available at www.arthroscopyjournal.org).

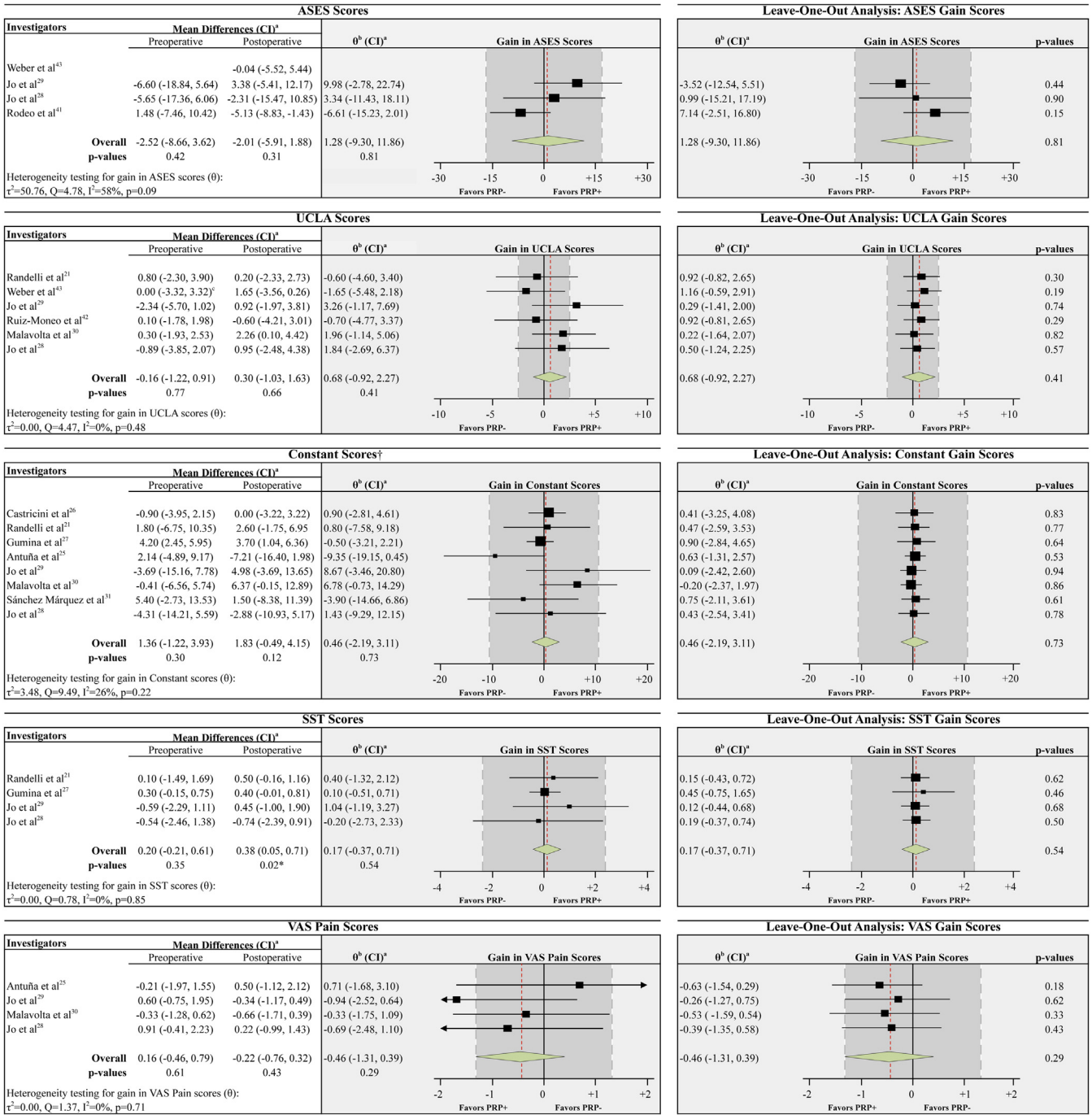
Clinical Outcomes

Figure 3 summarizes the results of the meta-analyses regarding overall clinical outcome scores. Each study found significant improvements in outcome scores when compared with preoperative baseline values. With the exception of postoperative SST scores, there were no statistically significant differences in pre- or postoperative outcome scores between the PRP+ and PRP− treatment groups ($P > .05$). There were also no statistically significant differences in the gain in outcome scores between PRP+ and PRP− treatment groups. Leave-one-out analyses revealed that exclusion of any single study would not result in a categorically different statistical conclusion (i.e., change from $P > .05$ to $P < .05$) regarding the overall effect of PRP treatment for any of the 5 outcome measures.

Figure 4 summarizes the results of subgroup meta-analyses for Constant scores across the 6 analyzed covariates (Appendices B1 and B2 [available at www.arthroscopyjournal.org] for full meta-regression data set for Constant scores). PRP treatment by injection over the surface of the repaired tendon showed a significantly decreased gain in the Constant score when compared with PRP treatment through application at the tendon-bone interface (−6.88 points v +0.78 points, respectively; $P = .046$).

Figure 5 illustrates the recovery paths of both Constant and UCLA scores at 3-, 6-, and 12-month intervals. There were no statistically significant differences in Constant or UCLA scores between the PRP+ and PRP− treatment groups at any point along their respective recovery paths ($P > .05$). These data suggest that functional improvement may not be accelerated by PRP application in arthroscopic repair of full-thickness rotator cuff tears.

Figure 6 illustrates the results of sensitivity power analysis of each included study. In general, the sample sizes of the included studies were only powered to detect large differences in outcome scores between treatment groups. Castricini et al.[26] had the largest enrollment among studies in the analysis and was the only study with at least 80% power to detect the previously reported MCID for Constant scores between PRP+ and PRP− treatment groups. For ASES scores, Rodeo et al.,[41] and both studies by Jo et al.[28,29] were powered to detect a difference in ASES scores within the range of MCIDs reported by Tashjian et al.[33] None of the studies that reported SST scores were powered to detect a difference smaller than the reported MCID for SST scores.



†See Appendices B1 and B2 for the full meta-regression results for Constant scores.
**Indicates a statistically significant difference between PRP+ and PRP- groups.*
[a]CI = 95% Confidence Interval.
[b]θ = Gain in outcomes scores (Postoperative Difference - Preoperative Difference).
[c]Confidence interval derived from imputed standard deviations.
Note: Boundaries of shaded areas represent Minimum Clinically Important Differences (MCIDs) that have been reported in the literature.[32-35]

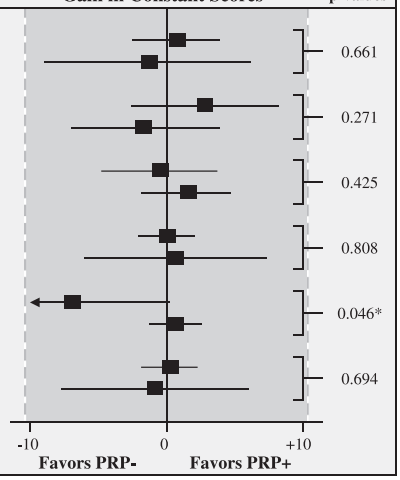
Fig 3. Meta-analyses and leave-one-out analyses for outcomes scores after a minimum 12-month follow-up period.

Structural Outcomes

The results of the meta-analyses regarding structural outcomes are presented in Figure 7. Overall, there were no statistically significant differences in retear rates between the PRP+ and PRP− treatment groups; however, after exclusion of data from Antuña et al.[25] (by leave-one-out analysis), a statistically significant increase in the relative risk of a retear developing was found in the PRP− group ($P = .05$). Meta-regression showed that the overall effect of PRP treatment on retear rates was not significantly different among the 6 previously mentioned

Subgroup Meta-Regression for Constant Scores†

Covariate	Subgroup	# Studies	Mean Differences (CI)[a]		θ[b] (CI)[a]	p-values[c]
			Preoperative	Postoperative		
Evidence Level	Level I Evidence	6	1.34 (-1.49, 4.17)	2.21 (-0.42, 4.83)	0.77 (-2.46, 3.99)	0.661
	Level II Evidence	2	0.97 (-8.51, 10.45)	-1.14 (-7.38, 5.11)	-1.23 (-8.82, 6.37)	
Initial Tear Size	< 3 cm Sagittal Length	2	-0.80 (-3.54, 1.93)	2.53 (-3.58, 8.64)	2.90 (-2.56, 8.36)	0.271
	> 3 cm Sagittal Length	4	3.97 (2.32, 5.62)	1.69 (-2.93, 6.30)	-1.49 (-7.02, 4.03)	
Repair Technique	Single-Row	5	3.75 (2.17, 5.33)	2.66 (-0.35, 5.67)	-0.48 (-4.71, 3.75)	0.425
	Double-Row	3	-1.35 (-4.17, 1.48)	0.17 (-2.65, 3.00)	1.55 (-1.82, 4.92)	
PRP Preparation	Manual System	3	1.84 (-2.24, 5.92)	2.18 (-0.17, 4.54)	0.04 (-2.08, 2.16)	0.808
	Commercial System	5	0.53 (-3.01, 4.07)	0.93 (-4.12, 5.99)	0.76 (-5.91, 7.44)	
PRP Application	Injection over tendon	2	0.97 (-8.51, 10.45)	-3.06 (-11.58, 5.47)	-6.88 (-14.12, 0.37)	0.046*
	Tendon-Bone Interface	6	0.65 (-2.57, 3.87)	2.40 (0.29, 4.51)	0.78 (-1.19, 2.76)	
PRP Consistency	Fibrin Matrix	4	0.40 (-3.94, 4.74)	1.75 (-1.14, 4.64)	0.31 (-1.81, 2.42)	0.694
	Liquid	4	1.84 (-1.80, 5.48)	1.65 (-3.18, 6.48)	-0.84 (-7.80, 6.12)	



†See Appendices B1 and B2 for full meta-regression data set for Constant scores.
**Indicates a statistically significant difference between subgroups.*
[a]CI = 95% Confidence Interval. Confidence intervals that include 0 are not statistically significant.
[b]θ = Gain in outcomes scores (Postoperative Difference - Preoperative Difference).
[c]Stated p-values compare the overall effect of PRPs on gain in Constant scores between subgroups.
Note: Boundary of shaded area represents the Minimum Clinically Important Difference (MCIDs) reported by Kukkonen et al.[32]

Fig 4. Subgroup meta-regression highlighting the effects of the 6 covariates on preoperative, postoperative, and gain in Constant scores.

covariates (Fig 8; Appendices C1 and C2 [available at www.arthroscopyjournal.org] for full meta-regression data set for retear rates). Among initial tear sizes greater than 3 cm in anterior-posterior length, the PRP+ group exhibited a larger retear reduction effect after double-row repairs when compared with the PRP− group (25.9% *v* 57.1%, respectively; $P = .046$) and for PRFM when compared with liquid-based PRPs (14.8% *v* 46.8%, respectively; $P = .054$ [Appendices C1 and C2, available at www.arthroscopyjournal.org]).

Discussion

The results of these meta-analyses partially confirmed our hypothesis that there would be no statistically significant differences in clinical or structural outcomes between PRP+ and PRP− treatment groups. Although there were no overall differences in outcome scores or retear rates, meta-regression indicated that the overall gain in the Constant score was significantly increased when PRPs were placed at the tendon-bone interface rather than over the surface of the repaired tendon ($P = .046$). In the PRP+ group, those with cuff tears greater than 3 cm in anterior-posterior length that were repaired using a double-row technique showed a statistically significant reduction in retear rates when compared with the rest of the study population ($P = .046$). Retear rates were also decreased when PRFMs (as opposed to liquid-based PRPs) were used to supplement the repairs ($P = .054$); however, this result did not reach statistical significance.

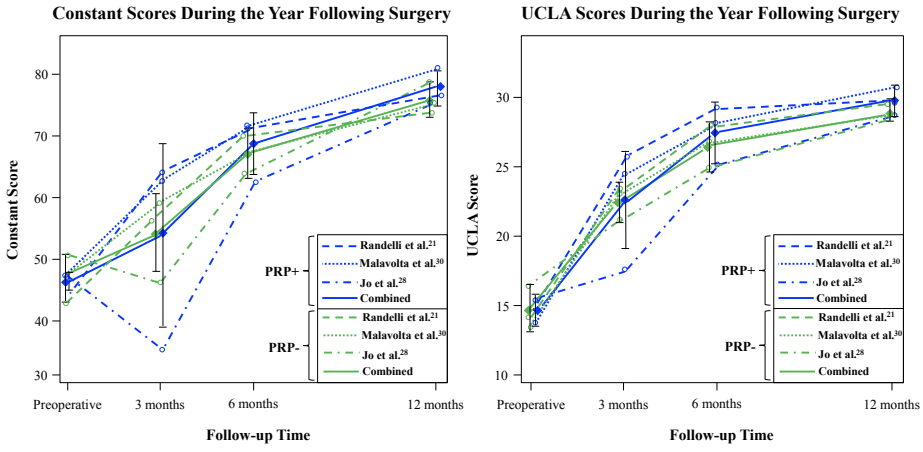


Fig 5. Recovery paths of Constant and University of California Los Angeles (UCLA) scores up to 12 months postoperatively.

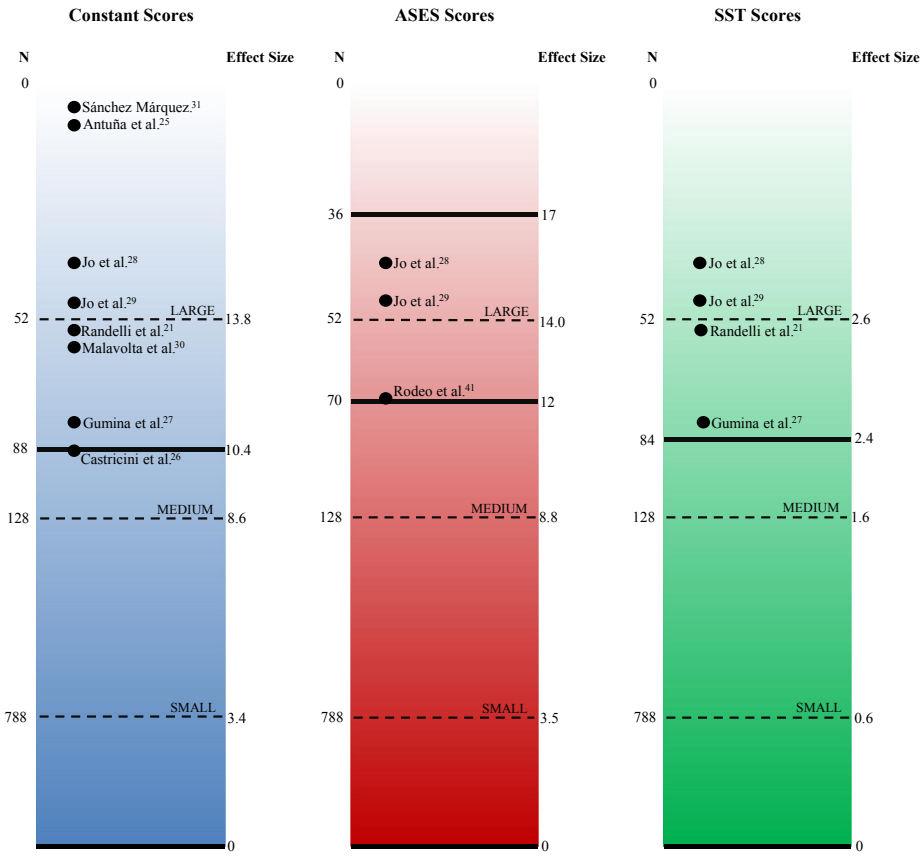
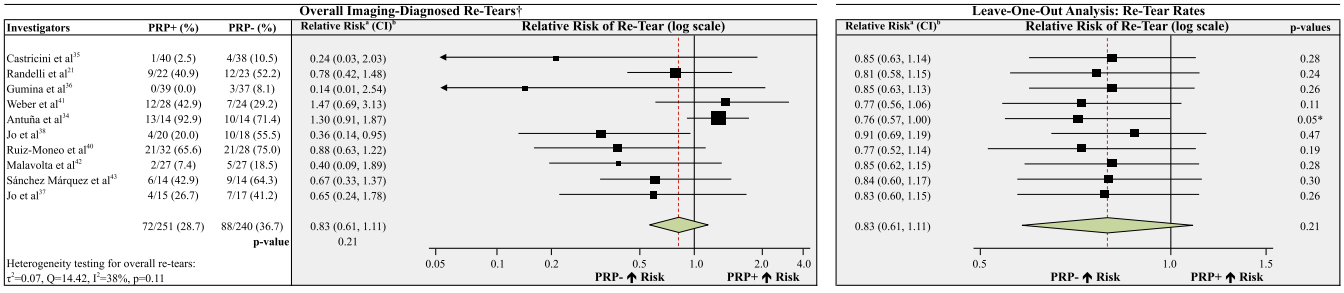


Fig 6. Plots showing the relation of sample size and effect size able to be detected with 80% power in the 3 clinical outcome scores given global standard deviation estimates.[32,33] Data points represent the smallest difference in outcomes gain scores between the PRP+ and PRP− groups that could be detected with 80% power given the sample sizes reported in each study. Solid lines represent minimum clinically important difference (MCID) estimates found in the literature.[32,33] Moving from low to high, dashed lines indicate small, medium, and large effect sizes as described by Cohen.[36] (ASES, American Shoulder and Elbow Surgeons; SST, Simple Shoulder Test.)

In this study, a random-effects model was chosen because standard diagnostic tests showed evidence of heterogeneity for the calculations combining relatively many studies and are known to be substantially underpowered when combining several studies only[44]; there were also considerable differences in experimental methodology, the potential for biases, and sample demographics among the included studies, and random-effects models allow for better generalizability of conclusions when extrapolating to different surgeons, surgical techniques, and patient populations.[45]

It was also critical to recognize and address several important confounding factors that may have influenced our overall results:

1. The inclusion of Level II studies in a meta-analysis has been purported to increase the potential for various biases, which may produce skewed results.[46]
2. As shown by Carbonel et al.[47] and Park et al.,[48] initial tear size may play a role in postoperative outcome scores after minimum 2-year follow-up.

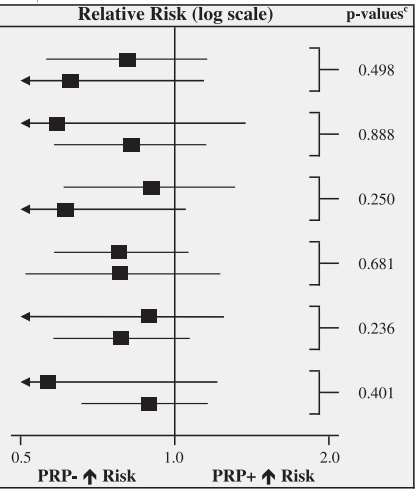


†*See Appendix C1 and C2 for full meta-regression results of imaging-diagnosed re-tears.*
[a]*Relative Risk: Values of greater than 1.0 indicate an increased risk of re-tears in the PRP+ group while values of less than 1.0 indicate an increased risk of re-tears in the PRP- group.*
[b]*CI = 95% Confidence Interval*
**Indicates statistical significance*

Fig 7. Meta-analyses and leave-one-out analyses of overall re-tear rates and relative risk ratios of sustaining a retear before final follow-up.

Subgroup Meta-Regression for All Imaging-Diagnosed Re-Tears†

Covariate	Subgroup	# Studies	PRP+ (%)	PRP- (%)	Relative Risk[a] (CI)[b]
Evidence Level	Level I Evidence	8	62/222 (27.9)	72/209 (34.5)	0.85 (0.59, 1.21)
	Level II Evidence	2	10/29 (34.5)	16/31 (51.6)	0.66 (0.37, 1.19)
Initial Tear Size	< 3 cm Sagittal Length	5	17/116 (14.7)	24/116 (20.7)	0.62 (0.26, 1.46)
	> 3 cm Sagittal Length	7	34/103 (33.0)	43/96 (44.8)	0.86 (0.61, 1.21)
Repair Technique	Single-Row	6	42/144 (29.2)	46/139 (33.1)	0.95 (0.64, 1.40)
	Double-Row	4	30/107 (28.0)	42/101 (41.6)	0.65 (0.40, 1.07)
PRP Preparation	Manual System	4	22/133 (16.5)	40/119 (33.6)	0.82 (0.61, 1.10)
	Commercial System	6	41/118 (34.7)	48/114 (42.1)	0.82 (0.52, 1.31)
PRP Application	Injection over tendon	2	10/29 (34.5)	16/31 (51.6)	0.66 (0.37, 1.19)
	Tendon-Bone Interface	8	72/251 (28.7)	88/240 (36.7)	0.83 (0.61, 1.11)
PRP Consistency	Fibrin Matrix	5	21/142 (14.8)	31/134 (23.1)	0.59 (0.27, 1.28)
	Liquid	5	51/95 (53.7)	57/106 (53.8)	0.92 (0.70, 1.22)



†See Appendices C1 and C2 for full meta-regression data set for imaging-diagnosed re-tears.

[a]Relative Risk: Values of greater than 1.0 indicate an increased risk of re-tears in the PRP+ group while values of less than 1.0 indicate an increased risk of re-tears in the PRP- group.

[b]CI = 95% Confidence Interval. Confidence intervals that include 1.0 are not statistically significant.

[c]Stated p-values compare the overall effect of PRPs on relative risk of re-tears between subgroups.

Fig 8. Subgroup meta-regression highlighting the overall effects of the 6 covariates on the relative risk of retears between the PRP+ and PRP− treatment groups.

3. Single- versus double-row repair constructs may also have an impact on clinical outcomes; however, a recent meta-analysis of Level I randomized trials comparing single- versus double-row rotator cuff repair revealed no differences in clinical outcomes after a mean 23.2-month follow-up period.[2]
4. Many of the studies in this review also reported varying PRP preparation protocols that may have produced PRP solutions with widely variable platelet concentrations, biochemical activation cascades, and leukocyte concentrations.[49-55]
5. Some investigators manually prepared the PRP using basic centrifugation devices,[21,26,27,42] whereas others used commercially available PRP preparation systems,[25,28-31,41,43] which have been theorized to produce more consistent results.[54,55]
6. The method of PRP application to the repaired tendon also varied across each study. Some investigators injected the final liquid-based PRP into the arthroscopic working portal after rotator cuff repair and evacuation of subacromial fluid,[25,31,42] whereas others strategically placed the PRP liquid (or gel) at the tendon-bone interface where healing occurs.[21,26-30,43]

To account for these potentially confounding variables, we performed meta-regression analyses to evaluate the effect of each of the 6 mentioned covariates on overall clinical and structural outcomes after rotator cuff repair with or without PRP augmentation. Injection of a PRP liquid over the previously repaired tendon produced a significant decrease in the overall gain in Constant scores when compared with those in which PRP was inserted at the tendon-bone interface. These data suggest that the effect of PRPs on clinical outcomes may be optimized when applied directly to the site at which healing is desired; however, it should be noted that a statistically significant difference does not necessarily indicate clinical relevance.

In accordance with the claims of others,[56-58] Randelli et al.[21] found that PRPs may accelerate functional recovery. Although there were no differences in outcome scores after 6-, 12-, or 24-month follow-up periods in their study, Randelli et al.[21] found statistically significant improvements in Constant, UCLA, and SST scores in the PRP+ group after a 3-month follow-up period when compared with the PRP− group. To test the theory of accelerated recovery, we also evaluated Constant and UCLA scores after 3-, 6-, and 12-month follow-up periods through meta-analysis. Ultimately, we found no statistically significant differences in Constant or UCLA scores at any of these time intervals throughout the recovery paths of each treatment group.

Despite the statistically significant decrease in retear rates in the PRP+ group shown by Jo et al.,[29] meta-analysis of data from 10 studies and 530 shoulders (Rodeo et al.[41] excluded because of short follow-up) revealed no differences in retear rates after a mean 11.8-month imaging follow-up period. Similar to our analysis of clinical outcomes, we performed a subgroup meta-regression for each of the 6 previously mentioned covariates. None of the covariates resulted in a significant change in the overall effect of PRP treatment on retear rates; however, initial tear sizes, repair

techniques, and PRP consistency may have had substantial individual effects on retear rates.

Limitations

There are several additional limitations to this study that should be considered. First, the potential for selection bias, performance bias, detection bias, attrition bias, and reporting bias is expected with any meta-analysis. Therefore, we conducted a thorough risk of bias assessment and presented the results in Figure 2 to aid in data interpretation. Second, we were unable to perform a meta-analysis on the effects of other potential confounders (such as the volume of whole blood used, the inclusion or exclusion of leukocytes, and the use or nonuse of thrombin for platelet activation) because of lack of reporting. Third, the Constant score has not been specifically validated for use in rotator cuff disease; however, its use has been widely reported in the literature.

Conclusions

There were no statistically significant differences in overall gain in outcome scores or retear rates between treatment groups. Gain in Constant scores were significantly increased when PRPs were applied at the tendon-bone interface when compared with application over the top of the repaired tendon. Retear rates were significantly decreased when PRPs were used for the treatment of tears greater than 3 cm in anterior-posterior length using a double-row technique. Most of the included studies were only powered to detect large differences in outcome scores between treatment groups. In addition, an increased risk for selection, performance, and attrition biases was found.

Acknowledgment

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