Check for updates

Platelet-Rich Plasma Versus Alternative Injections for Osteoarthritis of the Knee

CME

A Systematic Review and Statistical Fragility Index–Based Meta-analysis of Randomized Controlled Trials

Jacob F. Oeding,*†‡ MS, Nathan H. Varady,§ MD, MBA, Forrest W. Fearington,† BS, Ayoosh Pareek,§ MD, Sabrina M. Strickland,§ MD, Benedict U. Nwachukwu,§ MD, MBA, Christopher L. Camp,‖ MD, and Aaron J. Krych,‖ MD
Investigation performed at Mayo Clinic, Rochester, Minnesota, USA

Background: Based in part on the results of randomized controlled trials (RCTs) that suggest a beneficial effect over alternative treatment options, the use of platelet-rich plasma (PRP) for the management of knee osteoarthritis (OA) is widespread and increasing. However, the extent to which these studies are vulnerable to slight variations in the outcomes of patients remains unknown.

Purpose: To evaluate the statistical fragility of conclusions from RCTs that reported outcomes of patients with knee OA who were treated with PRP versus alternative nonoperative management strategies.

Study Design: Systematic review and meta-analysis; Level of evidence, 2.

Methods: All RCTs comparing PRP with alternative nonoperative treatment options for knee OA were identified. The fragility index (FI) and reverse FI were applied to assess the robustness of conclusions regarding the efficacy of PRP for knee OA. Meta-analyses were performed to determine the minimum number of patients from ≥1 trials included in the meta-analysis for which a modification on the event status would change the statistical significance of the pooled treatment effect.

Results: In total, this analysis included outcomes from 1993 patients with a mean ± SD age of 58.0 ± 3.8 years. The mean number of events required to reverse significance of individual RCTs (FI) was 4.57 ± 5.85. Based on random-effects meta-analyses, PRP demonstrated a significantly higher rate of successful outcomes when compared with hyaluronic acid (P = .002; odds ratio [OR], 2.19; 95% CI, 1.33-3.62), as well as higher rates of patient-reported symptom relief (P = .019; OR, 1.55; 95% CI, 1.07-2.24), not requiring a reintervention after the initial injection treatment (P = .002; OR, 2.17; 95% CI, 1.33-3.53), and achieving the minimal clinically important difference (MCID) for pain improvement (P = .007; OR, 6.19; 95% CI, 1.63-23.42) when compared with all alternative nonoperative treatments. Overall, the mean number of events per meta-analysis required to change the statistical significance of the pooled treatment effect was 8.67 ± 4.50.

Conclusion: Conclusions drawn from individual RCTs evaluating PRP for knee OA demonstrated slight robustness. On meta-analysis, PRP demonstrated a significant advantage over hyaluronic acid as well as improved symptom relief, lower rates of reintervention, and more frequent achievement of the MCID for pain improvement when compared with alternative nonoperative treatment options. Statistically significant pooled treatment effects evaluating PRP for knee OA are more robust than approximately half of all comparable meta-analyses in medicine and health care. Future RCTs and meta-analyses should consider reporting FIs and fragility quotients to facilitate interpretation of results in their proper context.

Keywords: fragility index; randomized controlled trial; platelet-rich plasma; knee osteoarthritis

Knee osteoarthritis (OA) is a highly prevalent degenerative joint disease affecting 20% of all adults >45 years old in the United States,[46] with >654 million people affected globally.[10] Disproportionately affecting older adults, women, and those who are overweight or obese,[46] knee OA is a leading cause of disability and functional limitation, resulting in reduced quality of life, increased health care costs, and lost productivity. Nonsurgical treatments such as physical therapy, anti-inflammatory

The American Journal of Sports Medicine
2024;52(12):3147–3160
DOI: 10.1177/03635465231224463
© 2024 The Author(s)

medications, and intra-articular corticosteroid injections (CSIs) remain the standard of care for nonoperative management of symptoms. Recently, however, treatments such as platelet-rich plasma (PRP) have increased in popularity due in large part to research suggesting beneficial effects over alternative nonoperative treatment options for knee OA, with nearly 1000 publications on the subject over the past 12 years alone.[11]

PRP is derived from the patient's own blood and contains platelets, growth factors, and cytokines that may stimulate tissue regeneration and reduce inflammation.[19] As the applications for PRP have grown, so too have the variety of proprietary PRP preparation devices and preparations.[20] While intra-articular PRP injections have been proposed as a potential treatment for knee OA, the evidence for PRP in knee OA is conflicting, with some studies showing significant benefits while others showed no difference compared with control treatments.[38] Currently, the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline on management of OA of the knee states that PRP "may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee," with a strength of recommendation of "limited."[1] This recommendation was downgraded 2 levels from "strong" to "limited" based on concerns including the heterogeneity of results.[1]

The fragility index (FI) and reverse FI (RFI) are statistical tools that have recently garnered increased attention in the orthopaedic literature.[8,12,18,22,44] The FI measures the minimum number of events (in this case, treatment successes or failures) that would need to change from one group to the other to alter the conclusions of a statistically significant trial, while the RFI measures the number of flipped outcome events needed to convert a statistically nonsignificant trial to a significant one. In short, calculation entails simultaneously adding and subtracting outcome events and nonevents in a sequential manner until a reversal of statistical significance is achieved.[47] To standardize fragility to the sample size of each randomized controlled trial (RCT), the fragility quotient (FQ) can also be calculated by dividing the FI by the respective RCT sample size for each study. Thus, smaller FQs demonstrate a less robust study outcome, while larger FQs correspond to more robust study outcomes. These tools can be used to evaluate the robustness of study findings and help identify studies that may be at higher risk of being fragile, meaning that the results could change with just a few additional events.[3] For example, a recent review of statistically significant findings from RCTs in hip and knee arthroplasty found that the median FI was 1, meaning that reversing the outcome of a single patient in either treatment group of each trial would alter the results of the trial from significant to nonsignificant.[18]

Given that RCTs are often considered the gold standard for evidence in medical literature and that significant findings may lead to the portrayal of PRP as a panacea with regenerative capacities by the media and popular press, resulting in patients seeking out PRP treatment independently despite its significant out-of-pocket cost and lack of reimbursement by many insurance providers, there is a need to evaluate evidence for PRP for the management of knee OA through a careful lens. Thus, the purpose of this study was to (1) evaluate the statistical fragility of RCTs assessing the effectiveness of PRP in knee OA and (2) determine whether meta-analyses of individual RCTs affect the robustness of conclusions that can be drawn regarding the effectiveness of PRP for knee OA. We hypothesized that some individual high-level studies using PRP for knee OA would be statistically fragile, but that meta-analyses would demonstrate greater robustness of findings. By identifying studies with higher risk of fragility, we aim to provide clinicians and researchers with a better understanding of the reliability of the evidence for PRP in knee OA and highlight the need for further research to confirm or refute the effectiveness of this treatment option.

METHODS

Search Strategy

This study followed the recommendations provided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[33] The PubMed, OVID/Medline, and Cochrane libraries were searched to perform a comprehensive review of the literature investi-

*Address correspondence to Jacob F. Oeding, MS, School of Medicine, Mayo Clinic Alix School of Medicine, 226 2nd St SW, Rochester, MN 55905, USA (email: jacoboeding@gmail.com) (Twitter: @JacobOeding).
†School of Medicine, Mayo Clinic Alix School of Medicine, Rochester, Minnesota, USA.
‡Department of Orthopaedics, Institute of Clinical Sciences, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.
§Department of Orthopedic Surgery, Hospital for Special Surgery, New York, New York, USA.
‖Department of Orthopedic Surgery and Sports Medicine, Mayo Clinic, Rochester, Minnesota, USA.
Submitted July 12, 2023; accepted November 15, 2023.

One or more of the authors has declared the following potential conflict of interest or source of funding: J.F.O. has received consulting fees from Kaliber.ai. A.P. has received support for education from Smith & Nephew and hospitality payments from Medical Device Business Services. S.M.S. has received consulting fees from Moximed, Smith & Nephew, Miach Orthopaedics, Vericel, and Flexion Therapeutics; research support from Vericel and JRF; speaking fees from Organogenesis and Vericel; and royalties from Organogenesis; and holds stock or stock options in Engage and Stryker. B.U.N. has received consulting fees from Stryker, Wright Medical, and Zimmer Biomet; support for education from Arthrex and Smith & Nephew; consulting fees from Figur8; and a grant from Arthrex; and holds stock or stock options in BICMD. C.L.C. has received consulting fees from Arthrex; research support from Major League Baseball; and publishing royalties from Springer. A.J.K. has received consulting fees from Joint Restoration Foundation, Arthrex, and Responsive Arthroscopy; honoraria from Joint Restoration Foundation; royalties from Arthrex and Responsive Arthroscopy; a grant from DJO; and research support from Aesculap/B.Braun; and serves on the medical board of trustees for the Musculoskeletal Transplant Foundation. 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.

gating the use of PRP for the treatment of knee OA. The final search was performed in March 2023 and included studies from database conception to the time of the search. Search terms included the following: ("platelet rich plasma" OR "PRP") AND ("knee") AND ("osteoarthritis" OR "OA" OR "gonarthrosis" OR "cartilage"). Inclusion criteria consisted of RCTs reporting categorical data with associated *P* values. Only titles and abstracts for articles published in the English language were reviewed. Studies that did not focus on the application of PRP for knee OA were excluded. In addition, abstracts, technique papers, cadaveric or animal studies, review articles, and letters to the editor were excluded.

Study Review and Data Abstraction

Article titles, abstracts, and full texts were screened by 2 authors (J.F.O., F.W.F.) to identify articles that met the inclusion and exclusion criteria. In total, 204 full texts were reviewed, the references of which were screened to capture any additional studies potentially missed in the initial search. In total, 16 RCTs investigating the use of PRP for knee OA and reporting dichotomous outcomes were ultimately included in this systematic review (Figure 1).

Data extraction was performed independently by 2 authors (J.F.O., F.W.F.) using a standardized form for data collection. Collected data included raw categorical data, associated *P* values, the particular formulation of PRP used (leukocyte-rich PRP [LR-PRP], leukocyte-poor PRP [LP-PRP], or not specified), whether the injections were guided by ultrasound, and the number of patients lost to follow-up. Study methodological quality and risk of bias were assessed via the Cochrane risk of bias tool.[24] This tool focuses on identification of specific features within each study to allow for the assessment of allocation sequence generation and concealment. RCTs were screened for potential sources of bias including selective outcome reporting; unavailable or missing data; patients deemed lost to follow-up; blinding of patients, surgeons, and outcome assessors; and other potential sources of bias.[24]

Statistical Analysis

Data extracted from each study were summarized in both narrative and table format. The FI for each dichotomous outcome was calculated according to the method previously described by Walsh et al,[47] which involves manipulating the reported outcome events using the Fisher exact test in a 2×2 contingency table until a reversal of significance is achieved, with statistical significance defined as $P < .05$ (Figure 2). In short, this entails simultaneously adding and subtracting outcome events and nonevents in a sequential manner until the Fisher exact test determines a reversal of statistical significance. For example, assuming a study reports significantly more patients reporting improved symptoms after a particular treatment, the number of patient outcome events (ie, the number of patients moved from the "improved symptoms" group to the "no improved symptoms" group) required to raise the *P* value above .05 was determined. This number of outcome events represents the FI and provides a measure of the statistical fragility of that reported outcome. Likewise, if a study reported a nonsignificant outcome event, the number of patient outcome events required to shift the *P* value <.05 was determined, corresponding to the RFI.

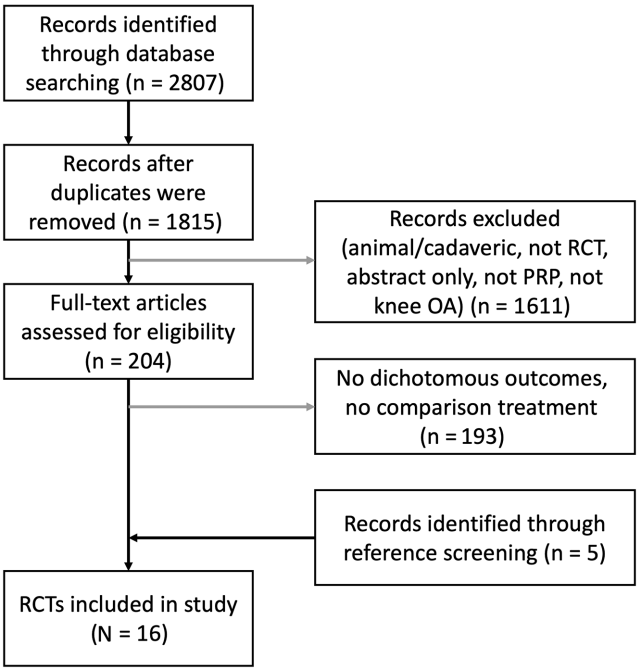

Figure 1. Flowchart of the systematic review process showing the number of articles reviewed at each time point and those included in the final study group. OA, osteoarthritis; PRP, platelet-rich plasma; RCT, randomized controlled trial.

While no universal standard for what makes a study fragile or robust has been defined, various interpretations have been proposed, as a function of both overall events and patients in the study.[49] Specifically, Xing and Lin[49] proposed the following FI cutoffs based on an empirical assessment of the FIs of a large database of clinical studies in the Cochrane Library: ≤1 event (extremely fragile), 1 to 3 events (moderately fragile), 2 to 4 events (slightly fragile), 5 to 14 events (slightly robust), 10 to 26 events (moderately robust), and ≥27 events (extremely robust). For the RFI, these ranges were as follows: ≤1 event (extremely fragile), 2 or 3 events (moderately fragile), 3 or 4 events (slightly fragile), 5 to 7 events (slightly robust), 7 to 12 events (moderately robust), and ≥13 events (extremely robust).[49] To standardize fragility to the sample size of each RCT, the FQ was also calculated. This involved dividing the FI by the respective RCT sample size for each study. Thus, smaller FQs demonstrate a less robust study outcome, while larger FQs correspond to more robust study outcomes. Similar to the FI ranges above, the following ranges have been proposed for the FQ of significant studies: ≤0.01 (extremely fragile), 0.01 to 0.02 (moderately fragile), 0.02 to 0.03 (slightly fragile), 0.03 to 0.07 (slightly robust), 0.04 to 0.15 (moderately robust), and ≥0.15

	Treatment Failure	Treatment Success		Treatment Failure	Treatment Success
PRP	6	89	PRP	7	88
HA	15	79	HA	15	79
P-Value		0.039	P-Value		0.073

Figure 2. Illustration of a sample fragility index (FI) calculation. The alteration of just 1 event results in the reversal of statistical significance and a resultant FI of 1. This would correspond to a very fragile (less robust) study outcome. HA, hyaluronic acid; PRP, platelet-rich plasma.

(extremely robust).[49] For nonsignificant studies, these ranges were ≤0.01 (extremely fragile), 0.01 to 0.03 (moderately fragile), 0.02 to 0.04 (slightly fragile), 0.05 to 0.09 (slightly robust), 0.07 to 0.14 (moderately robust), and ≥0.15 (extremely robust).[49] In addition, *P* values were calculated for all outcome events and compared with those reported (if any) by each study to verify accuracy and claims of significance. This was done using the 2-tailed Fisher exact test.

Finally, meta-analyses were performed based on the treatment to which PRP was compared and the outcome metric used in cases of ≥3 comparable RCTs. Outcome variables were assessed by random-effects meta-analysis using Mantel-Haenszel methods[31] and Paule-Mandel estimators,[39] and forest plots with pooled odds ratios (ORs) and 95% CIs were presented. Assessments of heterogeneity were performed independently using the Higgins and Thompson I^2,[25] DerSimonian-Laird τ^2,[14] and Cochran *Q* tests of heterogeneity. The FI or RFI of each meta-analysis was calculated and is defined as the minimum number of patients from ≥1 trials included in the meta-analysis for which a modification on the event status would change the statistical significance of the pooled treatment effect. For studies evaluating a single outcome metric at multiple time points, the patient status at the most recent follow-up was used. All analyses were performed in R Version 4.2.2 (R Foundation for Statistical Computing) and Microsoft Excel (Microsoft Corporation).

RESULTS

Literature Search

A total of 2807 records were identified through the initial literature search, 1815 of which remained after duplicates were removed. Titles and abstracts from these studies were screened according to the inclusion and exclusion criteria described above, which resulted in 204 full-text articles further assessed for eligibility. In total, 16 RCTs were ultimately included in this review (Figure 1).

Study Characteristics

This analysis consisted of outcomes from 1993 patients with a mean (± SD) age of 58.0 ± 3.8 years. Ten of the 16 RCTs represented level 1 evidence. Six RCTs represented level 2 evidence based on either a follow-up of <80%, poor blinding and randomization, or lack of a power analysis. Based on the risk of bias assessment, 11 studies demonstrated a low risk of bias, while 5 studies had a high risk of bias (Table 1). With respect to the reporting of a power analysis, 13 RCTs reported performance of an a priori power analysis, while 3 failed to report performance of a power analysis, either a priori or a posteriori.

One RCT consisting of 203 knees compared outcomes after treatment with PRP versus ozone or plasma rich in growth factor. One RCT consisting of 66 knees compared outcomes after treatment with PRP versus daily nonsteroidal anti-inflammatory drug administration. One RCT consisting of 192 knees performed a direct comparison between LP-PRP and LR-PRP. Overall, 7 RCTs reported use of LP-PRP, 5 RCTs reported use of LR-PRP, and 5 RCTs failed to report whether the PRP used was LP-PRP or LR-PRP. Regarding the dichotomous outcomes analyzed, 5 evaluated patient perception of symptom relief, 4 evaluated treatment failure as defined by the need for a new surgical or injection procedure due to the persistence or worsening of knee symptoms (reintervention), 2 evaluated achievement of the minimal clinically important difference (MCID) in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (>21.1% improvement), 2 evaluated pain relief as defined by >50% from baseline per the visual analog scale (VAS) score, 1 evaluated achievement of the MCID on the International Knee Documentation Committee Subjective Knee Evaluation Form, 1 evaluated cartilage defect progression via magnetic resonance imaging (MRI), 1 evaluated joint space increases in excess of 0.05 cm per T2-weighted MRI scan, 1 evaluated achievement of >1 grade improvement on MRI via the modified Shahriaree Classification system, 1 evaluated achievement of the Patient Acceptable Symptom State criteria for the Knee injury and Osteoarthritis Outcome Score Symptoms scale, and 1 evaluated "significant clinical improvement" per a WOMAC pain score decrease of >25% compared with baseline. The mean sample size of the included RCTs was 124.56 ± 79.22 patients. Table 1 provides a summary of the included RCTs, including study and patient characteristics.

There were 48 outcomes analyzed in the original studies, 14 of which were statistically significant ($P < .05$) (Figure 3). Of these statistically significant results, all favored PRP over the alternative injection therapy. The mean

TABLE 1
Overview of Randomized Controlled Trials Reporting Dichotomous Outcomes After Management of Knee Osteoarthritis With PRP[a]

Author	Total No. of Patients	Mean Age, y	PRP Comparison	LOE	Risk of Bias	Power Analysis	Outcome	Time of Evaluation, mo	Lost to FU/ Excluded
PRP vs HA									
Sdeek et al, 2021[42]	200	59.9	LP	1	Low	NR	Reintervention	18	11
							Reintervention	24	
							Reintervention	30	
							Reintervention	36	
Raeissadat et al, 2021[41]	238	56.9	NR	1	High	A priori	Symptom relief	12	17
Di Martino et al, 2019[16]	189	55.1	LR	1	Low	NR	Symptom relief	12	22
							Symptom relief	24	
							Symptom relief	36	
							Symptom relief	48	
							Symptom relief	60	
							Symptom relief	72	
							Reintervention	24	
Lisi et al, 2018[29]	54	55.3	NR	1	Low	A priori	>1-grade improvement on MRI via modified Shahriaree Classification system	6	8
Filardo, et al, 2015[21]	192	55.4	LR	1	High	A priori	Symptom relief	12	13
Wu et al, 2022[48]	46	61.7	LP	1	Low	A priori	MCID in WOMAC pain scores (>21.1% function improvement)	1	1
								3	
								6	
								12	
Szwedowski et al, 2022[45]	75	56	LP	1	Low	A priori	WOMAC pain score decrease of >25% compared with baseline	1.5	1
								3	
								6	
Montañez-Heredia et al, 2016[34]	55	63.9	LP	2	Low	A priori	>50% decrease in pain per VAS	3	2
								6	
Buendía-López et al, 2018[9]	106	56.4	LP	2	Low	A priori	MCID in WOMAC pain scores (>21.1% function improvement)	6	6
								12	
PRP vs CSI									
Joshi Jubert et al, 2017[26]	65	66.8	NR	2	Low	A priori	Symptom relief	6	1
Szwedowski et al, 2022[45]	75	56	LP	1	Low	A priori	WOMAC pain score decrease of >25% compared with baseline	1.5	1
								3	
								6	
PRP vs saline									
Bennell et al, 2021[7]	285	61.9	LP	1	Low	A priori	Symptom relief	2	5
							Symptom relief	12	
							Cartilage defect progression per MRI score	12	
Qamar et al, 2021[40]	100	59.4	NR	2	High	NR	Pain relief >50% from baseline per VAS score	6	NR
PRP vs MAT									
Zaffagnini et al, 2022[50]	108	54.3	LR	1	Low	A priori	MCID in IKDC scores	6	10
								12	
							Reintervention	24	
Louis et al, 2021[30]	30	47	NR: LD[b]	2	High	A priori	Joint spacing increase of >0.05 cm per T2-weighted MRI scan	6	0
			NR: HD[b]					6	
			NR: LD[b]					12	
			NR: HD[b]					12	
Baria et al, 2022[4]	58	53.9	LR	2	High	A priori	PASS criteria for KOOS symptoms scale	6	1
PRP vs PRGF									
Raeissadat et al, 2021[41]	103	56.9	NR	1	High	A priori	Symptom relief	12	16

(continued)

TABLE 1
(continued)

Author	Total No. of Patients	Mean Age, y	PRP Comparison	LOE	Risk of Bias	Power Analysis	Outcome	Time of Evaluation, mo	Lost to FU/ Excluded
PRP vs ozone									
Raeissadat et al, 2021[41]	100	56.9	NR	1	High	A priori	Symptom relief	12	19
PRP vs NSAID									
Buendía-López et al, 2018[9]	66	56.4	LP	2	Low	A priori	MCID in WOMAC pain scores (>21.1% function improvement)	6	4
								12	
LP-PRP vs LR-PRP									
Di Martino et al, 2022[15]	192	55.4	LP/LR	1	Low	A priori	Symptom relief	6	6
							Symptom relief	12	
							Reintervention	12	

[a]CSI, corticosteroid injection, FU, follow-up; HA, hyaluronic acid; HD, high dose; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; LD, low dose; LOE, level of evidence; LP, leukocyte poor; LR, leukocyte rich; MAT, microfragmented adipose tissue; MCID, minimal clinically important difference; MRI, magnetic resonance imaging; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PASS, Patient Acceptable Symptom State; PRGF, plasma rich in growth factor; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Louis et al[30] reported the use of LD and HD PRP but did not report whether the PRP was LR-PRP or LP-PRP.

number of events required to reverse significance (FI) was 4.57 ± 5.85 (range, 1-21). This corresponded to an FQ of 0.060 ± 0.075, meaning the significance of the results was contingent on 6 events per 100 participants. For nonsignificant outcome events, the mean number of events required to reverse statistical nonsignificance (RFI) was 4.41 ± 2.22 (range, 1-11). This corresponded to a reverse FQ (RFQ) of 0.065 ± 0.056, meaning the nonsignificance of the results was contingent on 6.5 events per 100 participants (Table 2). Overall, the mean number of events per meta-analysis required to change the statistical significance of pooled treatment effects was 8.67 ± 4.50.

PRP Versus Hyaluronic Acid

Overall, 9 RCTs consisting of 1155 knees reported outcomes after management of knee OA with PRP versus hyaluronic acid (HA). This corresponded to 25 total outcomes analyzed with a mean time of evaluation of 18.94 ± 18.92 months (range, 1-72 months). For these 9 RCTs, the mean FI (reversal of significance to nonsignificance) was 2.56 ± 3.00 with a mean FQ of 0.028 ± 0.026. The mean RFI (reversal of nonsignificance to significance) was 4.46 ± 2.67 with a mean RFQ of 0.056 ± 0.035.

Results of the random-effects model are shown in Figure 4. Of the 525 total outcome events corresponding to patients whose knee OA was managed with HA, 315 (60.0%) corresponded to successful outcomes. Of the 548 outcome events corresponding to patients whose knee OA was managed with PRP, 399 (72.8%) outcome events corresponded to successful outcomes. The meta-analysis of the corresponding RCTs resulted in a P value of .002 (OR, 2.19; 95% CI, 1.33-3.62), favoring successful outcomes with PRP over HA. This meta-analysis demonstrated an FI of 8 and FQ of 0.007, meaning that 8 event status modifications from ≥1 trials included in the meta-analysis would alter the significance of the meta-analysis to nonsignificance.

PRP Versus CSI

Two RCTs consisting of 140 knees reported outcomes after management of knee OA with PRP versus CSI. This corresponded to 4 total outcomes analyzed with a mean time of evaluation of 4.13 ± 2.25 months (range, 1.5-6 months). For these 2 RCTs, the mean FI was 7 ± 7.07 with a mean FQ of 0.143 ± 0.144. The mean RFI was 4.5 ± 2.12 with a mean FQ of 0.085 ± 0.053.

PRP Versus Saline

Two RCTs consisting of 385 knees reported outcomes after management of knee OA with PRP versus saline. This corresponded to 4 total outcomes analyzed with a mean time of evaluation of 8.00 ± 4.90 months (range 2-12 months). For these 2 RCTs, the mean FI was 11.00 ± 14.14 with a mean FQ of 0.107 ± 0.146. The mean RFI was 4.50 ± 0.71 with a mean FQ of 0.017 ± 0.002.

PRP Versus Microfragmented Adipose Tissue

Three RCTs consisting of 196 knees reported outcomes after treatment with PRP versus microfragmented adipose tissue (MAT). This corresponded to 8 total outcomes analyzed with a mean time of evaluation of 10.50 ± 6.21 months (range, 6-24 months). For these 3 RCTs, the mean RFI was 4.00 ± 2.00 with a mean FQ of 0.122 ± 0.076.

Of the 140 total outcome events corresponding to patients whose knee OA was managed with PRP, 67 (47.9%) corresponded to successful outcomes. Of the 135 total outcome events corresponding to patients whose knee OA was managed with MAT, 64 (47.4%) outcome events corresponded to successful outcomes. The corresponding meta-analysis demonstrated a P value >.99

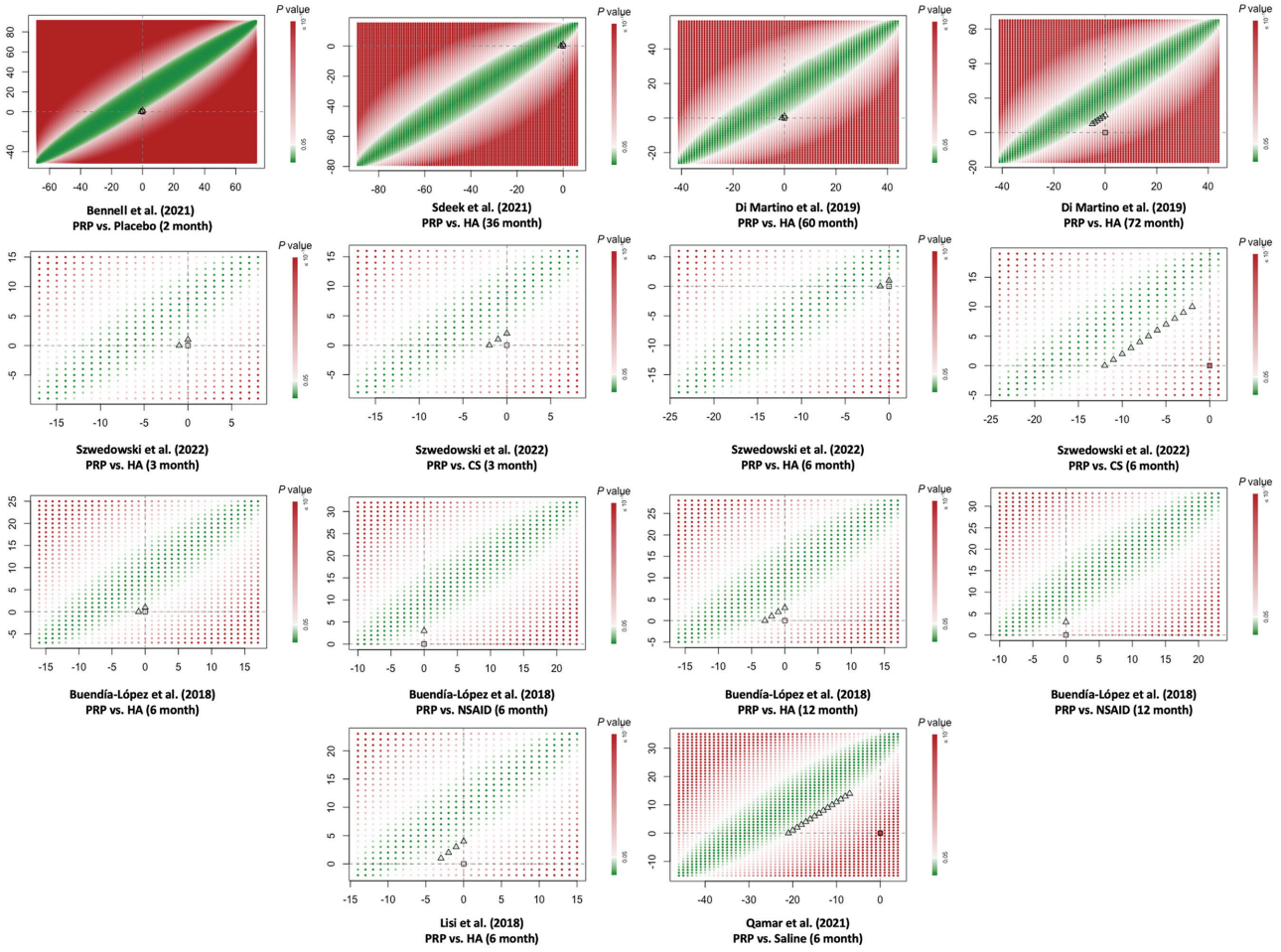

Figure 3. Visualizations of the statistical fragility of statistically significant findings of randomized controlled trials evaluating platelet-rich plasma (PRP) for the management of knee osteoarthritis. Green points or areas indicate nonsignificant results, while red points or areas indicate significant results. Dashed lines represent no modifications in the corresponding groups. Square points represent the original *P* value, and triangle points indicate minimal modifications that alter the significance.[28] Event statuses are modified in both groups, with modifications in the PRP group indicated on the *x*-axis and modifications in the alternative treatment group on the *y*-axis. The follow-up time at which the outcome was evaluated is indicated in parentheses underneath each plot. Each point represents the extent of the *P* value corresponding to a specific combination of event status modifications in both the PRP and alternative treatment groups. The density of points corresponds to sample size, with lower density indicating a smaller randomized controlled trial. CS, corticosteroid; HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug.

(OR, 1.00; 95% CI, 0.57-1.75) and an RFI of 15 (RFQ, 0.06) for nonsignificance altered to significance.

Symptom Relief

Five RCTs compared patient-reported symptom relief after treatment with PRP versus an alternative. Of the 509 total outcome events corresponding to evaluation of patient-reported symptom relief at the most recent time of evaluation for patients treated with PRP, 330 (64.8%) corresponded to successful outcomes. Of the 490 total outcome events corresponding to evaluation of patient-reported symptom relief at the most recent time of evaluation for patients treated with a therapy other than PRP, 271 (55.3%) corresponded to successful outcomes.

Meta-analysis of the corresponding RCTs demonstrated a *P* value of .019 (OR, 1.55; 95% CI, 1.07-2.24) (Figure 5) in favor of PRP over all control treatments. The FI and FQ of the meta-analysis were 3 and 0.003, respectively, indicating that 3 patients in $\geq$1 of the RCTs would need to experience a modification in treatment outcome to flip the results of the meta-analysis from significant to nonsignificant.

Reinterventions After Initial Treatment

Three RCTs compared reintervention rates after treatment with PRP versus an alternative. Of the 230 total outcome events corresponding to the need for a subsequent surgical or follow-up injection after the initial set of injections at the most recent time of evaluation for patients treated

TABLE 2
FI and FQ of Randomized Controlled Trials Reporting Dichotomous Outcomes After Management of Knee Osteoarthritis With PRP[a]

Author	FI/RFI	FQ/RFQ, %	*P* (reported)	*P* (calculated)
PRP vs HA				
Sdeek et al, 2021[42]	5	2.60	NR	>.999
	2	1.10	NR	.169
	5	2.60	NR	.767
	1[b]	0.50[b]	NR	.039
Raeissadat et al, 2021[41]	7	6.90	NR	.657
Di Martino et al, 2019[16]	11	6.60	NR	.756
	3	1.80	NR	.122
	2	1.20	NR	.086
	4	2.40	NR	.159
	1[b]	0.60[b]	NR	.04
	10[b]	6.00[b]	NR	.001
	1	0.60	.036	.061
Lisi et al, 2018[29]	4[b]	7.40[b]	.003	.002
Filardo et al, 2015[21]	6	3.30	NR	.815
Wu et al, 2022[48]	5	11.10	.793	>.999
	2	4.40	.243	.243
	3	6.70	.608	.608
	3	6.70	.489	.489
Szwedowski et al, 2022[45]	2	4.10	NR	.128
	1[b]	2.00[b]	NR	.046
	1[b]	2.00[b]	.038	.049
Montañez-Heredia et al, 2016[34]	3	4.70	.227	.193
	7	13.20	>.999	>.999
Buendía-López et al, 2018[9]	1[b]	1.50[b]	<.001	.038
	3[b]	4.60[b]	<.001	.001
PRP vs CSI				
Joshi Jubert et al, 2017[26]	3	4.70	.472	.193
Szwedowski et al, 2022[45]	6	12.20	NR	.778
	2[b]	4.10[b]	NR	.023
	12[b]	24.50[b]	.001	.001
PRP vs saline				
Bennell et al, 2021[7]	1[b]	0.40[b]	.02	.041
	5	1.80	.09	.147
	4	1.50	.14	.17
Qamar et al, 2021[40]	21[b]	21.00[b]	.001	.001
PRP vs MAT				
Zaffagnini et al, 2022[50]	2	2.00	NR	.091
	8	8.20	NR	.687
	3	3	NR	.227
Louis et al, 2021[30]	3	17.60	NR	.637
	4	23.50	NR	>.999
	3	17.60	NR	.644
	3	15.00	NR	.37
Baria et al, 2022[4]	6	10.30	.99	>.999
PRP vs PRGF				
Raeissadat et al, 2021[41]	8	7.80	NR	>.999
PRP vs ozone				
Raeissadat et al, 2021[41]	6	6.00	NR	.512
PRP vs NSAID				
Buendía-López et al, 2018[9]	3[b]	4.50[b]	<.001	.007
	3[b]	4.50[b]	<.001	.001
LP-PRP vs LR-PRP				
Di Martino et al, 2022[15]	7	4.00	NR	.499
	5	2.90	NR	.239
	3	1.70	.331	.331

[a]CSI, corticosteroid injection; FI, fragility index; FQ, fragility quotient; HA, hyaluronic acid; LP, leukocyte poor; LR, leukocyte rich; MAT, microfragmented adipose tissue; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PRGF, plasma rich in growth factor; PRP, platelet-rich plasma; RFI, reverse fragility index; RFQ, reverse fragility quotient.

[b]Indicates reversal of significance to nonsignificance (FI). All other values correspond to the RFI (reversal of nonsignificance to significance).

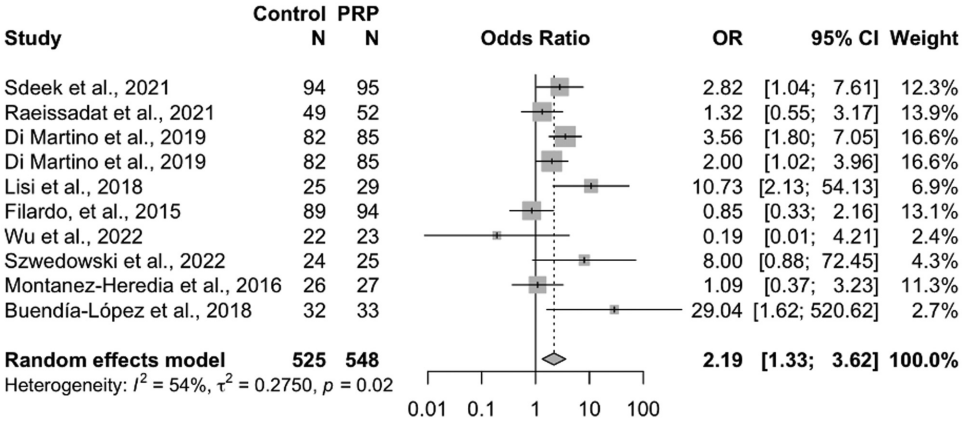

Figure 4. Random-effects meta-analysis comparing outcomes after treatment with platelet-rich plasma (PRP) versus hyaluronic acid. OR, odds ratio.

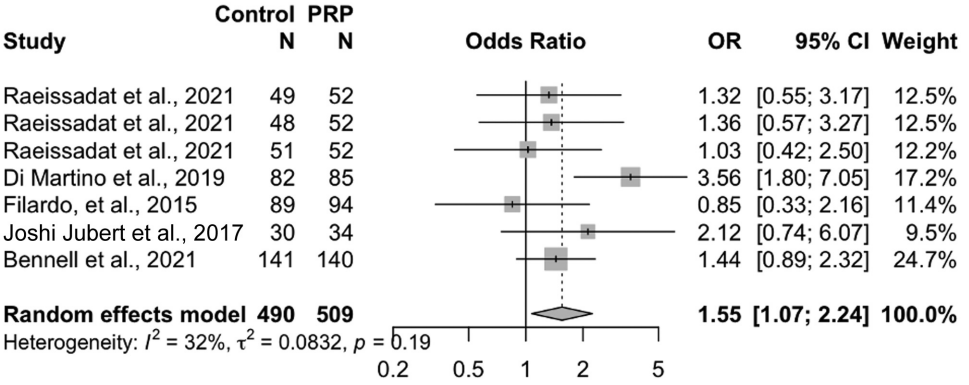

Figure 5. Random-effects meta-analysis comparing patient-reported symptom relief after treatment with platelet-rich plasma (PRP) versus all other control treatments. OR, odds ratio.

with PRP, 169 (73.5%) corresponded to successful outcomes. Of the 225 total outcome events corresponding to reinterventions at the most recent time of evaluation for patients treated with a therapy other than PRP, 139 (61.8%) corresponded to successful outcomes.

Meta-analysis of these RCTs produced a *P* value of .002 (OR, 2.17; 95% CI, 1.33-3.53) (Figure 6). The FI and FQ of this meta-analysis were 7 and 0.02, respectively, indicating that 7 outcome events would need to be modified to change the significance of the meta-analysis to nonsignificance.

Cartilage Status on MRI

Three RCTs evaluated cartilage status via MRI. Of the 179 total outcome events corresponding to the cartilage status of patients treated with PRP, 133 (74.3%) corresponded to successful outcomes. Of the 167 total outcome events corresponding to the cartilage status of patients treated with a therapy other than PRP, 126 (75.4%) corresponded to successful outcomes.

The random-effects meta-analysis demonstrated a *P* value of .865 (OR, 1.20; 95% CI, 0.15-9.62), an RFI of 13, and RFQ of 0.04 (Figure 7).

Pain Improvement

Five RCTs compared patient-reported outcome metrics for pain, including WOMAC and VAS scores, between PRP and control treatment options. Of the 216 total outcome events corresponding to achievement of the predetermined level of pain improvement by each study (range, ~20%-50% improvement from baseline) for patients treated with PRP, 147 (68.1%) corresponded to successful outcomes. Of the 211 total outcome events corresponding to pain improvement for patients treated with a therapy other than PRP, 84 (39.8%) corresponded to successful outcomes.

The *P* value of the random-effects meta-analysis was .007 (OR, 6.19; 95% CI, 1.63-23.42) favoring PRP over control treatments (Figure 8). The FI of this meta-analysis was 6, with an FQ of 0.01. In other words, if 6 outcome

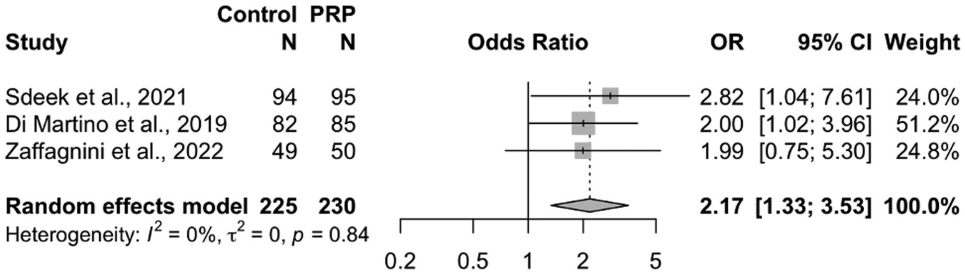

Figure 6. Random-effects meta-analysis comparing reintervention rates after treatment with platelet-rich plasma (PRP) versus all other control treatments. OR, odds ratio.

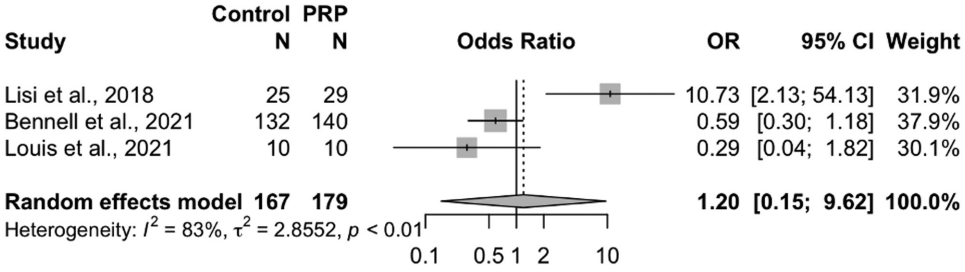

Figure 7. Random-effects meta-analysis comparing cartilage status on magnetic resonance imaging after treatment with platelet-rich plasma (PRP) versus all other control treatments. OR, odds ratio.

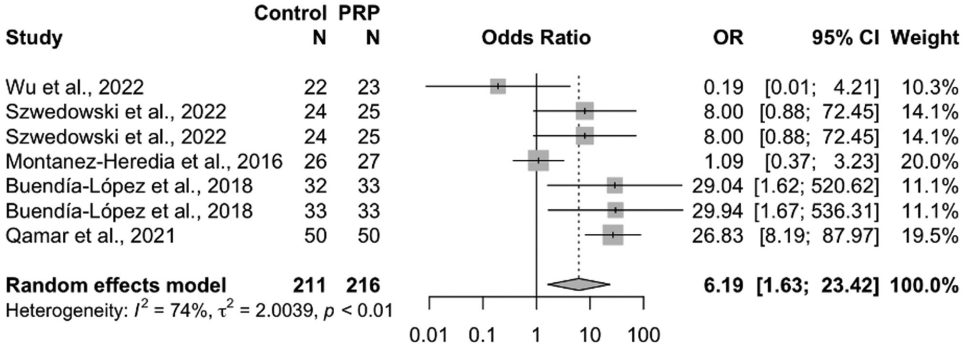

Figure 8. Random-effects meta-analysis comparing pain improvement after treatment with platelet-rich plasma (PRP) versus all other control treatments. OR, odds ratio.

events in this meta-analysis were flipped, the meta-analysis would change from significant to nonsignificant.

DISCUSSION

We performed a comprehensive evaluation of the statistical fragility of RCTs comparing PRP with alternative nonoperative treatment options for the management of knee OA. The primary finding was that individual RCTs demonstrated slight robustness based on both the FI and the FQ and with respect to both significant and nonsignificant findings. The mean number of events required to reverse significance (FI) was nearly 5 outcome events per RCT, which means that 5 events would have needed to have a different outcome to change the significance of the RCT. Likewise, the mean number of events required to reverse the statistical significance of conducted meta-analyses was 6. Meta-analyses based on the treatment to which PRP was compared and the outcome metric used for the comparison demonstrated robust evidence in support of PRP over HA as well as for avoidance of a reintervention after the initial injection treatment and achievement of the MCID for pain improvement when compared with all alternative treatments.

Currently, the AAOS clinical practice guideline on management of OA of the knee states that PRP "may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee," with a strength of

recommendation of "limited."[1] This recommendation was downgraded 2 levels from "strong" to "limited" based on concerns discussed in the Evidence to Decision framework, including the heterogeneity of results.[1] This study provides an additional metric to heterogeneity that can be used to evaluate the strength of evidence in support for or against PRP for the management of knee OA. In particular, the finding that individual RCTs were overall more robust than fragile supports the current clinical practice guideline but suggests that the strength of recommendation may be able to be upgraded from "limited." Meta-analysis demonstrated robust findings with respect to PRP over alternative treatment options for statistically significant improvement in WOMAC and VAS pain scores, with an OR of 2.17 for achievement of the MCID when receiving PRP versus alternative treatments and an overall FI of 7 (FQ, 0.02), meaning 7 event status modifications from $\geq$1 trials included in the meta-analysis would need to take place to alter the significance of the meta-analysis to nonsignificance. Furthermore, meta-analysis of studies comparing PRP with HA demonstrated robust and significant findings in support of PRP over HA when evaluating all outcome metrics, including patient-reported symptom relief, reintervention rates, cartilage status on MRI, and achievement of the MCID for pain improvement. These results align with and provide additional support to the findings of Belk et al,[5] who, in their systematic review and meta-analysis of RCTs comparing PRP with HA for knee OA, concluded that patients undergoing treatment for knee OA with PRP can be expected to experience improved clinical outcomes when compared with patients treated with HA based on studies using the WOMAC and VAS scores. In our meta-analysis, we found that 8 total event status modifications (FQ, 0.007) from $\geq$1 trials would need to take place to suggest no difference in outcomes achieved with PRP versus HA.

Although only compared by 2 studies each in this systematic review and thus ineligible for meta-analysis, findings suggesting superiority of PRP over saline and CSI included studies with the 2 highest FIs in the systematic review (21 and 12 for saline and CSI, respectively). Again, these findings align with and add further support to a recent meta-analysis of both dichotomous and nondichotomous outcomes that found PRP injections produce superior outcomes when compared with CSIs, including improved pain management, less joint stiffness, and improved participation in sports, with the maximal difference observed at 6-month follow-up.[32] Our findings add further support to these results and suggest that improved outcomes of PRP over CSI and saline for knee OA may be a robust conclusion. Similarly, the meta-analysis with one of the highest RFIs (RFI, 13) was with respect to studies evaluating the cartilage status of patients on MRI. There is strong evidence that PRP does not regenerate cartilage.[9,23,43] Thus, it is not surprising that similar outcomes were found between PRP and all alternative treatment options when cartilage status on MRI was used as the outcome of interest.

It is important to note that while findings were overall robust, there was also heterogeneity among the included RCTs. For example, an I^2 of 74% resulted from the meta-analysis evaluating PRP for pain improvement. Thus, despite an OR of 6.19 in favor of PRP over all alternative treatment strategies, there was still moderate to high heterogeneity among the included outcomes. This finding is not uncommon when evaluating patient outcomes using WOMAC and VAS pain scores, however. A recent systematic review and meta-analysis found that patients who receive PRP or concentrated bone marrow aspirate injections have better outcomes than patients who receive HA and reported I^2 values ranging from 81% to 98% for WOMAC and VAS pain scores.[6] Heterogeneity may be due to several factors, including differences in preparation protocols and PRP compositions, differences in the definition of success used, the form by which patients reported results (such as on paper vs on a tablet or computer), the timing at which results were reported (such as at home vs after a physical therapy visit), and the length of follow-up. While these factors may certainly contribute to heterogeneity at the study level, it is also important to note the substantial variability at the patient level that is inherent to patient-reported metrics of pain associated with knee OA. For example, it is well known that there is substantial variability at the individual patient level with respect to the experience of pain.[13,17,37] In other words, it is possible for a patient with Kellgren-Lawrence grade 4 knee OA to have high functional ability and limited pain, while a patient with no joint space narrowing could have debilitating pain and disability. Thus, it is extremely challenging to control for the subjective experience and response to pain by individual patients even in the presence of objective diagnoses of knee OA, and this variable may have a substantial effect on the variability in patient response to biologic injections such as PRP, particularly in regard to outcomes such as patient-reported symptom relief and achievement of the MCID for WOMAC and VAS pain scores.

In this study, the mean number of patients from $\geq$1 trials included in each meta-analysis for which a modification on the event status would change the statistical significance of the pooled treatment effect was 8.67 $\pm$ 4.50. In a cross-sectional analysis of 906 meta-analyses of trials with a binary outcome from the Cochrane Database of Systematic Reviews, it was found that one-third of all meta-analyses depended on the event status of $\leq$5 participants from $\geq$1 trials.[2] More specifically, for statistically significant meta-analyses with sample sizes between 200 and 500, as was the case for the majority of meta-analyses in the present study, 50.1% of statistically significant meta-analyses had an FI of $\leq$5.[2] For statistically significant meta-analyses in the present study, the mean FI was 6.00 $\pm$ 2.16. Thus, statistically significant findings favoring PRP over alternative injection therapies were found to be more robust than the majority of significant meta-analyses of similar size included in the Cochrane Database of Systematic Reviews, which is currently the largest database of systematic reviews in health care.[2] Although there are few FI-based meta-analyses in the orthopaedic literature specifically, the median FI of statistically significant findings from individual RCTs related to sports medicine and arthroscopic surgery was found to be just 2 patients.[27]

A recent review of the most influential studies in PRP research found that the majority of the top 50 cited studies were of level 1 or 2 evidence, with RCTs being the most common study design and knee OA the most represented topic on the list of clinical studies.[35] Thus, there is evidence that suggests immense clinical and research interest in RCTs focused on PRP for knee OA; nevertheless, there continues to be substantial debate on the topic. This study showed that the FI can serve as an additional metric to evaluate the strength of evidence in support for or against the use of PRP for knee OA. For this reason, the authors advocate the reporting of FIs and FQs in future RCTs evaluating outcomes after PRP injections in patients with knee OA.

Limitations

The results of this study should be interpreted in the context of its limitations. First, it is important to note that FIs can only be applied to categorical data with dichotomous outcomes. As a result, a number of RCTs were excluded because they did not report binary outcomes that could be assessed using the FI or RFI. While achievement of a certain outcome metric such as the MCID in the WOMAC pain score provides a useful means to measure the success or failure of a treatment, it is of course possible that a range of symptom states exist and depend on a variety of patient-specific factors. In addition, the present study possesses a number of limitations inherent to all systematic reviews and meta-analyses. These include the inability to control for biases introduced by individual studies, such as patient selection, randomization, and blinding, as well as heterogeneity in methodology and outcome metrics. It is also important to note that substantial heterogeneity in PRP platelet concentrations may exist among the included studies based on individual PRP preparation protocols,[36] and the effects of platelet dosing on outcomes after treatment with PRP injections have yet to be fully evaluated. The longest follow-up of any included study was 72 months; thus, the effects of PRP and alternative injection therapies beyond this point were not evaluated, and further research with longer-term follow-ups is needed. Finally, as the FI and RFI are relatively new tools for evaluating scientific literature, future work is needed to enhance their interpretability and ensure that results are understood in their proper context.

CONCLUSION

Individual RCTs evaluating PRP for knee OA possess slight robustness with respect to both significant and nonsignificant findings. Upon meta-analysis, PRP demonstrated a significant advantage over HA as well as improved symptom relief, lower rates of reintervention, and more frequent achievement of the MCID for pain improvement when compared with alternative nonoperative treatment options, but it showed no evidence of increased improvement of cartilage status on MRI. Statistically significant pooled treatment effects evaluating PRP for knee OA are more robust than approximately half of all comparable meta-analyses in medicine and health care. Future RCTs and meta-analyses should consider reporting FIs and FQs to facilitate interpretation of results in their proper context.

ORCID iDs

Jacob F. Oeding https://orcid.org/0000-0002-4562-4373
Christopher L. Camp https://orcid.org/0000-0003-3058-7327
Aaron J. Krych https://orcid.org/0000-0003-3248-8007

An online CME course associated with this article is available for 1 *AMA PRA* Category 1 Credit™ at https://education.sportsmed.org/Public/Catalog/Home.aspx?CourseSearch=1&Criteria=9&Option=25. In accordance with the standards of the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of The American Orthopaedic Society for Sports Medicine that authors, editors, and planners disclose to the learners all financial relationships during the past 12 months with any commercial interest (A 'commercial interest' is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients). Any and all disclosures are provided in the online journal CME area which is provided to all participants before they actually take the CME activity. In accordance with AOSSM policy, authors, editors, and planners' participation in this educational activity will be predicated upon timely submission and review of AOSSM disclosure. Noncompliance will result in an author/editor or planner to be stricken from participating in this CME activity.

REFERENCES

1. American Academy of Orthopaedic Surgeons. *Management of Osteoarthritis of the Knee (Non-Arthroplasty): Evidence-Based Clinical Practice Guideline*. Accessed March 8, 2022. https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf
2. Atal I, Porcher R, Boutron I, Ravaud P. The statistical significance of meta-analyses is frequently fragile: definition of a fragility index for meta-analyses. *J Clin Epidemiol*. 2019;111:32-40.
3. Baer BR, Gaudino M, Fremes SE, Charlson M, Wells MT. Reassembling the fragility index: a demonstration of statistical reasoning. *J Clin Epidemiol*. 2022;142:317-318.
4. Baria M, Pedroza A, Kaeding C, et al. Platelet-rich plasma versus microfragmented adipose tissue for knee osteoarthritis: a randomized controlled trial. *Orthop J Sports Med*. 2022;10(9):23259671221120678.
5. Belk JW, Kraeutler MJ, Houck DA, et al. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med*. 2021;49(1):249-260.
6. Belk JW, Lim JJ, Keeter C, et al. Patients with knee osteoarthritis who receive platelet-rich plasma or bone marrow aspirate concentrate injections have better outcomes than patients who receive hyaluronic acid: systematic review and meta-analysis. *Arthroscopy*. 2023;39(7):1714-1734.
7. Bennell KL, Paterson KL, Metcalf BR, et al. Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: the RESTORE randomized clinical trial. *JAMA*. 2021;326(20):2021-2030.
8. Bragg JT, Ruelos VCB, McIntyre JA, et al. Reverse fragility index comparing rates of rerupture after open Achilles tendon repair versus

early functional rehabilitation: a systematic review of randomized controlled trials. *Am J Sports Med*. Published online June 12, 2023. doi:10.1177/03635465231178831
9. Buendía-López D, Medina-Quirós M, Fernández-Villacañas Marín M. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. *J Orthop Traumatol*. 2018;19(1):3.
10. Cui A, Li H, Wang D, et al. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine*. 2020;29-30:100587.
11. Cui Y, Lin L, Wang Z, et al. Research trends of platelet-rich plasma therapy on knee osteoarthritis from 2011 to 2021: a review. *Medicine (Baltimore)*. 2023;102(2):e32434.
12. Davey MS, Hurley ET, Doyle TR, et al. The fragility index of statistically significant findings from randomized controlled trials comparing the management strategies of anterior shoulder instability. *Am J Sports Med*. 2023;51(8):2186-2192.
13. Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC Musculoskelet Disord*. 2016;17(1):425.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
15. Di Martino A, Boffa A, Andriolo L, et al. Leukocyte-rich versus leukocyte-poor platelet-rich plasma for the treatment of knee osteoarthritis: a double-blind randomized trial. *Am J Sports Med*. 2022;50(3):609-617.
16. Di Martino A, Di Matteo B, Papio T, et al. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. *Am J Sports Med*. 2019;47(2):347-354.
17. Edwards RR, Dolman AJ, Martel MO, et al. Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskelet Disord*. 2016;17:284.
18. Ekhtiari S, Gazendam AM, Nucci NW, Kruse CC, Bhandari M. The fragility of statistically significant findings from randomized controlled trials in hip and knee arthroplasty. *J Arthroplasty*. 2021;36(6):2211-2218.e2211.
19. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. *Int J Mol Sci*. 2020;21(20):7794.
20. Everts PA, van Erp A, DeSimone A, Cohen DS, Gardner RD. Platelet rich plasma in orthopedic surgical medicine. *Platelets*. 2021;32(2):163-174.
21. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1575-1582.
22. Forrester LA, McCormick KL, Bonsignore-Opp L, et al. Statistical fragility of surgical clinical trials in orthopaedic trauma. *J Am Acad Orthop Surg Glob Res Rev*. 2021;5(11):e20.00197.
23. Hart R, Safi A, Komzák M, et al. Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. *Arch Orthop Trauma Surg*. 2013;133(9):1295-1301.
24. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:D5928.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
26. Joshi Jubert N, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis: a prospective, randomized, double-blinded clinical trial. *Orthop J Sports Med*. 2017;5(2):2325967116689386.
27. Khan M, Evaniew N, Gichuru M, et al. The fragility of statistically significant findings from randomized trials in sports surgery: a systematic survey. *Am J Sports Med*. 2017;45(9):2164-2170.
28. Lin L, Chu H. Assessing and visualizing fragility of clinical results with binary outcomes in R using the fragility package. *PLoS One*. 2022;17(6):e0268754.
29. Lisi C, Perotti C, Scudeller L, et al. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. *Clin Rehabil*. 2018;32(3):330-339.
30. Louis ML, Dumonceau RG, Jouve E, et al. Intra-articular injection of autologous microfat and platelet-rich plasma in the treatment of knee osteoarthritis: a double-blind randomized comparative study. *Arthroscopy*. 2021;37(10):3125-3137.e3123.
31. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22(4):719-748.
32. McLarnon M, Heron N. Intra-articular platelet-rich plasma injections versus intra-articular corticosteroid injections for symptomatic management of knee osteoarthritis: systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2021;22(1):550.
33. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341.
34. Montañez-Heredia E, Irízar S, Huertas PJ, et al. Intra-articular injections of platelet-rich plasma versus hyaluronic acid in the treatment of osteoarthritic knee pain: a randomized clinical trial in the context of the Spanish National Health Care System. *Int J Mol Sci*. 2016; 17(7):1064.
35. Oeding JF, Lansdown DA, Leucht P, et al. Influential studies in orthopaedic platelet-rich plasma research are recent and consist of high levels of evidence: a review of the top 50 most cited publications. *J Knee Surg*. 2023;36(8):900-910.
36. Oudelaar BW, Peerbooms JC, Huis In 't Veld R, Vochteloo AJH. Concentrations of blood components in commercial platelet-rich plasma separation systems: a review of the literature. *Am J Sports Med*. 2019;47(2):479-487.
37. Paradowski PT, Englund M, Lohmander LS, Roos EM. The effect of patient characteristics on variability in pain and function over two years in early knee osteoarthritis. *Health Qual Life Outcomes*. 2005;3:59.
38. Park YB, Kim JH, Ha CW, Lee DH. Clinical efficacy of platelet-rich plasma injection and its association with growth factors in the treatment of mild to moderate knee osteoarthritis: a randomized double-blind controlled clinical trial as compared with hyaluronic acid. *Am J Sports Med*. 2021;49(2):487-496.
39. Paule RC, Mandel J. Consensus values, regressions, and weighting factors. *J Res Natl Inst Stand Technol*. 1989;94(3):197-203.
40. Qamar A, Mohsin S, Siddiqui U, Naz S, Danish S. Effectiveness of platelet rich plasma for the management of knee osteoarthritis: a randomized placebo controlled trial. *Pakistan J Med Health Sci*. 2021;15(7):1553-1556.
41. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, et al. The comparison effects of intra-articular injection of platelet rich plasma (PRP), plasma rich in growth factor (PRGF), hyaluronic acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. *BMC Musculoskelet Disord*. 2021;22(1):134.
42. Sdeek M, Sabry D, El-Sdeek H, Darweash A. Intra-articular injection of platelet rich plasma versus hyaluronic acid for moderate knee osteoarthritis. A prospective, double-blind randomized controlled trial on 189 patients with follow-up for three years. *Acta Orthop Belg*. 2021;87(4):729-734.
43. Şen E, Yıldırım MA, Yeşilyurt T, Kesiktaş FN, Dıraçoğlu D. Effects of platelet-rich plasma on the clinical outcomes and cartilage thickness in patients with knee osteoarthritis. *J Back Musculoskelet Rehabil*. 2020;33(4):597-605.
44. Sudah SY, Moverman MA, Masood R, et al. The majority of sports medicine and arthroscopy-related randomized controlled trials reporting nonsignificant results are statistically fragile. *Arthroscopy*. 2023;39(9):2071-2083.e1.
45. Szwedowski D, Mobasheri A, Moniuszko A, Zabrzyński J, Jeka S. Intra-articular injection of platelet-rich plasma is more effective than hyaluronic acid or steroid injection in the treatment of mild to moderate knee osteoarthritis: a prospective, randomized, triple-parallel clinical trial. *Biomedicines*. 2022;10(5):991.
46. Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proc Natl Acad Sci U S A*. 2017;114(35):9332-9336.

47. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol*. 2014;67(6):622-628.
48. Wu YT, Li TY, Lee KC, et al. Efficacy of a novel intra-articular administration of platelet-rich plasma one-week prior to hyaluronic acid versus platelet-rich plasma alone in knee osteoarthritis: a prospective, randomized, double-blind, controlled trial. *J Clin Med*. 2022;11(11):3241.
49. Xing A, Lin L. Empirical assessment of fragility index based on a large database of clinical studies in the Cochrane Library. *J Eval Clin Pract*. 2023;29(2):359-370.
50. Zaffagnini S, Andriolo L, Boffa A, et al. Microfragmented adipose tissue versus platelet-rich plasma for the treatment of knee osteoarthritis: a prospective randomized controlled trial at 2-year follow-up. *Am J Sports Med*. 2022;50(11):2881-2892.

For reprints and permission queries, please visit Sage's Web site at http://www.sagepub.com/journals-permissions