Systematic Review

# A Greater Platelet Dose May Yield Better Clinical Outcomes for Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Systematic Review

William A. Berrigan, M.D., Zach Bailowitz, M.D., Anna Park, M.Phil., Aakash Reddy, Ryan Liu, and Drew Lansdown, M.D.

**Purpose:** To determine whether the platelet dose administered during a platelet-rich plasma (PRP) injection for knee osteoarthritis (OA) affects clinical outcomes. **Methods:** A systematic review was performed by searching PubMed, Cochrane Library, and Embase for randomized controlled trials with at least 1 study arm using PRP for knee OA. Only studies that provided a platelet count, concentration, or dose with a minimum of 6-month outcome scores were included. Studies in which the PRP group had statistically significant positive outcomes were separated from those without statistical significance. The average platelet doses for studies with positive outcomes in the PRP group were compared with those without positive outcomes. **Results:** After exclusion criteria were applied, 29 studies were analyzed. Of the 29, there were 31 arms that used PRP as a treatment method, of which 28 had statistically significant positive outcomes at 6 months compared with the control group. The mean platelet dose in the 28 with a positive outcome was $5,500 \pm 474 \times 10^6$, whereas the 3 that had no positive difference had a mean platelet dose of $2,302 \pm 437 \times 10^6$ ($P < .01$). There were 18 studies with 12-month outcomes, with 16 of 18 having positive outcomes. The positive studies had an average platelet dose of $5,464 \pm 511$, whereas the studies that had no statistical difference had an average platelet dose of $2,253 \pm 753 \times 10^6$ ($P < .05$). **Conclusions:** Improved clinical outcomes from PRP injections for knee OA may be related to a greater platelet dose. **Level of Evidence:** Level II, systematic review of Level I and II studies.

*See commentary on page 818*

Platelet-rich plasma (PRP) is a mixture of concentrated platelets and growth factors prepared through the centrifugation of autologous whole blood. PRP injections increasingly are used for the treatment of knee osteoarthritis (OA), showing promise as a safe and effective treatment option.[1-4] Although initial in vitro studies showed that PRP may function by promoting tissue regeneration, more recent research leans toward its anticatabolic and immunomodulatory effects.[5] In the context of knee OA, this may help to temper cartilage degeneration and decrease the inflammatory components of pain and dysfunction, although the exact mechanisms for its efficacy remain unclear.[6]

Despite the theoretical importance of factors such as platelet, growth factor, or leukocyte concentration, there is no standardized way of preparing PRP. The 2017 Minimum Information for Biologics in Orthopedics guidelines define important characteristics for standardizing reporting in studies involving biologics in orthopaedic research, including platelet concentration, leukocyte differential, and volume injected.[7] Despite these reporting guidelines, no standardized platelet dosage or injection regimen for the treatment of knee OA has been established.

Previous studies have called attention to the heterogeneity in PRP literature regarding the composition and preparation of PRP, injection protocols, platelet dosage, and postinjection rehabilitation.[8-10] Platelet dosage is one of many factors that may influence PRP outcomes and has substantial heterogeneity in the literature. Platelet dosage is a measure of the total number of

*From the Department of Orthopaedics, University of California San Francisco, San Francisco, California, U.S.A. (W.A.B., D.L.); Department of Orthopedics, Kaiser Permanente Oakland, Oakland, California, U.S.A. (Z.B.); University of California San Francisco School of Medicine, San Francisco, California, U.S.A. (A.P.); and University of California Berkeley, Berkeley, California, U.S.A. (A.R., R.L.).*

*Received November 18, 2023; accepted March 10, 2024.*

*Address correspondence to William A. Berrigan, M.D., 1500 Owens St., San Francisco, California, U.S.A. E-mail: bill.berrigan@ucsf.edu*



*0749-8063/231643*
*https://doi.org/10.1016/j.arthro.2024.03.018*

platelets delivered in a PRP treatment and is determined by the product of platelet count (usually in platelets/microliter), volume injected, and total number of injections. A recent review characterizes the importance of platelet dosing in initiating angiogenic pathways necessary for microvascular networks that supply oxygen and nutrients to impaired tissues.[11] Other research into platelet dosage in PRP found an absolute count of 10 billion platelets to be an important threshold for sustained chondroprotection at 1 year for patients with moderate knee OA.[12]

The purpose of this study was to determine whether the platelet dose administered during a PRP injection for knee OA affects clinical outcomes. We hypothesized that total platelet dosage would be correlated with improvements in patient-reported outcome measures.

## Methods

This systematic review was registered in PROSPERO on March 6, 2023, and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[13]

### Data Sources and Search Strategy

We searched the PubMed, Cochrane Library, and Embase databases for publications through February 2023. The electronic search strategy used was as follows: "PRP" AND "knee osteoarthritis" AND "injection" AND "intra-articular." In total, 882 studies were extracted with 328 duplicate manuscripts removed, leaving 554 for title and abstract review.

### Eligibility Criteria

To be included in the study, the study had to (1) be original research in the form of randomized controlled trials that compared various preparations of intra-articular PRP (autologous blood concentration, autologous conditioned plasma, or plasma rich in growth factor) with other groups (saline, hyaluronic acid, corticosteroid, microfragmented adipose tissue, bone marrow aspirate concentrate); (2) include raw data: platelet count (injected), volume injected, and outcomes scores at different time points; (3) be published after the year 2000, as PRP applications to musculoskeletal structures were not adequately described before this time period; (4) be written in English; and (5) have a minimum of 6 months of follow-up time. If the study described the same cohort of patients that had already been screened, only the most recent publication was included.

### Data Extraction

Two reviewers (A.R., R.L.) independently screened the titles and abstracts of the articles identified by the search and performed study selection based on inclusion criteria. A third reviewer resolved discrepancies (W.A.B.). Full texts were retrieved after the initial title and abstract review. Data were extracted using a standardized data-collection form. The following data were extracted: general study information (lead author, year published, sample size, comparator, follow-up time period); details of the participants (age, body mass index [BMI], race, socioeconomic status, Kellgren-Lawrence [KL] grade for severity of OA); details of PRP procedure (centrifuge speed and time, number of spins, activations, platelet number, injection volume, number of injections, use of image guidance, leukocyte concentration, light activation); and outcome measures. The average platelet dosage was calculated for each study by multiplying the average platelet concentration by the amount injected to obtain the average total platelet dosage received by each participant.

### Study Outcome

Study outcomes were classified by whether they reported a positive effect for the PRP group in the main study outcome at 6 months and 1 year. Positive effects were defined as a statistically significant improvement in the main outcome measure.

### Statistical Analysis

Descriptive statistics were used to compare the demographics and characteristics of studies with positive effects to those without. Two-sample *t*-tests were used to compare average age and BMI. The Shapiro-Wilk test was used to determine normality in the distribution of average platelet dosages for the group of studies reporting positive outcomes and for those not reporting positive outcomes. Wilcoxon rank test was then used to compare the average platelet dosage between the 2 groups. Significance was defined as $P \leq .05$.

### Quality and Risk of Bias Assessment

The quality of the included studies was evaluated using the Cochrane Collaboration Tool for Risk of Bias.[14] This tool consists of random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each item was graded as high, low, or unclear risk.

## Results

In total, 554 studies were retrieved for title and abstract screening. The full texts of 132 studies were reviewed and, of these, 29 randomized clinical trials met the eligibility criteria (Fig 1). The demographics and study details are included in Appendix Tables 1 and 2, available at www.arthroscopyjournal.org. The risk of bias is shown in Figure 2. All details regarding PRP treatment protocols are found in Table 1.[12,15-42]

Of the 29 studies reviewed, 31 study arms used PRP as a treatment method. Of the 31, 28 showed PRP to have significantly improved outcomes compared with their respective control groups at 6 months. The remaining 3 had no statistical difference. The studies that showed improved outcomes had an average platelet dose of $5{,}500 \pm 474 \times 10^6$ with a median of 5,267, whereas the studies that had no statistical difference had an average platelet dose of $2{,}302 \pm 437 \times 10^6$ ($P < .01$) with a median of 2,400. Of the 18 studies that tracked outcomes out to 12 months, 16 showed significant improvements in the PRP group, whereas 2 showed no

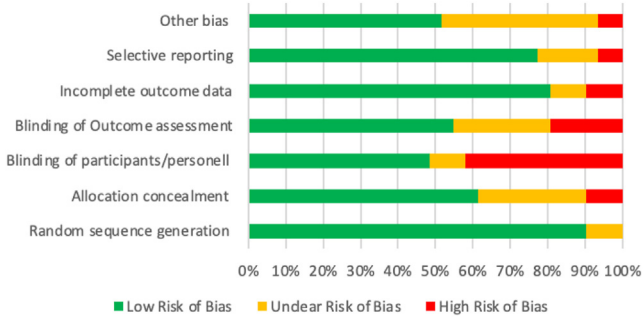


**Fig 2.** Risk of bias assessment.

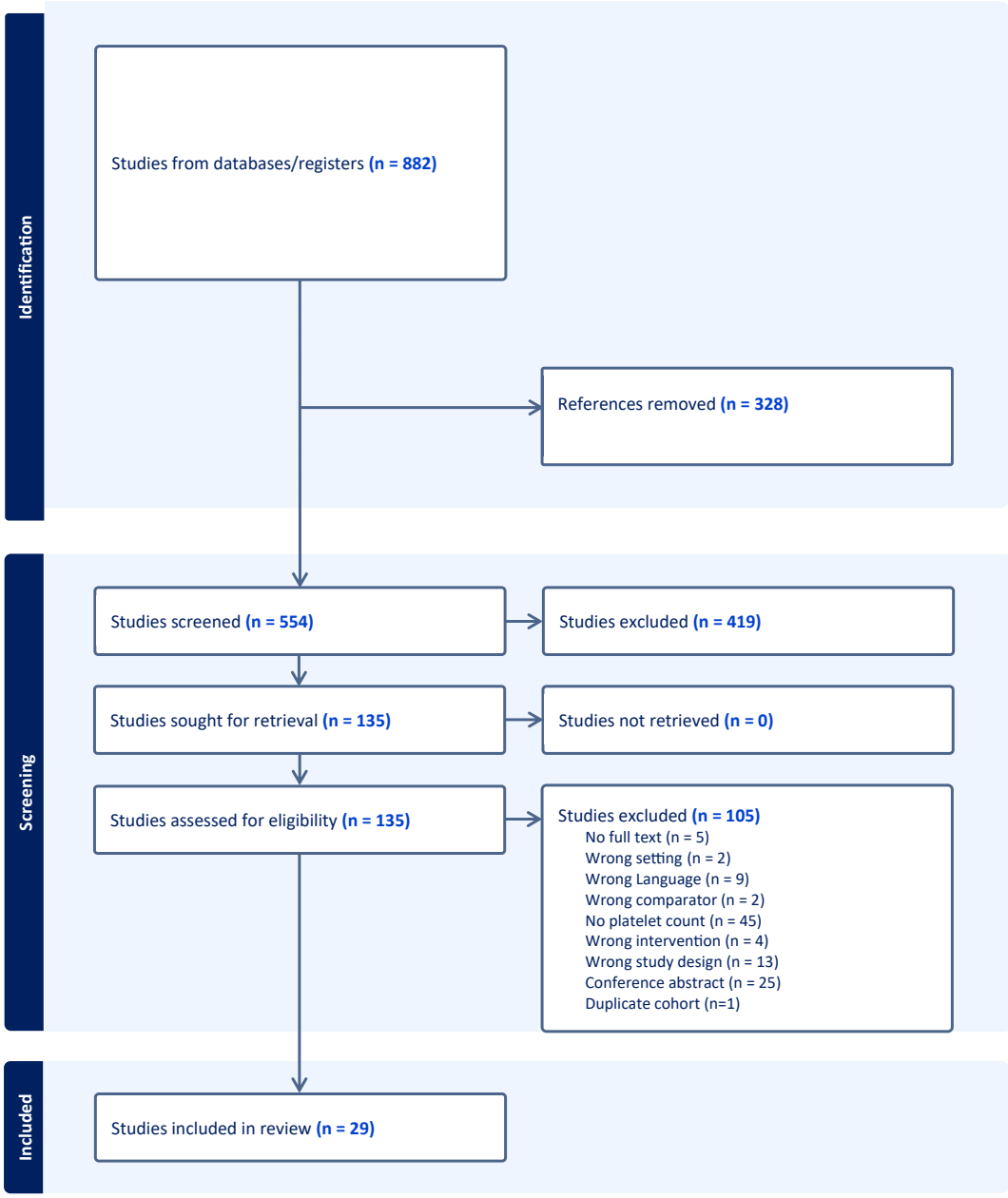


**Fig 1.** Preferred Reporting for Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

**Table 1.** PRP Treatment Protocol

| Lead Author (Year) | LOE | LP/LR | Centrifuge Speed, min | No. of Spins | PRP Kit | Activation | Light Activation | Use of Image Guidance | No. of Injections | Platelet Number, per microliter × $10^3$ | Injection Volume, mL | Total Platelet Dose, × $10^6$ | 6Months (+/−) | 1 Year (+/−) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anz (2022)[15] | I | LP-PRP | 3,800 (1.5)/3,800 (5) | 2 | EmCyte PurePRP | N | N | Y | 1 | 1,216 | 7 | 8,512 | + | + |
| Bansal (2021)[12] | I | LP-PRP | 600 (10)/4,000 (15) | 2 | NR | N | N | N | 1 | 1,438 | 8 | 10,450 | + | + |
| Baria (2022)[16] | II | LR-PRP | NR | 2 | Arthrex Angel cPRP | N | N | Y | 1 | 2,673 | 5.12 | 13,685.76 | + | NA |
| Barman (2022)[17] | II | LR-PRP | 1,400 (10)/3,000 (10) | 2 | NR | N | N | Y | 1 | 857.7 | 8 | 6,861.6 | + | NA |
| Buendía-López (2018)[18] | II | LP-PRP | 1,050 (15)/2,000 (10) | 2 | Tubex | Y | N | N | 1 | 1,095 | 5 | 5,475 | + | + |
| Chu (2022)[19] | I | LP-PRP | 3,200 (3)/3,300 (5) | 2 | NR | N | N | N | 3 | 832.1 | 5 | 4,160.5 | + | + |
| Di Martino (2022)[20] | II | LR-PRP | 1,490 (6)/3,400 (15) | 2 | NR | Y | N | N | 1 | 1,000 | 5 | 5,000 | + | + |
| Di Martino (2022)[21] | I | LR-PRP | 1,800 (10)/3,500 (10) | 2 | NR | Y | N | N | 3 | 1,146.8 | 5 | 5,734 | + | + |
| Di Martino (2022)[21] | II | LP-PRP | 1,801 (10)/3,500 (10) | 2 | NR | Y | N | N | 3 | 1,074.9 | 5 | 5,374.5 | + | + |
| Duan (2022)[22] | I | LP-PRP | 3,200 (5)/3,300 (3) | 2 | NR | N | N | N | 3 | 751.25 | 4 | 3,005 | − | − |
| Elik (2020)[23] | I | LR-PRP | 2,000 (10)/4,000 (5) | 2 | RevMed | N | N | N | 3 | 1,000 | 4 | 4,000 | + | NA |
| Forogh (2016)[24] | I | NR | 1,600 (6)/2,000 (6) | 2 | Tubex | Y | N | N | 1 | 1,501 | 5 | 7,505 | + | NA |
| Görmeli (2017)[25] | I | LR-PRP | 1,500 (6)/3,500 (12) | 2 | NR | Y | N | N | 3 | 1,118 | 5 | 5,590 | + | NA |
| Görmeli (2017)[25] | I | LR-PRP | 1,500 (6)/3,500 (12) | 2 | NR | Y | N | N | 1 | 1,152 | 5 | 5,760 | + | NA |
| Joshi Jubert (2017)[26] | I | LP-PRP | 280g (15)/680g (20) | 2 | NR | N | N | N | 1 | 990 | 4 | 3,960 | + | NA |
| Kaszyński (2022)[27] | II | LP-PRP | 2,320g (7) | 1 | NR | N | N | N | 3 | 1,720 | 3 | 5,160 | + | + |
| Lana (2016)[28] | I | LR-PRP | 300g (5)/700g (17) | 2 | NR | Y | N | Y | 3 | 1,200 | 5 | 6,000 | + | + |
| Louis (2018)[29] | I | LP-PRP | 130g (15)/250g (15) | 2 | NR | Y | N | Y | 1 | 800 | 3 | 2,400 | − | NA |
| Montañez-Heredia (2016)[30] | I | LP-PRP | 1,800 (15)/3,500 (10) | 2 | NR | Y | N | N | 3 | 952 | 5 | 4,760 | + | NA |
| Nunes-Tamashiro (2022)[31] | I | NR | 1,200 (10) | 1 | NR | N | N | N | 1 | 1,119.588 | 6 | 6,717.528 | + | + |
| Park (2021)[32] | I | LR-PRP | 3,200 (15) | 1 | GPS III Platelet Concentration System; Zimmer Biomet | Y | N | N | 1 | 976 | 3 | 2,928 | + | NA |
| Rayegani (2014)[33] | II | LR-PRP | 1,600 (15)/2,800 (7) | 2 | Rooyagen | N | N | N | 2 | 1,346 | 5 | 6,730 | + | NA |
| Sdeek (2021)[34] | I | LP-PRP | 160g (20)/400g (15) | 2 | NR | N | N | N | 3 | 2,664 | 2.5 | 6,660 | + | + |
| Simental-Mendia (2016)[35] | II | LP-PRP | 1,800 (10)/3,400 (12) | 2 | NR | Y | N | N | 3 | 513.25 | 3 | 1,539.75 | + | + |
| Singh (2022)[36] | II | NR | 1,500 (15) | 1 | NR | N | N | N | 1 | 1,019 | 4.5 | 4,585.5 | + | + |
| Su (2018)[37] | II | LR-PRP | 1,480 (6)/3,400 (15) | 2 | NR | Y | N | N | 1 | 789.68 | 6 | 4,738.08 | + | + |
| Sun (2021)[38] | II | LP-PRP | 500-1,200 (8) | 1 | NR | N | N | N | 1 | 463.83 | 3 | 1,391.49 | + | NA |
| Tschopp (2022)[39] | I | LP-PRP | 1,500 (5) | 1 | ACP System; Arthrex | N | N | Y | 1 | 500 | 3 | 1,500 | − | − |
| Tucker (2021)[40] | II | LP-PRP | 3,000 (4) | 1 | Cytonics APIC | Y | N | Y | 1 | 703.73 | 5 | 3,518.65 | + | + |
| Wang (2022)[41] | I | LR-PRP | 1,450 (10)/3,370 (10) | 2 | NR | Y | N | N | 1 | 857.4 | 4 | 3,429.6 | + | NA |
| Xu (2021)[42] | II | LP-PRP | 160g (10)/250g (15) | 2 | NR | N | N | Y | 3 | 950 | 4 | 3,800 | + | + |

LOE, level of evidence; LP, leukocyte poor; LR, leukocyte rich; N, no, No., number; NR, not recorded; PRP, platelet-rich plasma; Y, yes.

statistical significance. The studies that showed improved outcomes at 12 months had an average platelet dose of 5,464 ± 511 × $10^6$ with a median of 5,160, whereas the studies that had no statistical difference had an average platelet dose of 2,253 ± 753 × $10^6$ ($P < .05$) with a median of 2,252.5.

The average age in the studies that tracked outcomes at 6 months was 58.0 ± 0.8 years in the improved outcome group and 48.7 ± 9.2 years in the group without statistical differences ($P = .28$). The average age in the studies that tracked outcomes at 12 months was 57.1 ± 1.0 years in the improved outcome group and 46.5 ±15.5 years in the group without statistical differences ($P = .82$).

The average BMI in the studies that tracked outcomes at 6 months was 27.5 ± 0.4 in the improved outcome group and 25.2 ± 0.6 in the group without statistical differences ($P = .09$). The average BMI in the studies that tracked outcomes at 12 months was 27.3 ± 0.5 in the improved outcome group and 25.0 ± 1.0 in the group without statistical differences ($P = .16$).

The average KL severity in the studies that tracked outcomes at 6 months was 2.3 ± 0.1 in the improved outcome group. Only 1 study reported KL average in the group without statistical significance at 2.1 ± 0.0. The average KL score in the studies that tracked outcomes at 12 months was 2.1 ± 0.12 in the improved outcome group and 2.1 ± 0.0 in the group, without statistical difference shown.

Three studies analyzed the number of patients who met the minimal clinically important difference (MCID). Di Martino et al. described 73% and 60% meeting the MCID of the International Knee Documentation Committee at 6 and 12 months and 63% and 56% for Knee Injury and Osteoarthritis Outcome Score Pain subscale (dosage 5,000 × $10^6$).[20,43] Buendía-López et al.[18] described a 20% change in Western Ontario and McMaster Universities Arthritis Index for 48% of participants at 6 months and 30% at 12 months (dosage 5,475 × $10^6$). Park et al.[32] noted 40% of participants met Western Ontario and McMaster Universities Arthritis Index MCID,[44] 54% for VAS,[45] and 60% for International Knee Documentation Committee[46] (dosage 2,928 × $10^6$) at 6 months.

## Discussion

Through this systematic review, we observed that a greater platelet dosage may yield better clinical outcomes when PRP is used in the treatment of symptomatic knee OA. Studies that demonstrated a statistically significant difference post-PRP treatment averaged a greater dose (5,464 ± 511 × $10^6$ when compared with those with negative results [2,253 ± 753 × $10^6$]). In addition, we observed that inconsistent reporting regarding platelet doses and other factors continues to be a limiting factor in interpreting and synthesizing the currently available research on PRP for knee OA.

Both in vitro and in vivo studies support the role of platelets in angiogenesis and tissue repair. In vivo studies have proposed mechanisms for the effect of platelet dosing on PRP outcomes. Platelets are rich sources of growth factors and cytokines, including vascular endothelial growth factor platelet-derived growth factor, fibroblast growth factor, and epidermal growth factor, which are instrumental in angiogenesis.[12,47] In vitro studies consistently demonstrate that increasing platelet concentrations in PRP preparations leads to a greater release of these angiogenic factors.[48-52] This heightened release of growth factors stimulates endothelial cell proliferation, migration, and differentiation, thereby facilitating angiogenesis.[11,53] Gentile and Garcovich[54] in a recent systematic review found that this optimally occurs at a concentration of 1-1.5 × $10^6$ platelets/microliter.

It is crucial to acknowledge the inherent variability in PRP preparation methods and the resulting heterogeneity in platelet concentrations and PRP contents. PRP can be produced via a single-spin or double-spin method at different centrifugation speeds, acceleration, and temperatures. Kahn et al.[55] found the centrifugal acceleration of 3,731g for 4 minutes to be the optimal condition for obtaining the greatest platelet concentration, whereas others suggested 2 spins at 200g, or 1,000g and 3,000g for varied time periods.[56,57] In regard to spins, Oh et al.[58] found that a double-spin method produced a greater level of platelets and growth factor than a single spin. In our review, most studies used a double-spin method, but there were 28 different centrifugation speeds with varying processing durations that reinforced the high inconsistency in preparation.

There are at least 50 commercial PRP systems on the market, each with its own methodology and product. Not all these products are able to produce the high-level platelet concentrations suggested, and some systems may not yield a supraphysiological level of platelets. This does not meet the minimum standards of PRP which, defined by the Food and Drug Administration, must contain at least 250,000 platelets per microliter, or as others have suggested, 1 million platelets per microliter.[59] The large variability leads to a theoretical range in dosage from 300 million to 12.8 billion platelets and a mix of clinical results.[60] This highlights the importance of standardizing PRP-preparation techniques to ensure consistency in platelet dosages and PRP contents across studies. It also emphasizes the need for caution when extrapolating the findings of individual studies to broader clinical practice, as the specific PRP preparation method used may affect treatment efficacy.

Beyond preparation, age can influence the final content and outcomes. Rossi et al.[61] showed that sex

and BMI did not influence PRP composition; however, increased age was associated with lower platelet concentration in PRP and therefore reduced growth factor and cytokines. Age, sex, and BMI did not significantly affect the results of our review. The studies with no statistical difference in outcomes had a younger patient population with lower BMI. This suggests that even in cohorts with potentially less favorable baseline characteristics, greater platelet dosages remained associated with improved outcomes. Nevertheless, individual patient characteristics may still play a role in treatment response, both in regards to the composition of injected PRP and other confounding factors known to affect outcomes, such as activity level. Further research is necessary to better understand their influence on PRP therapy and to better characterize how patient demographics affect optimal platelet dose.

It should be noted that the distribution of dosing regimens in our study was not normal. Consequently, we are unable to assert that our findings accurately reflect the optimal level of platelet dosing or establish a clear dose-dependent relationship. The existence of a dosing ceiling remains uncertain, and there is a possibility that elevated dosing could potentially inhibit angiogenesis.[51,62] Monitoring this aspect in future research is advisable. In addition, other likely factors should be considered beyond dosage. Failing to recognize the significance of this could be an oversight, as recent findings propose that treatment outcomes may be influenced by other biological aspects of PRP. These include the existence of anti-inflammatory or anticatabolic factors and distinct proteomics, warranting additional exploration in this area.[63,64]

### Limitations

Primarily, the analysis is limited by the design of the trials. The initial goal was to synthesize the data quantitatively, but the variability was too high to conduct a meta-analysis or network meta-analysis because of the heterogeneity of the control groups. There were 12 control groups with multiple outcome measures. This precluded any pooling of the data. Second, the review excludes randomized clinical trials that do not report cell counts. The 2017 Minimum Information for Studies Evaluating Biologics in Orthopaedics established the reporting of cell counts as the standard for research in the field.[7] Therefore, it was decided to not include studies without these discrete data even if it could be inferred from manufacturers' standards. Consequently, studies such as the PEAK (PRP treatment in Early osteoArthritis of the Knee) trial, published in 2022, which use systems known to produce low-dose PRP, are not included.[65] Third, there is a predominance of positive PRP studies with fewer negative trials. The number of positive versus negative studies limits our ability to compare the 2 groups. It also suggests the likelihood of publication bias that may skew the overall assessment of PRP's efficacy. Studies with negative outcomes may be under-represented in the literature, potentially affecting the application of our findings. Fourth, the study did not account for differences between leukocyte-rich or leukocyte-poor PRP preparations. Finally, only 3 trials analyzed the percentage of patients who met the MCID.[18,20,32] Therefore, the relationship between the outcomes to the MCID was reported but not analyzed.

## Conclusions

Improved clinical outcomes from PRP injections for knee OA may be related to a greater platelet dose.

## Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D.L. reports relationships with Vericel Corporation and AlloSource that include consulting or advisory. All other authors (W.A.B., Z.B., A.P., A.R., R.L.) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Appendix Table 1.** Demographic Information

| Lead Author (Year) | Age | BMI | Race | Socioeconomic Status |
|---|---|---|---|---|
| Anz (2022)[15] | 52.2 | 27.9 | N | N |
| Bansal (2021)[12] | 64.4 | 24.9 | N | N |
| Baria (2022)[16] | 51.9 | 31 | Y | N |
| Barman (2022)[17] | 57 | 25.63 | N | N |
| Buendía-López (2018)[18] | 56 | 25 | N | N |
| Chu (2022)[19] | 53.9 | 27.5 | N | N |
| Di Martino[7] (2022)[20] | 54.1 | 28 | N | N |
| Di Martino (2022)[21] | 55.2 | 26.1 | N | N |
| Di Martino (2022)[21] | 55.2 | 26.1 | N | N |
| Duan (2022)[22] | 31 | 24 | N | N |
| Elik (2020)[23] | 61.3 | 30.37 | N | N |
| Forogh[1] (2016)[24] | 59.1 | 28.9 | N | Education level |
| Görmeli[12] (2017)[25] | 53.8 | 28.4 | N | N |
| Görmeli[12] (2017)[25] | 53.8 | 28.4 | N | N |
| Joshi Jubert[13] (2017)[26] | 65.56 | 31.2 | N | N |
| Kaszyński (2022)[27] | 57 | 26 | N | N |
| Lana (2016)[28] | 60.9 | 27.42 | Y | N |
| Louis (2018)[29] | 53.2 | 25.6 | N | N |
| Montañez-Heredia (2016)[30] | 66.3 | 29 | N | N |
| Nunes-Tamashiro (2022)[31] | 67.6 | 29.22 | Y | Work and education |
| Park (2021)[32] | 60.6 | 25.5 | N | N |
| Rayegani (2014)[33] | 58.07 | 28.23 | N | N |
| Sdeek (2021)[34] | 60.2 | 27.9 | N | N |
| Simental-Mendia (2016)[35] | 55.6 | 29.5 | N | N |
| Singh (2022)[36] | 53.23 | 28.88 | N | Y |
| Su (2018)[37] | 54.16 | 28.17 | N | N |
| Sun (2021)[38] | 58.4 | 24.8 | N | Y |
| Tschopp (2022)[39] | 62 | 26 | N | N |
| Tucker (2021)[40] | 57.5 | 30.9 | N | N |
| Wang (2022)[41] | 64.9 | 23.4 | N | N |
| Xu (2021)[42] | 56.9 | 22.5 | N | N |

BMI, body mass index; N, not reported; Y, data included.

**Appendix Table 2.** Study Characteristics

| Lead Author (Year) | Sample Size | Control Group | KL Severity (KL Range) | Follow-Up Time, mo | Outcome Measures |
|---|---|---|---|---|---|
| Anz (2022)[15] | 90 | BMAC | 1.9 (1-3) | 1, 3, 6, 9, 12, 18, 24 | WOMAC, IKDC |
| Bansal (2021)[12] | 150 | HA | 2.79 (1-3) | 1, 3, 6, 12 | WOMAC, IKDC, 6MW |
| Baria (2022)[16] | 58 | MFAT | 2.74 (1-4) | 1, 3, 6 | KOOS, VAS |
| Barman (2022)[17] | 50 | IO PRP | 3 (3) | 1.5, 3, 6 | VAS, KOOS, satisfaction |
| Buendía-López (2018)[18] | 106 | NSAIDs, HA | 1.5 (1-2) | 6, 12 | WOMAC, VAS |
| Chu (2022)[19] | 610 | Saline | 1.96 (1-3) | 3, 6, 12, 24, 60 | WOMAC, IKDC, VAS |
| Di Martino[7] (2022)[20] | 118 | MFAT | 2.57 (1-4) | 1, 3, 6, 12, 24 | IKDC, KOOS, EQ-VAS, EQ-5D |
| Di Martino (2022)[21] | 192 | LP-PRP | 2.33 (1-3) | 2, 6, 12 | IKDC, KOOS, EQ-VAS, Tegner score |
| Di Martino (2022)[21] | 192 | LR-PRP | 2.33 (1-3) | 2, 6, 12 | IKDC, KOOS, EQ-VAS, Tegner score |
| Duan (2022)[22] | 190 | Saline | NR (NR) | 1, 3, 6, 12, 24 | WOMAC, VAS, HJHS, SF-36 |
| Elik (2020)[23] | 60 | Saline | 2.35 (1-3) | 1 ,6 | VAS, WOMAC, SF-36 |
| Forogh[1] (2016)[24] | 48 | Steroid | 2.71 (2-3) | 2, 6 | KOOS, VAS |
| Görmeli[12] (2017)[25] | 182 | HA, saline | NR (0-4) | 6 | EQ-VAS, IKDC |
| Görmeli[12] (2017)[25] | 182 | HA, saline | NR (0-4) | 6 | EQ-VAS, IKDC |
| Joshi Jubert[13] (2017)[26] | 65 | Steroid | 3.71 (3-4) | 1, 3, 6 | VAS, KOOS, SF-36 |
| Kaszyński (2022)[27] | 60 | Adipose tissue | 2.4 (1-3) | 1, 3, 6, 12 | VAS, KOOS, WOMAC, IKDC, EQ-5D-5L |
| Lana (2016)[28] | 105 | HA, HA + PRP | 2.1 (1-3) | 1, 3, 6, 12 | WOMAC, VAS, CRP |
| Louis (2018)[29] | 54 | HA | NR (2-4) | 1, 3, 6 | WOMAC, VAS, satisfaction |
| Montañez-Heredia (2016)[30] | 53 | HA | 2.3 (1-3) | 3, 6 | EuroQOL, KOOS |
| Nunes-Tamashiro (2022)[31] | 100 | Steroid, saline | 2.59 (2-3) | 1, 2, 3, 12 | VAS, VAS, WOMAC, SF-36, TUG, 6MW, Likert, % improvement |
| Park (2021)[32] | 110 | HA | 2.44 (1-3) | 1.5, 3, 6 | IKDC, VAS, WOMAC, Patient Global Assessment |
| Rayegani (2014)[33] | 65 | Acetaminophen + exercise | 2.33 (1-4) | 1, 2, 6 | WOMAC, SF-36, medication use |
| Sdeek (2021)[34] | 200 | HA | NR (2-3) | 0.5, 2, 6, 12, 24, 30, 36 | WOMAC, IKDC, VAS |
| Simental-Mendia (2016)[35] | 75 | Acetaminophen | 1.65 (1-2) | 1.5, 3, 6, 12 | VAS, WOMAC, SF-12 |
| Singh (2022)[36] | 70 | Arthroscopy | 2.44 (2-3) | 3, 6, 9 | WOMAC, VAS |
| Su (2018)[37] | 86 | IO PRP, HA | 1.48 (2-3) | 1, 3, 6, 12, 18 | WOMAC, VAS |
| Sun (2021)[38] | 85 | HA + PRP | 2 (2) | 1, 3, 6 | VAS, WOMAC, Lequesne, SLS |
| Tschopp (2022)[39] | 120 | Steroid, HA | 2.13 (1-3) | 3, 6, 9, 12, 15, 18, 21, 24 | NRS, WOMAC, TAS |
| Tucker (2021)[40] | 17 | Saline | NR (2-3) | 0.5, 3, 6, 12 | ELISA, PCR, WOMAC, VAS |
| Wang (2022)[41] | 100 | HA | 2.15 (1-3) | 3, 6, 78.9 | WOMAC, VAS |
| Xu (2021)[42] | 150 | HA, PRP+HA | 1.48 (2-3) | 1, 6, 12, 24 | WOMAC, VAS, Lequesne, Lysholm |

6MW, 6-minute walk test; BMAC, bone marrow aspirate concentrate; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; EQ-5D, EuroQol 5 Dimension 5 Level; EQ-VAS, EuroQol visual analog scale; HA, hyaluronic acid; HJHS, Hemophilia Joint Health Score; IKDC, International Knee Documentation Committee; IO PRP, intraosseous platelet-rich plasma; KOOS, Knee Injury and Osteoarthritis Outcome Score; LP-PRP, leukocyte-poor platelet-rich plasma; MFAT, microfragmented adipose tissue; N, not reported; NRS, Numeric Rating Scale; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; PRP, platelet-rich plasma; SF-36, Short-Form 36; SLS, single-leg stance; TAS, Tegner Activity Scale; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index; Y, data included.