



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

John W. Belk, B.A., Joseph J. Lim, Carson Keeter, M.S., Patrick C. McCulloch, M.D., Darby A. Houck, B.A., Eric C. McCarty, M.D., Rachel M. Frank, M.D., and Matthew J. Kraeutler, M.D.

Purpose: To systematically review the literature to compare the efficacy and safety of platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and hyaluronic acid (HA) injections for the treatment of knee osteoarthritis (OA). **Methods:** A systematic review was performed by searching PubMed, the Cochrane Library, and Embase to identify Level I studies that compared the clinical efficacy of at least 2 of the following 3 injection therapies: PRP, BMAC, and HA for knee OA. The search phrase used was *knee AND osteoarthritis AND randomized AND ("platelet rich plasma" OR "bone marrow aspirate" OR "hyaluronic acid")*. Patients were primarily assessed based on patient-reported outcome scores (PROs) including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS) for pain, and Subjective International Knee Documentation Committee (IKDC) score. **Results:** Twenty-seven studies (all Level I) met inclusion criteria, including 1,042 patients undergoing intra-articular injection(s) with PRP (mean age 57.7 years, mean follow-up 13.5 months), 226 patients with BMAC (mean age 57.0 years, mean follow-up 17.5 months), and 1,128 patients with HA (mean age 59.0 years, mean follow-up 14.4 months). Nonnetwork meta-analyses demonstrated significantly better postinjection WOMAC ($P < .001$), VAS ($P < .01$), and Subjective IKDC scores ($P < .001$) in patients who received PRP compared with patients who received HA. Similarly, network meta-analyses demonstrated significantly better postinjection WOMAC ($P < .001$), VAS ($P = .03$), and Subjective IKDC ($P < .001$) scores in patients who received BMAC compared with patients who received HA. There were no significant differences in postinjection outcome scores when comparing PRP with BMAC. **Conclusions:** Patients undergoing treatment for knee OA with PRP or BMAC can be expected to experience improved clinical outcomes when compared with patients who receive HA. **Level of Evidence:** Level I, meta-analysis of Level I studies.

Osteoarthritis (OA) is one of the most common articular cartilage pathologies in the United States and is a leading cause of chronic disability worldwide.¹ It has been estimated that 16.7% of people older than

45 years have symptomatic knee OA, with 27.8% showing radiographic signs of cartilage degeneration.² The clinical efficacy of platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and

From the University of Colorado School of Medicine, Aurora, Colorado (J.W.B., D.A.H.); University of Colorado Boulder, Boulder, Colorado (J.J.L.); University of Colorado School of Medicine, Department of Orthopedics, Aurora, Colorado (C.K., E.C.M., R.M.F.); and Houston Methodist Hospital, Department of Orthopedics & Sports Medicine, Houston, Texas (P.C.M., M.J.K.), U.S.A.

The authors report the following potential conflicts of interest or sources of funding: E.C.M. reports consultant for Biomet; royalties from Zimmer Biomet and Elsevier; and research support from Arthrex, Breg, DJ Orthopaedics, Mitek, Ossur, and Smith & Nephew, outside the submitted work. R.M.F. reports consultant and payment for lectures, including service on speakers bureaus for AlloSource, Arthrex, and JRF Ortho; royalties from Elsevier; and research support from Arthrex, Smith & Nephew, outside the submitted work.

P.C.M. reports consultant for Arthrex and research support from Smith & Nephew, outside the submitted work. Full ICMJE author disclosure forms are available for this article online, as [supplementary material](#).

Received November 16, 2022; accepted March 1, 2023.

Address correspondence to Matthew J. Kraeutler, M.D., Department of Orthopedics & Sports Medicine, Houston Methodist Hospital, 6445 Main St., Suite 2300, Houston, TX 77030. E-mail: matthewkraeutlermd@gmail.com

© 2023 by the Arthroscopy Association of North America

0749-8063/221506/\$36.00

<https://doi.org/10.1016/j.arthro.2023.03.001>

hyaluronic acid (HA) injections has recently gained significant attention as nonoperative treatment options for knee OA in the orthopaedic sports medicine community.^{3,4}

HA, a naturally occurring glycosaminoglycan found in synovial fluid, has been demonstrated as a safe and effective way to treat knee OA.^{5,6} With the benefit of insurance coverage, HA increases the mechanical and viscoelastic properties of the synovial fluid as well as overall joint lubrication, which promotes pain relief and functional improvements in osteoarthritic knee, hip, and ankle joints.^{7,8} However, HA injections are synthetically manufactured and have shown inconsistent effects on inflammation,⁹ leading many clinicians to adopt PRP and other injection therapies as first-line treatment options for degenerative knee OA.¹⁰ PRP involves the modulation of the intra-articular environment by introducing autologous blood products in the joint, which can reduce inflammatory distress and promote chondrogenesis.^{3,11,12} Multiple studies have shown the antinociceptive and cell proliferative properties of PRP to be effective inhibitors of the OA process,^{13,14} although the clinical indications of PRP remain unclear. In addition, PRP injections are expensive and not currently covered by most insurance companies. BMAC is one of the few cell-based therapies currently available as an injectable treatment option in the United States.¹⁵ The presence of bone marrow stromal cells (BMSCs) makes BMAC an attractive option and distinguishes this injectable from PRP or HA. The purpose of this study was to systematically review the literature to compare the efficacy and safety of PRP, BMAC, and HA injections for the treatment of knee OA. The authors hypothesized that patients with PRP or BMAC injections would experience improved clinical outcomes when compared with patients with HA injections.

Methods

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using a PRISMA checklist. Two independent reviewers (J.W.B., J.J.L.) searched PubMed, Embase, and the Cochrane Library up to August 15, 2022. The electronic search strategy used was as follows: *knee AND osteoarthritis AND randomized AND ("platelet rich plasma" OR "bone marrow aspirate" OR "hyaluronic acid")*. A total of 1,216 studies were reviewed by title and/or abstract to determine study eligibility based on inclusion criteria. In cases of disagreement, a third reviewer (M.J.K.) made the final decision. Inclusion and exclusion criteria followed the participants, interventions, comparators, outcomes, study design (i.e., PICOS) strategy. Studies selected for

inclusion met the following criteria: (1) participants: patients diagnosed with knee OA based on radiographic evaluation using a validated scoring system; (2) intervention: intra-articular injections of PRP, BMAC, or HA; (3) comparator: intra-articular injections of PRP, BMAC, or HA; (4) outcomes: clinical efficacy and adverse events, (5) study design: Level I randomized controlled trials that were published in English. Exclusion criteria included Level II-V studies and those that did not meet any of the aforementioned inclusion criteria. Twenty-seven studies were determined to meet inclusion criteria (Fig 1). Data extraction from each study was performed independently and then reviewed by a second author (M.J.K.). There was no need for funding or a third party to obtain any of the collected data. Risk of bias was assessed according to the Cochrane Collaboration's risk of bias tool,¹⁶ which incorporates an assessment of randomization, blinding, completeness of outcomes data, selection of outcomes reported, and other sources of bias.

Reporting Outcomes

Outcomes assessed included patient-reported outcomes (PROs). PROs included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score,¹⁷ the visual analog scale (VAS) for pain, the Subjective International Knee Documentation Committee (IKDC) score,¹⁸ the Lequesne Index score,¹⁹ and the Knee Injury and Osteoarthritis Outcome Score (KOOS).²⁰ For the VAS, all scores were standardized to a 100-point scale. A meta-analysis was performed to compare differences in PROs.

Study Methodology Assessment

The Modified Coleman Methodology Score (MCMS)²¹ was used to evaluate study methodology quality. The MCMS has a scaled potential score ranging from 0 to 100. Scores ranging from 85 to 100 are excellent, 70 to 84 are good, 55 to 69 are fair, and less than 55 are poor. The primary outcomes assessed by the MCMS are study size and type, follow-up time, attrition rates, number of interventions per group, and proper description of study methodology.

Statistical Analysis

A weighted average was calculated for numerical demographics (age, follow-up). In studies in which standard deviations were not provided,²²⁻²⁵ a quarter of the mean was used as the standard deviation, as previously described.²⁶ When data from 3 or more studies were available, the outcomes were summarized in a forest plot or a network forest plot when appropriate. Continuous outcome data of these studies were stratified by follow-up time and either mean differences (MDs) or standardized mean differences (SMDs), with

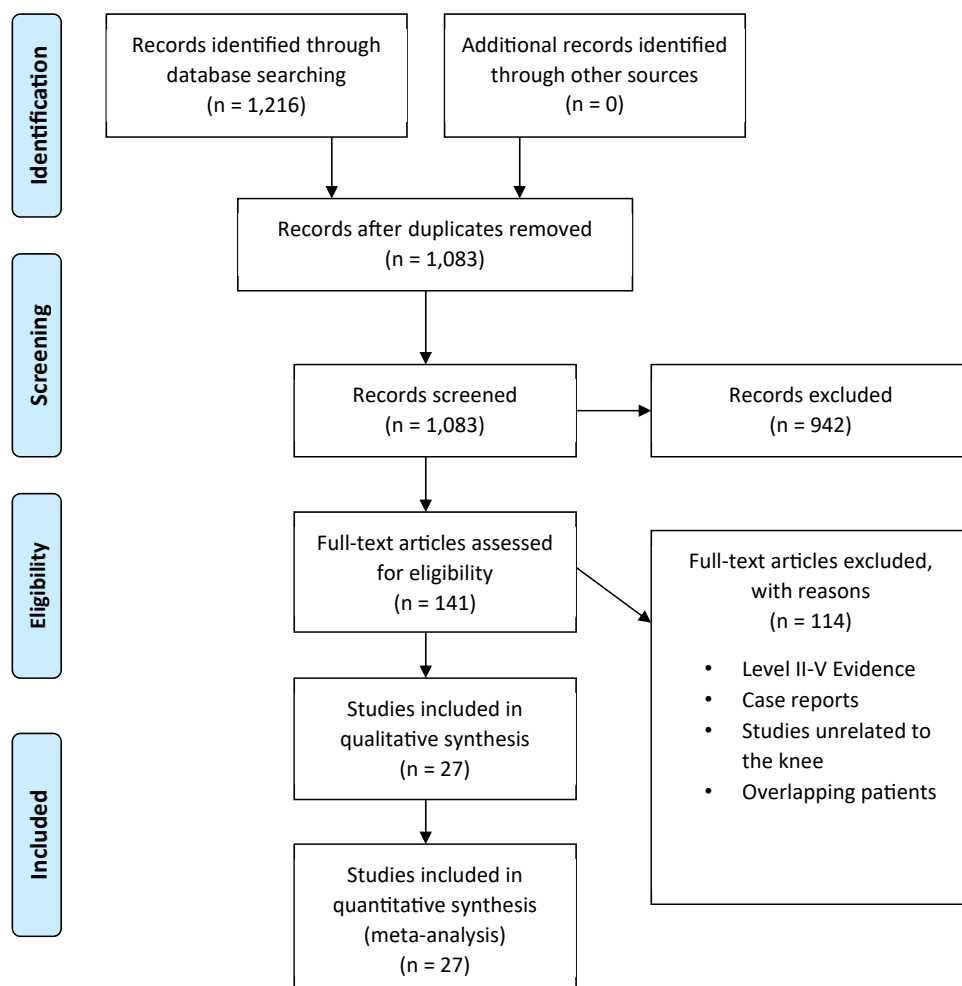


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

95% confidence intervals (CIs) calculated using either random or fixed-effects models depending on the analysis type and included in the forest plot. For non-network meta-analyses, a random-effects model was used because these models incorporate between-study heterogeneity into the overall summary measures. When there is no between-study heterogeneity, a random-effects model equals a fixed-effects model.²⁷ To quantify the degree of heterogeneity due to between-study characteristics, I^2 statistics were used to calculate heterogeneity. To indirectly compare the effects of leukocyte-poor (LP-PRP) and leukocyte-rich PRP (LR-PRP), a meta-analysis was performed using a random effects model for each continuous outcome variable.²⁸ Both network and non-network meta-analyses statistics and generation of network plots were constructed using R, version 4.2.2, and the Netmeta R package (R Foundation for Statistical Computing, Vienna, Austria). Risk of bias figures were performed using a combination of RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and R, version 4.2.2 (R Foundation for Statistical Computing).

Results

Twenty-seven studies met inclusion and exclusion criteria (Fig 1), including a total of 2,396 patients (PRP, $n = 1,042$; BMAC, $n = 226$; HA, $n = 1,128$). The mean patient age at the time of injection(s) was 57.7, 57.0, and 59.0 years in the PRP, BMAC, and HA groups, respectively, and the mean follow-up time was 13.5, 17.5, and 14.4 months in the PRP, BMAC, and HA groups, respectively (Table 1). The percentage of male patients was 38.5%, 54.5%, and 39.4% in the PRP, BMAC, and HA groups, respectively.

Outcomes Reported

Fifteen studies^{23-25,29-40} used the WOMAC score, 18 studies^{12,22-25,31-33,36,38,41-47} used the VAS, 9 studies^{12,22,24,30,34,41-44} used the Subjective IKDC score, 5 studies^{25,35,39,46,48} used the Lequesne Index (LEQ) score, and 6 studies^{12,30,42,45,47,49} used the KOOS score.

PRP Preparation and Treatment Method

All patients underwent harvest of peripheral venous blood from the antecubital vein, which was then

Table 1. Studies Included

Study	n (PRP, HA)	Patient Age, y (PRP)	Patient Age, y (HA)	Follow-up, mo (PRP)	Follow-up, mo (HA)	Sex Distribution, % Male (PRP, HA)		
PRP vs HA								
Ahmad et al., 2018 ⁴¹	45, 44	56.2 ± 6.8	56.8 ± 7.4	6.0	6.0	31.1%, 31.2%		
Cerza et al., 2012 ²⁹	60, 60	66.5 ± 11.3	66.2 ± 10.6	6.0	6.0	41.6%, 46.7%		
Cole et al., 2017 ²²	49, 50	55.9 ± 10.4	56.8 ± 10.5	12.0	12.0	57.1%, 40.0%		
Di Martino et al., 2019 ⁴³	85, 82	52.7 ± 13.2	57.5 ± 11.7	24.0	24.0	62.5%, 57.3%		
Duymus et al., 2017 ³¹	33, 34	60.4 ± 5.1	60.3 ± 9.1	12.0	12.0	3.0%, 2.9%		
Filardo et al., 2015 ¹²	94, 89	53.3 ± 13.2	57.6 ± 11.8	12.0	12.0	63.8%, 58.4%		
Görmeli et al., 2017 ⁴⁴	39, 39	53.8 ± 13.4	53.5 ± 14.0	6.0	6.0	42.2%, 43.5%		
Huang et al., 2019 ³²	40, 40	54.5 ± 1.2	54.8 ± 1.1	12.0	12.0	62.5%, 47.5%		
Jivan et al., 2021 ⁴⁵	10, 10	52.2	55.1	12.0	12.0	10.0%, 0.0%		
Lana et al., 2016 ⁴⁶	36, 36	60.9 ± 7.0	60.0 ± 6.6	12.0	12.0	19.4%, 8.3%		
Lin et al., 2019 ³⁴	31, 29	61.2 ± 13.1	62.5 ± 9.9	12.0	12.0	29.0%, 34.5%		
Lisi et al., 2018 ³⁵	25, 22	53.5 ± 15.1	57.1 ± 10.0	6.0	6.0	67.0%, 57.0%		
Montanez-Heredia et al., 2016 ⁵¹	27, 26	66.3 ± 8.3	61.5 ± 8.6	6.0	6.0	44.4%, 34.6%		
Paterson et al., 2016 ⁴⁷	10, 9	49.9 ± 13.7	52.7 ± 10.3	3.0	3.0	72.7%, 70.0%		
Raeissadat et al., 2015 ³⁷	77, 62	56.9 ± 9.1	61.1 ± 7.5	12.0	12.0	10.4%, 24.2%		
Raeissadat et al., 2017 ³⁶	36, 33	57.0 ± 7.2	59.5 ± 7.5	6.0	6.0	18.2%, 19.4%		
Raeissadat et al., 2021 ²³	52, 49	56.1 ± 6.0	57.9 ± 6.7	12.0	12.0	25.0%, 24.5%		
Sánchez et al., 2012 ⁴⁸	79, 74	60.5 ± 7.9	58.9 ± 8.2	6.0	6.0	48.0%, 48.0%		
Sdeek et al., 2021 ²⁴	95, 94	60.2	59.5	36.0	36.0	15.8%, 17.0%		
Su et al., 2018 ³⁸	27, 30	50.7 ± 8.7	53.1 ± 6.4	18.0	18.0	37.0%, 40.0%		
Vaquerizo et al., 2013 ³⁹	48, 48	62.4 ± 6.6	64.8 ± 7.7	11.0	11.0	33.3%, 45.8%		
Vasavilbaso et al., 2017 ⁴⁰	10, 30	60.3 ± 9.5	64.8 ± 10.4	18.0	18.0	40.0%, 56.7%		
Total	1,008, 990	57.6	59.1	13.5	13.7	38.3%, 37.8%		
Study	n (BMAC, HA)	Patient Age, y (BMAC)		Patient Age, y (HA)	Follow-up, mo (BMAC)	Follow-up, mo (HA)	Sex Distribution, % Male (BMAC, HA)	
BMAC vs HA								
Boffa et al., 2022 ⁴²	56, 56	57.8 ± 8.9		57.8 ± 8.9	24.0	24.0	62.5%, 62.5%	
Goncars et al., 2017 ⁴⁹	28, 28	53.4 ± 15.0		58.6 ± 13.0	12.0	12.0	53.6%, 35.7%	
Lamo-Espinosa et al., 2018 ³³	16, 9	61.9		60.6	48.0	48.0	62.5%, 77.8%	
Vega et al., 2015 ²⁵	15, 15	56.6 ± 9.6		57.3 ± 9.4	12.0	12.0	40.0%, 33.3%	
Total	135, 118	57.1		58.2	22.9	21.2	57.4%, 52.8%	
Study	n (PRP, BMAC, HA)	Patient age, y (PRP)	Patient Age, y (BMAC)	Patient Age, y (HA)	Follow-up, mo (PRP)	Follow-up, mo (BMAC)	Follow-up, mo (HA)	Sex Distribution, % Male (PRP, BMAC, HA)
PRP vs BMAC vs HA								
Dulic et al., 2021 ³⁰	34, 111, 30	58.8 ± 11.2	56.9 ± 10.8	59.4 ± 14.0	12.0	12.0	12.0	44.1%, 51.4%, 43.3%

NOTE. Patient age is reported as a mean ± standard deviation (when reported), follow-up duration is reported as a minimum follow-up, and the "Total" row reported as a weighted average. BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; PRP, platelet-rich plasma.

centrifuged to isolate the red blood cells from the upper plasma layer. The upper plasma layer was carefully collected using a serological pipette and placed into a new centrifuge tube. In 16 of 23 studies^{12,22-24,32,34,36-38,43-48,51} (69.6%) using PRP, the remaining erythrocyte layer was then centrifuged again to separate the platelet-poor plasma layer from the platelet-rich plasma layer. PRP was then activated by adding calcium chloride through low-level ultraviolet irradiation and used for intra-articular injection. In 12 studies,^{12,23,24,30-32,34,36,43-45,51} platelet concentration was between 1.8- to 9.8-times baseline values. Eleven studies^{22,29,35,37-41,46-48} did not report on platelet concentration. Systems used for PRP preparation were highly variable and largely unreported. For the injection itself, 11 studies^{23,29,31,35-40,44,46} (47.8%) described using a superolateral approach, in which the patient was placed in a supine position with the knee slightly bent. Two studies^{34,47} (8.7%) described using an anteromedial approach, in which patients were positioned in a chair with their knees in 90° of flexion. One study³² (4.3%) described administering the injection through a suprapatellar approach but did not specify lateral or medial. Nine studies^{12,22,24,30,41,43,45,48,51} (39.1%) did not describe the method of injection.

HA Preparation and Treatment Method

For HA, patients were treated with high-molecular weight HA (>1.5 million Daltons) in 15 studies^{12,22,24,30,31,34,37,39-41,43,44,46,48,51} (55.6%) and low-molecular weight HA (0.5-1.5 million Daltons) in 6 studies^{23,29,32,36,38,49} (22.2%). Six studies^{25,33,35,42,45,47} (22.2%) did not specify HA composition. All 23 studies^{1,15,17,20-23,28,33,34,39,42,43,45-49,54,55,56,59,60} that compared HA with PRP had identical injection methods to those described in the PRP section. For the remaining 4 studies^{25,33,42,49} that used HA, 2 studies^{33,42} described using a superolateral approach in which the patient was placed in a supine position with the knee in extension. One study²⁵ stated using a superomedial approach with no further description of patient positioning, and one study⁴⁹ did not describe the method of injection.

BMAC Preparation and Treatment Method

For BMAC, 3 studies^{25,33,42} described harvesting BMAC in the operating room. Two studies^{30,42} described placing patients in the supine position for the aspiration. One study²⁵ used allogeneic BMAC that did not require aspiration from the study participants. All syringes and bone marrow needles were washed with heparin. Bone marrow was aspirated from the proximal tibia in 2 studies^{30,42} and from the iliac crest in 3 studies.^{25,33,49} After sterile skin preparation, draping, and local anesthesia in the targeted area, a puncture was performed using a trocar into the medullary space, and 45 to 100 mL of bone marrow was aspirated while

Table 2. Number of Injections

Injectable	Number of Injections (Mean)	Most Commonly Used Number (Mode)	Range
PRP	2.7	3	1-4
BMAC	2.6	1	1-3
HA	1.4	3	1-5

BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; PRP, platelet-rich plasma.

adjusting the needle in different positions. All samples were kept and transferred at room temperature or lower and processed within 24 hours of aspiration. After centrifugation, the sample was loaded into a syringe and injected in the range of 1.5 to 6 mL. The 4 studies^{25,33,42,49} that compared BMAC with HA described identical injection methods to those described in the HA section. The one study³⁰ that compared all 3 groups (PRP, HA, and BMAC) had an identical injection procedure for all the groups as described in the PRP section.

PRP Leukocyte Content

Nine studies^{12,30,31,37,38,41,43,46,47} used LR-PRP and 9 studies^{22,24,29,32,34,36,39,48,51} used LP-PRP. Five studies^{2,35,40,44,45} did not report whether they used LR- or LP-PRP. In studies that did report leukocyte content, leukocyte concentration was largely unreported.

PRP/HA/BMAC Administration Strategy

Of the 22 studies^{12,22-24,29,32,31,34-41,43-48,51} that compared PRP with HA, 15 studies^{12,22,24,29,31,34,35,40,41,43,45,46,47,48,51} had identical administration strategies between groups (Table 2). Six studies^{12,22,34,43,47,48} administered 3 intra-articular injections at 1-week intervals, 5 studies^{24,31,41,46,51} administered 3 intra-articular injections with a 2-week interval between injections, one study²⁹ administered 4 intra-articular injections at 1-week intervals, one study³⁵ administered 3 intra-articular injections with a 4-week interval between injections, and 2 studies^{40,45} administered only 1 intra-articular injection. The remaining 7 studies^{23,32,36-39,44} that compared PRP and HA had nonidentical administration strategies between groups. Two studies^{39,44} administered 3 intra-articular injections at 1-week intervals for patients receiving PRP and only one intra-articular injection for patients receiving HA. One study³² administered 3 intra-articular injections with a 3-week interval between injections for patients receiving PRP and 3 intra-articular injections at 1-week intervals for patients receiving HA. Three studies^{23,36,37} administered 2 intra-articular injections at 3-week intervals for patients receiving PRP and 3 intra-articular injections at 1-week intervals for patients receiving HA. One study³⁸ administered 2 intra-articular injections with a

Table 3. Modified Coleman Methodology Score (MCMS)

Study	MCMS
Boffa et al., 2022 ⁴²	94
Raeissadat et al., 2015 ³⁷	93
Cerza et al., 2012 ²⁹	92
Huang et al., 2019 ³²	91
Raeissadat et al., 2021 ²³	91
Görmeli et al., 2017 ⁴⁴	90
Sánchez et al., 2012 ⁴⁸	90
Di Martino et al., 2019 ⁴³	89
Raeissadat et al., 2017 ³⁶	89
Filardo et al., 2015 ¹²	86
Paterson et al., 2016 ⁴⁷	85
Vasavilbaso et al., 2017 ⁴⁰	85
Lana et al., 2016 ⁴⁶	84
Lin et al., 2019 ³⁴	84
Sdeek et al., 2021 ²⁴	84
Duymus et al., 2017 ³¹	83
Ahmad et al., 2018 ⁴¹	82
Cole et al., 2017 ²²	82
Lamo-Espinosa et al., 2018 ³³	82
Montanez-Heredia et al., 2016 ⁵¹	82
Vaquerizo et al., 2013 ³⁹	82
Su et al., 2018 ³⁸	81
Lisi et al., 2018 ³⁵	80
Dulic et al., 2021 ³⁰	79
Goncars et al., 2017 ⁴⁹	78
Vega et al., 2015 ²⁵	78
Jivan et al., 2021 ⁴⁵	74
Total	84.8 ± 5.1

2-week interval between injections for patients receiving PRP and 5 intra-articular injections at 1-week intervals for patients receiving HA.

Of the 4 studies^{25,33,42,49} that compared HA with BMAC, 3 studies^{25,33,42} had an identical administration strategy of only 1 intra-articular injection for each group. One study⁴⁹ described a nonidentical administration strategy of only one intra-articular injection for BMAC patients and 3 injections at 1-week intervals for HA.

The one study³⁰ that compared all 3 groups (PRP, HA, and BMAC) described an identical administration

strategy of 3 injections at 1-week intervals among the groups.

Modified Coleman Methodology Score

Table 3 shows the MCMS scores from the 27 included studies. Twelve studies^{12,23,29,32,36,37,42-44,47,48,40} received excellent scores and 15 studies^{22,24,25,30,31,33,34,35,38,39,41,45,46,49,51} received good scores.

Demographics

Three studies^{12,37,43} reported a significant difference in age between the PRP and HA groups, in which the patients receiving HA were significantly older in all 3 studies ($P < .05$). One study³⁷ reported a significant difference in sex between groups, in which there was a significantly greater proportion of female patients in the PRP group. Twenty-three studies^{4,12,22-24,29-32,34,35,38-48,51} reported no differences in sex, 21 studies^{2,23,24,29-32,34-36,38-42,44-48,51} reported no differences in age, and 20 studies^{12,22-24,30-32,36-44,46-48,51} reported no differences in body mass index (BMI) between groups. Lin et al.³⁴ reported a significant difference in BMI between groups, in which patients with HA had a significantly greater BMI ($P = .01$). No studies found a significant difference in preinjection Kellgren-Lawrence OA grades⁵⁰ between groups.

Risk of Bias Assessment

The results of the methodologic quality assessment of included studies using the Cochrane Collaboration's risk of bias tool are presented in Figure 2. Sequence generation and allocation were adequately reported by most studies included, except in 14 studies where the concealment of allocation from the investigators was unclear (unclear risk of bias)^{22,24,30,32,37,38,43,41,45,49} or not concealed (high risk of bias).^{23,29,31,33} All studies were deemed to be at low risk for detection bias because of the blinding of the outcome assessor except in 10 studies^{29-33,37,38,41,45,49} in which the outcome assessor

Fig 2. Risk of bias graph. Risk of bias is presented as a percentage across all included studies (green, low risk; yellow, unclear; red, high risk).

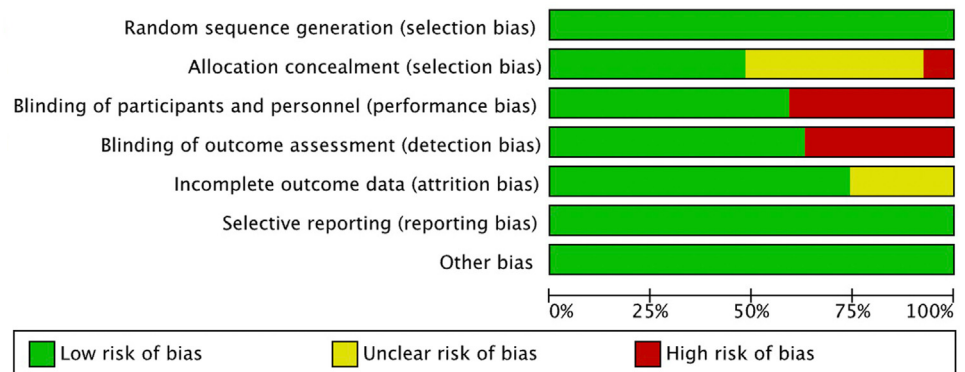


Table 4. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Total Score

Study	WOMAC							
	PRP		HA		BMAC			
	Preinjection	Postinjection	Preinjection	Postinjection	Preinjection	Postinjection	Preinjection	Postinjection
Cerza et al., 2012 ²⁹	79.6 ± 9.5		75.4 ± 10.7					
Dulic et al., 2021 ³⁰	48.1 ± 17.0		46.4 ± 15.0		44.3 ± 18.7			
Duymus et al., 2017 ³¹	76.1 ± 9.4		77.0 ± 2.5					
Huang et al., 2019 ³²	48.2 ± 5.0		47.2 ± 5.4					
Lisi et al., 2018 ³⁵	37.0 ± 3.3		28.5 ± 2.2					
Raeissadat et al., 2015 ³⁷	39.5 ± 17.1		28.7 ± 16.7					
Raeissadat et al., 2017 ³⁶	42.9 ± 13.5		38.8 ± 12.6					
Raeissadat et al., 2021 ²³	42.7 ± 7.7		42.8 ± 11.1					
Sdeek et al., 2021 ²⁴	66.5 ± 16.6		66.9 ± 16.7					
Su et al., 2018 ³⁸	50.2 ± 1.1		49.9 ± 1.5					
Vaquerizo et al., 2013 ³⁹	45.9 ± 12.7		50.8 ± 18.4					
Vasavilbaso et al., 2017 ⁴⁰	54.8 ± 11.3		58.7 ± 15.6					
Vega et al., 2015 ²⁵			45.0 ± 11.3		41.0 ± 10.3			

NOTE. Scores are reported as a mean ± standard deviation at latest follow-up (n = 12).

BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; PRP, platelet-rich plasma; NR, not reported; n.s., not significant.

was not blinded (high risk of bias). Patients in most studies were blinded to their intervention group (low risk of bias), except in 11 studies^{29-33,36-38,40,45,49} in which patients were aware of their treatment group (high risk of bias). Seven studies^{23,30,31,33,38,45,46} reported a minor loss of follow-up between 10% and 20% without proper explanation (unclear risk of bias),

while no other studies reported significant loss of follow-up (low risk of bias).

Patient-Reported Outcomes (PROs)

WOMAC Scores

Fifteen studies^{23-25,29-40} reported results of the WOMAC total score (Table 4), 11^{25,29-32,34,36-40} of

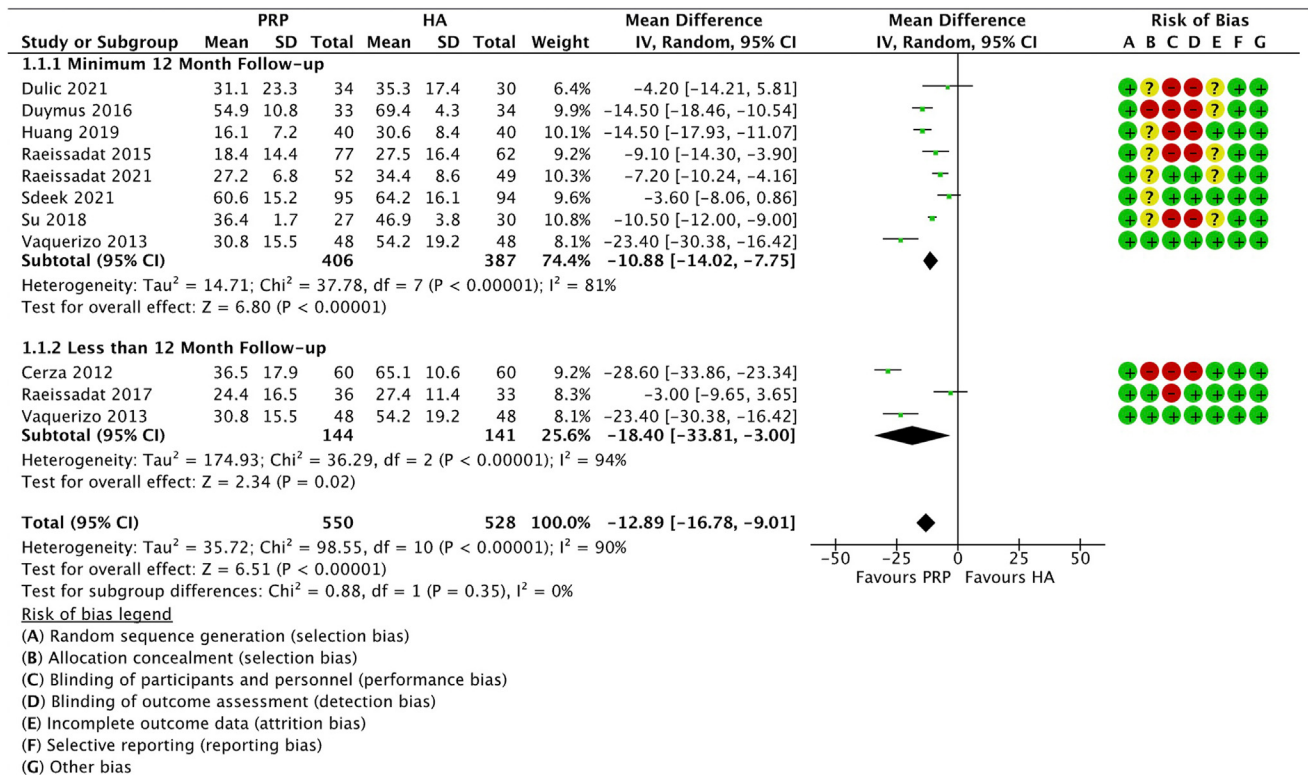


Fig 3. Non-network meta-analysis forest plot of PRP versus HA WOMAC scores. (CI, confidence interval; HA, hyaluronic acid; IV, weighted mean difference; PRP, platelet-rich plasma; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

which provided P values on pre- to posttreatment scores within each group. Of the 13 studies^{23,24,29-32,34-40} that evaluated PRP and included the WOMAC score, 9 studies^{29-32,36-40} (69.2%) found patients who received PRP to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 15 studies^{23-25,29-32,33-40} that evaluated HA and included the WOMAC score, 5 studies^{29,30,32,36,40} (33.3%) found patients who received HA to improve significantly ($P < .05$) from pretreatment to latest follow-up. Both studies^{25,30} that evaluated BMAC and included the WOMAC score found patients who received BMAC to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 13 studies^{23,24,29-32,34-40} that compared PRP with HA and reported WOMAC scores, 8 studies^{23,29,31,32,34,37-39} (61.5%) found patients who received PRP to report significantly better WOMAC scores ($P < .05$) at latest follow-up. Both studies^{25,30} that compared BMAC with HA and reported WOMAC scores found patients who received BMAC to report significantly better WOMAC scores ($P < .05$) at latest follow-up. No studies found patients who received HA to report significantly better WOMAC scores when compared with patients who received PRP or BMAC. The one study³⁰ that compared all 3 groups (PRP, BMAC, and HA) found no significant difference in WOMAC scores between BMAC and PRP.

Two studies^{33,34} that reported WOMAC scores are not included in Table 4. One of these studies³³ reported medians, in which pretreatment WOMAC scores between groups were not significantly different. Lin et al.³⁴ defined improved WOMAC outcomes as an increased score when compared with baseline, whereas all other studies reported improved WOMAC outcomes as a decreased score when compared with baseline. This study³⁴ found patients who received PRP to report significantly better WOMAC scores ($P < .05$) at latest follow-up, with no difference in preinjection scores between groups.

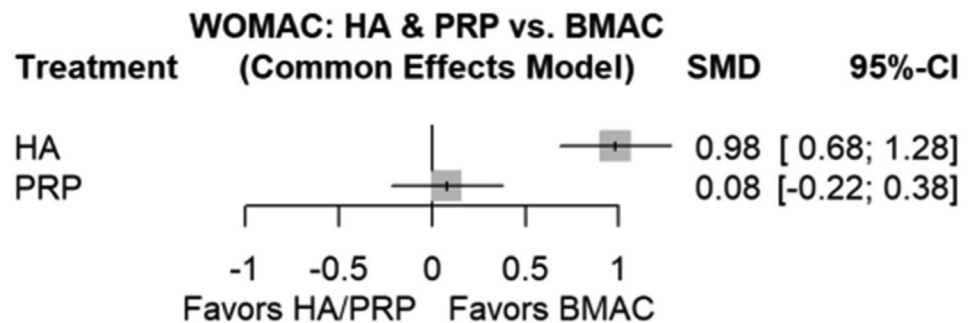
In the non-network meta-analysis, pooled analysis from 8 studies^{23,24,30-32,37-39} with mean follow-up of at least 12 months demonstrated that the PRP group had significantly better postinjection WOMAC total scores

as compared with the HA group (MD, -10.88 ; 95% CI, -14.02 to -7.75 , $P < .00001$) (Fig 3). Statistical evaluation of heterogeneity found for postinjection WOMAC total scores was $I^2 = 81\%$, suggesting that moderate-to-high heterogeneity may be present. Pooled analysis from 3 studies^{29,36,39} with mean follow-up less than 12 months demonstrated that the PRP group had significantly better postinjection WOMAC total scores as compared with the HA group (MD, -18.40 ; 95% CI, -33.81 to -3.00 , $P = .02$) (Fig 3). Statistical evaluation of heterogeneity found for postinjection WOMAC total scores was $I^2 = 94\%$, suggesting that significant heterogeneity may be present. In the network meta-analysis, pooled analysis from 8 studies^{23,24,30-32,37-39} with mean follow-up of at least 12 months demonstrated that the PRP group did not have significantly better postinjection WOMAC total scores as compared with the BMAC group (SMD, 0.0773 ; 95% CI, -0.2217 to 0.3763) (Fig 4). Statistical evaluation of heterogeneity found for postinjection WOMAC total scores was $I^2 = 91.6\%$, suggesting that high heterogeneity may be present. Pooled analysis from 3 studies^{29,36,39} with mean follow-up less than 12 months demonstrated that the BMAC group had significantly better postinjection WOMAC total scores as compared with the HA group (SMD, 0.9803 ; 95% CI, 0.6833 – 1.2774 ; $P < .001$) (Fig 4). There are no estimates in the network model that had to be inferred by indirect evidence alone (Fig 5). In addition, since the mean path length for all studies is less than 2, the comparison estimate does not need to be interpreted with particular caution. To check for consistency in the network, net splitting was used to determine the contribution of direct and indirect evidence. There is consistency in the difference between the direct and indirect comparisons between HA and BMAC, and HA and PRP but inconsistent differences between PRP and BMAC (Fig 6).

VAS Scores

Eighteen studies^{12,22-25,31-33,35,36,38,41-47} reported results of the VAS score (Table 5). Of the 15 studies^{12,22-24,31,32,35,36,38,41,43-47} that evaluated PRP and included the VAS score, 6 studies^{32,36,38,41,43,45}

Fig 4. Network forest plot of WOMAC scores. (BMAC, bone marrow aspirate concentrate; CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)



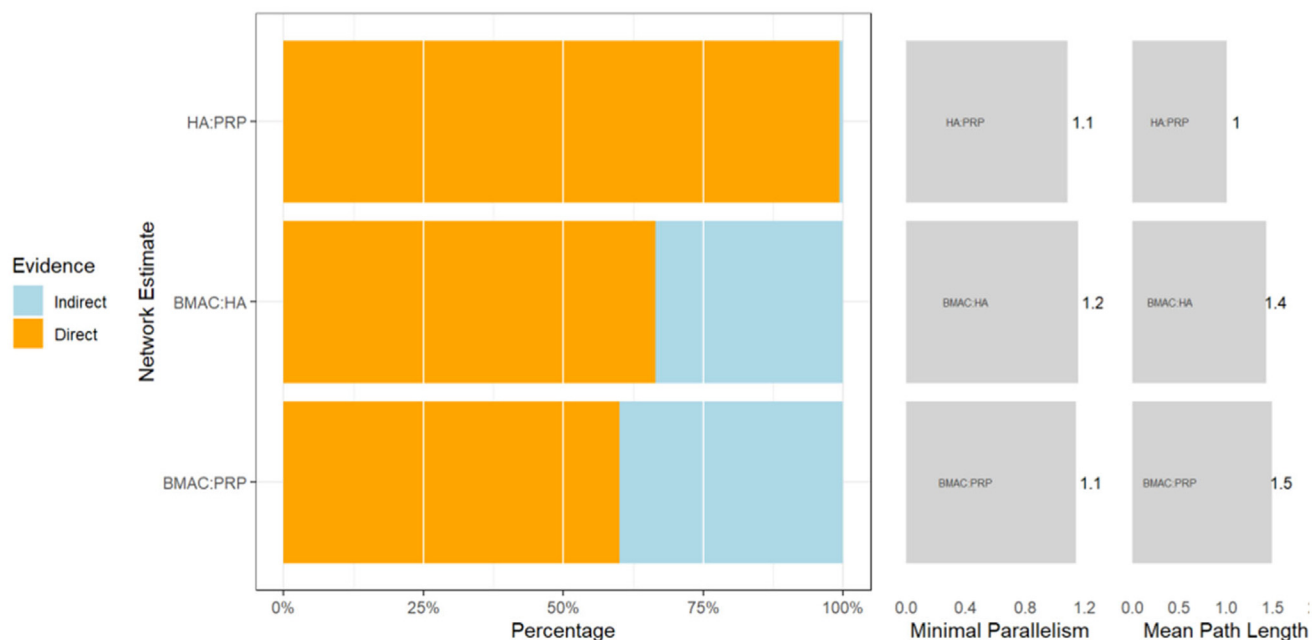


Fig 5. Direct evidence plot of WOMAC scores. (BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

(40.0%) found patients who received PRP to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 18 studies^{1,22-25,31-33,35,36,38,41-47} that evaluated HA and included the VAS score, 4^{25,32,36,42} (22.2%) found patients who received HA to improve significantly ($P < .05$) from pretreatment to latest follow-up. Both studies^{25,42} that evaluated BMAC and included the VAS score found patients who received BMAC to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 15 studies^{12,22-24,31,32,35,36,38,41,43-46} that compared PRP with HA and reported VAS scores, 8

studies^{41,22,23,31,38,44,45,46} (53.3%) found patients who received PRP to report significantly less pain ($P < .05$) at latest follow-up. Both studies^{25,42} that compared BMAC with HA and reported VAS scores found patients who received BMAC to report significantly less pain ($P < .05$) at latest follow-up. No studies found patients who received HA to report significantly less pain when compared with patients who received PRP or BMAC.

Three studies^{33,44,46} that reported VAS scores are not included in Table 5. Two of these studies^{33,46} reported medians, in which pretreatment VAS scores between groups were not significantly different. At the 12-month

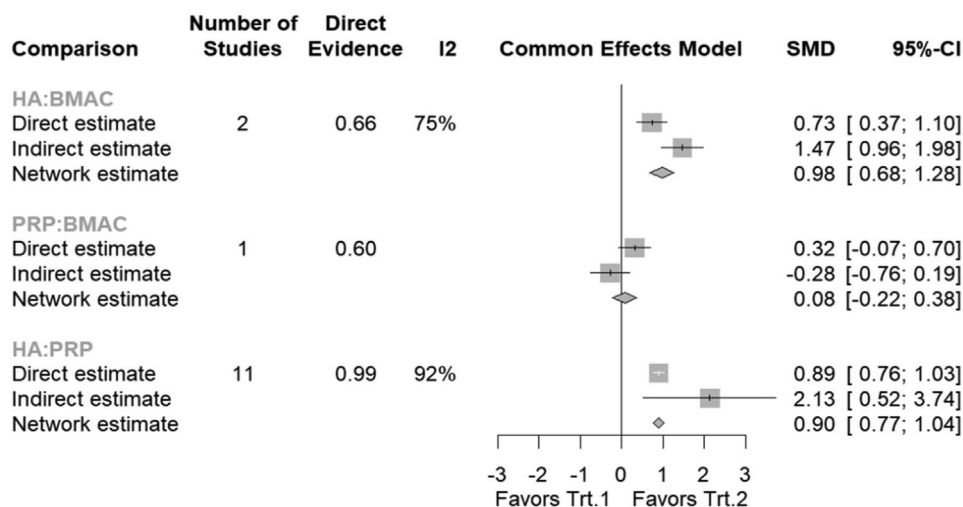


Fig 6. Network split plot of WOMAC scores. (BMAC, bone marrow aspirate concentrate; CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SMD, standardized mean difference; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.)

Table 5. Visual Analog Scale (VAS) Scores for Pain Severity

Study	VAS							
	PRP		HA		BMAC			
	Preinjection	Postinjection	Preinjection	Postinjection	Preinjection	Postinjection	Postinjection	P Value
Ahmad et al., 2018 ⁴¹	58.0 ± 19.0		61.0 ± 17.0			41.0 ± 14.0	60.0 ± 15.0	.01
Boffa et al., 2022 ⁴²			57.0 ± 20.0		62.0 ± 17.0		43.0 ± 28.0	<.05
Cole et al., 2017 ²²	57.2 ± 14.3		62.9 ± 15.7			34.6 ± 3.2	48.6 ± 3.7	.01
Di Martino et al., 2019 ⁴³	72.7 ± 12.3		71.2 ± 13.3			71.9 ± 13.6	66.6 ± 14.2	n.s.
Duymus et al., 2017 ³¹	74.0 ± 10.0		83.0 ± 4.0		<.001	51.0 ± 13.0	68.0 ± 1.0	<.001
Filardo et al., 2015 ¹²	73.2 ± 12.0		71.6 ± 13.4		n.s.	77.6 ± 11.1	73.4 ± 15.2	n.s.
Huang et al., 2019 ³²	45.7 ± 6.1		45.4 ± 6.0		n.s.	19.8 ± 14.4	21.4 ± 15.2	n.s.
Jivan et al., 2021 ⁴⁵	64.0 ± 5.0		54.0 ± 5.0		n.s.	46.0 ± 6.0	69.0 ± 7.0	.023
Lisi et al., 2018 ³⁵	63.0 ± 6.0		54.0 ± 4.0		n.s.	NR	NR	n.s.
Paterson et al., 2016 ⁴⁷	48.1 ± 23.8		39.7 ± 21.9		n.s.	36.9 ± 25.4	14.1 ± 9.3	n.s.
Raeissadat et al., 2017 ³⁶	76.0 ± 18.0		74.0 ± 15.0		n.s.	46.0 ± 28.0	48.0 ± 24.0	n.s.
Raeissadat et al., 2021 ²³	79.2 ± 10.0		82.2 ± 11.0		n.s.	46.2 ± 11.6	56.2 ± 14.1	<.01
Sdeek et al., 2021 ²⁴	57.8 ± 14.5		59.3 ± 14.8		n.s.	40.9 ± 10.2	60.3 ± 15.1	n.s.
Su et al., 2018 ³⁸	71.0 ± 3.0		70.0 ± 3.0		n.s.	38.0 ± 3.0	65.0 ± 3.0	<.05
Vega et al., 2015 ²⁵			64.0 ± 16.0		54.0 ± 13.5		51.0 ± 12.8	<.02

NOTE. Scores are reported as a mean ± SD at latest follow-up (n = 14).

BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; PRP, platelet-rich plasma; NR, not reported; n.s., not significant; VAS, visual analog scale.

follow-up, the one study³³ that evaluated BMAC found patients who received BMAC to have significantly less pain compared with the HA group ($P < .01$), whereas the other study⁴⁶ that evaluated PRP

found patients who received PRP to have significantly lower VAS scores compared with the HA group ($P < .01$). The remaining study⁴⁴ defined improved VAS outcomes as an increased score when compared with baseline, whereas

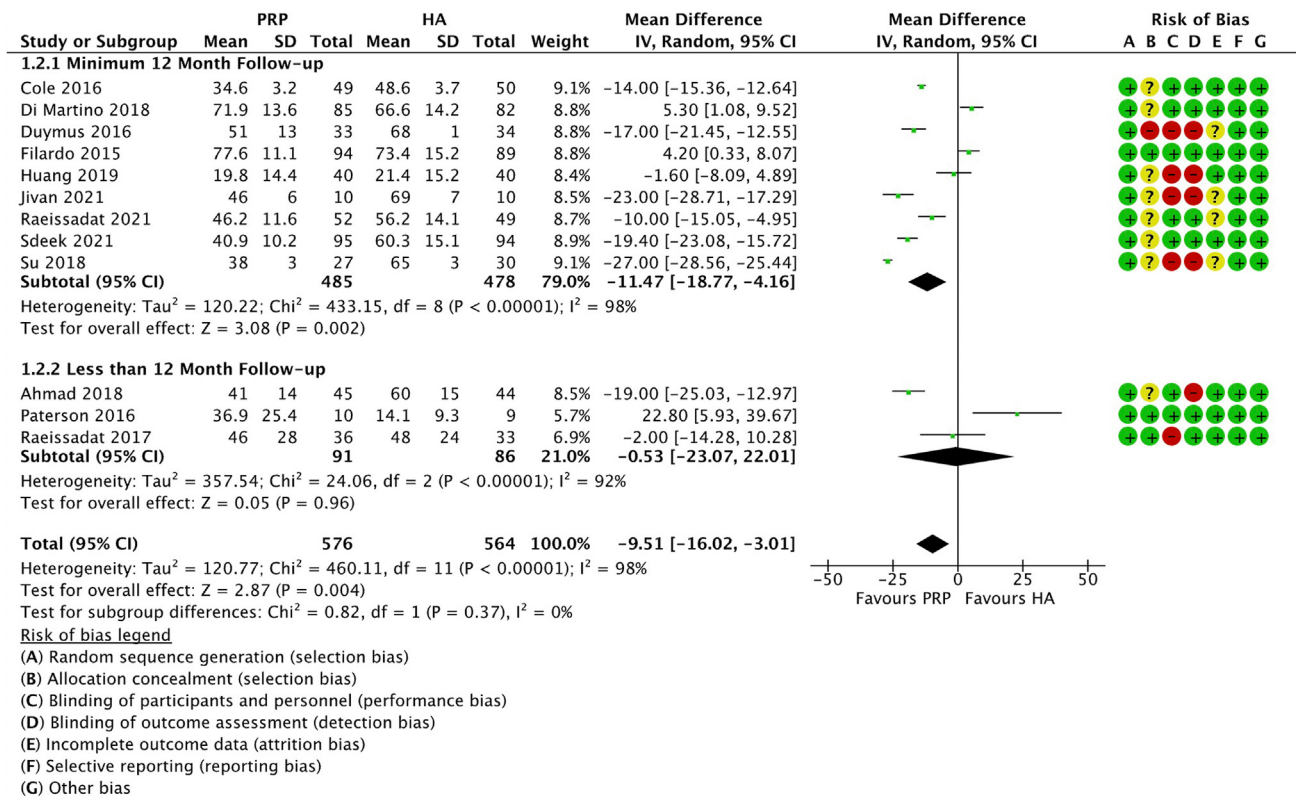


Fig 7. Non-network meta-analysis forest plot of PRP versus HA VAS scores. (CI, confidence interval; HA, hyaluronic acid; IV, weighted mean difference; PRP, platelet-rich plasma; SD, standard deviation; VAS, visual analog scale.)

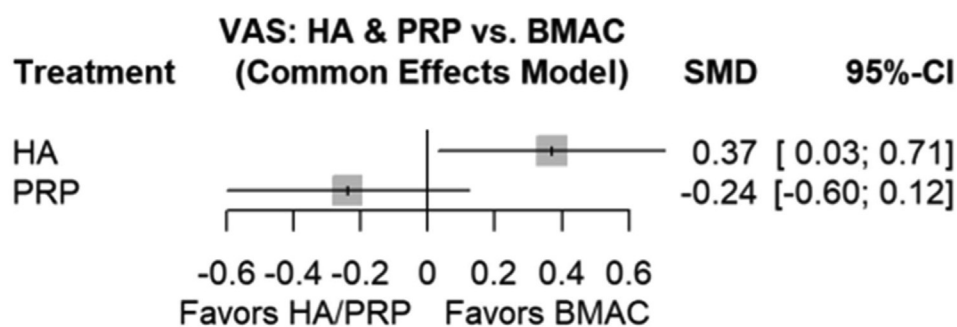


Fig 8. Network forest plot of VAS scores. (BMAC, bone marrow aspirate concentrate; CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SMD, standardized mean difference; VAS, visual analog scale.)

all other studies reported improved VAS outcomes as a decreased score when compared with baseline. This study²⁸ found PRP patients to report significantly improved VAS scores ($P < .05$) at latest follow-up with no difference in preinjection scores between groups.

In the non-network meta-analysis, pooled analysis from 9 studies^{12,22-24,31,32,38,43,45} with mean latest follow-up of at least 12 months demonstrated the PRP group had significantly better postoperative VAS pain scores as compared with the HA group (MD, -11.47; 95% CI, -18.77 to -4.16; $P = .002$) (Fig 7). Statistical evaluation of heterogeneity found for VAS pain scores was $I^2 = 98\%$, suggesting that high heterogeneity may be present. Pooled analysis from 3 studies^{36,41,47} with mean follow-up less than 12 months demonstrated no significant differences in VAS pain scores between the groups (MD, -0.53; 95% CI, -23.07 to 22.01; $P = .96$) (Fig 7). Statistical evaluation of heterogeneity found for VAS pain scores was $I^2 = 92\%$, suggesting that high

heterogeneity may be present. In the network meta-analysis, pooled analysis from 9 studies^{13,22-24,31,32,38,43,45} with mean latest follow-up of at least 12 months demonstrated the PRP group had significantly better postoperative VAS pain scores as compared with the HA group (MD, -11.47; 95% CI, -18.77 to -4.16, $P = .002$; Fig 8). Statistical evaluation of heterogeneity found for VAS pain scores was $I^2 = 96.8\%$ (95% CI, 95.7-97.6), suggesting that high heterogeneity may be present. Pooled analysis from 3 studies^{36,41,47} with mean follow-up less than 12 months demonstrated significant differences in VAS pain scores between HA and BMAC (SMD, 0.3696, 95% CI, 0.0310-0.7081; $P = .032$) but not between PRP and BMAC (SMD, -0.24; 95% CI, -0.6022 to 0.1227; $P = .19$) (Fig 8). There are no estimates in the network model that had to be inferred by indirect evidence alone (Fig 9). However, since the mean path length for all BMAC and PRP studies is equal to 2, the comparison

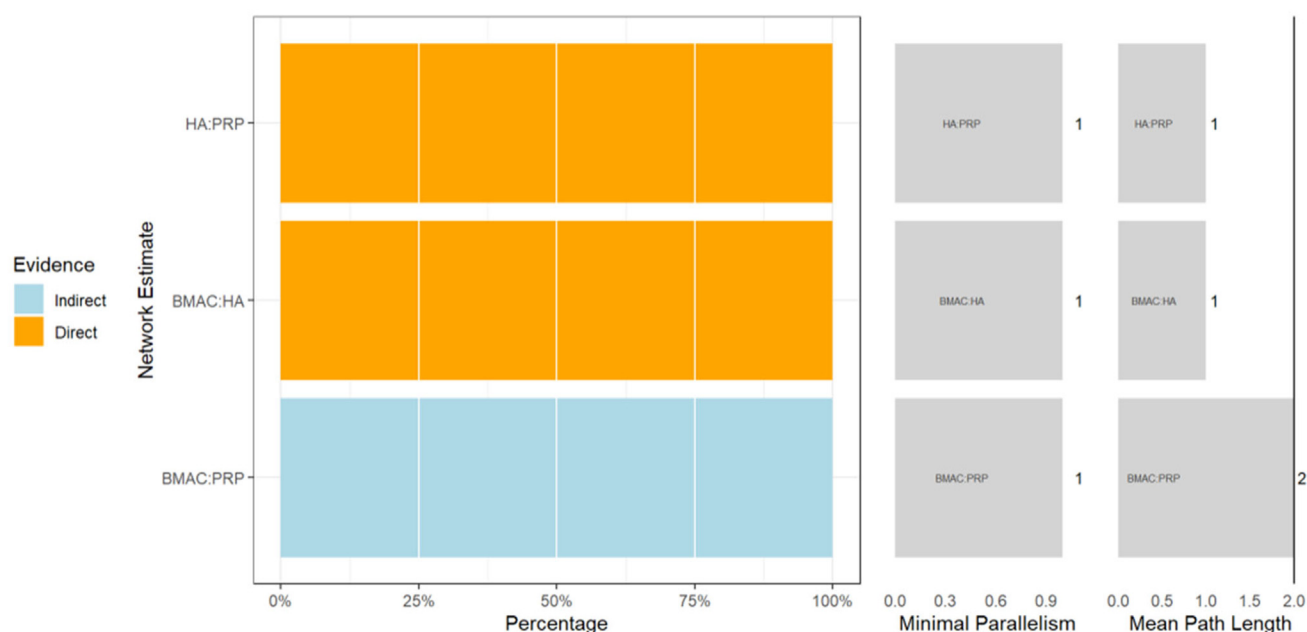
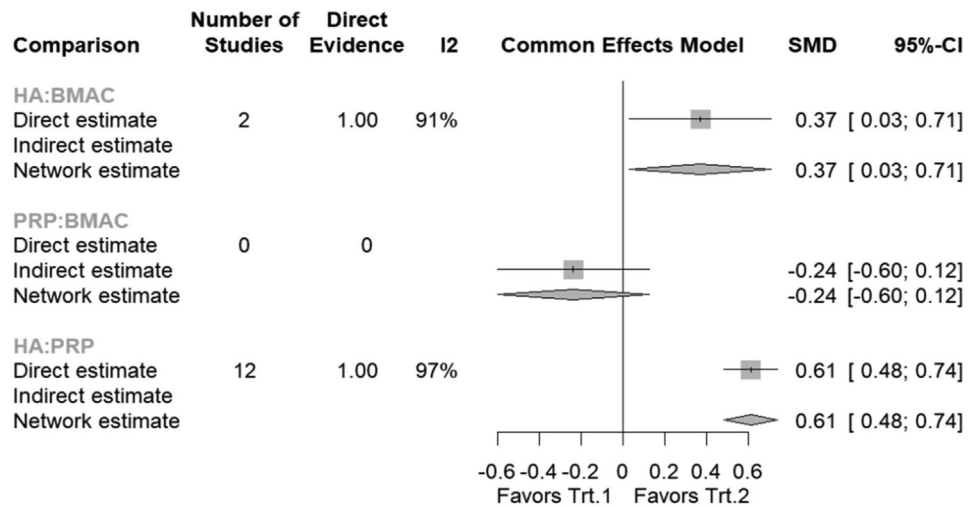


Fig 9. Direct evidence plot of VAS scores. (BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; PRP, platelet-rich plasma; VAS, visual analog scale.)

Fig 10. Network split plot of VAS scores. (BMAC, bone marrow aspirate concentrate; CI, confidence interval; HA, hyaluronic acid; PRP, platelet-rich plasma; SMD, standardized mean difference; VAS, visual analog scale.)



estimate needs to be interpreted with particular caution. To check for consistency in the network, net splitting was used to determine the contribution of direct and indirect evidence. There is consistency in the difference between the direct and indirect comparisons between HA and BMAC, HA and PRP, and PRP and BMAC (Fig 10).

Subjective IKDC Scores

Nine studies^{22,24,30,31,34,41-44} reported results of the Subjective IKDC score (Table 6). Of the 8 studies^{1,22,24,30,34,41,44} that evaluated PRP and included the Subjective IKDC score, 5^{1,22,30,34,43} (62.5%) found patients with PRP to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 9 studies^{12,22,24,30,34,41-44} that evaluated HA and included the Subjective IKDC score, 3^{12,30,43} (33.3%) found patients who received HA to improve significantly ($P < .05$) from pretreatment to latest follow-up. Both studies^{30,42} that evaluated BMAC and included the

Subjective IKDC score found patients who received BMAC to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 8 studies^{1,22,24,30,34,41,43,44} that compared PRP with HA and reported Subjective IKDC scores, 3 studies^{22,41,44} (37.5%) found patients who received PRP to report significantly better scores ($P < .05$) at latest follow-up. The one study³⁰ that compared all 3 groups (PRP, HA, and BMAC) found patients who received BMAC to report significantly better Subjective IKDC scores ($P < .05$) when compared with patients who received HA at latest follow-up with no significant difference compared with patients who received PRP. No studies found patients who received HA to report significantly better Subjective IKDC scores when compared with patients who received PRP or BMAC.

In the non-network meta-analysis, pooled analysis from 8 studies^{1,22,24,30,34,41,43,44} demonstrated that the PRP group had significantly better postoperative Subjective IKDC scores as compared with the HA group

Table 6. Subjective IKDC Scores

Study	Subjective IKDC							
	PRP	HA	BMAC	P Value	PRP	HA	BMAC	P Value
	Preinjection	Preinjection	Preinjection		Postinjection	Postinjection	Postinjection	
Ahmad et al., 2018 ⁴¹	49.2 ± 14.9	47.2 ± 16.2		n.s.	75.7 ± 15.1	65.6 ± 16.9		.004
Boffa et al., 2022 ⁴²		49.5 ± 16.6	48.5 ± 16.5	n.s.		55.4 ± 18.7	58.3 ± 19.1	n.s.
Cole et al., 2017 ²²	NR	NR		n.s.	65.5 ± 3.6	55.8 ± 3.8		.01
Di Martino et al., 2019 ⁴³	53.3 ± 14.3	50.3 ± 13.2		n.s.	72.5 ± 19.0	68.6 ± 18.8		n.s.
Dulic et al., 2021 ³⁰	32.9 ± 12.8	28.6 ± 11.4	36.2 ± 14.2	.02	48.6 ± 20.8	42.4 ± 17.6	57.6 ± 21.8	.002
Filardo et al., 2015 ¹²	52.4 ± 14.1	49.7 ± 13.0		n.s.	66.2 ± 16.7	64.2 ± 18.0		n.s.
Görmeli et al., 2017 ⁴⁴	40.4 ± 5.0	40.6 ± 4.5		n.s.	60.8 ± 9.8	48.4 ± 6.2		<.05
Lin et al., 2019 ³⁴	35.7 ± 13.8	35.9 ± 12.7		n.s.	49.9 ± 17.7	38.6 ± 16.1		n.s.
Sdeck et al., 2021 ²⁴	49.1 ± 12.3	47.3 ± 11.8		n.s.	55.2 ± 13.8	46.1 ± 11.5		n.s.

NOTE. Scores are reported as a mean ± standard deviation at latest follow-up (n = 9).

BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; NR, not reported; n.s., not significant.

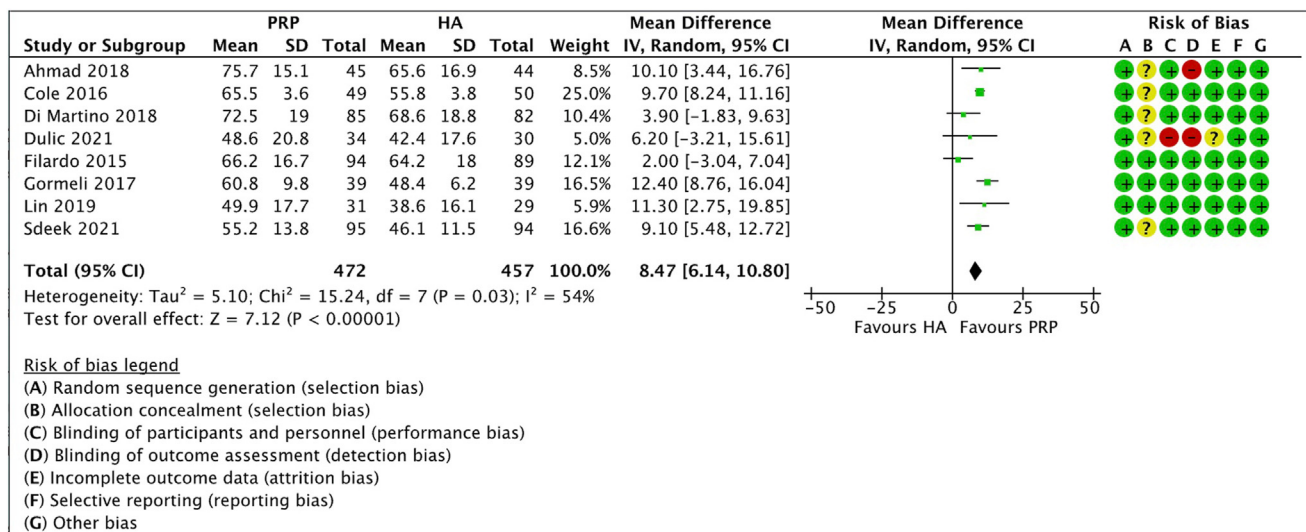


Fig 11. Non-network meta-analysis forest plot of PRP versus HA Subjective IKDC scores. (CI, confidence interval; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; IV, weighted mean difference; PRP, platelet-rich plasma; SD, standard deviation.)

(MD, 8.47; 95% CI, 6.14-10.80; $P < .0001$) (Fig 11). Statistical evaluation of heterogeneity found for post-operative Subjective IKDC scores was $I^2 = 54\%$, suggesting that moderate-to-high heterogeneity may be present. In the network meta-analysis, pooled analysis from 8 studies^{1,22,24,30,34,41,43,44} demonstrated that the BMAC group had significantly better postoperative Subjective IKDC scores as compared with the HA group (SMD, 0.98; 95% CI, 0.68-1.28; $P < .0001$) (Fig 12). There are no estimates in the network model that had to be inferred by indirect evidence alone (Fig 13). In addition, since the mean path length for all studies is less than 2, the comparison estimate does not need to be interpreted with particular caution. To check for consistency in the network, net splitting was used to determine the contribution of direct and indirect evidence. There is consistency in the difference between the direct and indirect comparisons between HA and BMAC, but inconsistent differences between HA and PRP and PRP and BMAC (Fig 14).

LEQ Scores

Five studies^{23,25,35,39,48} reported results of the LEQ score (Table 7). Of the 4 studies^{23,35,39,48} that evaluated PRP and included the LEQ score, 2 studies^{23,39} (50.0%) found patients who received PRP to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 5 studies^{23,35,39,40,48} that evaluated HA and included the LEQ score, one²³ (20.0%) found patients who received HA to improve significantly ($P < .05$) from pretreatment to latest follow-up. Of the 4 studies^{23,39,45,48} that compared PRP with HA and reported LEQ scores, 2 studies^{23,39} (50.0%) found patients who received PRP to report significantly better LEQ scores ($P < .05$) at latest follow-up. No studies found patients who received HA to report significantly better LEQ scores when compared with patients who received PRP or BMAC. The one study²⁵ not included in Table 7 used an LEQ scale from 0-100, while all other studies used a LEQ scale out of 24. The one study²⁵ that compared BMAC with HA found patients who received

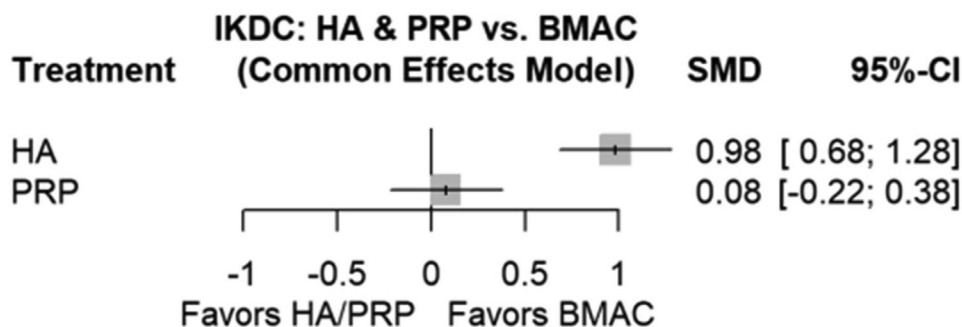


Fig 12. Network forest plot of Subjective IKDC scores. (BMAC, bone marrow aspirate concentrate; CI, confidence interval; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; SMD, standardized mean difference.)

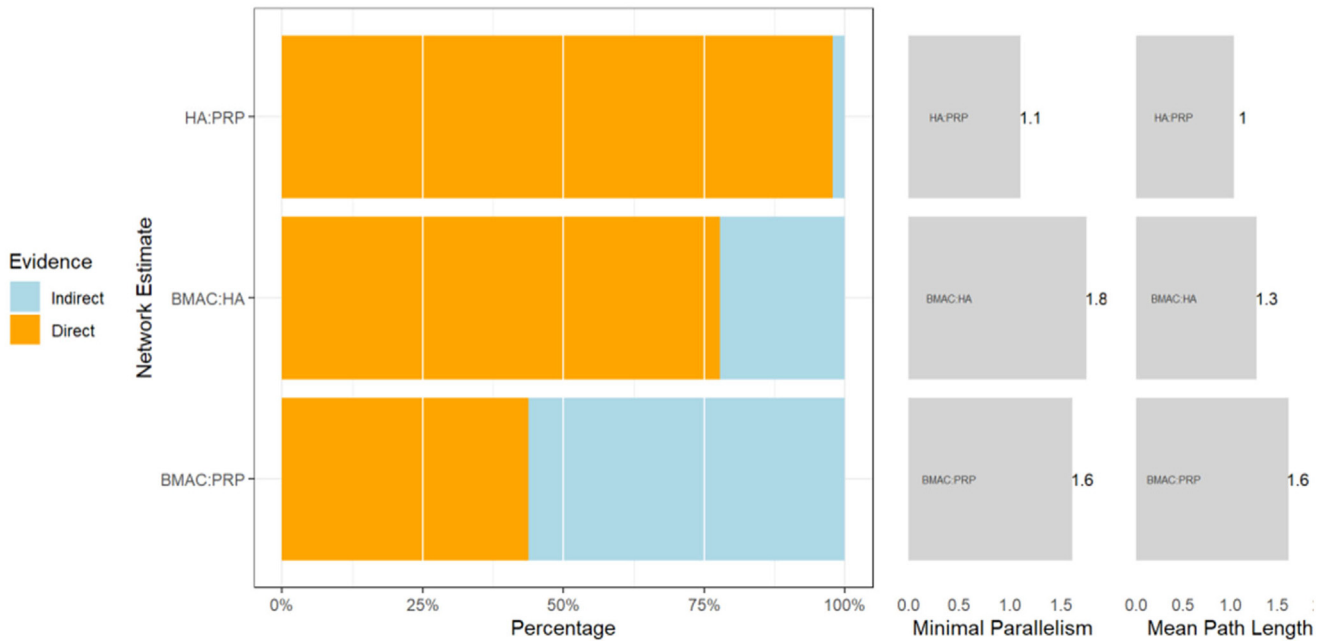


Fig 13. Direct evidence plot of Subjective IKDC scores. (BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma.)

BMAC to report significantly better LEQ scores ($P < .05$) at latest follow-up with no significant difference in pretreatment scores between groups.

Pooled analysis from 3 studies^{23,39,48} demonstrated that there was no difference in postoperative LEQ scores between the PRP and HA groups (MD, -2.45 ; 95% CI, -5.19 to 0.29 ; $p = .08$; Fig 15). Statistical evaluation of heterogeneity found for LEQ scores was $I^2 = 94\%$, suggesting that high heterogeneity may be present. Because at least 3 studies are needed per group to include in the meta-analysis, BMAC could not be included for LEQ scores as only one study reporting on BMAC also reported on LEQ scores.

KOOS Scores

Six studies^{12,30,42,45,47,49} reported using KOOS scores. Five studies^{12,42,45,47,49} reported posttreatment results on multiple KOOS subscores (Table 8), and one study³⁰ reported posttreatment results on overall KOOS scores. Of the 4 studies^{12,30,45,47} that compared PRP with HA and reported multiple KOOS subscores, one⁴⁵ (25.0%) found patients who received PRP to report significantly better posttreatment KOOS Pain, activities of daily living, and knee-related Quality of Life (QOL) scores ($P < .05$) at latest follow-up. Of the 3 studies^{30,42,49} that compared BMAC with HA and reported multiple KOOS subscores, one⁴² (33.3%) found BMAC patients to

Fig 14. Network split plot of Subjective IKDC scores. (BMAC, bone marrow aspirate concentrate; CI, confidence interval; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; SMD, standardized mean difference.)

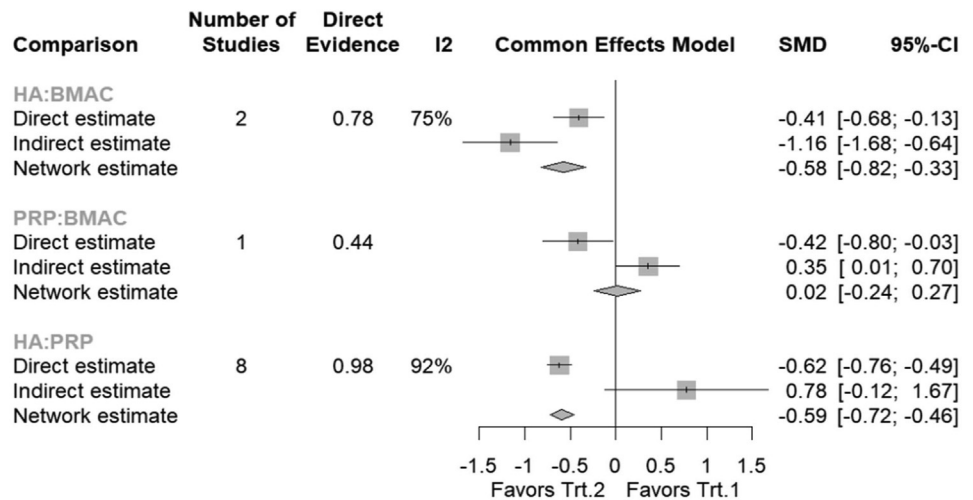


Table 7. Lequesne Index (LEQ) Scores

Study	LEQ					
	PRP		<i>P</i> Value	HA		<i>P</i> Value
	Preinjection	Postinjection		Preinjection	Postinjection	
Lisi et al., 2018 ³⁵	11.2 ± 0.9	9.0 ± 0.6	n.s.	NR	NR	n.s.
Raeissadat et al., 2021 ²³	12.6 ± 1.6	12.8 ± 2.2	n.s.	9.8 ± 2.5	11.6 ± 2.9	<.001
Sanchez et al., 2012 ⁵⁴	9.5 ± 3.0	9.1 ± 3.2	n.s.	5.2 ± 3.4	5.4 ± 3.3	n.s.
Vaquerizo et al., 2013 ³⁹	12.8 ± 3.8	13.1 ± 3.8	n.s.	8.9 ± 3.7	14.4 ± 3.8	<.001

NOTE. Scores are reported as a mean ± standard deviation at latest follow-up.

HA, hyaluronic acid; PRP, platelet-rich plasma; NR, not reported; n.s., not significant.

report significantly better KOOS Sport subscores ($P < .05$) at latest follow-up. No studies found HA patients to report significantly better KOOS scores when compared with patients who received PRP or BMAC. The one study⁴⁹ not included in Table 8 reported multiple KOOS subscores as a mean score change from baseline without reporting pretreatment results in all KOOS subscores. This study⁴⁹ compared BMAC with HA and found patients who received BMAC to report significantly better KOOS Pain subscores ($P < .05$) at latest follow-up. No studies reported significant differences in preinjection KOOS scores between groups ($P > .05$).

Subanalysis on Studies Using LP-PRP

Of the 9 studies^{22,24,29,32,34,36,39,48,51} that used LP-PRP, 6^{1,4,27,45,46,50} reported WOMAC scores, 4^{22,24,32,36} reported VAS scores, 3 studies^{22,24,34} reported Subjective IKDC scores, and 2^{39,48} reported LEQ scores (Table 9). Five of 6 studies^{29,32,34,36,39} reporting on WOMAC scores, 2 of 4 studies^{32,36} reporting on VAS, 2 of 3 studies^{22,34} reporting on Subjective IKDC scores, and 1 of 2 studies³⁹ reporting on LEQ scores found patients who received PRP to improve significantly ($P < .05$) from preinjection to latest follow-up. The one study³⁴ not included in Table 9 in the WOMAC section defined improved WOMAC outcomes

as an increased score when compared with baseline, whereas all other studies reported improved WOMAC outcomes as a decreased score when compared with baseline. This study³⁴ found patients who received PRP to report significantly better WOMAC scores ($P < .05$) at latest follow-up, with no difference in preinjection scores between groups. Overall, when comparing patients who received LP-PRP and HA at latest follow-up, 7 of 15 outcome scores (46.7%) demonstrated a significantly improved score in patients undergoing treatment with PRP compared with HA, whereas none (0%) demonstrated superiority with HA.

Subanalysis on Studies Using LR-PRP

Of the 9 studies^{12,30,31,37,38,41,43,46,47} that used LR-PRP, 4 studies^{30,31,37,38} reported WOMAC scores, 7 studies^{12,31,38,41,43,46,47} reported VAS scores, 4 studies^{12,30,41,43} reported Subjective IKDC scores, and none reported LEQ scores (Table 10). All 4 studies^{30,31,37,38} reporting on WOMAC score, 3 of the 7 studies^{38,41,43} reporting on VAS, and 3 of 4 studies^{12,30,43} reporting on Subjective IKDC scores found patients who received PRP to improve significantly ($P < .05$) from preinjection to latest follow-up. The one study⁴⁶ not included in Table 10 in the VAS section reported medians, in which preinjection VAS scores between groups were not significantly different.

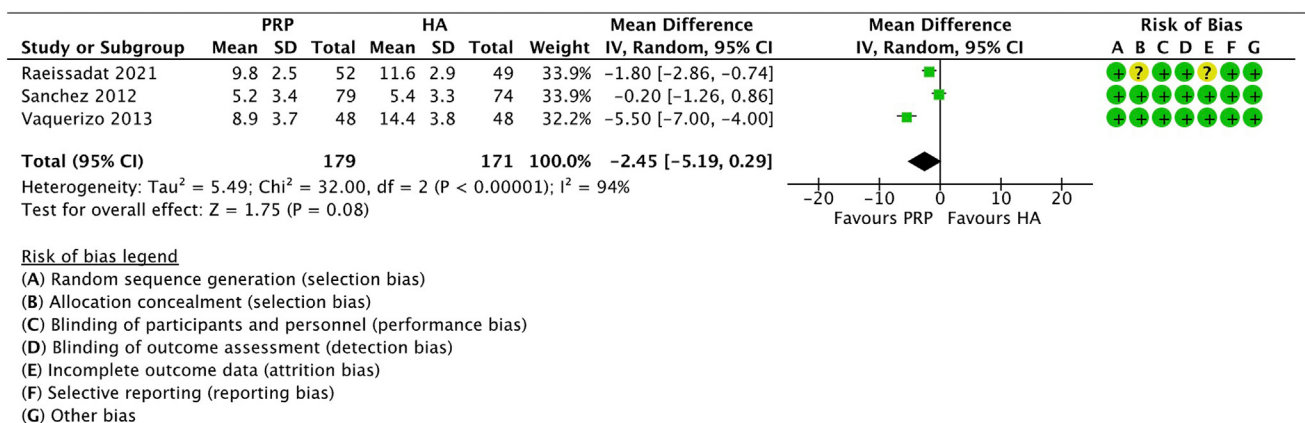


Fig 15. Non-network meta-analysis forest plot of PRP versus HA LEQ scores. (CI, confidence interval; HA, hyaluronic acid; IV, weighted mean difference; LEQ, Lequesne; PRP, platelet-rich plasma; SD, standard deviation.)

Table 8. Postinjection KOOS Subscores

Study	KOOS Subscores											
	Symptoms			Pain			ADLs			Sport		
	PRP	HA	BMAC	PRP	HA	BMAC	PRP	HA	BMAC	PRP	HA	BMAC
Boffa et al., 2022 ⁴²	74.9 ± 16.9	72.8 ± 16.8	71.6 ± 19.7	71.0 ± 20.6	77.2 ± 17.3	77.9 ± 18.4	41.3 ± 25.0	46.3 ± 28.1	49.3 ± 28.6	41.0 ± 27.8	52.8 ± 25.2	53.8 ± 25.9
Filardo et al., 2015 ¹²	73.9 ± 17.2	73.9 ± 18.4	74.9 ± 19.3	75.4 ± 19.0	78.4 ± 20.7	78.4 ± 19.3	49.3 ± 28.6	46.3 ± 28.1	49.3 ± 28.6	41.0 ± 27.8	50.9 ± 24.4	50.8 ± 24.0
Jivan et al., 2021 ⁴⁵	51.1 ± 2.6	44.2 ± 4.8	56.7 ± 6.1*	36.2 ± 6.8	56.0 ± 5.4*	37.8 ± 6.2	21.0 ± 7.0	18.0 ± 4.1	21.0 ± 7.0	18.0 ± 4.1	34.8 ± 6.1*	38.7 ± 4.7
Peterson et al., 2016 ⁴⁷	57.8 ± 22.8	80.2 ± 8.4	68.9 ± 15.8	79.3 ± 9.3	78.7 ± 15.9	90.0 ± 7.3	41.0 ± 27.8	64.4 ± 23.6	41.0 ± 27.8	64.4 ± 23.6	38.8 ± 28.4	54.9 ± 9.8

NOTE. Scores are reported as a mean ± standard deviation at latest follow-up.

ADLs, activities of daily living; BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; KOOS, Knee Injury and Osteoarthritis Outcome Score; NR, not reported; QOL, quality of life; PRP, platelet-rich plasma.

*Indicates a significant difference between groups.

When we compared patients who received LR-PRP and HA at latest follow-up, 9 of 15 outcome scores (60%) demonstrated significantly improved scores in patients undergoing treatment with PRP compared with HA, whereas none (0%) demonstrated superiority with HA.

LP-PRP Versus LR-PRP

Pooled analysis of studies that compared LR-PRP and LP-PRP found no significant differences in the efficacy of LR-PRP and LP-PRP in terms of WOMAC, VAS, or Subjective IKDC scores.

Analysis of the effects of LR-PRP versus LP-PRP on WOMAC scores was performed between 5 studies^{24,29,32,36,39} comparing LP-PRP with HA and 4 studies^{30,31,37,38} comparing LR-PRP with HA. Pooled analysis found no evidence of a statistically significant difference in the effects of LP-PRP versus LR-PRP on WOMAC scores.

Analysis of the effects of LR-PRP versus LP-PRP on VAS scores was performed between 4 studies^{22,24,32,36} comparing LP-PRP with HA and 6 studies^{12,31,38,41,43,47} comparing LR-PRP with HA. Pooled analysis found no evidence of a statistically significant difference in the effects of LP-PRP versus LR-PRP on VAS scores.

Finally, analysis of the effects of LR-PRP versus LP-PRP on Subjective IKDC scores was performed between 3 studies^{22,24,34} comparing LP-PRP with HA and 4 studies^{12,30,41,43} comparing LR-PRP with HA. Pooled analysis found no evidence of a statistically significant difference in the effects of LP-PRP versus LR-PRP on Subjective IKDC scores.

Outcomes by OA Grade

Because 21 of the 27 included studies (77.8%) did not analyze postinjection outcomes based on OA grades, the authors could not perform a subanalysis based on OA grade. Four studies^{22,29,45,49} that only included patients with Kellgren-Lawrence grade I-III OA analyzed outcomes based on preinjection OA grade. Three studies^{29,45,49} found no significant differences in any outcome at latest follow-up between patients with either grade I, II, or III OA. Cole et al.²² found that patients who received PRP or HA with grade I OA experienced significantly improved Subjective IKDC scores when compared with patients with grade III OA ($P = .005$). However, there were no significant differences in outcomes between grade I/II patients or between grade II/III patients. No differences were found in WOMAC or VAS scores between patients with either grade I, II, or III OA. Two studies^{42,44} that included patients with grade IV OA analyzed results based on preinjection OA grades. Boffa et al.⁴² found that patients who received BMAC with grade I-II OA experienced significantly better KOOS Sport and QOL scores at latest follow-up when compared with patients who

Table 9. Patient-Reported Outcomes in Studies Using Leukocyte-Poor PRP

Study	PRP	HA	<i>P</i> Value	PRP	HA	<i>P</i> Value
	Preinjection	Preinjection		Postinjection	Postinjection	
WOMAC						
Cerza et al., 2012 ²⁹	79.6 ± 9.5	75.4 ± 10.7	n.s.	36.5 ± 17.9	65.1 ± 10.6	.001
Huang et al., 2019 ³²	48.2 ± 5.0	47.2 ± 5.4	n.s.	16.1 ± 7.2	30.6 ± 8.4	<.01
Raeissadat et al., 2017 ³⁶	42.9 ± 13.5	38.8 ± 12.6	n.s.	24.4 ± 16.5	27.4 ± 11.4	n.s.
Sdeek et al., 2021 ²⁴	66.5 ± 16.6	66.9 ± 16.7	n.s.	60.6 ± 15.2	64.2 ± 16.1	n.s.
Vaquerizo et al., 2013 ³⁹	45.9 ± 12.7	50.8 ± 18.4	n.s.	30.8 ± 15.5	54.2 ± 19.2	<.001
VAS						
Cole et al., 2017 ²²	57.2 ± 14.3	62.9 ± 15.7	n.s.	34.6 ± 3.2	48.6 ± 3.7	.01
Huang et al., 2019 ³²	45.7 ± 6.1	45.4 ± 6.0	n.s.	19.8 ± 14.4	21.4 ± 15.2	n.s.
Raeissadat et al., 2017 ³⁶	76.0 ± 18.0	74.0 ± 15.0	n.s.	46.0 ± 28.0	48.0 ± 24.0	n.s.
Sdeek et al., 2021 ²⁴	57.8 ± 14.5	59.3 ± 14.8	n.s.	40.9 ± 10.2	60.3 ± 15.1	n.s.
Subjective IKDC						
Cole et al., 2017 ²²	NR	NR	n.s.	65.5 ± 3.6	55.8 ± 3.8	.01
Lin et al., 2019 ³⁴	35.7 ± 13.8	35.9 ± 12.7	n.s.	49.9 ± 17.7	38.6 ± 16.1	n.s.
Sdeek et al., 2021 ²⁴	49.1 ± 12.3	47.3 ± 11.8	n.s.	55.2 ± 13.8	46.1 ± 11.5	n.s.
LEQ						
Sanchez et al., 2012 ⁵⁴	9.5 ± 3.0	9.1 ± 3.2	n.s.	5.2 ± 3.4	5.4 ± 3.3	n.s.
Vaquerizo et al., 2013 ³⁹	12.8 ± 3.8	13.1 ± 3.8	n.s.	8.9 ± 3.7	14.4 ± 3.8	<.001

NOTE. Scores are reported as a mean ± standard deviation at latest follow-up.

HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; NR, not reported; n.s., not significant; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

received BMAC with grade III-IV OA ($P = .015$). Görmeli et al.⁴⁴ found that patients with grade I-III OA experienced significantly better VAS and Subjective IKDC scores at latest follow-up when compared with patients with grade IV OA ($P < .005$).

Discussion

The most important findings from this systematic review were consistently better results with PRP and

BMAC compared with HA injections for patients with knee OA. In both the non-network and network meta-analyses, these results were statistically significant in terms of the WOMAC, VAS, and Subjective IKDC scores. These results parallel those of a previous systematic review by Belk et al.⁵²

The improved results of PRP over HA may be explained by several biological advantages of PRP. In particular, PRP stimulates proliferation of various

Table 10. Patient-Reported Outcomes in Studies Using Leukocyte-Rich PRP

Study	PRP	HA	P Value	PRP	HA	P Value
	Preinjection	Preinjection		Postinjection	Postinjection	
WOMAC						
Dulic et al., 2021 ³⁰	48.1 ± 17.0	46.4 ± 15.0	n.s.	31.1 ± 23.3	35.3 ± 17.4	<.001
Duymus et al., 2017 ³¹	76.1 ± 9.4	77.0 ± 2.5	n.s.	54.9 ± 10.8	69.3 ± 4.3	< .001
Raeissadat et al., 2015 ³⁷	39.5 ± 17.1	28.7 ± 16.7	<.001	18.4 ± 14.4	27.5 ± 16.4	.0001
Su et al., 2018 ³⁸	50.2 ± 1.1	49.9 ± 1.5	n.s.	36.4 ± 1.7	46.9 ± 3.8	<.05
VAS						
Ahmad et al., 2018 ⁴¹	58.0 ± 1.90	61.0 ± 17.0	n.s.	41.0 ± 14.0	60.0 ± 15.0	.01
Di Martino et al., 2019 ⁴³	72.7 ± 12.3	71.2 ± 13.3	n.s.	71.9 ± 13.6	66.6 ± 14.2	n.s.
Duymus et al., 2017 ³¹	74.0 ± 10.0	83.0 ± 4.0	<.001	51.0 ± 13.0	68.0 ± 1.0	<.001
Filardo et al., 2015 ¹²	73.2 ± 12.0	71.6 ± 13.4	n.s.	77.6 ± 11.1	73.4 ± 15.2	n.s.
Paterson et al., 2016 ⁴⁷	48.1 ± 23.8	39.7 ± 21.9	n.s.	36.9 ± 25.4	14.1 ± 9.3	n.s.
Su et al., 2018 ³⁸	71.0 ± 3.0	70.0 ± 3.0	n.s.	38.0 ± 3.0	65.0 ± 3.0	<.05
Subjective IKDC						
Ahmad et al., 2018 ⁴¹	49.2 ± 14.9	47.2 ± 16.2	n.s.	75.7 ± 15.1	65.6 ± 16.9	.004
Di Martino et al., 2019 ⁴³	53.3 ± 14.3	50.3 ± 13.2	n.s.	72.5 ± 19.0	68.6 ± 18.8	n.s.
Dulic et al., 2021 ³⁰	32.9 ± 12.8	28.6 ± 11.4	.02	48.6 ± 20.8	42.4 ± 17.6	.002
Filardo et al., 2015 ¹²	52.4 ± 14.1	49.7 ± 13.0	n.s.	66.2 ± 16.7	64.2 ± 18.0	n.s.

NOTE. Scores are reported as a mean ± standard deviation at latest follow-up.

HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; NR, not reported; n.s., not significant; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

growth factors such as transforming growth factor- β , insulin-like growth factor, and vascular endothelial growth factor¹³ migration, and autocrine release of hepatocytic growth factors and HA.⁴⁸ Mechanical stress and growth factors play a pivotal role in modulating the expression of chondrocytes, and the abundance of these modulator cells obtained from PRP has been shown to decrease nuclear factor- $\kappa\beta$ activation, which is a major contributor to the inflamed and catabolic joint environment characterized by OA.⁵³ In addition, the autologous proteins found in the supernatant of PRP samples inhibit the generation of tumor necrosis factor- α —stimulated chondrocytes and matrix metalloproteinase enzymes, both of which have been demonstrated to promote inflammation and early-onset OA.⁵⁴ Unfortunately, PRP is currently not approved by insurance carriers and thus requires out-of-pocket payments by patients on the range of \$350 to \$1,700 per injection.⁵⁵ For patients who are able to afford these payments, we recommend PRP rather than HA injections.

Previous studies have demonstrated that LP-PRP serves as a superior line of treatment for OA in comparison with LR-PRP.^{56,57} Despite these results, other studies do not show improved clinical outcomes of LP-PRP, and thus the ideal PRP composition for the treatment of knee OA remains controversial.^{22,29,31,34,41,43} Of the studies using LR-PRP in this review, 60% of possible outcome scores resulted in patients who received PRP experiencing significantly improved postinjection results when compared with patients who received HA, whereas only 46.7% of outcome scores in studies using LP-PRP resulted in patients who received PRP experiencing significantly improved results when compared with patients who received HA. Although it is clear from the results of this study that PRP, regardless of leukocyte content, is a more effective treatment for OA when compared with HA, there is not a clear distinction in the superiority of LP- versus LR-PRP. This corroborates a recent network meta-analysis evaluating the effect of leukocyte concentration in PRP injections on outcomes for knee OA.⁵⁸ Further studies are necessary to directly compare the effects of PRP leukocyte content on outcomes in patients with knee OA.

The improved results of BMAC over HA also may be explained by several biological advantages of BMAC. BMAC has been found to be a safe and rich source of bone marrow stromal cells and is one of the few forms of stromal cell delivery approved by the United States Food and Drug Administration.^{59,60} These BMSCs have been found to be involved in chondrogenesis and generate anti-inflammatory effects.⁶¹ The presence of BMSCs in BMAC offers an advantage over HA. BMAC also contains several growth factors that may assist in the regenerative chondrogenesis process as well as an

increased number of platelets and white blood cells.⁶²⁻⁶⁴ Of the studies comparing BMAC and HA in this review, 72.7% (8/11) of possible outcome scores resulted in patients who received BMAC experiencing significantly improved postinjection results when compared with patients who received HA, whereas none demonstrated superiority in patients who received HA. This again corroborates a recent systematic review on BMAC injections for the treatment of knee OA.⁶⁵

Limitations

The limitations of this study should be noted. In particular, none of the included studies reported on knee survivorship, i.e., the number of patients who ultimately failed injection therapy and went on to require a total knee arthroplasty. Moderate-to-high heterogeneity may be present between studies. PRP, HA, and BMAC administration techniques and strategies were not identical across all studies, not all studies used the same PRP composition, and not all studies used the same PROs. Postinjection radiographic knee OA was not consistently reported in the included studies. In addition, follow-up times were short-term and highly variable, ranging from 3 to 48 months.

Conclusions

Patients undergoing treatment for knee OA with PRP or BMAC can be expected to experience improved clinical outcomes when compared with patients who receive HA.

References

1. Grazio S, Balen D. Obesity: Risk factor and predictor of osteoarthritis. *Lijec Vjesn* 2009;131:22-26.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:15-25.
3. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: A meta-analysis of randomized controlled trials. *Arthroscopy* 2017;33:659-670.
4. Filardo G, Di Matteo B, Kon E, Merli G, Marcacci M. Platelet-rich plasma in tendon-related disorders: Results and indications. *Knee Surg Sports Traumatol Arthrosc* 2018;26:1984-1999.
5. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—meta-analysis. *Osteoarthritis Cartilage* 2011;19:611-619.
6. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;43:593-599.
7. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in

- the osteoarthritic knee: A systematic review. *BMC Musculoskelet Disord* 2015;26:321.
8. Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. *Clin Transl Med* 2018;7:6.
 9. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis* 2010;69:113-119.
 10. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: A systematic review and network meta-analysis. *Ann Intern Med* 2015;162:46-54.
 11. Bennell KL, Hunter DJ, Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. *Curr Rheumatol Rep* 2017;19:24.
 12. 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;43:1575-1582.
 13. Kabiri A, Esfandiari E, Esmaeili A, Hashemibeni B, Pourazar A, Mardani M. Platelet-rich plasma application in chondrogenesis. *Adv Biomed Res* 2014;3:138.
 14. Sundman EA, Cole BJ, Karas V, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. *Am J Sports Med* 2014;42:35-41.
 15. Rodriguez-Fontan F, Piuze NS, Kraeutler MJ, Pascual-Garrido C. Early clinical outcomes of intra-articular injections of bone marrow aspirate concentrate for the treatment of early osteoarthritis of the hip and knee: A cohort study. *PM R* 2018;10:1353-1359.
 16. Higgins JP, Green S, eds. *Cochrane handbook for systematic reviews of interventions version 5.1.0*. [updated March 2011]. The Cochrane Collaboration, 2011.
 17. Bellamy N, Wilson C, Hendrikz J. Population-based normative values for the Western Ontario and McMaster (WOMAC) Osteoarthritis Index: Part I. *Semin Arthritis Rheum* 2011;41:139-148.
 18. Hefti F, Müller W, Jakob R, Stäubli H. Evaluation of knee ligament injuries with the IKDC form. *Knee Surg Sports Traumatol Arthrosc* 1993;1:226-234.
 19. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation—value in comparison with other assessment tests. *Scand J Rheumatol Suppl* 1987;65:85-89.
 20. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88-96.
 21. Coleman BD, Khan HM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: Clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. *Scand J Med Sci Sports* 2000;10:2-11.
 22. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: A prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. *Am J Sports Med* 2017;45:339-346.
 23. Raeissadat SA, 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;22:134.
 24. 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;87:729-734.
 25. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: A randomized controlled trial. *Transplantation* 2015;99:1681-1690.
 26. Weir CJ, Butcher I, Assi V, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: A systematic review. *BMC Med Res Methodol* 2018;18:25.
 27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558.
 28. Rucker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: Network Meta-Analysis using Frequentist Methods. R package version 1.1-0. <https://cran.r-project.org/web/packages/netmeta/netmeta.pdf> 2019. Accessed October 21, 2022.
 29. Cerza F, Carni S, Carcangui A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012;40:2822-2827.
 30. Dulic O, Rasovic P, Lalic I, et al. Bone marrow aspirate concentrate versus platelet rich plasma or hyaluronic acid for the treatment of knee osteoarthritis. *Medicina (Kaunas)* 2021;57:1193.
 31. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: Platelet-rich plasma, hyaluronic acid or ozone options. *Knee Surg Sports Traumatol Arthrosc* 2017;25:485-492.
 32. Huang Y, Liu X, Xu X, Liu J. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis: A prospective randomized controlled study. *Orthopade* 2019;48:239-247.
 33. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: Long-term follow up of a multicenter randomized controlled clinical trial (phase I/II). *J Transl Med* 2018;16:213.
 34. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: A randomized, double-blind, triple-parallel, placebo-controlled clinical trial. *Arthroscopy* 2019;35:106-117.
 35. 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;32:330-339.
36. Raeissadat SA, Rayegani SM, Ahangar AG, Abadi PH, Mojgani P, Ahangar OG. Efficacy of intra-articular injection of a newly developed plasma rich in growth factor (PRGF) versus hyaluronic acid on pain and function of patients with knee osteoarthritis: A single-blinded randomized clinical trial. *Clin Med Insights Arthritis Musculoskelet Disord* 2017;10:1179544117733452.
 37. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: Platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord* 2015;8:1-8.
 38. Su K, Bai Y, Wang J, Zhang H, Liu H, Ma S. Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis. *Clin Rheumatol* 2018;37:1341-1350.
 39. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: A randomized controlled trial. *Arthroscopy* 2013;29:1635-1643.
 40. Vasavilbaso C, Bello CD, Lopez E, et al. Benefits of different postoperative treatments in patients undergoing knee arthroscopic debridement. *Open Access Rheumatol* 2017;9:171-179.
 41. Ahmad HS, Farrag SE, Okasha AE, et al. Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. *Int J Rheum Dis* 2018;21:960-966.
 42. Boffa A, Di Martino A, Andriolo L, et al. Bone marrow aspirate concentrate injections provide similar results versus viscosupplementation up to 24 months of follow-up in patients with symptomatic knee osteoarthritis. A randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2022;30:3958-3967.
 43. 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;47:347-354.
 44. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2017;25:958-965.
 45. Jivan S, Monzavi SM, Zargaran B, et al. Comparative analysis of the effectiveness of intra-articular injection of platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: Results of an open-label trial. *Arch Bone Jt Surg* 2021;9:487-495.
 46. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med* 2016;12:69-78.
 47. Paterson KL, Nicholius M, Bennell KL, Bates D. Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: A double-blind, randomized controlled pilot study. *BMC Musculoskelet Disord* 2016;9:67.
 48. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070-1078.
 49. Goncars V, Jakobsons E, Blums K, et al. The comparison of knee osteoarthritis treatment with single-dose bone marrow-derived mononuclear cells vs. hyaluronic acid injections. *Medicina (Kaunas)* 2017;53:101-108.
 50. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 1957;16:494-502.
 51. Montanez-Heredia E, Irizar 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;17:1064.
 52. Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med* 2021;49:249-260.
 53. van Buul GM, Koevoet WL, Kops N, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. *Am J Sports Med* 2011;39:2362-2370.
 54. Woodell-May J, Matuska A, Oyster M, Welch Z, O'Shaughnessey K, Hoepfner J. Autologous protein solution inhibits MMP-13 production by IL-1 β and TNF α -stimulated human articular chondrocytes. *J Orthop Res* 2011;29:1320-1326.
 55. Alcerro JC, Lavernia CJ. Stem cells and platelet-rich plasma for knee osteoarthritis: Prevalence and cost in South Florida. *J Am Acad Orthop Surg* 2019;27:779-783.
 56. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: Single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc* 2012;20:2082-2091.
 57. Riboh JC, Slatzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med* 2016;44:792-800.
 58. Abbas A, Du JT, Dhotar HS. The effect of leukocyte concentration on platelet-rich plasma injections for knee osteoarthritis: A network meta-analysis. *J Bone Joint Surg Am* 2022;104:559-570.
 59. Chahla J, Alland JA, Verma NN. Bone marrow aspirate concentrate for orthopaedic use. *Orthop Nurs* 2018;37:379-381.
 60. McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. *J Orthop Res* 2009;27:1033-1042.
 61. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol* 2007;213:341-347.

62. Chiang H, Hsieh CH, Lin YH, Lin S, Tsai-Wu JJ, Jiang CC. Differences between chondrocytes and bone marrow-derived chondrogenic cells. *Tissue Eng Part A* 2011;17: 2919-2929.
63. Fortier LA, Potter HG, Rickey EJ, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. *J Bone Joint Surg Am* 2010;92:1927-1937.
64. Kraeutler MJ, Chahla J, LaPrade RF, Pascual-Garrido C. Biologic options for articular cartilage wear (platelet-rich plasma, stem cells, bone marrow aspirate concentrate). *Clin Sports Med* 2017;36:457-468.
65. Keeling LE, Belk JW, Kraeutler MJ, et al. Bone marrow aspirate concentrate for the treatment of knee osteoarthritis: A systematic review. *Am J Sports Med* 2022;50: 2315-2323.