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SYSTEMATIC REVIEW

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Comparison of hyaluronic acid and platelet-rich plasma in knee osteoarthritis: a systematic review

Hong Xu[1†], Weifeng Shi[1†], Hong Liu[1], Shasha Chai[1], Jindi Xu[1,2], Qingyu Tu[1,2], Jinwei Xu[1*] and Wei Zhuang[1*]

Abstract

Background Knee osteoarthritis (KOA) is a common joint disorder, and intra-articular injections of hyaluronic acid (HA) or platelet-rich plasma (PRP) are frequently employed therapeutic interventions. However, there remains controversy regarding their efficacy. This systematic review aims to compare the effectiveness and safety of HA and PRP through a meta-analysis, with the objective of identifying the optimal treatment protocol for KOA and enhancing its management.

Methods Randomized controlled trials evaluating the clinical outcomes of patients receiving intra-articular injections of either HA or PRP were included as eligible studies. Two independent investigators assessed the selected studies and evaluated their risk of bias. Primary outcome measures included the Visual Analog Scale (VAS) score, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, and other relevant assessment indices. Dichotomous variables were analyzed using risk ratios (RR) with 95% confidence intervals (CI). Data analysis was conducted using RevMan software (version 5.3).

Results A total of forty-two randomized controlled trials were included in this meta-analysis. No significant differences were observed between the patient populations in the two groups. The analysis demonstrated that PRP resulted in lower VAS and WOMAC scores compared to HA. Additionally, PRP exhibited superior performance across other evaluation indices. Notably, the incidence of adverse events was higher in the PRP group; however, all reported complications were mild.

Conclusions Based on the current evidence, intra-articular injection of PRP appears to be more effective than HA for the treatment of KOA, as indicated by the analysis of VAS, WOMAC scores, and other evaluation indices.

Trial registration Retrospectively registered.

Keywords Knee osteoarthritis, Hyaluronic acid, Platelet-rich plasma, Intra-articular injection, Meta-analysis

†Hong Xu and Weifeng Shi contributed equally to this work.

*Correspondence:
Jinwei Xu
xjw942100@163.com
Wei Zhuang
994397598@qq.com
[1] Department of Orthopaedics, Hangzhou Xiaoshan Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang Province, China
[2] Zhejiang Chinese Medical University, Zhejiang Province, China

Background

Knee osteoarthritis (KOA), a prevalent joint disease, is emerging as one of the leading causes of global disability. The incidence and prevalence of KOA in the general population have been increasing over the years. From 2008 to 2014, approximately 32.5 million individuals, representing 14% of the American population, were affected by osteoarthritis. It is estimated that the global prevalence of symptomatic knee osteoarthritis, confirmed by X-ray or other imaging modalities, was around 3.8%. However, this prevalence increased to 10% or more in individuals aged 60 years and older. Hereditary vulnerabilities, elevated body mass, certain occupations, and traumatic injuries are likely to augment the risk of developing KOA, while age remains the predominant risk factor [1]. KOA is with high health burden on patients, their families, and the society [2]. It is emerging as a major challenge for global health systems, particularly in the context of global aging and rising obesity rates [3].

Arthritis patients typically experience joint pain, stiffness, and difficulty in physical activity [1]. The impact of osteoarthritis (OA) on joints is gradual and progressive, leading to the continuous degradation of articular cartilage, subchondral bone, and surrounding synovial structures [4]. Approximately 80% of OA patients suffer from movement limitations, and one in four are unable to perform essential daily activities [5]. KOA constitutes at least 80% of all OA cases, and more than 19% of adults aged 45 and older in the United States have KOA [6]. KOA results in knee pain and functional impairment due to cartilage degeneration and joint space narrowing [7, 8].

The treatment of KOA aims to reduce pain and improve patient function. Most treatments, particularly invasive procedures such as total knee arthroplasty, carry potential adverse effects. While total knee arthroplasty is a surgical option, it is complex and associated with risks. However, this procedure is complicated and carries risks. Consequently, non-surgical interventions, including intra-articular injections, oral nonsteroidal anti-inflammatory drugs (NSAIDs), and physical therapy, have been extensively investigated. For patients with KOA, intra-articular injections are widely utilized. The most commonly administered injections are HA and PRP [9].

HA is a natural glycosaminoglycan in synovial fluid that enhances joint lubrication and improves viscoelastic properties. HA mechanically lubricates the joints to protect them from loads and impacts, and to restore the fluidity synovial fluid [10]. Additionally, HA interacts with inflammatory mediators to inhibit pain transmission, promote cartilage growth and extracellular matrix protein synthesis, and reduce apoptosis in osteoarthritic cartilage [11–14]. Consequently, HA functions as a physiologically active molecule and is commonly used as intra-articular injections [15–17]. Studies have demonstrated that HA can facilitate functional improvements in knee, hip, and ankle osteoarthritis [18, 19].

PRP, an autologous blood product, contains growth factors that promote angiogenesis, modulate inflammation, and recruit stem cells and fibroblasts to the injured area [20]. A small volume of peripheral blood is centrifuged to concentrate the platelets in the plasma. The concentration quality depends on the centrifugation equipment, gravity, centrifugation time and initial blood sample [21, 22]. Platelet α-granules (TGF-β1, bFGF, EGF and so on) contain a large number of growth factors. These factors can promote tissue healing such as cartilage repair, vascular remodeling and help regulate inflammation, when concentrated and injected into the knee joint [23, 24]. PRP has become an increasingly common and promising treatment for KOA in clinical practice in recent years.

The effectiveness of each intra-articular injection is controversial. While HA injections are common treatment for KOA, with its potential to benefit patients, studies on the efficacy have been inconsistent. The effectiveness of PRP injections appears to be less favorable in severe KOA patients. Additionally, the relatively expensive cost and the safety performance are questioned. This review aims to compare the effectiveness of PRP and HA or KOA through a meta-analysis. The goal is to determine the optimal treatment protocol for this condition and identify more effective management strategies.

Methods

Search strategy

PubMed, Web of science and the Cochrane Central Register of Controlled Trials were searched for randomized controlled trials (RCTs). Medical Subject Headings (MeSH) were used including 'knee osteoarthritis', 'hyaluronic acid', 'platelet-rich plasma' and "intra-articular".

Inclusion/exclusion criteria

Inclusion criteria primarily included: (1) clinical trial was randomly controlled, (2) random allocation was performed, (3) key data was recorded, including but not limited to age, sex, BMI, OA Grade, intervention, clinical outcomes including follow-up, VAS score, Western Ontario and McMaster Universities Arthritis Index (WOMAC score), International Knee Documentation Committee score (IKDC score), Knee injury and osteoarthritis outcome score (KOOS score), EuroQol visual analog scale (EQ-VAS), Lequesne index, satisfaction rate, Tegner activity scale and adverse events.

Exclusion criteria mainly including: (1) case report or review, (2) not involved with KOA treatment, (3) superfluous data were mixed in the comparison between PRP and HA, (4) without an English version. Disagreement was resolved through collective discussion.

Risks of bias assessment

Risks of bias were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. This included selection bias, performance bias, detection bias, attrition bias and reporting bias.

Potential effect modifiers and reasons for heterogeneity
Risk ratio (RR) and 95% confidence interval (CI) were calculated. Heterogeneity among the included studies was assessed using the I2 statistic at a significance level of $\alpha = 0.05$. A fixed-effect model was used if there was no evidence of heterogeneity ($I2 \leq 50\%$), otherwise a random effect model was used. The result robustness was tested by sequentially eliminating each study one by one and studies with $I2 > 50\%$ were excluded. A funnel plot was used to assess the potential publication bias if more than ten studies were included.

Data extraction
The following data were extracted: number of patients, characteristics of patients (age, sex, BMI, OA Grade, intervention), clinical outcomes including follow-up, VAS score, WOMAC score (total score, pain score, stiffness score), EQ-VAS score, Lequesne index, satisfaction rate, IKDC score, KOOS score and adverse events. Data extraction was conducted by reviewing the full test, and all relevant figures and tables were extracted end interpreted.

Data synthesis
Rev Man software (version 5.3) was employed for data analysis.

Ethical statement
Ethical approval was not required for this mete-analysis as all data were obtained from published studies.

Results
Study selection
Three hundred and sixty-one articles were identified from database searches. One hundred and forty-three duplicates were removed. Strict inclusion and exclusion criteria were applied. After reviewing the abstracts, ninety-eight records were excluded. Following full-text assessment, an additional thirty-eight studies were excluded. Ultimately, thirty-seven articles met the primary inclusion criteria and were included in this meta-analysis. Additionally, we manually reviewed the reference lists of relevant reviews to identify any additional eligible studies, which resulted in the inclusion of five more RCTs. The selection process is illustrated in the PRISMA Flow Diagram (Fig. 1).

Study characteristics
The forty-two identified RCTs [16, 25–65] included one RCT [58] conducted on KOA patients following knee arthroscopic debridement. Basic information was summarized in Table 1. A total of 3660 KOA patients were enrolled across the 42 RCTs, with 1839 assigned to the PRP group and 1821 to the HA group. The sample size of the these RCTs ranged from 21 to 192 patients. The majority of studies had a follow-up period of at least six months, with the shortest follow-up being three months. The OA severity was assessed using Kellgren and Lawrence (KL), Ahlbäck or Shahriaree Classification System, including patients with grades 0–4.

One article [45] did not report the mean age of each group, while two others [34, 53] reported the mean age without the standard deviation (SD). The remaining 39 RCTs indicated that patients in the PRP group were, to some extent, younger than those in the HA group ($p = 0.001$, Supplementary Fig. 1). Subgroup was employed to reduce I^2, and the result of 33 RCTs showed a similar trend ($p = 0.03$, Supplementary Fig. 1).

One article [56] did not provide the sex ratio and another [45] included only male patients The remaining 40 RCTs showed no statistic difference in sex ratio ($p = 0.23$, Supplementary Fig. 2).

Four articles [28, 42, 45, 65] did not report the mean BMI of each group, while another three [26, 34, 53] reported the mean BMI without the SD. The remaining 35 RCTs showed no statistic difference ($p = 0.28$, Supplementary Fig. 3). Subgroup was employed to reduce I^2 based on the funnel plot. And the result of 34 RCTs showed a similar trend ($p = 0.44$, Supplementary Fig. 3).

Data on OA grade were available in 30 studies, with one [34] not reporting the SD. No statistic difference was found in the OA grade ($p = 0.96$, Supplementary Fig. 4). Subgroup was employed. The result of 28 RCTs showed a similar trend ($p = 0.86$, Supplementary Fig. 4).

Risk of bias
Random sequence generation was reported in all RCTs. In most studies, random sequence generation was achieved using computers or other technology. Sealed envelope technique was employed in 25 studies. Blinding of participants was not achieved in 8 studies, leading to a high risk of performance bias. Evaluators were not concealed of the grouping in 6 studies, resulting in a high risk of detection bias (blinding of outcome assessment). Attrition bias and reporting bias were assessed as low or unclear. The authors' judgments regarding the risk of bias are summarized in Figs. 2 and 3.

VAS score
VAS score before intra-articular injection was available in 25 studies, with one [53] not reporting the SD. Data from 29 studies were used for analysis and no statistic difference was found ($p = 0.05$, Fig. 4). The VAS score at one to three months post-injection was available in 20 studies. The analysis revealed that patients in the PRP group had significantly lower VAS score ($p < 0.01$, Fig. 5). VAS

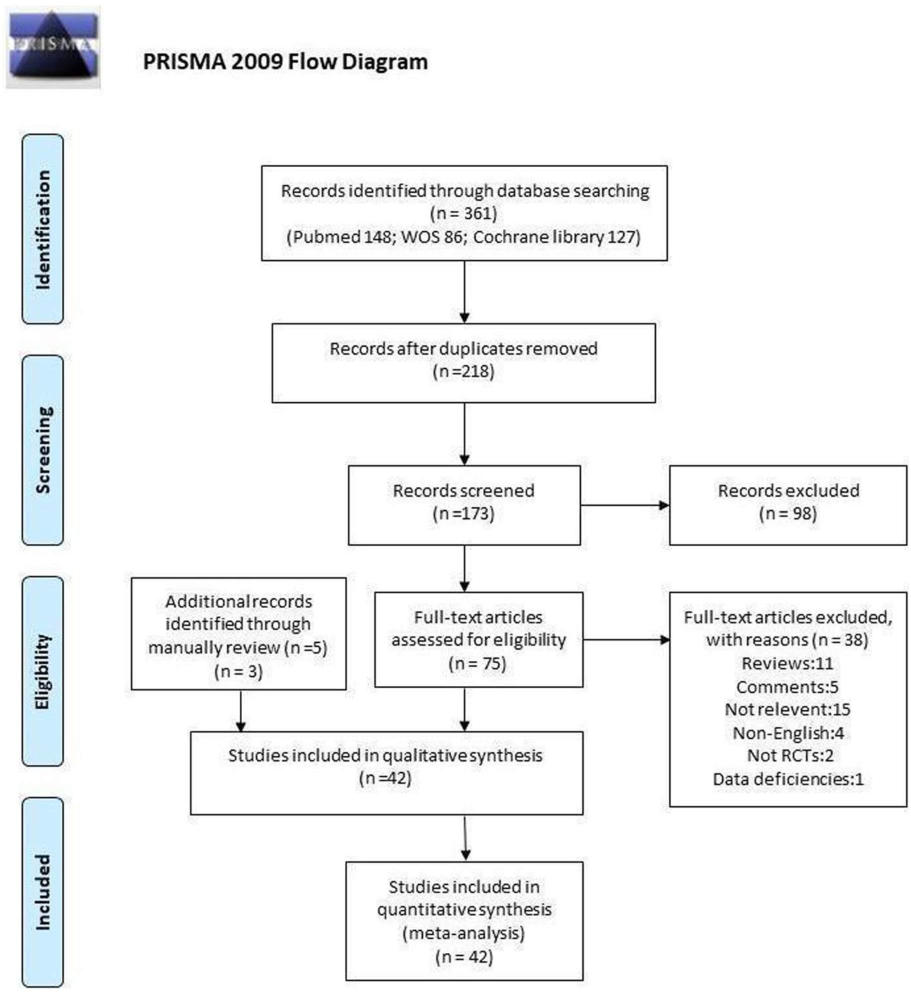

Fig. 1 PRISMA flow diagram

score at 6 months post-injection was available in 18 studies and the PRP group again showed significantly lower VAS scores ($p < 0.01$, Fig. 6). One-year follow-up analysis, based on 12 studies, also demonstrated the same trend ($p < 0.01$, Fig. 7).

WOMAC score

WOMAC total score

WOMAC total score before intra-articular injection was available in 28 studies. Analysis revealed no statistic difference ($p = 0.1$, Fig. 8). The follow-up at one to three months post-injection was available in 19 studies. Analysis showed that WOMAC total score was significantly lower in the PRP group ($p < 0.01$, Fig. 9). Same trend was observed at the six-month follow-up (23 RCTs, $p < 0.01$, Fig. 10) and one-year follow-up (16 RCTs, $p < 0.01$, Fig. 11).

WOMAC pain score

WOMAC pain score before injection was available in 20 studies. Analysis revealed no statistic difference ($p = 0.7$, Fig. 12). The follow-up at one to three months post-injection was available in 11 studies. Analysis showed no statistic ($p = 0.12$, Fig. 13). The follow-up at six months post-injection was available in 14 studies, and analysis showed that WOMAC pain score was significantly lower in the PRP group ($p < 0.01$, Fig. 14). At one year follow-up, the PRP group continued to perform better (12 RCTs, $p < 0.01$, Fig. 15).

WOMAC stiffness score

WOMAC stiffness score before injection was available in 18 studies. Analysis revealed that WOMAC stiffness score was lower in the HA group ($p < 0.01$, Fig. 16). Subgroup analysis was then employed and the result of 17 RCTs showed the same trend ($p < 0.01$). No statistic difference was found at the one to three-month follow-up

Table 1 Basic information of all the identified RCTs

Author.Year	Country	Group	N	Age, year	Sex M/F	BMI	OA Grade (KL)	OA Grade	Intervention (Dose,Times,Type)	Follow-up
Ahmad, H. S. 2018 [25]	Egypt	PRP	45	56.2 ± 6.8	14/31	26.7 ± 3.6	Grade 1–3; $P > 0.05$	2.83 ± 0.75	4 mL,3 times,2 weeks	6 m
		HA	44	56.8 ± 7.4	14/30	26.5 ± 3.5		2.25 ± 0.72	20 mg/2 mL,3 times,2 weeks	
Arliani, G. G. 2022 [26]	Brazil	PRP	14	62.78 ± 6.1	11/3	28.3	Grade 2–3; $P > 0.9999$	2.36 ± 0.50	5 mL,3 times,weekly	6 m
		HA	15	63.4 ± 4.99	13/2	28.1		2.4 ± 0.51	NA	
Buendía-López, D. 2018 [27]	Spain	PRP	33	56.15 ± 3.0	16/17	24.9 ± 0.32	Grade 1–2; $P > 0.05$	1.46 ± 0.51	5 mL,1 time	12 m
		HA	32	56.63 ± 2.9	15/17	24.9 ± 0.41		1.44 ± 0.50	60 mg/2 mL,1 time,DUROLANE	
Cerza, F. 2012 [28]	Italy	PRP	60	66.5 ± 11.3	25/35	NA	Grade 1–3; $P > 0.05$	1.9 ± 0.77	5.5 mL,4 times,weekly	6 m
		HA	60	66.2 ± 10.6	28/32			1.8 ± 0.78	20 mg/2 mL,4 times,weekly,HYALGAN	
Cole, B. J. 2017 [29]	USA	PRP	49	55.9 ± 10.4	28/21	27.4 ± 3.9	Grade 1–3; $P > 0.05$	2.35 ± 0.60	4 mL,3 times,weekly	12 m
		HA	50	56.8 ± 10.5	20/30	29.0 ± 6.4		2.45 ± 0.50	16 mg/2 mL,3 times,weekly	
Di Martino, A. 2019 [30]	Italy	PRP	85	52.7 ± 13.2	53/32	27.2 ± 7.6	Grade 1–3	2.0 ± 1.1	5 mL,3 times, weekly	24 m
		HA	82	57.5 ± 11.7	47/35	26.8 ± 4.3		2.0 ± 1.0	30 mg/2 mL,3 times,weekly,Hyalubrix	
Dong, C. 2022 [31]	China	PRP	24	56.64 ± 8.32	6/18	27.14 ± 3.16	Grade 3–4; $P > 0.05$	3.33 ± 0.48	3 ml,4 times, weekly,1 week postsurgery	12 m
		HA	25	55.18 ± 7.96	5/20	27.13 ± 3.04		3.4 ± 0.5	3 ml,4 times, weekly,1 week postsurgery	
Dulic, O. 2021 [32]	Serbia	PRP	34	58.8 ± 11.2	15/19	28.47 ± 4.54	Grade 2–4; $P > 0.05$	2.94 ± 0.81	NA	12 m
		HA	30	59.4 ± 14.0	13/17	29.98 ± 5.24		2.87 ± 0.86	20mg/2ml,3 times,weekly,Cartinorm	
Duymus, T. M. 2017 [33]	Turkey	PRP	33	60.4 ± 5.1	1/32	27.6 ± 4.6	Grade 2–3; $P > 0.05$	2.33 ± 0.48	5 mL,2 times,2 weeks	12 m
		HA	34	60.3 ± 9.1	1/33	28.4 ± 3.6		2.29 ± 0.46	40 mg/2 mL,1 time,OSTENIL PLUS	
Filardo, G. 2012 [34]	Italy	PRP	54	55	37/17	27	Grade 1–3	2.2	5 mL,3 times, weekly	12 m
		HA	55	58	31/24	26		2.1	3 times, weekly, Hyalubrix	
Filardo, G. 2015 [16]	Italy	PRP	94	53.32 ± 13.2	60/34	26.6 ± 4.0	Grade 1–3	2.0 ± 1.1	5 mL,3 times,weekly	12 m
		HA	89	57.55 ± 11.8	52/37	26.9 ± 4.4		2.0 ± 1.1	20 mg/2 mL,3 times,weekly,Hyalubrix	
Gormeli, G. 2017 [35]	Turkey	PRP	39	53.7 ± 13.1	16/23	28.7 ± 4.8	Grade 1–4	NA	5 mL,3 times,weekly	6 m
		HA	39	53.5 ± 14	17/22	29.7 ± 3.7			20 mg/2 mL,3 times,weekly,ORTHOVISC	
Huang, Y. 2019 [36]	China	PRP	40	54.5 ± 1.2	25/15	25.23 ± 4.15	Grade 1–2	NA	4 mL,1 time	12 m
		HA	40	54.8 ± 1.1	19/21	24.51 ± 3.09			2 mL,3 times, weekly	
Kesiktas, F. N. 2020 [37]	Turkey	PRP	18	52.7 ± 8.3	2/16	28.3 ± 4.4	Grade 2–4; $P > 0.05$	2 ± 0.77	2 ~ 3ml,1 time	3 m
		HA	18	55.1 ± 10.3	4/14	31.0 ± 4.9		2.06 ± 0.80	1 time,Biometics	
Kon, E. 2011 [38]	Italy	PRP	50	50.6 ± 13.8	30/20	24.6 ± 3.2	Grade 0–4	NA	5 mL,3 times,2 weeks	6 m
		HA	100	54.05 ± 12.77	52/48	25.5 ± 2.99			20 or 30 mg/2 mL,1 time	
Küçükakkaş, O. 2022 [39]	Turkey	PRP	20	57.5 ± 10.6	4/16	29.8 ± 6.8	Grade 2–3	NA	1 time	6 m
		HA	20	57.0 ± 10.1	6/14	28.9 ± 3.6			1 time	
Lana, J. F. 2016 [40]	Brazil	PRP	36	60.9 ± 7	7/29	27.42 ± 6.89	Grade 1–3; $P > 0.05$	2.11 ± 0.78	5 mL,1 time	12 m
		HA	36	60 ± 6.6	3/33	28.24 ± 8.77		2.06 ± 0.75	20 mg/2 mL,5 ~ 8 times	

Table 1 (continued)

Author.Year	Country	Group	N	Age, year	Sex M/F	BMI	OA Grade (KL)	OA Grade	Intervention (Dose,Times,Type)	Follow-up
Lin, K. Y. 2019 [41]	China	PRP	31	61.17 ± 13.08	9/22	23.98 ± 2.62	(Ah-lback) 1–3; $P > 0.05$	2.16 ± 0.69	5 mL,3 times,weekly	12 m
		HA	29	62.53 ± 9.9	10/19	26.26 ± 2.99		2.10 ± 0.72	20 mg/2 mL,3 times,weekly	
Lisi, C. 2018 [42]	Italy	PRP	30	53.5 ± 15.1	20/10	NA	(Shahriaree) 2–3	NA	3 times, monthly	12 m
		HA	28	57.1 ± 10	16/14				20 mg/2 mL,3 times,monthly,Hyalgan	
Louis, M. L. 2018 [43]	France	PRP	24	53.2 ± 11.7	14/10	25.6 ± 2.9	Grade 2–4	NA	3 mL,1 time	6 m
		HA	24	48.5 ± 11.5	11/13	27.0 ± 2.9			3 mL,1 time,DUROLANE	
Montañez-H, E. 2016 [44]	Spain	PRP	27	66.3 ± 8.3	12/15	29.0 ± 5.5	Grade 1–3; $P > 0.05$	2.26 ± 0.76	3 times,2 weeks	6 m
		HA	26	61.5 ± 8.6	9/17	30.4 ± 4.9		2.5 ± 0.65	25 mg/2.5 mL,3 times,2 weeks, Adant	
Papalia, R. 2016 [45]	Roma	PRP	23	37.2 ± 1.25	23/0	NA	NA	NA	5.5 mL,3 times	12 m
		HA	24		24/0				64mg/2ml,3 times,IBSA	
Park, Y. B. 2021 [46]	South Korea	PRP	55	60.6 ± 8.2	16/39	25.5 ± 2.2	Grade 1–3; $P > 0.05$	2.44 ± 0.79	3 mL,1 time	6 m
		HA	55	62.3 ± 9.6	8/47	25.9 ± 2.8		2.46 ± 0.77	30 mg/3 mL,1 time	
Paterson, K. L. 2016 [47]	Australia	PRP	11	49.91 ± 13.72	8/3	27.9 ± 11.94	Grade 2–3	NA	3 mL,3 times,weekly	3 m
		HA	10	52.70 ± 10.30	7/3	30.8 ± 5.64			3 mL,3 times,weekly,Hylan G-F 20	
Raeissadat, S. A. 2015 [50]	Iran	PRP	77	56.85 ± 9.13	8/69	28.20 ± 4.63	Grade 1–4; $P > 0.05$	2.56 ± 0.78	5 mL,2 times,monthly	12 m
		HA	62	61.13 ± 7.48	15/47	27.03 ± 4.15		2.69 ± 0.73	20 mg/2 mL,3 times,monthly	
Raeissadat, S. A. 2017 [49]	Iran	PRGF	36	57.0 ± 7.18	7/29	28.6 ± 2.82	Grade 2–3; $P > 0.05$	2.58 ± 0.5	5 mL,2 times,3 weeks	6 m
		HA	33	59.5 ± 7.54	6/27	27.5 ± 2.9		2.55 ± 0.5	20 mg,3 times,weekly,Hyalgan	
Raeissadat, S. A. 2021 [48]	Iran	PRP	52	56.09 ± 6.0	13/39	27.41 ± 2.6	Grade 2–3; $P > 0.05$	2.5 ± 0.50	2 times,2 weeks	12 m
		HA	49	57.91 ± 6.7	12/37	27.46 ± 2.2		2.45 ± 0.50	3 times,weekly,Hyalgan	
Sánchez, M. 2012 [51]	Spain	PRGF	89	60.5 ± 7.9	33/46	27.9 ± 2.9	(Ah-lback) 1–3; $P > 0.05$	1.63 ± 0.71	8 mL,3 times,weekly	6 m
		HA	87	58.9 ± 8.2	29/45	28.2 ± 2.7		1.64 ± 0.70	3 times,weekly	
Say, F. 2013 [52]	Turkey	PRP	45	55.2 ± 7.8	5/40	32.4 ± 4	Grade 1–3; $P > 0.05$	2.58 ± 0.54	2.5 mL,1 time	6 m
		HA	45	56.2 ± 5.1	6/39	32.3 ± 3.3		2.64 ± 0.53	25 mg/2.5 mL,3 times,weekly	
Sdeek, M. 2021 [53]	Egypt	PRP	95	60.2	15/80	27.9	Grade 2–3; $P > 0.05$	2.55 ± 0.50	3 times,2 weeks	36 m
		HA	94	59.5	16/78	27.1		2.48 ± 0.50	3 times,2 weeks	
Spaková, T. 2012 [54]	Slovakia	PRP	60	52.8 ± 12.43	33/27	27.9 ± 4.1	Grade 1–3; $P > 0.05$	2.28 ± 0.52	3 mL,3 times,weekly	6 m
		HA	60	53.2 ± 14.53	31/29	28.3 ± 4.0		2.32 ± 0.54	3 times,weekly	
Su, K. 2018 [55]	China	PRP	25	54.16 ± 6.56	11/14	28.17 ± 1.43	Grade 2–3; $P > 0.05$	2.48 ± 0.51	6 mL,2 times,2 weeks	18 m
		HA	30	53.13 ± 6.41	12/18	28.69 ± 1.13		2.53 ± 0.51	2 mL,5 times,weekly,Freda	
Szwedowski, D. 2022 [56]	Poland	PRP	25	57.92 ± 9.67	NA	27.48 ± 4.99	Grade 2–3	NA	1 time	26 w
		HA	24	52.58 ± 7.4	NA	26.82 ± 3.81			30 mg/mL,1 time	
Tavassoli, M. 2019 [57]	Iran	PRP	28	66.04 ± 7.58	6/22	29.61 ± 1.64	(Ah-lback) 1–2; $P < 0.05$	1.63 ± 0.49	4–6 mL,2 times,3 weeks	3 m
		HA	27	63.3 ± 8.87	8/19	28.94 ± 2.2		1.94 ± 0.24	30 mg/2 mL,3 times,weekly,Hyalgan	

Table 1 (continued)

Author.Year	Country	Group	N	Age, year	Sex M/F	BMI	OA Grade (KL)	OA Grade	Intervention (Dose,Times,Type)	Follow-up
Trueba V.2017 [58]	Mexico	PRP	10	60.3 ± 9.5	4/6	28 ± 3.6	Grade 1–2	NA	6 mL,1 time	18 m
		HA	30	64.77 ± 10.47	17/13	27.7 ± 3.05			NA	
Tschopp, M. 2022 [59]	Switzerland	PRP	30	62 ± 8.9	17/13	26.00 ± 5.48	Grade 1–3; $P > 0.05$	1.91 ± 0.89	3 mL,1 time	24 m
		HA	30	64 ± 12.78	19/11	25.50 ± 5.63		2.08 ± 0.93	6 mL,1 time	
Vaquerizo, V. 2013 [60]	Spain	PRGF	48	62.4 ± 6.6	16/32	30.7 ± 3.6	Grade 2–4; $P > 0.05$	2.88 ± 0.67	8 mL,3 times,2 weeks	12 m
		HA	48	64.8 ± 7.7	22/26	31.0 ± 4.6		2.81 ± 0.73	60 mg/3 mL,1 time	
Wang, Y. C. 2022 [61]	China	PRP	54	61.87 ± 5.46	12/42	24.07 ± 3.35	Grade 1–2; $P > 0.05$	1.46 ± 0.50	4 ml,1 time	6 m
		HA	56	63 ± 5.33	16/40	24.02 ± 2.39		1.29 ± 0.46	3 mL,1 time,SciVision Biotech	
Wang, Z. 2022 [62]	China	PRP	42	64.9 ± 11.8	11/31	23.4 ± 4.1	NA	NA	4 ml,3 times,weekly	6 m
		HA	43	62.3 ± 8.9	9/34	22.1 ± 3.6			25 mg/2.5 ml,3 times,weekly	
Xu, Z. 2021 [63]	China	PRP	30	56.9 ± 4.2	10/20	22.5 ± 2.3	Grade 2–3; $P > 0.05$	2.53 ± 0.51	4 ml,3 times,2 weeks	24 m
		HA	20	57.1 ± 3.4	5/15	22.8 ± 2.1		2.41 ± 0.50	2 ml/20 mg,3 times,2 weeks,SOFAST	
Yaradilmis, Y. U. 2020 [64]	Turkey	PRP	60	59.62 ± 6.96	17/53	31.9 ± 5.27	Grade 2–3; $P > 0.05$	2.6 ± 0.49	1 mL,3 times,weekly	12 m
		HA	30	63.0 ± 9.2	4/26	32.4 ± 4.2		2.73 ± 0.45	20mg/2ml,3 ~ 5 times,Ostenil	
Yu, W. 2018 [65]	China	PRP	104	46.2 ± 8.6	50/54	NA	Grade 1–4	NA	NA	12 m
		HA	88	51.5 ± 9.3	48/40				NA	
General	**Patients Number: PRP/HA=1839/1821; Age: (−0.60 [−0.97, −0.23],*p*<0.01; Sex (M): 1.09 [0.94, 1.26],*p*=0.23; BMI: −0.08 [−0.22, 0.06],*p*=0.28; OA Grade: 0.00 [−0.04, 0.05],*p*=0.96**									

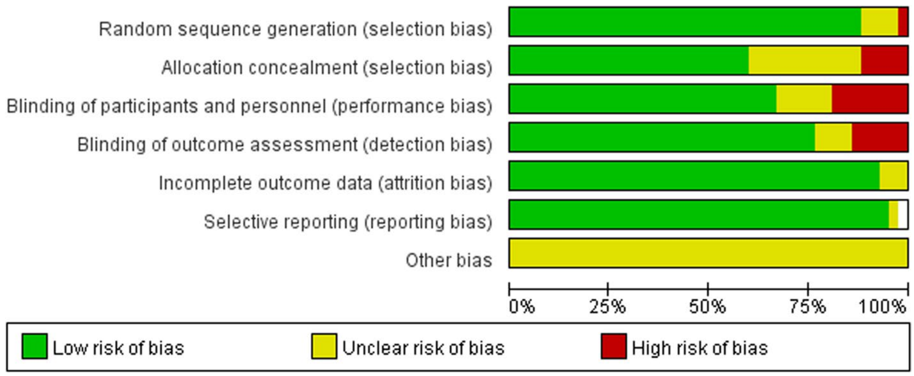

Fig. 2 Risks of bias graph

(9 RCTs, $p=0.87$, Fig. 17) or the six-month follow-up (12 RCTs, $p=0.61$, Fig. 18). However, one year later, the situation reversed, with the WOMAC stiffness score being higher in the HA group ($p<0.01$, Fig. 19).

WOMAC function score

WOMAC function score before injection was available in 16 studies. Analysisrevealed no statistic difference ($p=0.17$, Fig. 20). At the one to three-month, the function score was lower in the PRP group (9 RCTs, $p<0.01$, Fig. 21). Same trend was fobserved at the six-month follow-up (11 RCTs, $p<0.01$, Fig. 22) and one year (9 RCTs, $p<0.01$, Fig. 23).

IKDC score

Ten RCTs recorded the IKDC score before injection. No statistic difference was found ($p=0.82$, Supplementary Fig. 7.1). After intra-articular injection, the result at any follow-up point consistently showed that the IKDC score was higher in the PRP group (Supplementary Fig. 7.2, 7.3, 7.4).

KOOS score

Only 6 RCTs mentioned the KOOS score. The analysis found no statistic difference between the two groups before injection, at 6 months, or at 12 months post-injection (Supplementary Fig. 8.1, 8.2, 8.3). However, at one to three-month follow-up, the KOOS score was higher in the PRP group (6 RCTs, $p=0.03$, Supplementary Fig. 8.4).

EQ-VAS score

Only 4 RCTs reported the EQ-VAS score. The analysis found no statistic difference before the injection ($p=0.45$, Supplementary Fig. 9.1). During the first six months of follow-up, the EQ-VAS score was higher in the PRP group (Supplementary Fig. 9.2,9.3). Follow-up data at one year post-injection were not available.

Lequesne index

Six RCTs reported the Lequesne index score before injection and no statistic difference was found ($p=0.78$, Supplementary Fig. 10.1). No difference was observed at the one to three-month follow-up ($p=0.39$, Supplementary Fig. 10.2). However, at the six-month and one-year follow-ups, the score was lower in the PRP group ($p<0.01$, Supplementary Fig. 10.3, 10.4).

Satisfaction rate

Satisfaction rate was reported in only in 5 RCTs post-injection. Despite the small number of included studies, subgroup analysis was employed due to the extreme heterogeneity of one study [38]. In the remaining 4 studies, satisfaction rate was 81.2% in the PRP group and 78.92% in the HA group, with no statistic difference ($p=0.58$, Supplementary Fig. 11). In Kon, E.'s study [38], satisfaction rate was obviously higher in the PRP group (82% vs 33%).

Adverse event

Adverse events, occurring after the injection or during the follow-up, were reported in 21 RCTs. The adverse event rate was higher in the PRP group (12.86% vs 9.27%, $p=0.02$, Supplementary Fig. 12). However, all studies declared that the adverse events were mild and could be treated with oral medications or required no treatment.

Discussion

This meta-analysis was designed to compare the efficacy of the PRP and HA in the treatment of KOA within 12 months. The primary evaluating indicators included VAS score and WOMAC score (total score, pain score, stiffness score). Additional recorded measures were EQ-VAS score, Lequesne index, satisfaction rate, IKDC score, and adverse events. Statistical analysis indicated that PRP, in

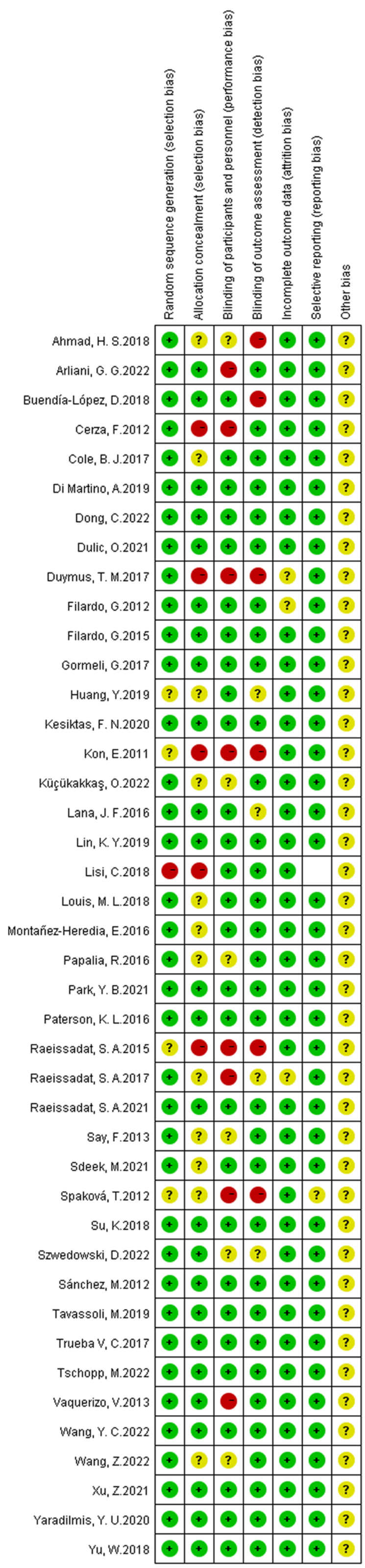

Fig. 3 Risks of bias summary

some respects, achieved better performance compared to HA.

Pain is typically the chief complaint of KOA patients. The analgesia effect assessment of injection is a crucial indicator. PRP achieves lower VAS score at all follow-up times within 12 months. Regarding another assessment criterion, WOMAC pain score, the analysis showed no statistic difference between the two groups during the first three months of follow-up. However, the WOMAC pain score was lower in the PRP group at six months and one year post injection. Last year, Khalid S and colleagues published a systematic review on a similar topic. They found that PRP treatment resulted in significant pain relief compared to HA injections, as evidenced by improved WOMAC pain and VAS scores, with the most significant improvement observed at 6 months [19]. Costa LAV's review also reported that at 6-month follow-up, PRP was as effective as and, in some studies, more effective than other therapies in terms of pain, function, and stiffness [66]. These findings are consistent with our clinical experience, where patients often report better pain relief after using PRP.

Analysis of WOMAC stiffness and function score indicated that PRP performed better. The WOMAC stiffness score was lower in the HA group before injection, and showed no statistic difference three months post-injection. However, one year later, it was higher in the HA group, reversing initial trend. The WOMAC function score showed no statistic difference before injection but was lower in the PRP group in subsequent evaluations within 12 months.

The IKDC score was used to comprehensively evaluate the subjective symptoms and objective signs of KOA patients. KOOS score is a scale assessing the extent of knee injury and the effectiveness of treatment for osteoarthropathy. This scale evaluates pain, symptoms, the ability to perform activities of daily living, sports and recreation, and life quality related to the knee joint in KOA patients. EQ-VAS score was used to measure the general health of the patients. Lequesne index, initially developed in France, is a tool for assessing the severity and functional status of KOA patients. Though these scales were less used than the VAS score and WOMAC score in the included studies, data analysis showed better performance of PRP. Satisfaction rate was available only in 5 RCTS, with most showing no statistic difference between the two groups. However, in Kon, E.'s study [38], the satisfaction rate was significantly higher in the PRP group.

According to the review and analysis, the adverse event rate was higher in the PRP group. It was declared that the adverse events were all mild, which could be treated with oral medications or required no therapy. Both treatment

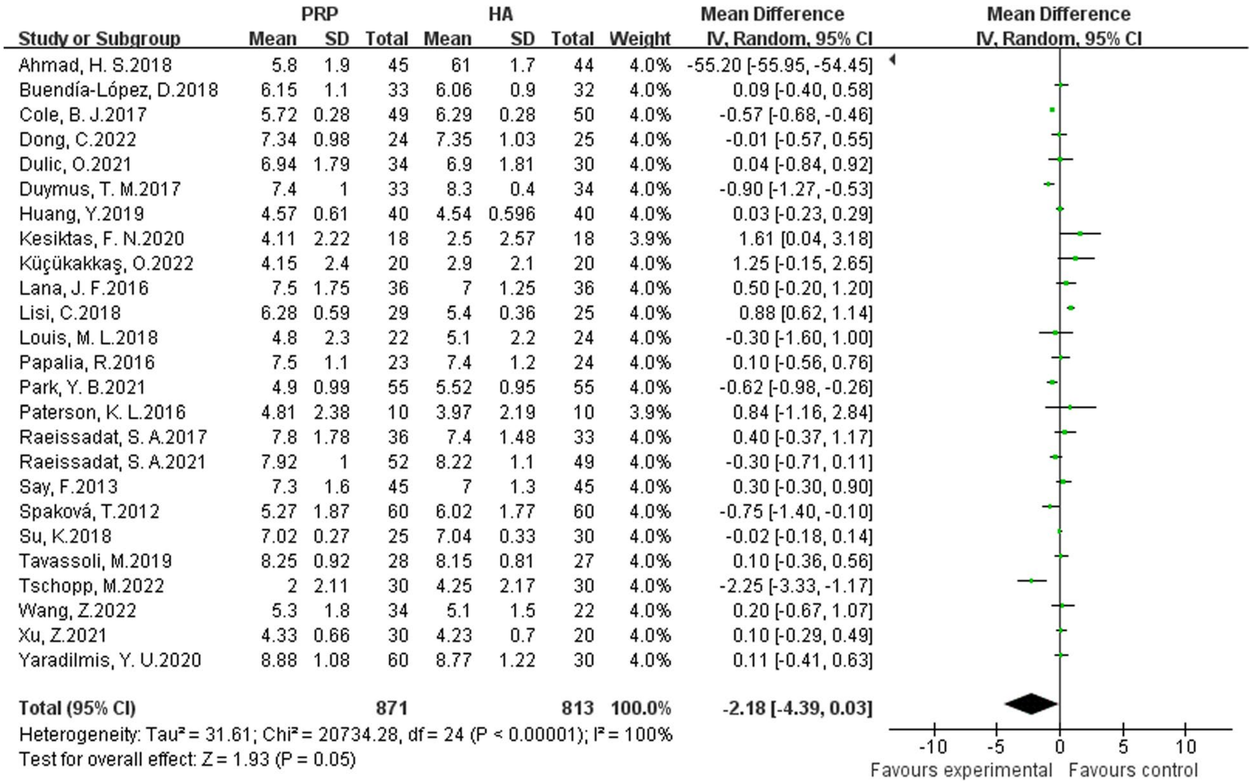

Fig. 4 VAS score before treatment

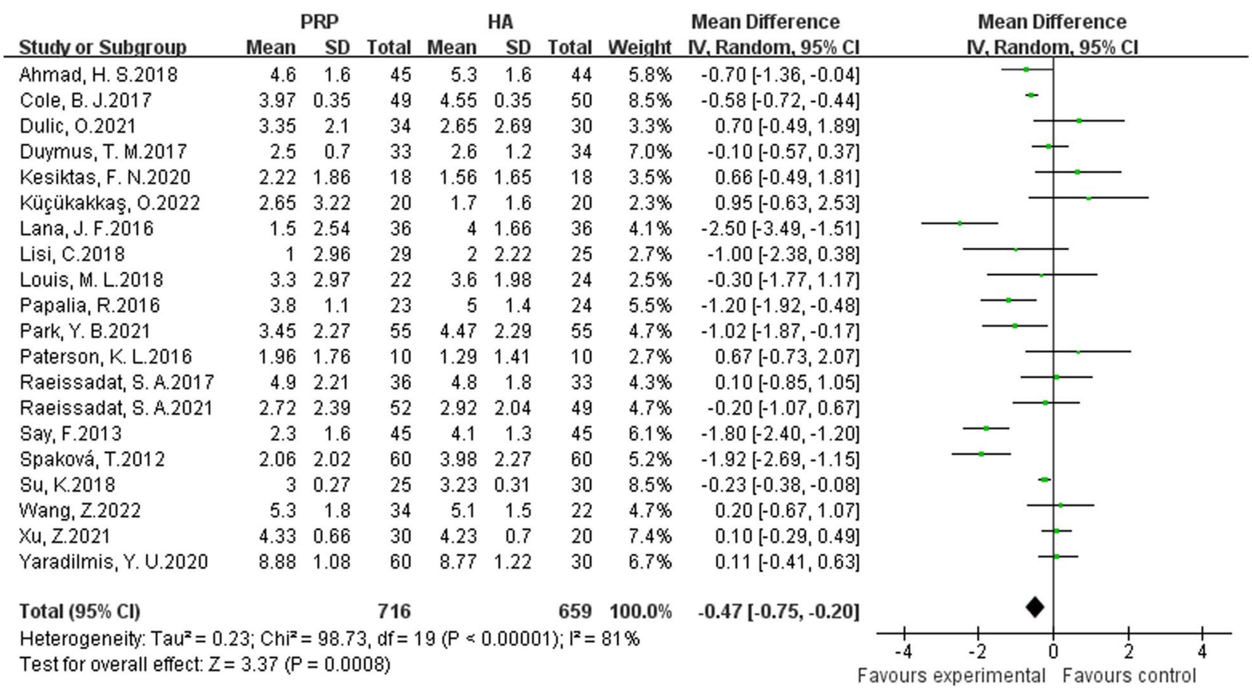

Fig. 5 VAS score, 3 months after treatment

Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI
Ahmad, H. S.2018	4.14	1.44	45	5.95	1.52	44	6.1%	-1.81 [-2.43, -1.19]
Buendía-López, D.2018	4.9	0.52	33	5.21	0.6	32	7.0%	-0.31 [-0.58, -0.04]
Cole, B. J.2017	3.44	0.33	49	4.85	0.38	50	7.2%	-1.41 [-1.55, -1.27]
Duymus, T. M.2017	4	1.3	33	4.3	1.3	34	6.1%	-0.30 [-0.92, 0.32]
Huang, Y.2019	0.99	3.79	40	1.07	3.68	40	3.1%	-0.08 [-1.72, 1.56]
Küçükakkaş, O.2022	2.35	1.92	20	1.4	1.88	20	4.3%	0.95 [-0.23, 2.13]
Lana, J. F.2016	2.5	2.18	36	4	3.15	36	4.0%	-1.50 [-2.75, -0.25]
Lisi, C.2018	1	1.48	29	2	2.22	25	4.7%	-1.00 [-2.02, 0.02]
Papalia, R.2016	2.9	0.8	23	3.3	0.9	24	6.5%	-0.40 [-0.89, 0.09]
Park, Y. B.2021	2.81	2.28	55	4.16	2.14	55	5.4%	-1.35 [-2.18, -0.52]
Raeissadat, S. A.2017	4.6	2.78	36	4.8	2.39	33	4.1%	-0.20 [-1.42, 1.02]
Raeissadat, S. A.2021	3.32	2.1	52	4.02	2.04	49	5.5%	-0.70 [-1.51, 0.11]
Say, F.2013	1.7	1.4	45	3	1	45	6.5%	-1.30 [-1.80, -0.80]
Spaková, T.2012	2.69	1.86	60	4.3	2.07	60	5.8%	-1.61 [-2.31, -0.91]
Su, K.2018	4.26	0.35	25	4.44	0.64	30	7.0%	-0.18 [-0.45, 0.09]
Wang, Z.2022	4.1	1.4	34	4.7	1.8	22	5.2%	-0.60 [-1.49, 0.29]
Xu, Z.2021	1.92	0.75	30	4.4	0.88	20	6.6%	-2.48 [-2.95, -2.01]
Yaradilmis, Y. U.2020	2.4	1.84	70	3.7	2.51	30	4.8%	-1.30 [-2.30, -0.30]
Total (95% CI)			**715**			**649**	**100.0%**	**-0.92 [-1.29, -0.54]**

Heterogeneity: Tau² = 0.50; Chi² = 168.82, df = 17 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.77 (P < 0.00001)

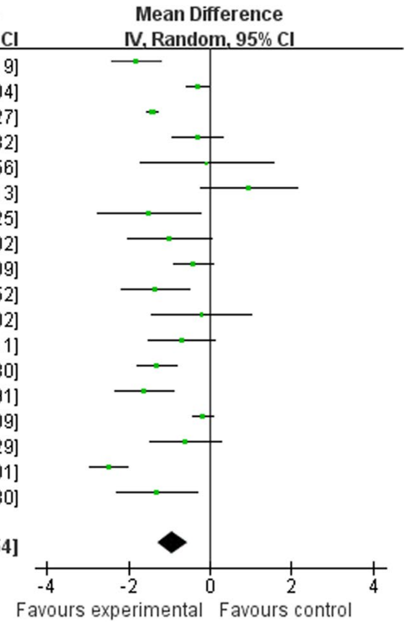

Fig. 6 VAS score, 6 months after treatment

Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI
Buendía-López, D.2018	5.03	1.7	33	6.25	0.4	32	8.4%	-1.22 [-1.82, -0.62]
Cole, B. J.2017	4.37	0.48	49	5.95	0.37	50	10.0%	-1.58 [-1.75, -1.41]
Dong, C.2022	1.72	0.53	24	3.24	0.67	25	9.5%	-1.52 [-1.86, -1.18]
Duymus, T. M.2017	5.1	1.3	33	6.8	0.1	34	9.1%	-1.70 [-2.14, -1.26]
Lana, J. F.2016	2.5	2.18	36	5	2.6	36	5.9%	-2.50 [-3.61, -1.39]
Lisi, C.2018	0	1.48	29	1	2.22	25	6.3%	-1.00 [-2.02, 0.02]
Papalia, R.2016	3.2	0.7	23	3.4	0.8	24	9.2%	-0.20 [-0.63, 0.23]
Raeissadat, S. A.2021	4.62	2.39	52	5.62	1.73	49	7.3%	-1.00 [-1.81, -0.19]
Su, K.2018	4.78	0.19	25	5.45	0.38	30	10.0%	-0.67 [-0.83, -0.51]
Wang, Z.2022	4.9	1	34	5.8	0.8	22	9.0%	-0.90 [-1.37, -0.43]
Xu, Z.2021	1.88	0.52	30	4.47	0.71	20	9.5%	-2.59 [-2.95, -2.23]
Yaradilmis, Y. U.2020	3.2	2.51	60	4.97	2.67	30	5.7%	-1.77 [-2.92, -0.62]
Total (95% CI)			**428**			**377**	**100.0%**	**-1.36 [-1.77, -0.94]**

Heterogeneity: Tau² = 0.44; Chi² = 158.00, df = 11 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.42 (P < 0.00001)

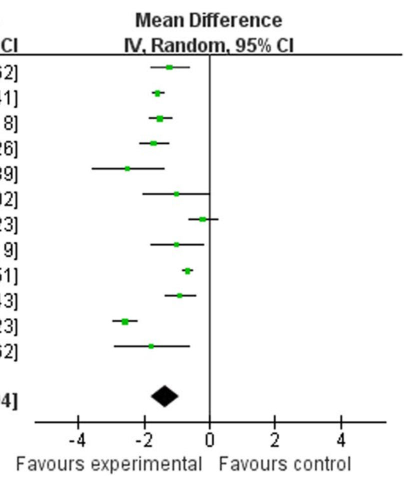

Fig. 7 VAS score, 12 months after treatment

methods were effective in improving pain and function over the study period and proven to be safe.

Though it was demonstrated that intra-articular injections (PRP and HA) were beneficial for pain treatment and function recovery in KOA patients, their effects tend to deteriorate over time and virtually disappear after the treatment [16, 26, 30]. Filardo's study declared that the effect of PRP or HA remain virtually stable nearly two months [16]. However, Sdeek, M. found the opposite conclusion, indicating that the benefits could persist for nearly one and half a year. PRP was found to be even better, although a second injection was required by the third year [53].This meta-analysis compared the treatment effect of PRP and HA for KOA patients only within 12 months, with no longer follow-up data available for analysis. It appears that both PRP and HA lose their therapeutic effects 6 months after injection, particularly HA.

Biochemical changes in articular cartilage are the primary features of KOA. This degenerative disease leads to progressive joint cartilage destruction and has a very limited self-renewal and repair capability.

HA is widely present in human tissues, particularly in synovial fluid, where it lubricates joint to prevent cartilage mechanical degradation. The synthesis and

Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI
Arliani, G. G.2022	42.5	17.9	14	41.1	15.5	15	1.2%	1.40 [-10.82, 13.62]
Buendía-López, D.2018	42.57	7.3	33	42.62	7.3	32	4.9%	-0.05 [-3.60, 3.50]
Cerza, F.2012	79.6	9.2	60	75.4	10.8	60	4.8%	4.20 [0.61, 7.79]
Dong, C.2022	69.54	12.83	24	72.63	11.49	25	2.8%	-3.09 [-9.92, 3.74]
Dulic, O.2021	48.12	17.02	34	46.41	14.98	30	2.3%	1.71 [-6.13, 9.55]
Duymus, T. M.2017	76.1	9.4	33	77	2.5	34	5.1%	-0.90 [-4.22, 2.42]
Huang, Y.2019	48.19	4.96	40	47.23	5.37	40	5.9%	0.96 [-1.31, 3.23]
Kesiktas, F. N.2020	61	26.6	18	44.7	15	18	0.9%	16.30 [2.19, 30.41]
Küçükakkaş, O.2022	50.8	20.4	20	53.4	13.1	20	1.5%	-2.60 [-13.23, 8.03]
Lin, K. Y.2019	52.81	18.14	31	52.67	18.06	29	1.9%	0.14 [-9.02, 9.30]
Lisi, C.2018	36.96	3.33	29	28.48	2.22	25	6.4%	8.48 [6.99, 9.97]
Louis, M. L.2018	36.5	16.8	24	34.7	21.8	24	1.4%	1.80 [-9.21, 12.81]
Park, Y. B.2021	38.6	15.4	55	33	11.8	55	3.7%	5.60 [0.47, 10.73]
Raeissadat, S. A.2015	39.5	17.06	77	28.69	16.69	62	3.4%	10.81 [5.17, 16.45]
Raeissadat, S. A.2017	42.9	13.51	36	38.8	12.62	33	3.1%	4.10 [-2.07, 10.27]
Raeissadat, S. A.2021	42.73	7.7	52	42.75	11.1	49	4.7%	-0.02 [-3.77, 3.73]
Spaková, T.2012	38.76	16.5	60	43.21	13.7	60	3.5%	-4.45 [-9.88, 0.98]
Su, K.2018	50.17	1.6	25	49.88	1.54	30	6.7%	0.29 [-0.54, 1.12]
Szwedowski, D.2022	53.84	14.96	25	53.92	15.19	24	2.1%	-0.08 [-8.53, 8.37]
Sánchez, M.2012	121.8	44.4	89	115.6	45.1	87	1.0%	6.20 [-7.02, 19.42]
Tavassoli, M.2019	63.71	9.87	56	63.11	8.94	54	4.9%	0.60 [-2.92, 4.12]
Trueba V, C.2017	54.8	11.26	10	58.7	16.43	30	1.9%	-3.90 [-13.03, 5.23]
Vaquerizo, V.2013	45.9	12.7	48	50.8	18.4	48	3.0%	-4.90 [-11.22, 1.42]
Wang, Y. C.2022	18.74	1.85	54	18.23	1.8	56	6.7%	0.51 [-0.17, 1.19]
Wang, Z.2022	37.8	13.7	34	37.5	11.4	22	2.9%	0.30 [-6.33, 6.93]
Xu, Z.2021	100	4	30	102.5	2.8	20	6.1%	-2.50 [-4.39, -0.61]
Yaradilmis, Y. U.2020	81.9	11.28	60	79.17	13.27	30	3.5%	2.73 [-2.81, 8.27]
Yu, W.2018	36.21	17.53	104	37.41	16.72	88	3.9%	-1.20 [-6.05, 3.65]
Total (95% CI)			**1175**			**1100**	**100.0%**	**1.24 [-0.23, 2.71]**

Heterogeneity: Tau² = 8.25; Chi² = 151.78, df = 27 (P < 0.00001); I² = 82%

Test for overall effect: Z = 1.65 (P = 0.10)

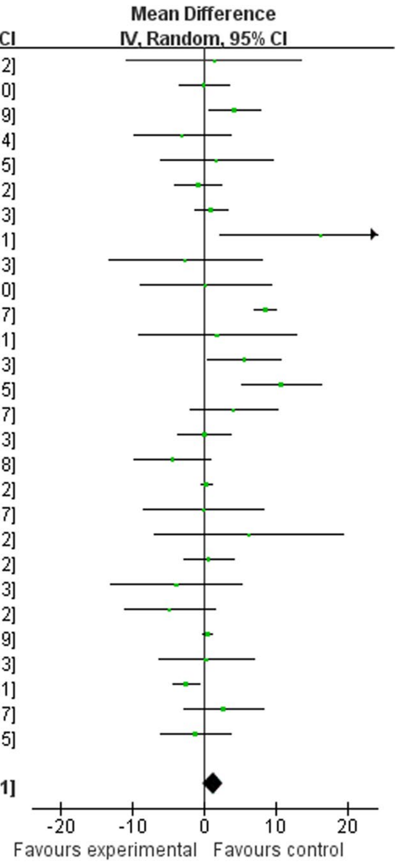

Fig. 8 WOMAC total score before treatment

Study or Subgroup	PRP Mean	PRP SD	PRP Total	HA Mean	HA SD	HA Total	Weight	Mean Difference IV, Random, 95% CI
Arliani, G. G.2022	29	16	14	24	14.6	15	1.3%	5.00 [-6.17, 16.17]
Cerza, F.2012	49.6	17.7	60	55.2	12.3	60	4.2%	-5.60 [-11.05, -0.15]
Dulic, O.2021	35.8	19.8	34	41.17	18.77	30	1.7%	-5.37 [-14.83, 4.09]
Duymus, T. M.2017	26.4	9.5	33	33.2	12.2	34	4.4%	-6.80 [-12.03, -1.57]
Huang, Y.2019	25.15	5.24	40	25.02	4.98	40	10.3%	0.13 [-2.11, 2.37]
Kesiktas, F. N.2020	24	25.7	18	22.3	15.1	18	0.9%	1.70 [-12.07, 15.47]
Küçükakkaş, O.2022	33.5	13.65	20	42.3	10.14	20	2.6%	-8.80 [-16.25, -1.35]
Lin, K. Y.2019	20.64	10.75	31	20.92	11.27	29	4.1%	-0.28 [-5.86, 5.30]
Lisi, C.2018	9	6.67	29	17	10.37	25	5.1%	-8.00 [-12.73, -3.27]
Louis, M. L.2018	26.8	16.2	24	24.9	16.6	24	1.8%	1.90 [-7.38, 11.18]
Park, Y. B.2021	28.9	9	55	27.9	11.17	55	6.6%	1.00 [-2.79, 4.79]
Raeissadat, S. A.2017	26.8	13.45	36	27.8	11.01	33	3.8%	-1.00 [-6.78, 4.78]
Raeissadat, S. A.2021	25.53	11.15	52	26.35	6.85	49	7.0%	-0.82 [-4.41, 2.77]
Spaková, T.2012	14.35	14.18	60	26.17	17.47	60	3.9%	-11.82 [-17.51, -6.13]
Su, K.2018	30.63	1.73	25	31.68	1.89	30	13.5%	-1.05 [-2.01, -0.09]
Wang, Y. C.2022	14.96	1.6	54	16.16	2.04	56	14.0%	-1.20 [-1.88, -0.52]
Wang, Z.2022	19.9	8.2	34	24.2	9.6	22	4.9%	-4.30 [-9.17, 0.57]
Xu, Z.2021	99.2	3	30	95.6	6.7	20	8.0%	3.60 [0.47, 6.73]
Yaradilmis, Y. U.2020	43.2	18.19	60	46.5	21.9	30	1.8%	-3.30 [-12.39, 5.79]
Total (95% CI)			**709**			**650**	**100.0%**	**-1.94 [-3.26, -0.61]**

Heterogeneity: Tau² = 3.13; Chi² = 48.43, df = 18 (P = 0.0001); I² = 63%

Test for overall effect: Z = 2.87 (P = 0.004)

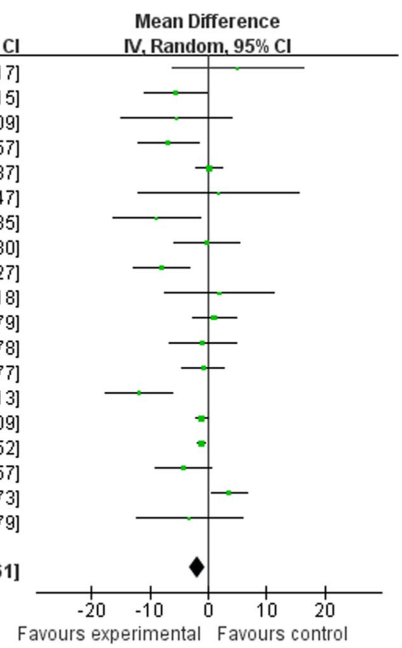

Fig. 9 WOMAC total score, 3 months after treatment

	PRP			HA				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Arliani, G. G.2022	41.1	24.8	14	35.7	35.7	15	0.7%	5.40 [-16.85, 27.65]
Buendía-López, D.2018	33.6	1.2	33	37.3	1.2	32	7.0%	-3.70 [-4.28, -3.12]
Cerza, F.2012	36.5	17.9	60	65.1	10.6	60	4.6%	-28.60 [-33.86, -23.34]
Dulic, O.2021	31.21	21.26	34	37.71	16.31	30	2.6%	-6.50 [-15.73, 2.73]
Duymus, T. M.2017	42.8	7.1	33	44.5	6.6	34	5.8%	-1.70 [-4.98, 1.58]
Huang, Y.2019	21.14	5.17	40	26.38	5.2	40	6.4%	-5.24 [-7.51, -2.97]
Küçükakkaş, O.2022	35	11.28	20	42.5	17.54	20	2.7%	-7.50 [-16.64, 1.64]
Lin, K. Y.2019	19.92	10.76	31	24.81	11.27	29	4.4%	-4.89 [-10.47, 0.69]
Lisi, C.2018	6	7.41	29	14	12.59	25	4.3%	-8.00 [-13.62, -2.38]
Louis, M. L.2018	27.4	22	24	26.6	26	24	1.5%	0.80 [-12.83, 14.43]
Park, Y. B.2021	32.2	17.24	55	26.5	11.17	55	4.5%	5.70 [0.27, 11.13]
Raeissadat, S. A.2017	24.4	16.54	36	27.4	11.38	33	3.8%	-3.00 [-9.65, 3.65]
Raeissadat, S. A.2021	23.73	11.15	52	28.05	6.85	49	5.6%	-4.32 [-7.91, -0.73]
Spaková, T.2012	18.85	14.09	60	30.9	16.57	60	4.4%	-12.05 [-17.55, -6.55]
Su, K.2018	34.37	1.22	25	38.84	1.6	30	6.9%	-4.47 [-5.22, -3.72]
Szwedowski, D.2022	24.1	6.3	25	34.9	4.2	24	6.0%	-10.80 [-13.79, -7.81]
Sánchez, M.2012	86.7	24.13	79	83.1	24.37	74	3.3%	3.60 [-4.09, 11.29]
Trueba V, C.2017	30.4	29.74	10	30.5	18.15	30	0.8%	-0.10 [-19.64, 19.44]
Vaquerizo, V.2013	27.2	15.1	48	50.4	23.2	48	3.2%	-23.20 [-31.03, -15.37]
Wang, Y. C.2022	14.39	1.56	54	13.88	1.91	56	7.0%	0.51 [-0.14, 1.16]
Wang, Z.2022	22.3	7.6	34	31.5	11.6	22	4.4%	-9.20 [-14.68, -3.72]
Xu, Z.2021	93.5	5.2	30	100.4	4	20	6.2%	-6.90 [-9.46, -4.34]
Yaradilmis, Y. U.2020	37.67	17.13	60	44.17	12.01	30	4.1%	-6.50 [-12.60, -0.40]
Total (95% CI)			**886**			**840**	**100.0%**	**-6.16 [-8.06, -4.26]**

Heterogeneity: Tau² = 13.40; Chi² = 323.80, df = 22 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.35 (P < 0.00001)

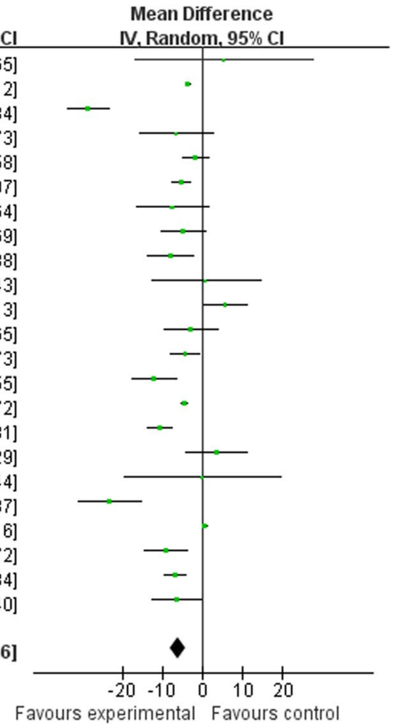

Fig. 10 WOMAC total score, 6 months after treatment

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Buendía-López, D.2018	34.51	1.2	33	42.65	0.9	32	11.1%	-8.14 [-8.65, -7.63]
Dong, C.2022	18.54	4.17	24	28.96	5.75	25	9.3%	-10.42 [-13.22, -7.62]
Dulic, O.2021	31.06	23.34	34	35.29	17.39	30	3.1%	-4.23 [-14.24, 5.78]
Duymus, T. M.2017	54.9	10.8	33	69.3	4.3	34	7.9%	-14.40 [-18.36, -10.44]
Huang, Y.2019	16.1	7.22	40	30.64	8.36	40	8.5%	-14.54 [-17.96, -11.12]
Lin, K. Y.2019	19.16	20.67	31	26.69	21.51	29	2.8%	-7.53 [-18.22, 3.16]
Lisi, C.2018	4	5.19	29	14	16.3	25	5.2%	-10.00 [-16.66, -3.34]
Raeissadat, S. A.2015	18.44	14.35	77	27.46	16.36	62	6.5%	-9.02 [-14.20, -3.84]
Raeissadat, S. A.2021	13.6	30.56	52	17.2	27.54	49	2.6%	-3.60 [-14.93, 7.73]
Su, K.2018	39.97	2.93	25	43.4	2.35	30	10.6%	-3.43 [-4.85, -2.01]
Trueba V, C.2017	30	35.11	10	29.1	23.83	30	0.7%	0.90 [-22.47, 24.27]
Vaquerizo, V.2013	30.8	15.5	48	54.2	19.2	48	4.9%	-23.40 [-30.38, -16.42]
Wang, Z.2022	38.8	8.6	34	44.6	9.9	22	6.7%	-5.80 [-10.85, -0.75]
Xu, Z.2021	93.5	5.3	30	100.4	3.5	20	9.7%	-6.90 [-9.34, -4.46]
Yaradilmis, Y. U.2020	42.83	20.67	60	51.33	21.89	30	3.4%	-8.50 [-17.92, 0.92]
Yu, W.2018	20.25	15.2	104	26.4	16.98	88	7.2%	-6.15 [-10.75, -1.55]
Total (95% CI)			**664**			**594**	**100.0%**	**-9.07 [-11.13, -7.01]**

Heterogeneity: Tau² = 9.91; Chi² = 89.63, df = 15 (P < 0.00001); I² = 83%
Test for overall effect: Z = 8.62 (P < 0.00001)

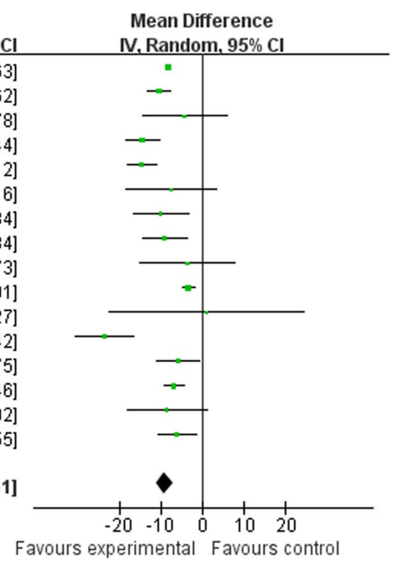

Fig. 11 WOMAC total score, 12 months after treatment

degradation of HA are abnormal in KOA patients, leading to reduced HA concentration and molecular weight. This lesion decreases the bioviscolelasticity of synovial fluid and damages cartilage. HA also has the anti-inflammatory effects to relieve pain and reduce damage [39]. However, HA can only alleviate pain and inflammation; it cannot prevent the degeneration and destruction of articular cartilage. Moreover, its effect tend to deteriorate gradually within one to six months, and the patients may return to their pre-treatment status [67].

PRP injections, as an alternative to HA, can relieve pain in patients with mild KOA. PRP's regenerative and

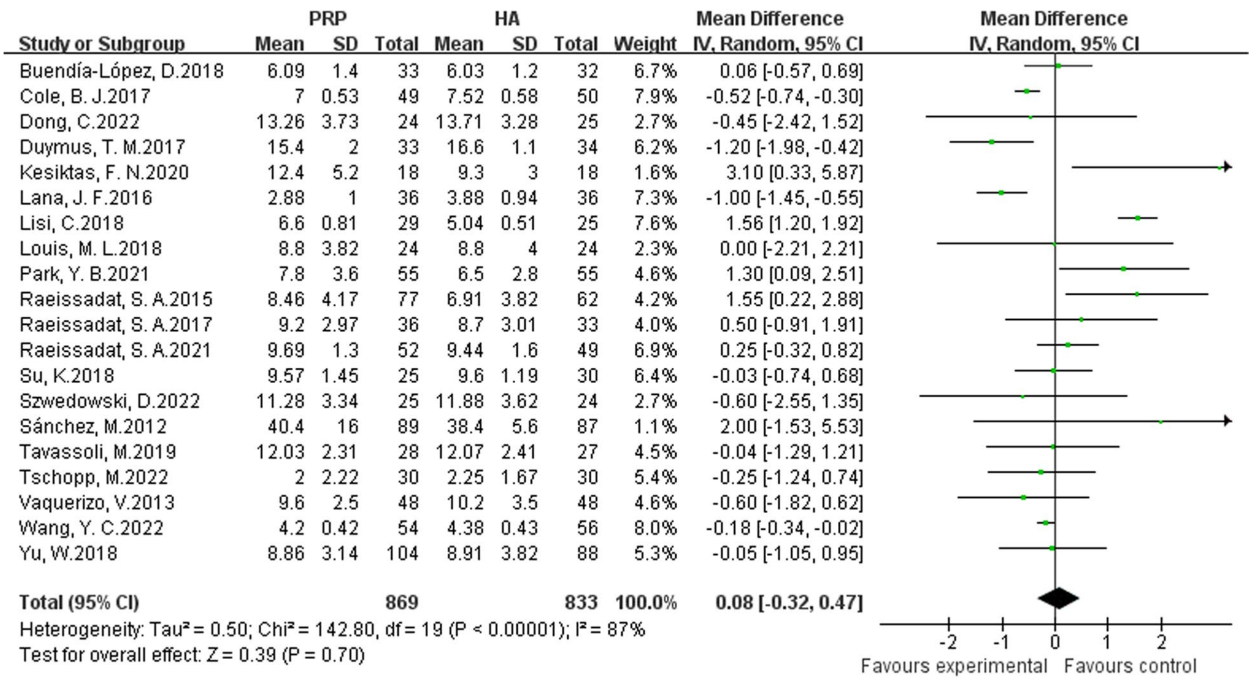

Fig. 12 WOMAC pain score before treatment

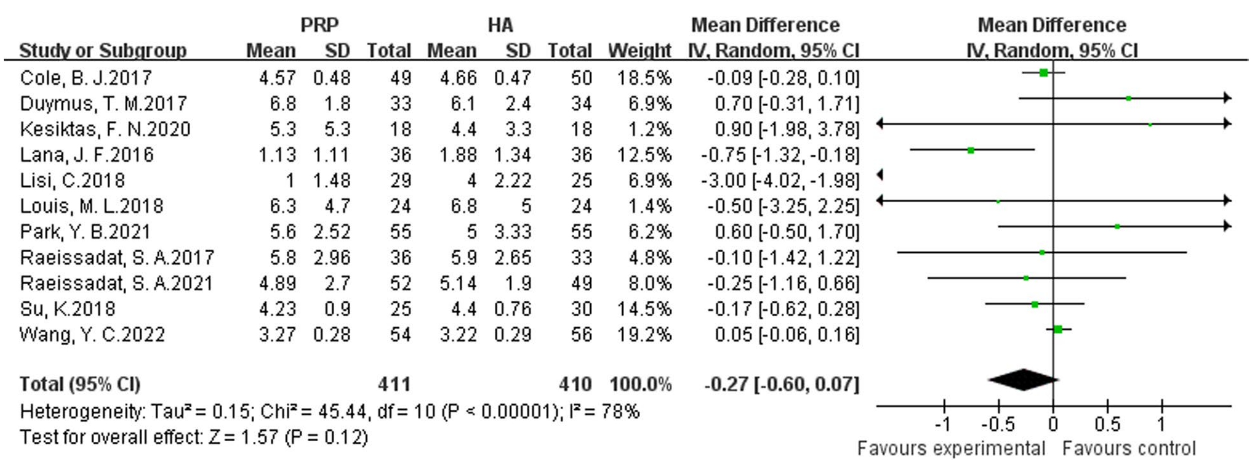

Fig. 13 WOMAC pain score, 3 months after treatment

anti-inflammatory effects are biochemically significant in cartilage repair. Macrophages and growth factors released by PRP can help to repair and regenerate articular cartilage, destroy necrotic tissue and reduce inflammatory response [22, 68]. In PRP, concentrated platelet-derived growth factors can stimulate chondrocyte proliferation and matrix secretion, and reduce the inflammatory factors expression and chondrocytes apoptosis [24]. PRP is also believed to stimulate the migration and proliferation of mesenchymal stem cells and their differentiation into joint chondrocytes, thereby ameliorating cartilage degeneration [39]. The controversial effects of PRP may be attributed to the different components of PRP used in various studies, particularly the concentration of white blood cells. Based on the concentration of white blood cells, PRP can be roughly categorized into two categories, leukocyte- and platelet-rich plasma (L-PRP) and pure platelet-rich plasma (P-PRP) [69]. The concentrations of IL-1βand TNF-α in PRP are closely related to the concentration of leukocyte, and they should perform adverse effects on chondrocytes [70, 71]. Therefore, the high concentration of leukocytes in L-PRP may adversely affect

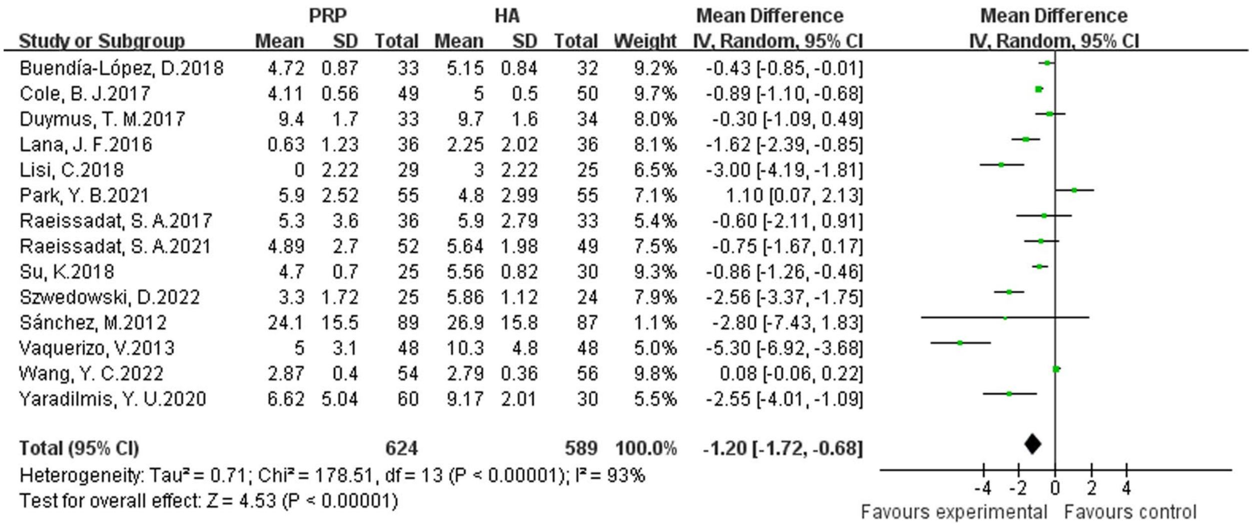

Fig. 14 WOMAC pain score, 6 months after treatment

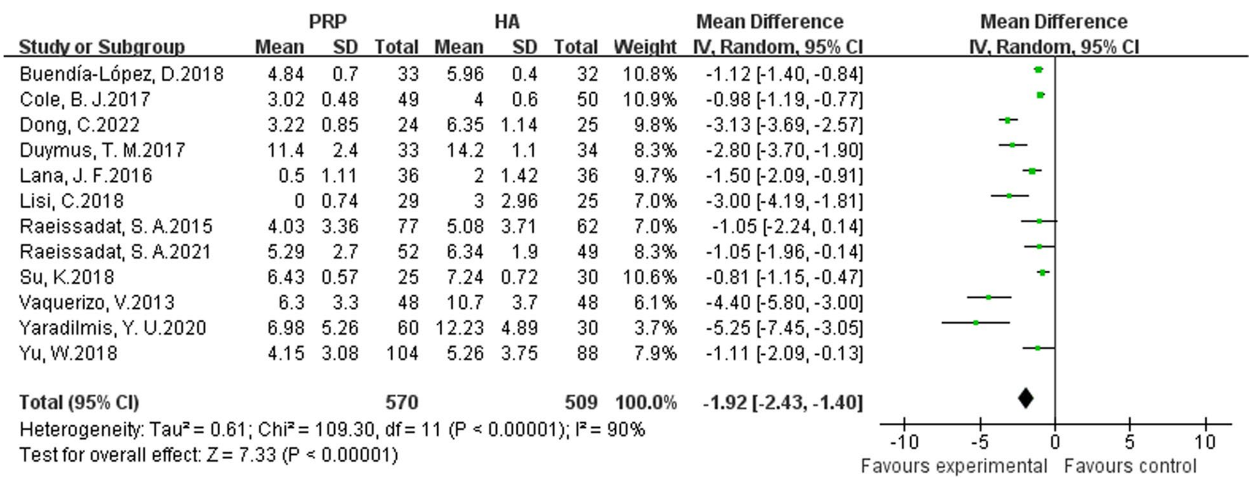

Fig. 15 WOMAC pain score, 12 months after treatment

cartilage repair by releasing IL-1β and TNF-α, potentially counteracting the positive effects of growth factors on cartilage repair and ultimately impacting the efficacy of L-PRP in treating osteoarthritis.

Clinicians tend to administer regular, multiple injections to stabilize the effect of PRP or HA. A new treatment combining HA and PRP has been proposed. Xu,Z and his team found the combination of HA and PRP is more effective than PRP or HA alone in inhibiting synovial inflammation and can effectively improve pain and function while reducing adverse reactions [63]. Gao et al. found the combination did not differ significantly from PRP alone but performed better than HA monotherapy with a lower incidence of adverse events [72]. Michelangelo Palco and his group combined HA and PRP in the conservative treatment of KOA and hip osteoarthritis (HOA) [73, 74]. They found the combination showed better results in improving knee mobility and function, while for HOA, L-PRP demonstrated better results in reducing VAS score over time. Li, B. performed a network meta-analysis in 2020 and found the combination with best clinical efficacy in improving physical performance, stiffness, and total scores, while PRP alone was more effective in relieving pain [75]. However, another review published in 2022 did not confirm the superior therapeutic effect of such combination, but considered it safer than PRP injections alone, based on the incidence of adverse events [76]. Further research is needed to determine whether the combination of HA and PRP is a better treatment option.

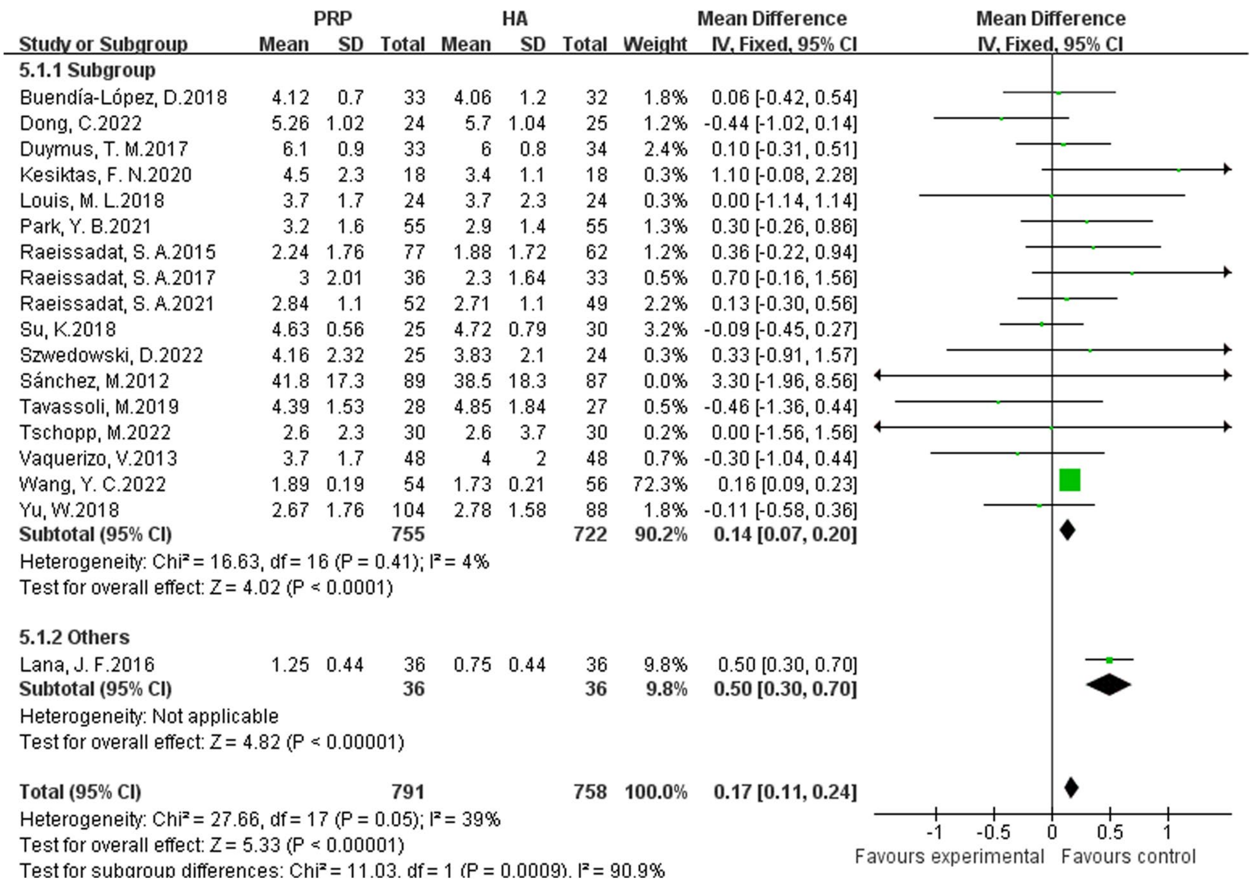

Fig. 16 WOMAC Stiffness score before treatment

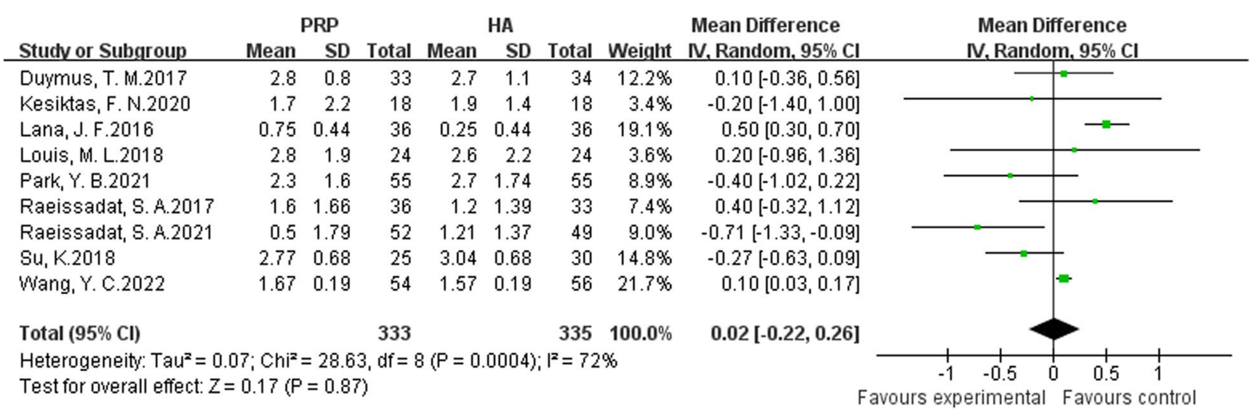

Fig. 17 WOMAC Stiffness score, 3 months after treatment

Patients with mild, moderate or severe OA should respond differently to injections. However, in this review, the clinical outcomes were not analyzed according to the KL-grade. Consequently, this review was unable to assess the effects in KOA patients with different KL-grades. Furthermore, the published studies vary in terms of injection frequency, making direct comparisons challenging. This variability may explain the differences in outcome. Intra-articular injections, with strong placebo effect, made subjective evaluation indices such as pain, stiffness and satisfaction susceptible more susceptible to bias. Significant heterogeneity in some of the analyses suggests the

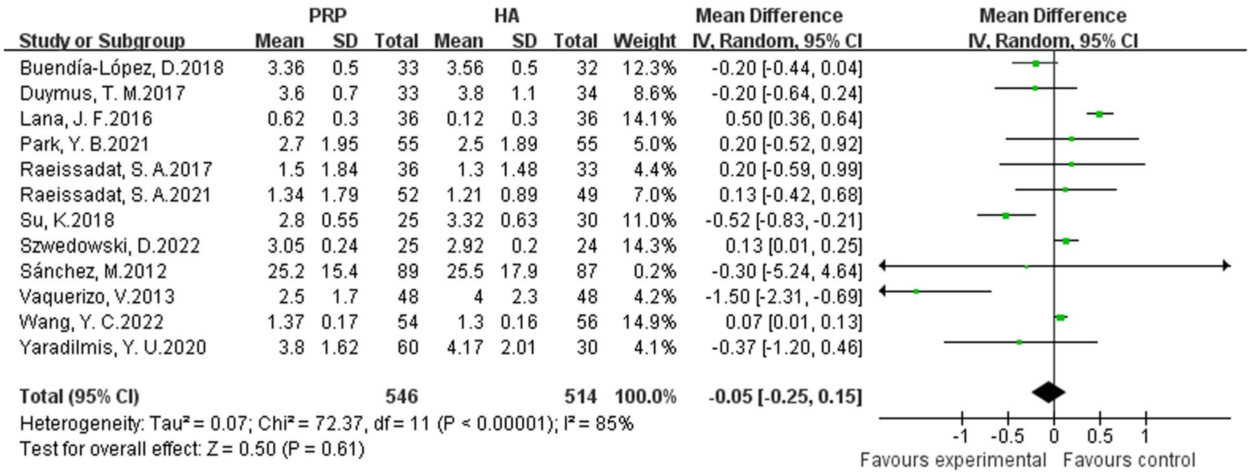

Fig. 18 WOMAC Stiffness score, 6 months after treatment

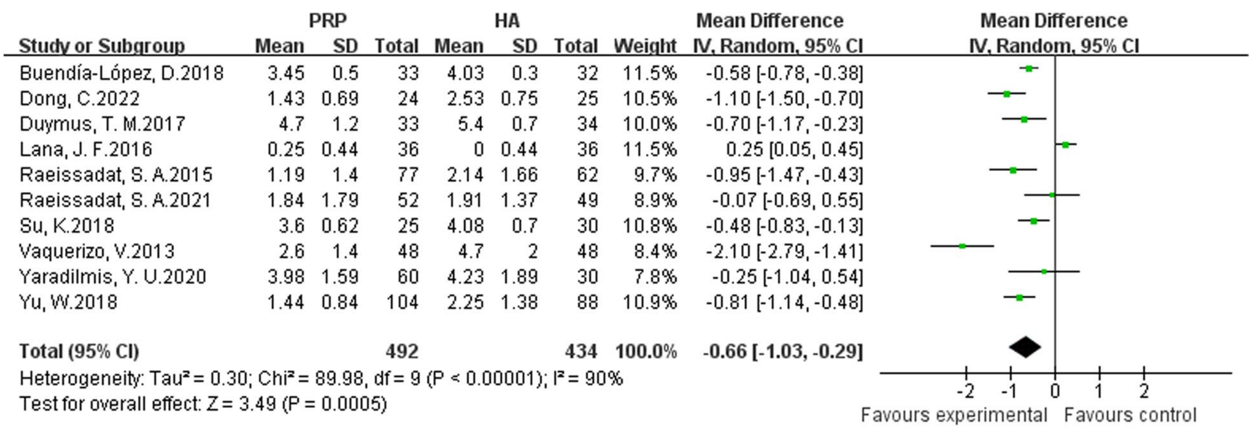

Fig. 19 WOMAC Stiffness score, 12 months after treatment

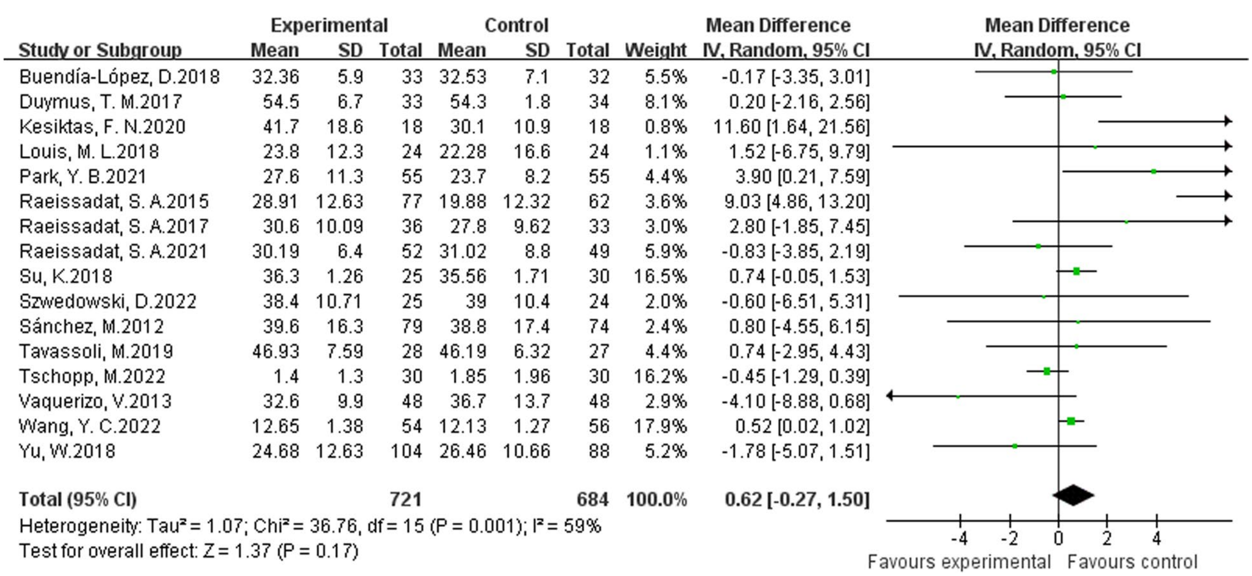

Fig. 20 WOMAC Function score before treatment

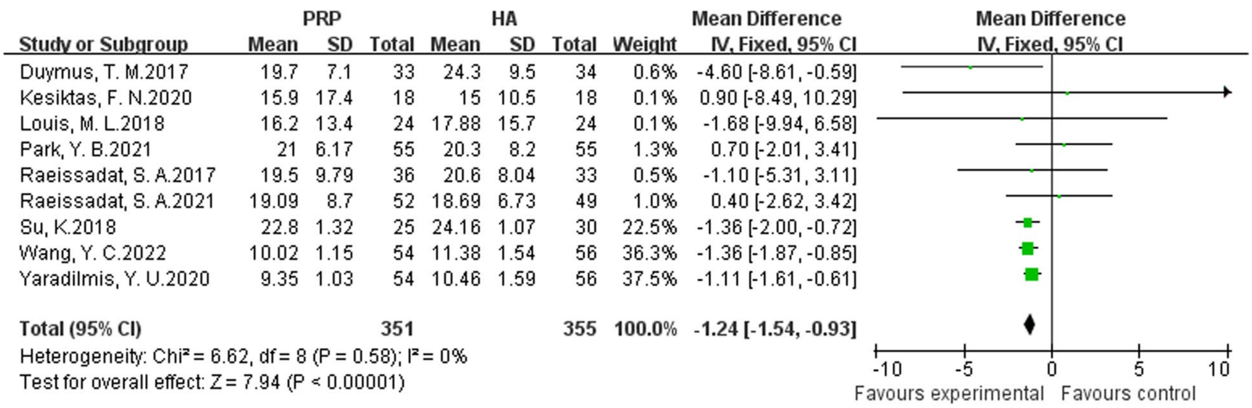

Fig. 21 WOMAC Function score, 3 months after treatment

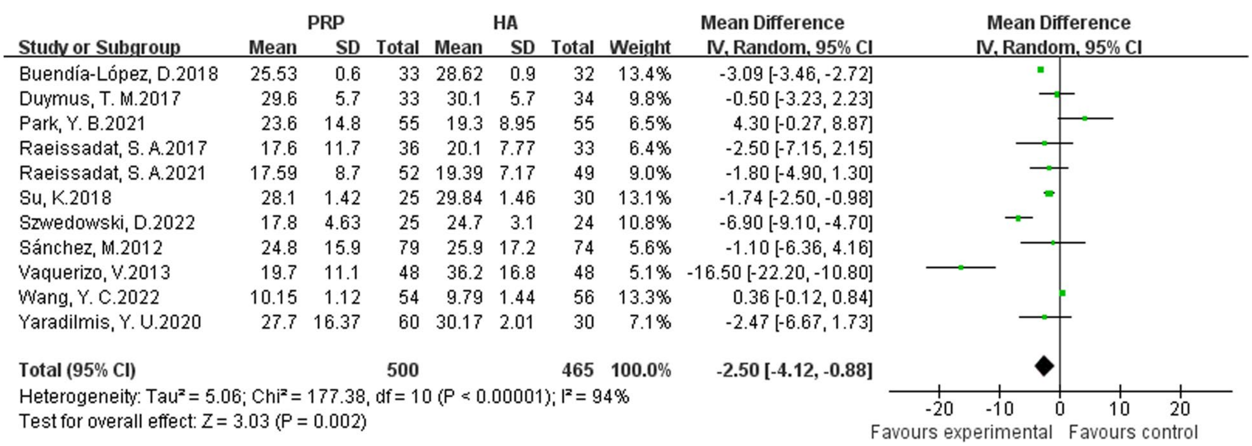

Fig. 22 WOMAC Function score, 6 months after treatment

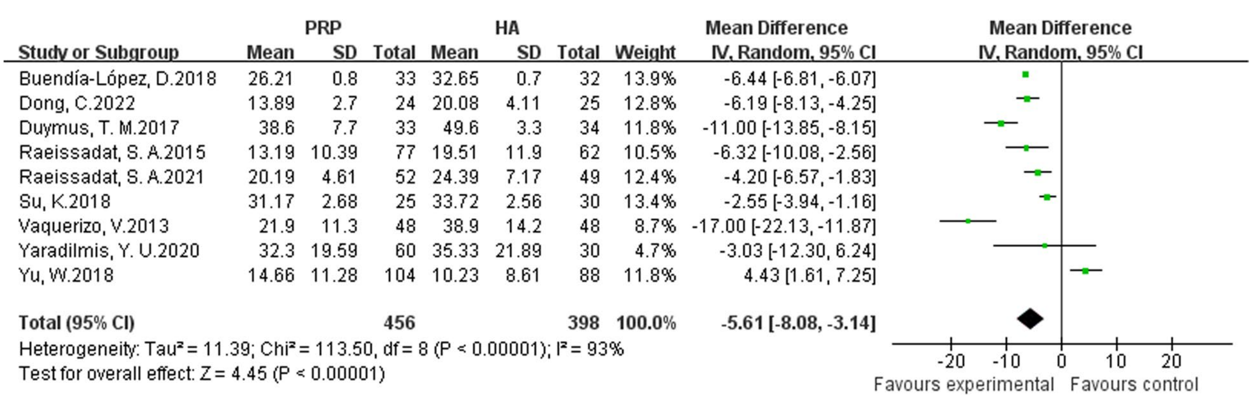

Fig. 23 WOMAC Function score, 12 months after treatment

evidence is mixed in certain areas. The reasons of this heterogeneity are diverse, primarily including variations in PRP preparation methods, differences in hyaluronic acid molecular weight and concentration, and differences in patient characteristics (age, BMI, OA grade) across studies. Khalid S [19] highlighted similar issues, noting the presence of high unexplained heterogeneity. 'Caution is advised when interpreting the results, and additional studies are required to gain a more thorough and unbiased understanding of the topic'.

Conclusions

Current evidence suggests that intra-articular injection of PRP shows potential advantages compared to HA for the KOA patients, based on the analysis of VAS score, WOMAC score, IKDC score, KOOS score and EQ-VAS score. However, significant heterogeneity in some analyses indicates that the evidence is mixed in certain areas, and further studies are needed to confirm these findings across diverse patient populations and KOA grades. Future studies with larger study cohorts are warranted to validate our findings.

Abbreviations

KOA	Knee osteoarthritis
HA	Hyaluronic acid
PRP	Platelet-rich plasma
RCT	Randomized controlled trial
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index score
IKDC	International Knee Documentation Committee score
KOOS	Knee injury and osteoarthritis outcome score
EQ-VAS	EuroQol visual analog scale
KL	Kellgren and Lawrence
RR	Risk ratio
CI	Confidence interval
CI	Confidence interval
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08474-6.

Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7
Supplementary Material 8
Supplementary Material 9
Supplementary Material 10
Supplementary Material 11
Supplementary Material 12

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None.

Authors' contributions
HX, WS, JX and WZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: HX and WS. Acquisition, analysis, or interpretation of data: HX, WS and HL Drafting of the manuscript: HX and WS. Critical revision of the manuscript for important intellectual content: All authors.

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Data availability
The data used to support the findings of this study are included within the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
I confirm that this original manuscript has been read and approved by all named authors for publication, and that the work is not under consideration in any other journal.

Competing interests
The authors declare no competing interests.

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