Platelet-rich plasma preserves cartilage thickness and delays total knee arthroplasty in osteoarthritis with an inflammatory phenotype: a 5-year follow-up retrospective study

Yang Chen
Third Xiangya Hospital of Central South University
Song Wu
Third Xiangya Hospital of Central South University
Zi Wen
Third Xiangya Hospital of Central South University
Xin-Xing Wang
Third Xiangya Hospital of Central South University
Yong Chen
Third Xiangya Hospital of Central South University
Guang Xia
Third Xiangya Hospital of Central South University
Xu Cao (hughcaoxu@hotmail.com)
Third Xiangya Hospital of Central South University

Research Article

Keywords: knee osteoarthritis, phenotype, platelet-rich plasma, sodium hyaluronate, total knee arthroplasty

Posted Date: November 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2280373/v1

Abstract

Background

This study aims to explore whether platelet-rich plasma (PRP) can delay the progression of disease, reduce the incidence of Total knee arthroplasty (TKA) and improve clinical symptoms in patients with typical inflammatory phenotype knee osteoarthritis (KOA)

Methods

This was a retrospective cohort study with 5-year follow-up. According to clinical manifestations, magnetic resonance imaging (MRI) Osteoarthritis Knee Score (MOAKS), and serum inflammation markers C-reactive protein (CRP), we selected patients with typical inflammatory phenotype of KOA. Patients were divided into groups based on whether they had received PRP, hyaluronic acid (HA), or other conservative treatment (OCT). The Kellgren-Lawrence (K-L) grade and Minimum joint space width (MJSW) in knee X-rays were used to evaluate the progression of KOA. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, Knee Society scores (KSS), minimal clinically important difference (MCID) and Osteoarthritis Research Society International Set Responder Criteria Osteoarthritis Clinical Trials Revisited (OMERACT-OARSI) tool were used to evaluate the improvement of KOA symptoms. The incidence and timing of TKA was statistically analyzed.

Results

A total of 646 patients were finally included, including 211 received PRP, 209 received HA and 226 received OCT. PRP showed better results in K-L grade and MJSW compared with HA and OCT (The results at 12m, 24m, 36m, 48m, 60m, respectively, were as follows; K-L grade, PRP vs. HA, $P = 0.957$, $P = 0.534$, $P = 0.230$, $P < 0.001$, $P < 0.001$; PRP vs. OCT, $P = 0.240$, $P = 0.012$, $P = 0.004$, $P < 0.001$, $P < 0.001$; MJSW, PRP vs. HA, $P = 0.249$, $P = 0.013$, $P < 0.001$, $P < 0.001$, $P < 0.001$; PRP vs. OCT, $P = 0.155$, $P = 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$). Compared with HA and OCT, PRP group exhibited significant lower TKA incidence (PRP vs. HA, $P = 0.001$; PRP vs. OCT, $P = 0.001$; HA vs OCT, $P = 0.732$) and delayed time to TKA (log-rank, PRP vs HA,$P < 0.001$, PRP vs OCT, $P < 0.001$, HA vs OCT, $P = 0.467$). The WOMAC, KSS and KSS-F in PRP group were significantly better than those in HA group and OCT group at each time point after treatment ($P < 0.05$).

Conclusions

Intra articular injection of PRP can delay progression of KOA, reduce or postpone occurrence of TKA and improve clinical symptoms in strictly screened patients with typical inflammatory phenotype KOA.

Level of Evidence:

III, retrospective cohort.

Background

Osteoarthritis (OA) has a high prevalence worldwide, with a greater burden in the elderly and women [1]. Clinical treatment for OA involves a step-wise strategy, in which systematic conservative treatment is usually adopted for early- and middle- stage OA, which mainly includes Self-management/education programs, physical exercise, oral and topical NSAIDs and hyaluronic acid (HA) injection [2].Although these can relieve pain and improve joint function to a certain extent, most existing studies concluded that none of these treatments can delay the progression of OA and postpone the need for total knee arthroplasty(TKA) [3, 4].

In past decade, intra-articular platelet-rich plasma (PRP) injections exhibited exciting efficacy in relieving clinical symptoms in patients with early- stage OA [5, 6]. Most of these studies have concluded that PRP has a significantly better outcome than conventional conservative treatment. However, apart from some animal studies showing that PRP benefits cartilage health [7–9], few clinical studies have investigated whether PRP can delay OA progression and the need for TKA. Recently, Sánchez M and colleagues reported that patients received PRP injections achieved a delay in the TKA of more than 1.5 years [10]. However, in contrast, Bennell KL and colleagues claimed that PRP injection did not result in a significant difference in symptoms or cartilage volume over 12 months compared to placebo [11]. This inconsistency may be attributed to multiple factors, including the length of follow-up, etc., while the heterogeneity of OA is most likely a key reason. Rather than being a single disease, OA is now considered a clinical syndrome consisting of multiple phenotypes [12]. The pathomechanistic features differ between the different phenotypes, implying inconsistent response and outcome to treatment [13]. Therefore, restricting the study subjects to specific OA phenotypes is necessary to clarify the therapeutic effects of PRP.

Although there is currently no unified classification for OA phenotyping, the most typical phenotype characterized by low-grade, chronic inflammation has been identified by most studies [12–18]. The interaction between prolonged or dysregulated inflammation and molecules released from failed tissue repair forms a progressive cycle leading to cartilage destruction [19]. This ‘inflammation-damage cycle’ represents the most typical OA pathomechanism and clinical features, providing opportunities to develop disease modifying approaches. In principle, PRP mainly acts by releasing growth factors and immuno regulatory cytokinesto activate tissue repair responses and alleviate inflammatory microenvironment [20]. Thus, PRP could suppress the above vicious cycle from both controlling damage and anti- inflammation respectively, and we can hypothesise that PRP might exhibit maximum therapeutic effect on the inflammatory phenotype. Based on this, this study aimed to investigate the effect of PRP on cartilage thickness and incidence of TKA in strictly screened OA patients with inflammatory phenotype, and to compare with HA and other conservative treatments (OCT).

Materials And Methods

Patients

The data of 2623 knee OA (KOA) patients who were first diagnosed in the Orthopaedic Medical Centre of our Hospital from 2012 to 2017 were retrospectively collected and screened according to the following criteria:

Inclusion criteria: (i) > 90% complete treatment records, at least including magnetic resonance imaging (MRI) of the knee at the first visit, weight-bearing plain radiographs of the knee at each follow-up time point, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and Knee Society scores (KSS); (ii) Age 40–70 years; (iii) Met the American College of Rheumatology (ACR) criteria for the diagnosis of KOA [21], with the baseline of Kellgren-Lawrence (K-L) grade I–III [18, 22]; (iv) Numeric rating scale (NRS) [23] score > 40; (v) With inflammatory OA phenotype: knees with either inter-condylar synovitis or whole knee effusion with MRI Osteoarthritis Knee Score (MOAKS) grade 3, with at least a MOAKS 2 in the other respective feature [18]; Serum inflammatory markers were higher than “OA geometric mean”: C-reactive protein (CRP) > 5.03ug/ml [24].

Exclusion criteria: (i) Patients who are allergic to pharmaceutical ingredients; (ii) Knee joint surgery other than TKA, or knee joint injection treatment (These include PRP, glucocorticoids, HA, or other drugs for intraarticular injection) within three months before or five years after the first visit; (iii) Systemic inflammatory diseases; (iv) Body mass index (BMI) ≧ 40kg/m^2 or metabolic diseases; (v) Mental illness; (vi) Patients in the PRP treatment group with a low platelet count (< 100×10^9/L), or a platelet count in PRP less than three times the baseline; (vii) Other complications or joint diseases (e.g., purulent arthritis, gout, rheumatoid arthritis, ankylosing spondylitis, etc.); (viii) Severe joint deformity; (ix) Patients with local or systemic joint infection, or with a history of active or recurrent infection.

Finally, 646 patients, including 211 received PRP (three injections, 2 weeks apart, for 5 years), 209 received HA (three injections, 2 weeks apart, for 5 years) (ARTZ® Japan) and 226 received other conservative treatments (OCT, mainly including oral and topical NSAIDs, weight loss and exercises) were included. The initial knee scores and imaging screening of the patients were completed by 6 senior orthopaedic surgeons, and the follow-up retrospective evaluation was completed by 2 radiologists and 2 orthopaedic attending physicians. Follow-up data collected by the two orthopaedic doctoral candidates, all patients visit every year follow-up rating and knee X-ray check, phone or email in combination with follow-up rating in the form of a questionnaire. The indication for TKA is severe symptoms that cannot be relieved by conservative treatment in patients with K-L grade IV. All the physicians involved in the treatment and evaluation had more than 8 years of joint surgery experience.

PRP preparation and application

In this study, RapidCell® PRP technology (China) was used to prepare the leukocyte- poor PRP, which is similar in principle to the secondary centrifugation method reported by Landersberg [25] Briefly, in

accordance with the guidelines of RapidCell® operation manual, 40ml of venous blood (mixed with sodium citrate anticoagulant at a ratio of 1:9) was extracted from each patient. The first- stage centrifugation (200g, 5 min) step was carried out to extract the upper- leukocyte- poor autologous conditioned plasma. Thereafter, second- stage centrifugation (280g, 10 min) was conducted, and the upper- layer platelet- poor plasma was discarded. Finally, 4–6 mL of LP-PRP was obtained, with 0.5 ml of PRP extracted for platelet count. All preparation processes were completed under strict aseptic conditions. Patients received injections within 30 minutes after the preparation. After successful puncture, the effusion in the joint cavity was first aspirated, following which the LP-PRP was injected.

Evaluation

Records of 646 patients, with average follow-up period of 60.18 months, were evaluated: (i) baseline information, including name, sex, age, treatment, BMI, CRP, IL-6, PLT count and Follow-up time; (ii) imaging data: K-L grade and Minimum joint space width (MJSW) that defined as the minimum distance medially from the femoral condyle to the tibial plateau [26, 27]. Elevation of K-L grade and decrease of MJSW more than 0.5mm were considered as KOA progression [28]; (iii) knee pain/function scores: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Society Score (KSS). The minimal clinically important difference [MCID] in the WOMAC measure is 12% of the baseline value or 6% of the maximal value [29]. With the use of ROC curve analysis, patients with an improvement of at least 9 points for KSS-knee and 10 points for KSS-function scores experience a clinically important change [30] (The MCID of K-L grade and MJSW are unknown). Treatment response rates based on scores prior to treatment and 12 months post-treatment, which were calculated using the Osteoarthritis Research Society International Set Responder Criteria Osteoarthritis Clinical Trials Revisited (OMERACT-OARSI) tool [31]. Patient's global assessment (PGA) was assessed on a 5-point Likert scale on which subjects indicate the amount of improvement of their knee complaints compared to baseline (1. fair improvement, 2. moderate improvement, 3. no change, 4. Moderate deterioration, 5. fair deterioration) [32]. (iv) The time undergoing TKA.

Statistical analysis

SPSS 25.0 software was used to process the collected data following collation. Rates of KOA imaging progression were calculated based on the number of patients meeting the radiographic criteria for KOA progression, based on changes in K–L grade and MSJW, and the differences among the three groups were compared using the chi-square test. In terms of clinical outcomes, the main dependent variables were WOMAC scores and KSS at final follow-up.

All data were normally distributed, and all measurements are expressed as standard deviations or confidence intervals (CIs). Variance analysis was used to compare different time points in the same group. Inter-group comparisons were conducted based on the least significant difference (Bonferroni correction) or using a Tamhane test, while pairwise comparisons among the three groups were conducted using one-way analyses of variance (ANOVA). Paired-samples *t*-tests were used for paired comparisons. The significance level was set at $P < 0.05$.

Based on OMERACT-OARSI criteria, a chi-square test was used to calculate the differences in response among the study groups after follow-up. The α value of the significance level was 0.05. The probability of loss to follow-up and undergoing surgery in each group was listed separately, and differences among the groups were compared using chi-square tests. The Kaplan–Meier survival method was used for time-event analysis, and a log-rank test was used to compare survival times according to different variables.

Results

Patient characteristics

Table 1 exhibits the characteristics of the 646 enrolled patients (PRP group, n = 211 patients; HA group, n = 209 patients; OCT group, n = 226 patients). 16, 38, and 44 patients in the PRP, HA and OCT groups received TKA, respectively. There were no statistically significant differences in age (P = 0.363), sex (P = 0.772), duration of pain (P = 0.891), BMI (P = 0.937), or follow-up time (P = 0.406) among the groups. The average time from first treatment to TKA in the PRP, HA and OCT groups was 54.63 (± 5.51) months, 44.68 (± 5.71) months and 41.48 (± 5.92) months, respectively, and the difference was statistically significant (P < 0.001). The average platelet concentration in the PRP group was 1,196.06(± 301.53)×10^9/L and 5.8×baseline (206.08 ± 45.44×10^9/L; P < 0.001). The percentage of patients who underwent both imaging and retreatment is shown in Table 1.

Table 1
Patient characteristics and groups

Groups	PRP	HA	OCT	*P* - value
Total (n)	211	209	226	
Follow-up (n)	195	171	182	0.001
TKA (n)	16	38	44	
Age (years)	57.25 ± 8.49	56.19 ± 8.55	57.19 ± 8.74	0.363
Sex (n)				0.772
Male	92	93	106	
Female	119	116	120	
Duration of pain (m)	6.09 ± 5.28	6.26 ± 5.37	6.32 ± 4.94	0.891
PLT count (WB $\times 10^9$)	206.08 ± 45.44	/	/	< 0.001
PLT count (PRP $\times 10^9$)	1196.06 ± 301.53	/	/	
BMI (kg/m^2, mean)	25.30 ± 3.92	25.16 ± 4.16	25.22 ± 3.92	0.937
CRP (ug/ml, mean)	8.27 ± 3.05	8.23 ± 3.07	8.25 ± 3.15	0.990
K-l classification				0.913
I	45	39	43	
II	54	61	63	
III	112	109	120	
Mean follow-up time (m)	60.13 ± 0.62	60.20 ± 0.64	60.21 ± 0.72	0.406
12m	9m-14m	11m-15m	9m-13m	
24m	20m-26m	23m-26m	22m-25m	
36m	33m-39m	33m-37m	34m-37m	
48m	m-52m	46m-50m	45m-48m	
60m	58m-61m	58m-62m	59m-62m	

Data are presented as n values or the mean ± standard deviation. Continuous variables were analysed using analyses of variance; categorical variables were analysed using chi-square tests. Comparisons between two groups were performed using t-tests. Statistical significance was set at $P < 0.05$

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HA, hyaluronic acid; IL-6, interleukin-6; K-L, Kellgren–Lawrence; m, months; n, number; OCT, other conservative treatment; PLT, platelet; PRP, platelet-rich plasma; TKA, total knee arthroplasty; WB, whole blood

Groups	PRP	HA	OCT	*P* - value
Average time to TKA (m)	54.63 ± 5.51	44.68 ± 5.71	41.48 ± 5.92	< 0.001

Data are presented as n values or the mean ± standard deviation. Continuous variables were analysed using analyses of variance; categorical variables were analysed using chi-square tests. Comparisons between two groups were performed using t-tests. Statistical significance was set at $P < 0.05$

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HA, hyaluronic acid; IL-6, interleukin-6; K-L, Kellgren–Lawrence; m, months; n, number; OCT, other conservative treatment; PLT, platelet; PRP, platelet-rich plasma; TKA, total knee arthroplasty; WB, whole blood

Main results

Table 2 and Fig. 4 show that there were no statistically significant differences in K-L grades among the groups prior to (ANOVA, $P = 0.551$) and 12 months after treatment (ANOVA, $P = 0.444$). PRP was statistically superior in improving K-L grade from month 48 onward compared to HA (PRP vs. HA, $P = 0.957$, $P = 0.534$, $P = 0.230$, $P = 0.012$, $P = 0.036$ at 12m, 24m, 36m, 48m, 60m, respectively) and from month 24 onward compared to OCT (PRP vs. OCT, $P = 0.240$, $P = 0.012$, $P = 0.004$, $P = 0.002$, $P = 0.005$ at 12m, 24m, 36m, 48m, 60m, respectively). Similarly, there were no statistically significant differences in MJSW among the groups prior to (ANOVA, $P = 0.835$) and 12 months after treatment (ANOVA, $P = 0.584$). PRP was statistically superior in improving MJSW from month 24 onward compared to HA and OCT (PRP vs. HA, $P = 0.413$, $P = 0.044$, $P = 0.009$, $P = 0.024$, $P = 0.014$ at 12m, 24m, 36m, 48m, 60m, respectively; PRP vs. OCT, $P = 0.350$, $P = 0.021$, $P = 0.005$, $P = 0.029$, $P = 0.026$, at 12m, 24m, 36m, 48m, 60m, respectively). There were no significant differences in K-L grade or MJSW between the HA and OCT groups during the five-year follow-up period ($P > 0.05$).

Table 2
Clinical results in each patient group (n = 548)

Outcomes	PRP	HA	OCT	P^a	P^b	P^c	P^d
K-L grade							
Baseline	2.26 ± 0.81	2.19 ± 0.78	2.18 ± 0.79	0.372	0.328	0.945	0.551
12m	2.29 ± 0.73	2.29 ± 0.74	2.38 ± 0.79	0.957	0.240	0.297	0.444
24m	2.29 ± 0.81	2.35 ± 0.75	2.52 ± 0.85	0.534	0.012	0.066	0.035
36m	2.33 ± 0.81	2.44 ± 0.73	2.60 ± 0.89	0.230	0.004	0.097	0.014
48m	2.40 ± 0.80	2.66 ± 0.95	2.72 ± 0.98	0.012	0.002	0.624	0.005
60m	2.56 ± 0.83	2.79 ± 1.02	2.87 ± 1.02	0.036	0.005	0.486	0.012
MJSW							
Baseline	3.53 ± 0.68	3.58 ± 0.68	3.58 ± 0.66	0.606	0.604	0.998	0.835
12m	3.46 ± 0.69	3.36 ± 0.70	3.34 ± 0.67	0.413	0.350	0.857	0.584
24m	3.38 ± 0.70	3.15 ± 0.74	3.08 ± 0.56	0.044	0.021	0.618	0.038
36m	3.30 ± 0.76	2.98 ± 0.79	2.90 ± 0.66	0.009	0.005	0.601	0.006
48m	3.04 ± 0.82	2.75 ± 0.75	2.69 ± 0.54	0.024	0.029	0.676	0.028
60m	2.83 ± 0.99	2.49 ± 0.74	2.39 ± 0.54	0.014	0.026	0.622	0.016

Patients who had undergone surgery during the follow-up period were excluded. Data are presented as n values or the mean ± standard deviation. Analysed via one-way analysis of variance. Statistical significance was set at $P < 0.05$

Pa, PRP and HA groups were compared; Pb, PRP and OCT groups were compared; Pc, HA and OCT group were compared; Pd, one-way ANOVA between groups

Abbreviations: HA, hyaluronic acid; K-L, Kellgren–Lawrence; m, months; MJSW, minimum joint space width; OCT, other conservative treatment; PRP, platelet-rich plasma

As shown in Table 3, rates of progression in K-L grade and MJSW were lower in the PRP group than in the HA and OCT groups (K-L grade, PRP vs. HA, $P = 0.001$; PRP vs. OCT, $P = 0.001$; HA vs. OCT, $P = 0.851$; MJSW, PRP vs. HA, $P = 0.001$; PRP vs. OCT, $P = 0.001$; HA vs. OCT, $P = 0.008$).

Table 3
Comparison of OA progression, incidence of TKA, and responders in each group

	PRP	HA	OCT	OR(95% CI)	*P*-value
OA Progression-1					
	29.86%	65.07%	/	0.23(0.15,0.34)	0.001
K-L grade	/	65.07%	65.93%	0.96(0.65,1.43)	0.851
	29.86%	/	65.93%	0.22(0.15,0.33)	0.001
OA Progression-2					
	36.02%	89.95%	/	0.06(0.04,0.11)	0.001
MJSW	/	89.95%	80.97%	2.10(1.20,3.68)	0.008
	36.02%	/	80.97%	0.13(0.09,0.20)	0.001
Surgery-3					
	7.58%	18.18%	/	0.37(0.20,0.69)	0.001
TKA	/	18.18%	19.46%	0.92(0.57,1.49)	0.732
	7.58%	/	19.46%	0.34(0.19,0.62)	0.001
OMERACT-OARSI					
	69.19%	53.11%	/	1.98(1.33,2.96)	0.001
Responder rate	/	53.11%	44.69%	1.40(0.96,2.05)	0.079
	69.19%	/	44.69%	2.78(1.88,4.12)	0.001
Patients who had undergone surgery during the follow-up period were excluded. Analysed using chi-square tests. Statistical significance was set at $P < 0.05$					
OA progression was recorded at 60 months of follow-up.					
The responder rate was determined using 12 months of follow-up data.					
Abbreviations: CI, confidence interval; HA, hyaluronic acid; K-L, Kellgren–Lawrence; MJSW, minimum joint space width; OCT, other conservative treatment; OMERACT-OARSI, Osteoarthritis Research Society International Set Responder Criteria Osteoarthritis Clinical Trials Revisited; OR, odds ratio; PRP, platelet-rich plasma; TKA, total knee arthroplasty					
1: K-L classification; 2: MJSW; 3: TKA incidence, A total of 98 patients underwent TKA, including 16 in the PRP group, 38 in the HA group, and 44 in the OCT group					

Table 3 shows that 98 patients underwent TKA during the five-year follow-up period, including 16 (7.58%) patients in the PRP group, 38 (18.18%) patients in the HA group, and 44 (19.46%) patients in the OCT group. TKA incidence was significantly lower in the PRP group than in the other two groups (PRP vs. HA,

P = 0.001; PRP vs. OCT, P = 0.001), while the difference between the HA and OCT groups was not significant (P = 0.732). Figure 5 shows the survival curves of the three groups and the distribution of time to TKA. Compared with HA and OCT, PRP reduced the incidence and significantly delayed the time of TKA (log-rank, PRP vs. HA, P < 0.001, PRP vs. OCT, P < 0.001, HA vs. OCT, P = 0.467).

Secondary results

Table 3 shows that at 12 months after treatment, the response rate of the PRP group was 69.19%, which was significantly higher than that in the HA (53.11%) and OCT groups (44.69%) (PRP vs. HA, P = 0.001; PRP vs. OCT, P = 0.001). There was no significant difference between the HA and OCT groups (P = 0.079).

As shown in Table 4 and Fig. 6, the results of WOMAC, KSS and KSS-F in PRP group were significantly better than those in HA group and OCT group at each time point after treatment (P < 0.05). But we observed differences in KSS baseline scores between the groups (P = 0.008). The results of WOMAC and KSS-F in the HA group were significantly better than those in the OCT group at 12 months after treatment (WOMAC, P = 0.001; KSS-F, P = 0.006)(Notably, a decrease in the WOMAC score indicated improvement in symptoms and function, while an increase in the KSS score indicated improvement in symptoms and function). The MCID of each score at each time point was the highest in PRP, but it gradually decreased over time (Table 4, Fig. 6).

Table 4
Clinical results in each patient group (n = 548)

Outcomes	PRP(n = 195)	HA (n = 171)	OCT(n = 182)	P^a	P^b	P^c	P^d
WOMAC							
Baseline	78.56 ± 15.71	75.55 ± 13.97	77.87 ± 16.01	0.060	0.662	0.154	0.150
Change (Baseline-12m)	-15.96 ± 12.07	-3.99 ± 3.34	-0.62 ± 8.77	< 0.001	< 0.001	0.001	< 0.001
N (%)	139 (71.28)	87 (50.88)	71 (39.01)				
Change (Baseline-24m)	-10.39 ± 9.23	-0.40 ± 5.26	1.19 ± 11.43	< 0.001	< 0.001	0.102	< 0.001
N (%)	111 (56.92)	59 (34.50)	61 (33.52)				
Change (Baseline-36m)	-6.47 ± 7.79	1.18 ± 7.26	1.70 ± 10.42	< 0.001	< 0.001	0.569	< 0.001
N (%)	99 (50.77)	52 (30.41)	53 (29.12)				
Change (Baseline-48m)	-4.83 ± 9.00	3.36 ± 9.72	3.48 ± 12.01	< 0.001	< 0.001	0.912	< 0.001
N (%)	88 (45.13)	43 (25.15)	41 (22.53)				
Change (Baseline-60m)	-4.05 ± 8.41	4.12 ± 11.31	5.14 ± 15.32	< 0.001	< 0.001	0.424	< 0.001
N (%)	84 (43.08)	33 (19.30)	30 (16.48)				
KSS							
Baseline	66.03 ± 8.05	68.58 ± 9.19	68.26 ± 8.87	0.005	0.013	0.724	0.008
Change (Baseline-12m)	8.53 ± 6.68	1.25 ± 9.46	0.76 ± 5.73	< 0.001	< 0.001	0.536	< 0.001
N (%)	131 (67.18)	87 (50.88)	81 (44.51)				

Outcomes	PRP(n = 195)	HA (n = 171)	OCT(n = 182)	P^a	P^b	P^c	P^d
Change (Baseline-24m)	5.70 ± 6.28	-0.43 ± 10.76	-0.03 ± 6.21	< 0.001	< 0.001	0.636	< 0.001
N (%)	103 (52.82)	71 (41.52)	74 (40.66)				
Change (Baseline-36m)	4.03 ± 6.44	-2.87 ± 10.67	-3.60 ± 6.73	< 0.001	< 0.001	0.395	< 0.001
N (%)	97 (49.74)	61 (35.67)	67 (36.81)				
Change (Baseline-48m)	1.51 ± 6.48	-6.63 ± 9.92	-6.51 ± 7.67	< 0.001	< 0.001	0.883	< 0.001
N (%)	87 (44.62)	37 (21.64)	36 (19.78)				
Change (Baseline-60m)	0.12 ± 7.66	-7.48 ± 11.53	-7.48 ± 8.11	< 0.001	< 0.001	0.997	< 0.001
N (%)	81 (41.54)	22 (12.87)	18 (9.89)				
KSS-F							
Baseline	68.08 ± 12.26	69.71 ± 13.41	70.85 ± 12.90	0.226	0.057	0.403	0.109
Change (Baseline-12m)	5.99 ± 8.18	2.40 ± 16.62	-0.68 ± 2.45	0.001	< 0.001	0.006	< 0.001
N (%)	137 (70.26)	87 (50.88)	80 (43.96)				
Change (Baseline-24m)	3.21 ± 10.12	-0.26 ± 17.23	-2.45 ± 14.02	0.018	< 0.001	0.142	< 0.001
N (%)	112 (57.44)	71 (41.52)	74 (40.66)				
Change (Baseline-36m)	2.13 ± 11.37	-2.81 ± 15.63	-4.62 ± 14.13	0.001	< 0.001	0.217	< 0.001
N (%)	106 (54.36)	56 (32.75)	52 (28.57)				

Outcomes	PRP(n = 195)	HA (n = 171)	OCT(n = 182)	P^a	P^b	P^c	P^d
Change (Baseline-48m)	0.23 ± 11.14	-3.77 ± 9.98	-6.26 ± 14.29	0.001	< 0.001	0.051	< 0.001
N (%)	98 (50.26)	47 (27.49)	48 (22.53)				
Change (Baseline-60m)	0.02 ± 11.72	-5.88 ± 10.19	-6.57 ± 14.52	< 0.001	< 0.001	0.599	< 0.001
N (%)	93 (47.69)	37 (21.64)	41 (22.53)				
Patients who had undergone surgery during the follow-up period were excluded.Data are presented as n values or the mean ± standard deviation. Analysed via one-way ANOVA. Statistical significance was set at $P < 0.05$							
Pa, PRP and HA groups were compared; Pb, PRP and OCT groups were compared; Pc, HA and OCT group were compared; Pd, one-way ANOVA analysis between groups							
Abbreviations:							
HA, hyaluronic acid; KSS, Knee Society score; KSS-F, KSS-function score; m, months; OCT, other conservative treatment; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; Change, Change from baseline; N (%), Number of patients with MCID (minimal							
clinically important difference), %							

Adverse reactions

During the follow-up period, some patients in the PRP and HA groups experienced pain following knee joint puncture, which resolved spontaneously in all cases (pain duration: ≤3 days), without requiring further treatment. No local infections were reported.

Discussion

The present study compared the efficacy of three treatment modalities (PRP, HA, and OCT) in patients with typical inflammatory phenotype KOA. We evaluated the delay of OA progression and the incidence of TKA at 5-year follow-up. Clinical studies of PRP have focused on controlling KOA symptoms. Although changes in OA-related symptoms can clearly reflect the curative effect of treatment, findings regarding PRP nonetheless remain controversial. A meta-analysis that included 23 randomized controlled trials (RCTs) showed [33] that PRP was more advantageous than HA, corticosteroids (CS), plasma rich in growth factors, and placebo treatment over at least six months of follow-up. The prospective study of Kon E [34] found that PRP exerted a better curative effect in young KOA patients with mild degeneration,

and when PRP was compared with HA, they observed no significant differences among older patients and those with severe cartilage degeneration. Yoshitomo Saita et al. [35] conducted a retrospective study with 517 patients followed for 12 months and reported a PRP OMERACT-OARSI response rate of 51.3% in patients with K-L grade IV (indicating severe OA) at 6 months after treatment, which was still 50.9% at 12 months, and the results were not significantly correlated with age. However, Jevsevar et al. [36] conducted a MATE-Analysis study that reported no difference in OA symptom improvement between PRP and placebo treatments, consistent with the conclusions of an RCT by Bennell et al [11]. In contrast, few studies have investigated the effect of PRP in delaying the progression of KOA. Sánchez et al. followed 667 patients who had received PRP for more than 5 years and 74.1% achieved a delay in the TKA of more than 1.5 years, with a median delay of 5.3 years [10]. The authors further noted that a greater number of PRP treatment cycles was associated with more delayed TKA. They concluded that PRP can reduce the incidence of TKA, which is consistent with the findings of our study, although they did not compare PRP with other conventional treatments. However, in Bennell KL's RCT study on 288 KOA patients, intra-articular injection of PRP did not exhibit the effect of delaying the progression of KOA within 12 months of follow-up compared with placebo [11]. This study based on changes in the volume of the medial tibial cartilage on MRI in 144 patients in the PRP group and 144 patients in the placebo group after 12 months of treatment. In addition, although we found that there was no significant difference in the effect of HA and OCT on TKA incidence, the average time to TKA was delayed by 3.2 months in the HA group, which is consistent with the findings of Delbarre A et al. and Concoff et al. [37, 38] and different from that of Shewale AR's study [39].

Given these discrepancies, some authors have proposed several factors influencing PRP treatment outcomes in treating KOA, such as the PRP preparation method, the white blood cell content in the PRP, patient characteristics, genetic factors, and duration of follow-up [40–42]. For example, our analysis demonstrated that PRP exerted a significant superior effect on K-L grade and MJSW only starting at 24 months after treatment compared with HA and OCT. This has the potential to partially explain the difference in outcomes between Bennell KL's study and others. Recently, studies have observed the influences of OA heterogeneity on the efficacy of treatments. This may explain the discrepancies of outcomes in OA treatments. Andia I et al. [17] argued that the application of PRP in KOA should be restricted only to patients with specific KOA phenotypes, especially the typical inflammatory phenotype, to achieve optimal outcomes. However, there is no uniform standard for the classification of KOA phenotypes currently. Nonetheless, various classification strategies have been proposed, including those based on clinical features, imaging features, biochemical markers, and computer classification based on high throughput “omics” data. Yuan et al. [13] collected cartilage, subchondral bone, and synovium samples from several clinical centres to construct an extensive transcriptome atlas of patients with KOA, which divided the patients into four phenotypes based on significant molecular characteristics using clustering analysis: (i) a glycosaminoglycan metabolic disorder phenotype; (ii) a collagen metabolic disorder phenotype; (iii) an activated sensory neuron phenotype; and (iv) an inflammatory phenotype. These phenotypes respectively corresponded to (i) clinical symptoms; (ii) osteophytes; (iii) pain; and (iv) inflammation and joint space stenosis. A systematic review by Deveza et al. [12] reported that pain

sensitivity, psychological distress, imaging severity, BMI, muscle strength, inflammation, and comorbidity were correlated with different clinical phenotypes. In these classification studies, there was a higher frequency of the phenotype characterized by intra-articular low-grade and prolonged inflammation and typical cartilage destruction [14].

PRP was reported to inhibit nuclear factor kappa β (NF-κβ) in cells by releasing growth factors and cytokines, thus limiting the inflammatory response in the joints [43, 44]. In addition, the derivatives of PRP have been shown to regulate immunity, induce chondrocyte proliferation, migration, and differentiation, as well as extracellular matrix (ECM) synthesis [45].In line with these mechanisms, research has demonstrated that an intra-articular injection of PRP can alleviate KOA symptoms by improving synovitis [46]. In theory, PRP has a relatively direct effect on "low-grade and prolonged inflammation [19]" and cartilage destruction and degradation, which are common in OA. However, there are no clear and consensus criteria for identifying this inflammatory phenotype of KOA. CRP (C-reactive protein) and other inflammatory indicators have been proved to be increased in patients with OA [24, 47], which provides a reference for identifying this phenotype. In this study, we selected patients with inflammatory KOA phenotype according to the typical clinical symptoms of KOA, MRI imaging characteristics, and the abnormalities of clinically commonly used serum inflammatory markers CRP. The therapeutic effect of PRP on this most typical KOA phenotype was investigated in these patients. Our findings support the hypothesis that PRP can exert a superior therapeutic effect in patients with this phenotype. This helps us to better select the treatment subjects for PRP.

Limitations

This study has some limitations. First, this study was a retrospective study with no sample size calculation, limited follow-up time, possible bias in patient screening, and slight differences in baseline pain and functional scores. A small number of patients may refuse medical intervention because of financial problems, the influence of which could not be completely eliminated in the study; second, in this study, PRP treatment was administered to patients with KOA who had the inflammatory degenerative phenotype, and the response rate was 69.19%. Some patients remained insensitive to treatment, which may have been due to continued progression or overlap of KOA phenotypes, and there is no uniform and clear definition for identifying KOA with different phenotypes. Third, the current results may not be generalisable to other PRP preparation methods.

Conclusions

The results of this retrospective study suggest that intraarticular injection of PRP can delay the radiographic progression of typical inflammatory phenotype of KOA and reduce or postpone the occurrence of TKA. In WOMAC, KSS, and KSS-F scores, PRP was associated with more patients achieving MCID than HA and OCT. Meanwhile, the response rate of OMERACt-OARSI in PRP group was higher than that in HA group and OCT group.

Abbreviations

BMI, body mass index;

CRP, C-reactive protein;

HA, hyaluronic acid;

IL-6, interleukin-6;

K-L, Kellgren–Lawrence;

KSS-F, KSS-function score; m, months;

MJSW, minimum joint space width;

OCT, other conservative treatment;

OMERACT-OARSI, Osteoarthritis Research Society International Set Responder Criteria Osteoarthritis Clinical Trials Revisited;

PLT, platelet;

PRP, platelet-rich plasma;

TKA, total knee arthroplasty;

WB, whole blood

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; Change

Declarations

Funding: This work was supported by the National Natural Science Foundation of China (82072501), Science and Technology Innovation Leading Planof High-Tech Industry in Hunan Province (2020SK2011), Youth Fund Project of Natural Science Foundation of Hunan Province (2020JJ5848), and Medical Research Development Fund Project (WS865C).

Competing interests: The authors declare no conflicts of interest.

Authors' contributions: All authors contributed equally to this paper. Study design: Xu Cao; conduction of the study: Yang Chen, Zi Wen, Xin-Xing Wang, and Xu Cao; data collection: Zi Wen, XinXing Wang, Yong Chen, and Guang Xia; data analysis: XinXing Wang, and Zi Wen; data interpretation: Zi Wen and Xu Cao; drafting of the manuscript: Yang Chen; revision of manuscript content, Xu Cao. Xu Cao take responsibility

for the integrity of the data analysis. All authors have read and agreed to the published version of the manuscript.

Ethics approval: The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of Xiangya Third Hospital of Central South University (Ethics Committee approval number: Kuai |22023).

Consent to participate: Written informed consent was obtained from all patients before the initiation of treatment.

Consent to publish: Not applicable.

Acknowledgments: The authors thank Editage (www.editage.cn) for English language editing.

Availability of data and materials: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to the protection of patients' privacy.

References

1. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthr Cartil. 2022;30:184–95. https://doi.org/10.1016/j.joca.2021.04.020
2. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: A review. JAMA. 2021;325:568–78. https://doi.org/10.1001/jama.2020.22171, PMID: 33560326, PMCID: PMC8225295
3. Weick JW, Bawa HS, Dirschl DR. Hyaluronic acid injections for treatment of advanced osteoarthritis of the knee: Utilization and cost in a national population sample. J Bone Joint Surg Am. 2016;98:1429–35. https://doi.org/10.2106/JBJS.15.01358, PMID: 27605686
4. Hafsi K, McKay J, Li J, Lana JF, Macedo A, Santos GS, et al. Nutritional, metabolic and genetic considerations to optimise regenerative medicine outcome for knee osteoarthritis. J Clin Orthop Trauma. 2019;10:2–8. https://doi.org/10.1016/j.jcot.2018.10.004. Epub 2018 Oct 15. PMID: 30705524, PMCID: PMC6349648
5. 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;49:249–60. https://doi.org/10.1177/0363546520909397
6. Dong Y, Zhang B, Yang Q, Zhu J, Sun X. The effects of platelet-rich plasma injection in knee and hip osteoarthritis: A meta-analysis of randomized controlled trials. Clin Rheumatol. 2021;40:263–77. https://doi.org/10.1007/s10067-020-05185-2
7. Sakata R, Reddi AH. Platelet-rich plasma modulates actions on articular cartilage lubrication and regeneration. Tissue Eng Part B Rev. 2016;22:408–19. https://doi.org/10.1089/ten.TEB.2015.0534. Epub 2016 Jun 27. PMID: 27109909

8. Milano G, Deriu L, Sanna Passino E, Masala G, Manunta A, Postacchini R, et al. Repeated platelet concentrate injections enhance reparative response of microfractures in the treatment of chondral defects of the knee: An experimental study in an animal model. Arthroscopy. 2012;28:688–701. https://doi.org/10.1016/j.arthro.2011.09.016
9. Akeda K, An HS, Okuma M, Attawia M, Miyamoto K, Thonar EJ, et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthr Cartil. 2006;14:1272–80. https://doi.org/10.1016/j.joca.2006.05.008
10. Sánchez M, Jorquera C, Sánchez P, Beitia M, García-Cano B, Guadilla J, et al. Platelet-rich plasma injections delay the need for knee arthroplasty: A retrospective study and survival analysis. Int Orthop. 2021;45:401–10. https://doi.org/10.1007/s00264-020-04669-9. Epub 2020 Jul 3. PMID: 32621139
11. Bennell KL, Paterson KL, Metcalf BR, Duong V, Eyles J, Kasza J, et al. Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: The RESTORE randomized clinical trial. JAMA. 2021;326:2021–30. https://doi.org/10.1001/jama.2021.19415, PMID: 34812863, PMCID: PMC8611484
12. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: A systematic review. Osteoarthr Cartil. 2017;25:1926–41. https://doi.org/10.1016/j.joca.2017.08.009. Epub 2017 Aug 25. PMID: 28847624
13. Yuan C, Pan Z, Zhao K, Li J, Sheng Z, Yao X, et al. Classification of four distinct osteoarthritis subtypes with a knee joint tissue transcriptome atlas. Bone Res. 2020;8:38. https://doi.org/10.1038/s41413-020-00109-x, PMID: 33298863, PMCID: PMC7658991
14. Van Spil WE, Kubassova O, Boesen M, Bay-Jensen AC, Mobasheri A. Osteoarthritis phenotypes and novel therapeutic targets. Biochem Pharmacol. 2019;165:41–8. https://doi.org/10.1016/j.bcp.2019.02.037. Epub 2019 Mar 1. PMID: 30831073
15. Roman-Blas JA, Mendoza-Torres LA, Largo R, Herrero-Beaumont G. Setting up distinctive outcome measures for each osteoarthritis phenotype. Ther Adv Musculoskelet Dis. 2020;12:1759720X20937966. https://doi.org/10.1177/1759720X20937966, PMID: 32973934, PMCID: PMC7491224
16. Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: A systematic review of the literature. BMC Musculoskelet Disord. 2016;17:425. https://doi.org/10.1186/s12891-016-1286-2, PMID: 27733199, PMCID: PMC5062907
17. Andia I, Atilano L, Maffulli N. Moving toward targeting the right phenotype with the right platelet-rich plasma (PRP) formulation for knee osteoarthritis. Ther Adv Musculoskelet Dis. 2021;13:1759720X211004336. https://doi.org/10.1177/1759720X211004336
18. Namiri NK, Lee J, Astuto B, Liu F, Shah R, Majumdar S, et al. Deep learning for large scale MRI-based morphological phenotyping of osteoarthritis. Sci Rep. 2021;11:10915. https://doi.org/10.1038/s41598-021-90292-6, PMID: 34035386, PMCID: PMC8149826

19. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12:580–92. https://doi.org/10.1038/nrrheum.2016.136. Epub 2016 Aug 19. PMID: 27539668, PMCID: PMC5500215
20. Rodríguez-Merchán EC. Intra-articular platelet-rich plasma injections in knee osteoarthritis: A review of their current molecular mechanisms of action and their degree of efficacy. Int J Mol Sci. 2022;23:1301. https://doi.org/10.3390/ijms23031301, PMID: 35163225, PMCID: PMC8836227
21. Damen J, van Rijn RM, Emans PJ, Hilberdink WKHA, Wesseling J, Oei EHG, et al. Prevalence and development of hip and knee osteoarthritis according to American College of Rheumatology criteria in the CHECK cohort. Arthritis Res Ther. 2019;21:4. https://doi.org/10.1186/s13075-018-1785-7, PMID: 30611305, PMCID: PMC6321652
22. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16:494–502. https://doi.org/10.1136/ard.16.4.494, PMID: 13498604, PMCID: PMC1006995
23. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol. 1990;17:1022–4. PMID: 2213777
24. Otterness IG, Swindell AC, Zimmerer RO, Poole AR, Ionescu M, Weiner E. An analysis of 14 molecular markers for monitoring osteoarthritis: Segregation of the markers into clusters and distinguishing osteoarthritis at baseline. Osteoarthr Cartil. 2000;8:180–5. https://doi.org/10.1053/joca.1999.0288, PMID: 10806045
25. Landesberg R, Roy M, Glickman RS. Quantification of growth factor levels using a simplified method of platelet-rich plasma gel preparation. J Oral Maxillofac Surg. 2000;58:297–300; discussion 300. https://doi.org/10.1016/s0278-2391(00)90058-2
26. Jeffrey D, Gesa N, Jingbo N, Saara T, Jose T, Christine D, et al. Comparison of radiographic joint space width to MRI cartilagemorphometry: Analysis of longitudinal data from the Osteoarthritis Initiative (OAI). Arthritis Care Res. 2010;62:932–7
27. Zhang Q, Xu W, Wu K, Fu W, Yang H, Guo JJ. Intra-articular pure platelet-rich plasma combined with open-wedge high tibial osteotomy improves clinical outcomes and minimal joint space width compared with high tibial osteotomy alone in knee osteoarthritis: A prospective study. Arthroscopy. 2022;38:476–85. https://doi.org/10.1016/j.arthro.2021.09.013. Epub 2021 Sep 25. PMID: 34571181
28. Cooper C, Adachi JD, Bardin T, Berenbaum F, Flamion B, Jonsson H, et al. How to define responders in osteoarthritis. Curr Med Res Opin. 2013;29:719–29. https://doi.org/10.1185/03007995.2013.792793. Epub 2013 Apr 17. PMID: 23557069, PMCID: PMC3690437
29. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities.

Arthritis Rheum. 2001;45:384–91. https://doi.org/10.1002/1529-0131(200108)45:4<384::AID-ART352>3.0.CO;2-0

30. Lizaur-Utrilla A, Gonzalez-Parreño S, Martinez-Mendez D, Miralles-Muñoz FA, Lopez-Prats FA. Minimal clinically important differences and substantial clinical benefits for Knee Society Scores. Knee Surg Sports Traumatol Arthrosc. 2020;28:1473–8. https://doi.org/10.1007/s00167-019-05543-x. Epub 2019 May 20. PMID: 31111184
31. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis research society international set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthr Cartil. 2004;12:389–99. https://doi.org/10.1016/j.joca.2004.02.001
32. Hermans J, Bierma-Zeinstra SMA, Bos PK, Niesten DD, Verhaar JAN, Reijman M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial. BMC Musculoskelet Disord. 2019;20:196. https://doi.org/10.1186/s12891-019-2546-8, PMID: 31064359, PMCID: PMC6503549
33. Singh H, Knapik DM, Polce EM, Eikani CK, Bjornstad AH, Gursoy S, et al. Relative efficacy of intra-articular injections in the treatment of knee osteoarthritis: A systematic review and network meta-analysis. Am J Sports Med. 2022:3635465211029659;50:3140–8. https://doi.org/10.1177/03635465211029659 [Epub ahead of print]. PMID: 34403285
34. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. Arthroscopy. 2011;27:1490–501. https://doi.org/10.1016/j.arthro.2011.05.011
35. Saita Y, Kobayashi Y, Nishio H, Wakayama T, Fukusato S, Uchino S, et al. Predictors of effectiveness of platelet-rich plasma therapy for knee osteoarthritis: A retrospective cohort study. J Clin Med. 2021;10:4514. https://doi.org/10.3390/jcm10194514
36. Jevsevar DS, Shores PB, Mullen K, Schulte DM, Brown GA, Cummins DS. Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: A network meta-analysis. J Am Acad Orthop Surg. 2018;26:325–36. https://doi.org/10.5435/JAAOS-D-17-00318
37. Delbarre A, Amor B, Bardoulat I, Tetafort A, Pelletier-Fleury N. Do intra-articular hyaluronic acid injections delay total knee replacement in patients with osteoarthritis - A Cox model analysis. PLOS ONE. 2017;12:e0187227. https://doi.org/10.1371/journal.pone.0187227
38. Concoff A, Niazi F, Farrokhyar F, Alyass A, Rosen J, Nicholls M. Delay to TKA and costs associated with knee osteoarthritis care using intra-articular hyaluronic acid: Analysis of an administrative database. Clin Med Insights Arthritis Musculoskelet Disord. 2021;14:1179544121994092. https://doi.org/10.1177/1179544121994092, PMID: 33814937, PMCID: PMC7989120
39. Shewale AR, Barnes CL, Fischbach LA, Ounpraseuth ST, Painter JT, Martin BC. Comparative effectiveness of intra-articular hyaluronic acid and corticosteroid injections on the time to surgical

knee procedures. J Arthroplasty. 2017;32:3591–3597.e24. https://doi.org/10.1016/j.arth.2017.07.007

40. Bansal H, Leon J, Pont JL, Wilson DA, Bansal A, Agarwal D, et al. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. Sci Rep. 2021;11:3971. https://doi.org/10.1038/s41598-021-83025-2. Erratum in: Sci Rep. PMID: 33597586; PMC ID: PMC7889864. 2021;11:18612. https://doi.org/10.1038/s41598-021-98365-2
41. Lana JF, Macedo A, Ingrao ILG, Huber SC, Santos GS, Santana MHA. Leukocyte-rich PRP for knee osteoarthritis: Current concepts. J Clin Orthop Trauma. 2019;10;Suppl 1:S179–82. https://doi.org/10.1016/j.jcot.2019.01.011. Epub 2019 Jan 14. PMID: 31700210, PMCID: PMC6823820
42. Shahid M, Kundra R. Platelet-rich plasma (PRP) for knee disorders. EFORT Open Rev. 2017;2:28–34. https://doi.org/10.1302/2058-5241.2.160004, PMID: 28607768, PMCID: PMC5444079
43. van Buul GM, Koevoet WL, Kops N, Bos PK, Verhaar JA, Weinans H, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med. 2011;39:2362–70. https://doi.org/10.1177/0363546511419278. Epub 2011 Aug 19. PMID: 21856929
44. Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, et al. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: Mechanisms of NF-κB inhibition via HGF. J Cell Physiol. 2010;225:757–66. https://doi.org/10.1002/jcp.22274, PMID: 20568106
45. Szwedowski D, Szczepanek J, Paczesny Ł, Zabrzyński J, Gagat M, Mobasheri A, et al. The effect of platelet-rich plasma on the intra-articular microenvironment in knee osteoarthritis. Int J Mol Sci. 2021;22:5492. https://doi.org/10.3390/ijms22115492, PMID: 34071037, PMCID: PMC8197096
46. Ahmad HS, Farrag SE, Okasha AE, Kadry AO, Ata TB, Monir AA, 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;21:960–6. https://doi.org/10.1111/1756-185X.13315, PMID: 29878617
47. Siebuhr AS, Petersen KK, Arendt-Nielsen L, Egsgaard LL, Eskehave T, Christiansen C, et al. Identification and characterisation of osteoarthritis patients with inflammation derived tissue turnover. Osteoarthr Cartil. 2014;22:44–50. https://doi.org/10.1016/j.joca.2013.10.020. Epub 2013 Nov 9. PMID: 24216059

Figures

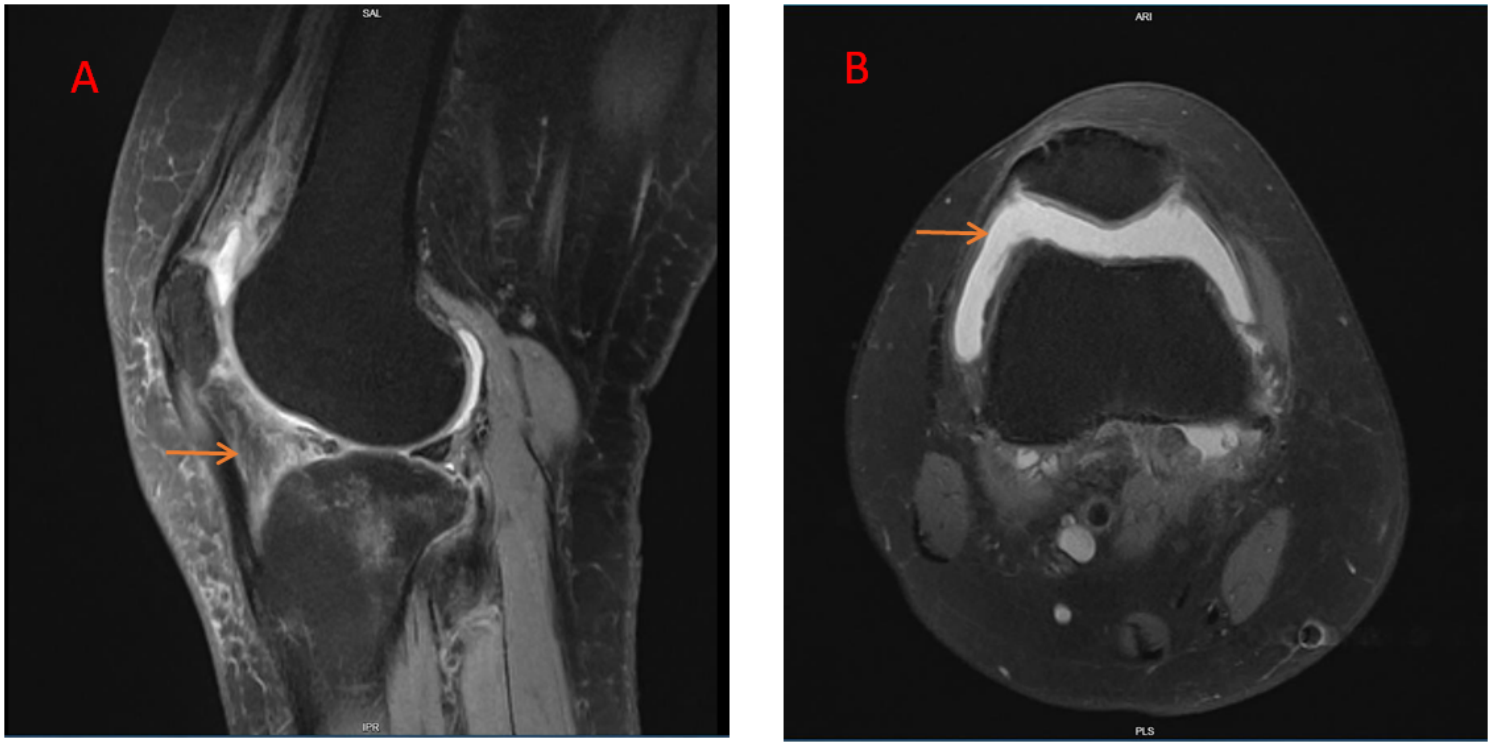

Figure 1

Inflammatory phenotype is defined as knees with either inter-condylar synovitis (A) or whole knee effusion with MRIO steoarthritis Knee Score (MOAKS) grade 3 (B)

Abbreviations: MRI, magnetic resonance imaging

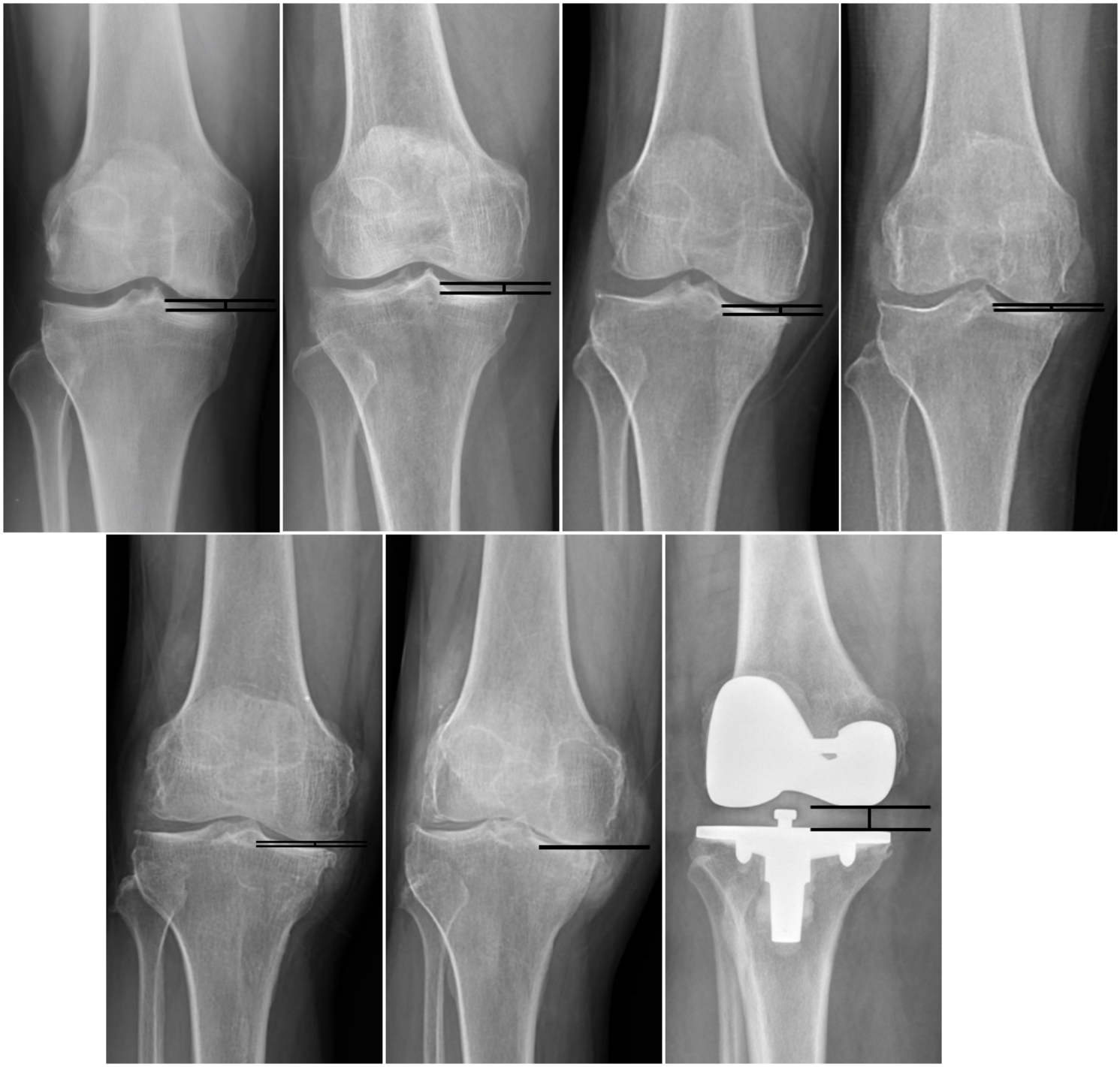

Figure 2

A 57-year-old woman had changes in MJSW series after PRP treatment.

The MJSW values were 3.6, 3.4, 2.7, 1.6, 0.3,0mm at pre-treatment, 12, 24, 36,48, and 58 months, respectively. Finally, the patient received TKA.

Abbreviations: MJSW, minimum joint space width; PRP, platelet-rich plasma; TKA, total knee arthroplasty

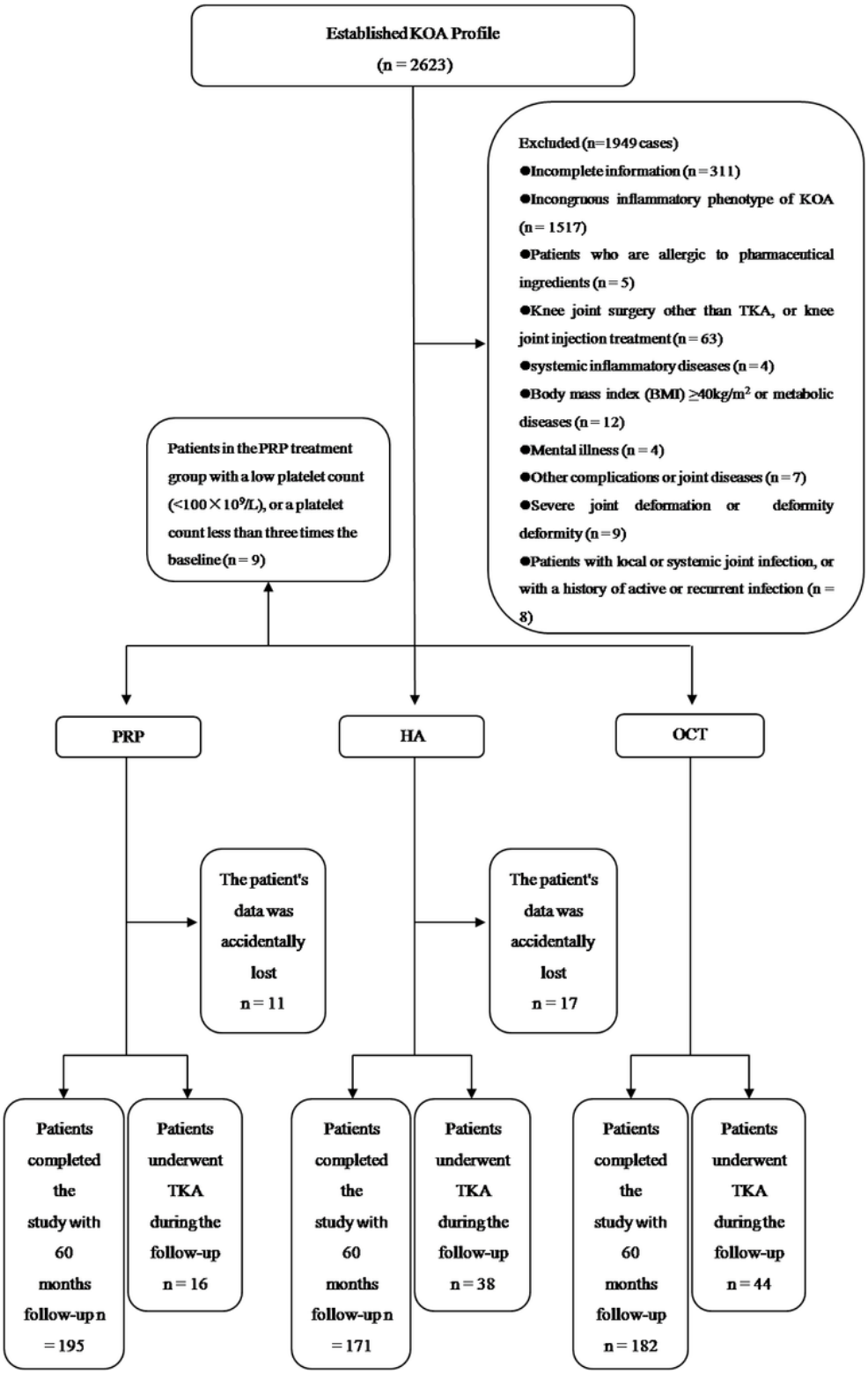

Figure 3

Flowchart of patient selection for the retrospective analysis

In total, 646 patients first diagnosed with KOA between 2012 and 2017, and those having an established KOA profile, were selected.

Abbreviations: HA, hyaluronic acid; OCT, other conservative treatment; PRP, platelet-rich plasma; TKA, total knee arthroplasty

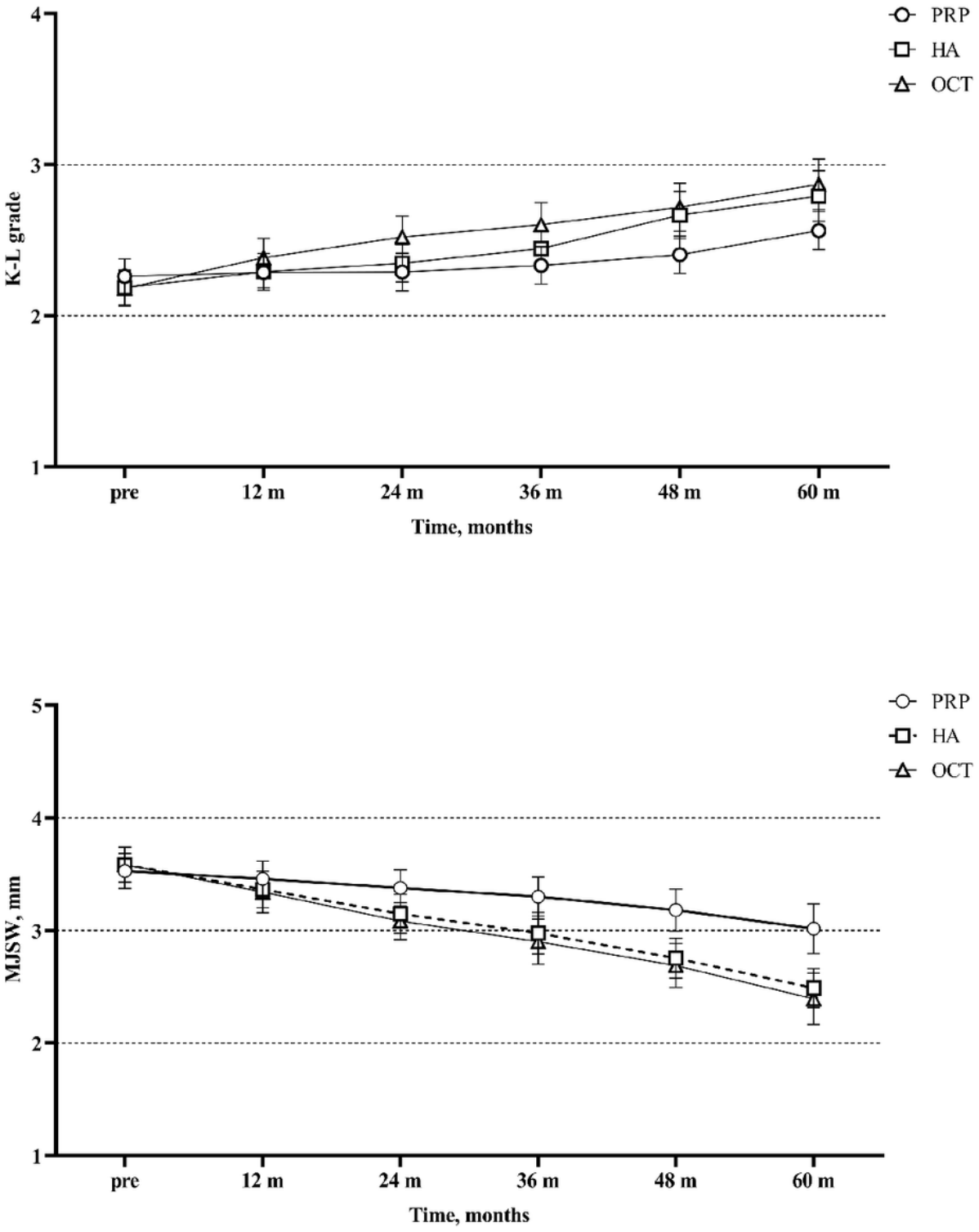

Figure 4

Serial changes in K-L grade and MJSW

Data represent the mean values; error bars represent 95% CIs.

Abbreviations: CIs, confidence intervals; HA, hyaluronic acid; K-L, Kellgren–Lawrence; MJSW, minimum joint space width; OCT, other conservative treatment;PRE, pre-treatment; PRP, platelet-rich plasma

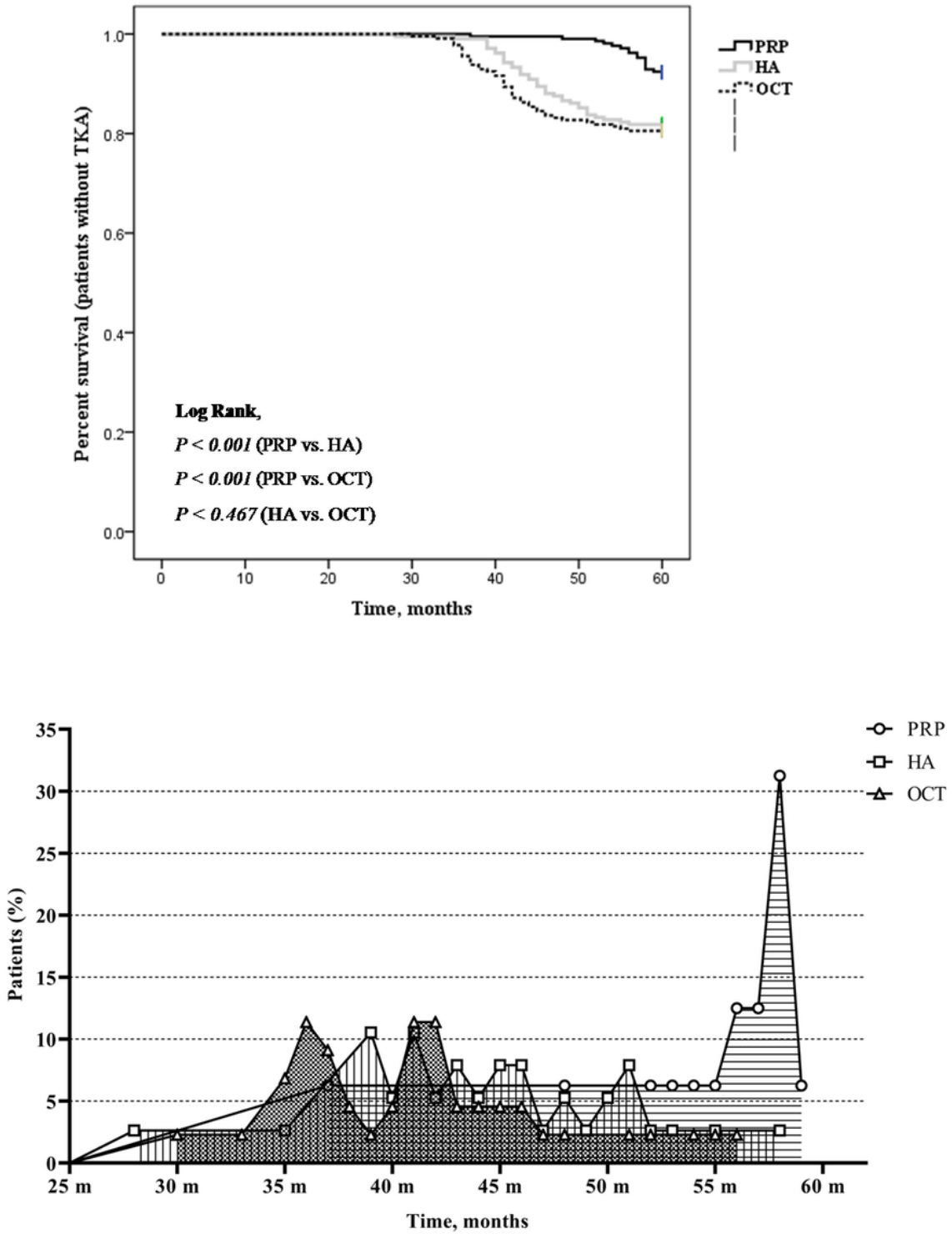

Figure 5

Kaplan–Meier survival analysis with total knee arthroplasty as the endpoint (**a**) and the percentage of patients who underwent TKA in each group at the time of TKA surgery (“Patients (%)” refers to just the patients in each group who underwent a TKA during the follow-up).

Data represent the mean values; error bars represent 95% CIs.

Abbreviations: CIs, confidence intervals; HA, hyaluronic acid; OCT, other conservative treatment; PRP, platelet-rich plasma

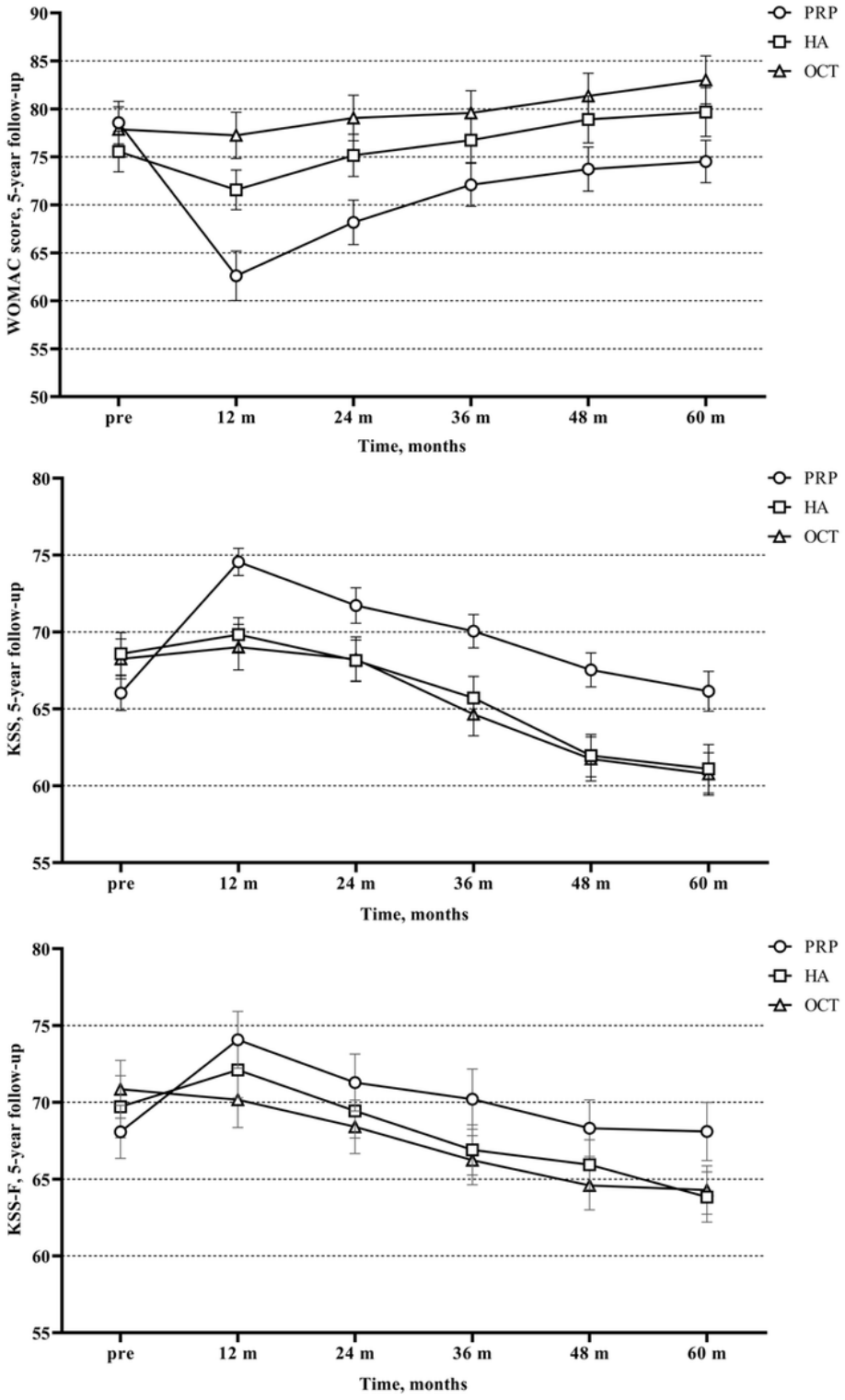

Figure 6

WOMAC, KSS, and KSS-F scores at each follow-up point

Data represent the mean values; error bars represent 95% CIs.

Abbreviations: KSS: Knee Society score; KSS-F, KSS-function score; PRE, pre-treatment; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities osteoarthritis index; CI, confidence interval.