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A model-based quantitative analysis of efficacy and associated factors of platelet rich plasma treatment for osteoarthritis

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Objective: While platelet rich plasma (PRP) has been extensively studied in treating osteoarthritis (OA), there has been an ongoing debate regarding the efficacy of PRP and the optimal subpopulation for PRP treatment remains unknown. The authors hereby aim to establish a pharmacodynamic model-based meta-analysis to quantitatively evaluate PRP efficacy, comparing with hyaluronic acid (HA) and identify relevant factors that significantly affect the efficacy of PRP treatment for OA.

Methods: The authors searched for PubMed and the Cochrane Library Central Register of Controlled Trials of PRP randomized controlled trials (RCTs) for the treatment of symptomatic or radiographic OA from the inception dates to 15 July 2022. Participants' clinical and demographic characteristics and efficacy data, defined as Western Ontario and McMaster Universities Osteoarthritis Index and visual analog scale pain scores at each time point were extracted.

Results: A total of 45 RCTs (3829 participants) involving 1805 participants injected with PRP were included in the analysis. PRP reached a peak efficacy at ~ 2–3 months after injection in patients with OA. Both conventional meta-analysis and pharmacodynamic maximal effect models showed that PRP was significantly more effective than HA for joint pain and function impairment (additional decrease of 1.1, 0.5, 4.3, and 1.1 scores compared to HA treatment at 12 months for Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, function, and visual analog scale pain scores, respectively). Higher baseline symptom scores, older age ($\geq$60 years), higher BMI ($\geq$30), lower Kellgren–Lawrence grade ($\leq$2) and shorter OA duration (<6 months) were significantly associated with greater efficacy of PRP treatment.

Conclusion: These findings suggest that PRP is a more effective treatment for OA than the more well-known HA treatment. The authors also determined the time when the PRP injection reaches peak efficacy and optimized the targeting subpopulation of OA. Further high-quality RCTs are required to confirm the optimal population of PRP in the treatment of OA.

Keywords: model-based meta-analysis, osteoarthritis, platelet rich plasma

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease with hyaline cartilage impairment and subchondral bone remodeling, affecting generally 10% of the global population[1]. Pain, limited function, swelling, stiffness, and reduced strength are usual symptoms of the disease[2]. Current treatment options mainly focus on relieving pain and improving function in the late stage. To date, no definitive therapy can reverse the progression of OA or prevent cartilage from degradation[3]. Therefore, there is an urgent need for new evidence-based therapeutic options.

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Platelet rich plasma (PRP) is an autologous concentrate of human platelets, derived from a participant's own plasma to concentrate and deliver growth factors and mediators from alpha granules found in platelets[4]. These growth factors and other molecules potentially facilitate critical tissue healing and pain-relieving effects through modulating inflammation, inhibiting chondrocyte apoptosis, synthesizing collagen, and regulating stem cells[5]. PRP has shown benefits for pain relief and functional improvement compared with placebo in OA treatment, especially for mild-moderate knee OA[6]. However, two recently published meta-analyses concluded that intra-articular PRP injection, compared with the hyaluronic acid (HA) injection, exerted inconsistent effects on joint symptoms or structural changes[7,8]. The inconsistencies between related trials regarding the effect of PRP in OA treatment may be due to the heterogeneity of participant characteristics and PRP preparations across studies.

Model-based meta-analysis (MBMA) is an efficient technique that integrates time-course and dose-effect relationships of drugs compared with conventional meta-analysis, by thoroughly utilizing covariates such as age, sex, dose, and disease duration[9,10]. By establishing a pharmacodynamic model with the MBMA, specified participant subgroups that may benefit from certain treatments can be identified and precise therapies could be eventually achieved[11]. Due to variations in mechanisms, risk factors, and clinically-relevant characteristics of participants, OA is increasingly recognized as a multifaceted chronic joint disease that no miracle treatment can be used for all OA participants[12]. Therefore, in this study, we aimed to quantitatively assess the efficacy of PRP treatment on symptoms of OA and further depict the optimal target population for PRP treatment. We also compared PRP with the commonest intra-articular HA injection in OA participants to explicitly demonstrate the therapeutic effect of the former. These results would provide significant information for current clinical practices and future clinical trial design.

HIGHLIGHTS

- The pharmacodynamic maximal effect models showed that platelet rich plasma (PRP) was significantly more effective than hyaluronic acid.
- PRP treatment reached a peak efficacy at about 2–3 months after injection in patients with osteoarthritis at Western Ontario and McMaster Universities Osteoarthritis Index subscales and visual analog scale pain scores.
- The subpopulation with higher baseline symptom scores, older age ($\geq$ 60 years), higher BMI ($\geq$ 30), lower Kellgren–Lawrence grade ($\leq$ 2) and shorter osteoarthritis duration (< 6 months) could have greater efficacy of PRP treatment.

Methods

Literature search

The public medical databases, PubMed, and the Cochrane Library Central Register of Controlled Trials were searched for randomized controlled trials (RCTs) related to PRP for OA treatment with a search deadline of 15 July 2022. The main terms used in the search were 'Osteoarthritis' and 'Platelet rich plasma'[13]. The detailed search strategies are described in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A201. This study has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14], Supplemental Digital Content 2, http://links.lww.com/JS9/A202, Supplemental Digital Content 3, http://links.lww.com/JS9/A203, and assessing the methodological quality of systematic reviews (AMSTAR), Supplemental Digital Content 4, http://links.lww.com/JS9/A204, Guidelines.

Inclusion and exclusion criteria

The inclusion criteria were as follows: RCTs on monotherapy of PRP injection for the treatment of OA; participants enrolled in the trials must suffer from symptomatic or radiographic OA; and the sample size was more than 10.

Exclusion criteria were as follows: literatures including conference abstracts, reviews, meta-analyses, posthoc analyses, biomarker, and animal model studies, and other nonclinical trials; literatures not published in English; the trials included participants who had undergone joint surgery or who had rheumatoid arthritis, ankylosing spondylitis, or other rheumatic diseases; and trials on the spine or temporomandibular joint OA.

Data extraction and literature quality assessment

Microsoft Excel (version 2016) was used to extract the following information by two independent researchers (YC and SH) from the included trials: literature characteristics (author, year of publication, and digital object unique identifier); trial design characteristics; baseline characteristics of participants; and primary clinical outcomes at baseline and each visit: [Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales and visual analog scale (VAS) pain scores].

The literature quality assessment was independently performed by two researchers (TF and MZ) using the revised Cochrane risk of bias tool for randomized trials (RoB 2)[15]. The details of data extraction and literature quality assessment can be seen (S1 Fig. and S1–3 Table).

Modeling analysis on the efficacy of PRP

Base model establishment

The outcome scores after PRP treatment showed a trend of decreasing and then increasing over time, and these data could be fitted by the Bateman Emax model, the structural model of which can be seen in Equation (Eq) 1[16].

$$E = E_0 - E_{\max} * (e^{-koff * time} - e^{-kon * time}) \quad (1)$$

This study used the first-order conditional estimation method to estimate the model parameters.

Covariate model establishment

A covariate model was established to screen for significant covariates that could potentially influence the pharmacodynamic

parameters. The covariates investigated in this study included: age, sex, BMI, disease duration, baseline Kellgren–Lawrence (K–L) grade, treatment duration, injection site (knee, hip, or foot), injection frequency, whether leukocyte was removed from PRP or not, PRP was activated or not (addition of calcium gluconate or $CaCl_2$)[17], blindness (whether the trial is double-blinded, single-blinded, or unblinded) and using intention-to-treat analysis or not. Covariates with a missing data rate greater than or equal to 30% were not investigated, and missing values for covariates with a missing rate of less than 30% would be filled with the median of the remaining data. The way covariates were introduced into the model depended on their data type. Categorical covariates were introduced in models by Eq. 2, and continuous covariates were introduced in models by Eq. 3 or Eq. 4.

$$P_{typical,i} = P_{typical} + COV_i * \theta_{\mathrm{cov}} \quad (2)$$

$$P_{typical,i} = P_{typical} * [1 + (COV_i - COV_{median}) * \theta_{\mathrm{cov}}] \quad (3)$$

$$P_{typical,i} = P_{typical} * e^{(COV_i - COV_{median}) * \theta_{\mathrm{cov}}} \quad (4)$$

A stepwise covariate model (SCM) was used to screen the covariates introduced into the final model[18].

Random effect model establishment

The variability of PRP efficacy between different studies at the same covariate level could be described as interstudy variability, and an additive or proportional error model was used in this study (Eqs. 5 and 6).

$$P_i = P_{typical,i} + \eta_p \quad (5)$$

$$P_i = P_{typical,i} * e^{\eta_p} \quad (6)$$

Unexplainable variability was considered to be a residual error. This study used an additive error model to explain the residual error (Eq. 7):

$$Y_{obs,i,j} = Y_{pred,i,j} + \frac{\varepsilon_{i,j}}{\sqrt{N_{i,j}}} \quad (7)$$

Model validation

Model diagnostic plots were used to assess the goodness-of-fit of the final model[19]. Visual predictive check plots were used to assess the consistency of predictions and observations, which can further evaluate the prediction ability of the model. The stability of the final model was assessed using the bootstrap method.

Typical efficacy analysis of PRP

After the final model was established, the typical PRP efficacy values and their 90% CIs at different covariate levels could be simulated by 1000 Monte Carlo simulations based on the model parameter estimations and their standard errors[20]. In addition, we performed subgroup analyses of certain covariates of particular clinical interest, including age, sex, BMI, disease duration, baseline K–L grade, treatment duration, injection site, injection frequency, leukocytes removed from PRP or not, and PRP activated or not. The analytical details can be found in the Supplement, Supplemental Digital Content 1, http://links.lww.com/JS9/A201.

Quantitative comparison of the efficacy of PRP and HA

HA is a drug commonly used as a parallel comparator with PRP. In order to further clarify the clinical efficacy of PRP, this study would extract the endpoints and covariates data of HA from the PRP literature database constructed above and establish a pharmacodynamic model of HA (the methods of model establishment and assessment are similar to those of PRP). Once the final model of HA was determined, the difference between the reduction from baseline of each clinical outcome of PRP and HA at a given level of covariates and its 90% CI were obtained by 1000 Monte Carlo simulations. The vertical axis indicates the efficacy calculated by subtracting the efficacy of HA from that of PRP; if its CI did not span 0, the efficacy of the two drugs was considered to be significantly different, and the larger this difference was, the better the efficacy of PRP could be considered than that of HA.

Results

Characteristics of the included studies

A total of 716 studies were initially identified. A total of 45 studies (3829 participants), including 54 PRP trial arms with 1805 participants were eventually included in the analysis. Of these, 23 studies reported WOMAC subscales and 41 studies reported VAS pain scores, and these two most commonly reported endpoints were the primary outcomes for modeling analysis in this study. The flow chart of the inclusion and exclusion of the literature, the detailed characteristics of the included literature and the results of the literature quality assessment can be found in Fig. 1, Supplementary Tables 2 and 3, Supplemental Digital Content 1, http://links.lww.com/JS9/A201, Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A201, respectively.

Model establishment and assessment

As only two studies reported follow-up data beyond 13 months, follow-up data within 13 months were analyzed to ensure model stability. To ensure the scores of the WOMAC subscales were comparable across studies, all reported WOMAC subscales were transformed to a standard WOMAC scale, which included 24 questions (5 for pain, 2 for stiffness, and 17 for physical function) with a total score of 0–96[21], and all reported VAS pain scores were converted to a 0–10 cm scale.

After screening by the SCM, baseline WOMAC pain scores, baseline WOMAC stiffness scores, baseline VAS pain scores, and baseline BMI were found to have significant effects on the E_{max}. The estimation of the model parameters and their relative standard errors are shown in Table 1. The efficacy of PRP in WOMAC subscales s and VAS pain scores can be expressed in

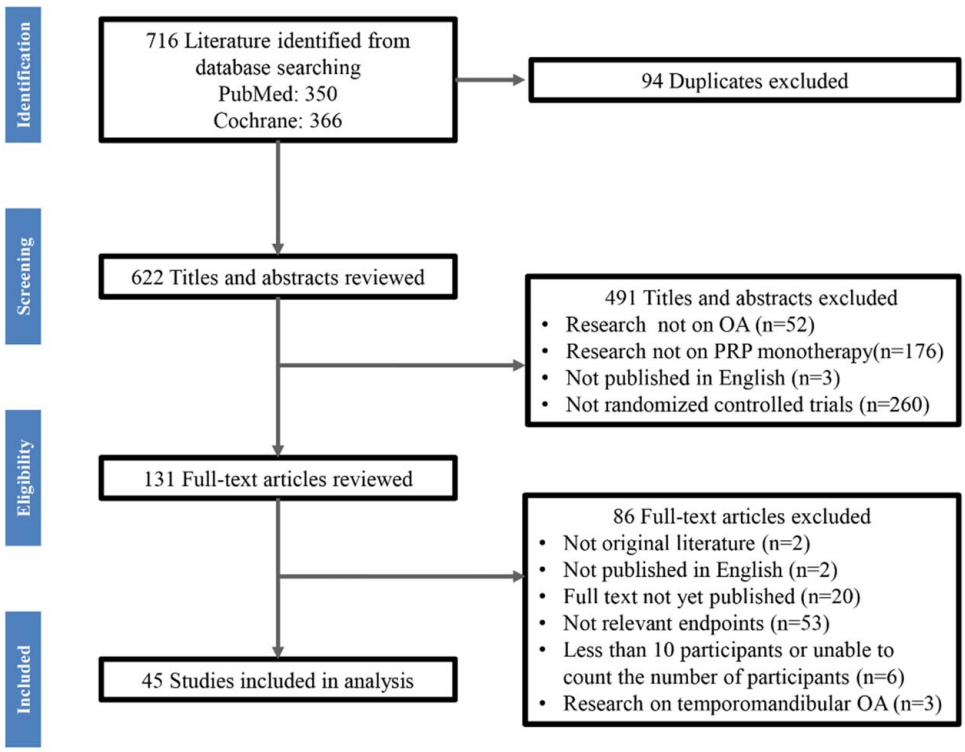

Figure 1. Flow chart demonstrating the inclusion and exclusion of studies into the analysis.

Eqs. 8 to 11:

$$E_{WOMACpain} = 6.51 * [1 + 0.103 * (Baselinepain - 10.6)] * (e^{-0.0325*t} - e^{-2.20*t}) \quad (8)$$

$$E_{WOMACstiffness} = 2.55 * e^{0.228*(Baseline_{stiffness}-4.4)} * [1 + 0.0797 * (BMI - 28.2)] * (e^{-0.0446*t} - e^{-1.97*t}) \quad (9)$$

$$E_{WOMACfunction} = 20.5 * (e^{-0.0616*t} - e^{-1.81*t}) \quad (10)$$

$$E_{VASpain} = 3.61 * e^{0.233*(Baseline_{vaspain}-6.4)} * (e^{-0.0385*t} - e^{-1.61*t}) \quad (11)$$

After PRP treatment, a larger improvement in participants' WOMAC pain, stiffness, and VAS pain scores were found when their baseline scores were higher, and this was consistent across different timepoints, while participants' baseline WOMAC function scores had no significant influence on the efficacy of PRP. In addition, the efficacy of PRP on WOMAC stiffness scores improved when baseline BMI increased (Fig. 4).

The goodness-of-fit plots of the PRP absolute efficacy model showed high consistency between the observations on population predictions and individual predictions, with conditional weighted residuals less than 4 (corresponding to $P < 0.05$) and randomly distributed around a straight line passing through zero (Supplementary Fig. 2, Supplemental Digital Content 1, http://links.lww.com/JS9/A201). The visual predictive check plots showed that the PRP efficacy values and their 90% CIs obtained from model simulations could cover most of the observations, indicating the model has good prediction performance (Supplementary Fig. 3, Supplemental Digital Content 1, http://links.lww.com/JS9/A201). The success rates of the 1000 times bootstrap methods for the PRP pharmacodynamic model with WOMAC pain, stiffness, function, and VAS pain scores were 98.9, 99.3, 97.5, and 94.2%, respectively. The median of the model parameters obtained by the bootstrap method was close to the model parameters estimated from the original dataset (Table 1), indicating that the model was relatively stable and unlikely to be influenced by specific studies. Overall, the results of the model assessment suggested that the established models could describe the observed data well.

Typical efficacy analysis of PRP

PRP efficacy simulation

Based on the parameters estimated by the final model, the typical absolute efficacy of PRP treatment in each WOMAC subscale and VAS pain score over 12 months at different baseline levels and their 90% CIs can be obtained by 1000 Monte Carlo simulations (Table 2). When the baseline WOMAC pain score was 10, PRP could be expected to reduce the WOMAC pain score by 5.2, 5.5, 5.0, and 4.1 points at 1, 3, 6, and 12 months, respectively. When the baseline WOMAC stiffness score was 4 and the BMI was 30, PRP could be expected to reduce the WOMAC stiffness score by 2.2, 2.3, 2.0, and 1.6 points at 1, 3, 6, and 12 months, respectively. The improvement of WOMAC function score by PRP treatment was not affected by common covariates, and PRP was expected to reduce the WOMAC function score by 15.6, 16.6, 13.9, and 9.6 points at 1, 3, 6, and 12 months, respectively. When the baseline VAS pain score was 5, PRP could be expected to

Table 1

Parameter estimations and bootstrap results of the PRP final model.

	WOMAC pain		WOMAC stiffness		WOMAC function		VAS pain	
Parameters	Estimates (RSE%)	Bootstrap median (5–95%CI)	Estimates (RSE%)	Bootstrap median (5–95%CI)	Estimates (RSE%)	Bootstrap median (5–95%CI)	Estimates (RSE%)	Bootstrap median (5–95%CI)
Pharmacodynamic parameters								
E_{max}	6.510 (4.9)	6.527 (5.980–7.222)	2.550 (8.2)	2.634 (2.288–3.034)	20.500 (12.1)	20.625 (16.812–25.165)	3.610 (8.9)	3.647 (3.122–4.271)
k_{on}	2.200 (25.0)	2.110 (1.520–3.392)	1.970 (23.9)	1.793 (1.241–3.870)	1.810 (26.7)	1.767 (1.236–3.105)	1.610 (22.0)	1.599 (1.100–2.474)
k_{off}	0.033 (26.2)	0.034 (0.014–0.059)	0.045 (36.1)	0.049 (0.024–0.085)	0.062 (28.4)	0.062 (0.034–0.093)	0.039 (24.1)	0.038 (0.025–0.058)
Covariate parameter								
θ_{Base}*	0.103 (12.1)	0.102 (0.070–0.126)	0.278 (19.5)	0.234 (0.118–0.323)	/	/	0.233 (23.0)	0.232 (0.144–0.315)
θ_{BMI}*	/	/	0.080 (33.2)	0.078 (0.029–0.123)	/	/	/	/
Inter-study variability								
η_{Emax}†	0.803 (27.1)	0.836 (0.482–1.562)	0.578 (25.3)	0.532 (0.225–0.861)	0.584 (17.3)	0.563 (0.393–0.730)	1.500 (17.0)	1.425 (0.753–1.861)
η_{kon}†	0.651 (23.2)	0.620 (0.355–0.948)	0.655 (26.2)	0.664 (0.313–1.225)	0.540 (20.2)	0.830 (0.537–1.209)	1.072 (19.6)	1.057 (0.707–1.423)
η_{koff}†	1.616 (19.7)	1.578 (0.966–2.337)	0.036 (26.4)	0.038 (0.023–0.088)	0.077 (21.2)	0.076 (0.051–0.114)	1.034 (15.1)	1.051 (0.764–1.312)
Residual error								
ε	2.665 (24.4)	2.494 (1.260–3.605)	1.446 (28.9)	1.382 (0.551–1.975)	2.439 (30.4)	2.320 (1.040–3.508)	1.277 (19.7)	1.277 (0.843–1.680)

Emax, theoretical maximal efficacy; Eq, equation; k_{on}, the PRP efficacy onset rate which can reflect the time required for the PRP to reach its maximum effect; k_{off}, the PRP efficacy loss rate which can reflect the rate of PRP efficacy decrease after reaching its maximum effect; PRP, platelet rich plasma; RSE, relative standard error; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*θ correction factor to the covariate of baseline, η the interstudy variability of the pharmacodynamic parameter, ε residual error.

†η_{Emax} of WOMAC pain, η_{Emax} and η_{koff} of WOMAC stiffness, η_{koff} of WOMAC function, η_{Emax} of VAS pain all meet the additive model (Eq. 2), the other inter-study variability parameters meet the exponential model (Eq. 3).

reduce the VAS pain score by 2.0, 2.3, 2.1, and 1.6 points at 1, 3, 6, and 12 months, respectively. Figure 2 shows that the efficacy of PRP treatment reached a peak at about 2–3 months and then gradually decreased, with the loss rates of about 3.2, 4.4, 6.0, and 3.8% per month for WOMAC pain, stiffness, function, and VAS pain scores, respectively.

Subgroup analysis of potential influencing factors

This study also performed subgroup analyses of potential influencing factors of clinical interest. As shown in Figure 3, older participants (≥60 years) obtained better treatment effects on WOMAC function. In addition, a significant association was found between K–L grades (K–L ≤2) and efficacy on WOMAC pain, and a trend towards higher efficacy of PRP on WOMAC stiffness, function, and VAS pain scores. Also, obese patients (BMI ≥30) obtained more efficacious results in WOMAC pain, function, and VAS pain. Notably, BMI was a significant covariate in the MBMA model for WOMAC stiffness. Shorter OA duration (<6 months) denoted better treatment effects in WOMAC pain and function. On the other hand, the association between sex and efficacy of PRP was inconsistent, and factors such as PRP activation or not, leukocyte removal, injection frequency, injection site, treatment duration, blindness (data not shown) or whether used intention-to-treat analysis (data not shown) had no significant influence on the efficacy (Supplementary Figure 4, Supplemental Digital Content 1, http://links.lww.com/JS9/A201).

Quantitative comparison of the efficacy between PRP and HA groups

The final model parameter estimations and model assessment results of HA can be found in Supplementary Table 4, Supplemental Digital Content 1, http://links.lww.com/JS9/A201 and Supplementary Figure S5–6, Supplemental Digital Content 1, http://links.lww.com/JS9/A201. We found that the baseline VAS pain scores and gender had significant influences on the pharmacodynamic parameter E_{max} of HA, and the efficacy of HA in each WOMAC subscale and VAS pain score can be expressed by Eq. 12–15, in which 6.2 was the median VAS pain score for the participants using HA.

$$E_{WOMAC\mathit{pain}} = 4.\,62*e^{-2.42*(Men-0.3)} *(e^{-0.0634*t} - e^{-3.74*t}) \quad (12)$$

$$E_{WOMAC\mathit{stiffness}} = 1.\,97*(e^{-0.0756*t} - e^{-3.47*t}) \quad (13)$$

$$E_{WOMAC\mathit{function}} = 14.\,5*(e^{-0.0842*t} - e^{-3.01*t}) \quad (14)$$

$$E_{VAS\mathit{pain}} = 2.\,26*e^{0.374*(Baseline_{VASpain}-6.2)} *(e^{-0.0636*t} - e^{-9.20*t}) \quad (15)$$

Simulation results (Fig. 4) showed that PRP was significantly more effective than HA or tended to be more effective than HA on all outcomes. At 12 months, for example, PRP treatment was significantly associated with an additional decrease of 1.1, 0.5, 4.3, and 1.1 scores compared to HA treatment for WOMAC pain, stiffness, function, and VAS pain scores, respectively. This finding was also in line with the conventional meta-analysis performed in this study. Conventional meta-analysis forest plots are shown in Supplementary Figures 7–10, Supplemental Digital Content 1, http://links.lww.com/JS9/A201.

Discussion

PRP has gained increasing attention for OA treatment due to its merits of releasing growth factors, cytokines, and adhesion protein[22]. By using MBMA, we found that compared with HA, PRP treatment relieved more pain, improved function, and stiffness in OA participants to a greater extent, which was consistent with results from a conventional meta-analysis. The efficacy of

Table 2

Model-estimated PRP efficacy at different time points.

Baseline	1 month typical efficacy (5–95%CI)	3 months typical efficacy (5–95%CI)	6 months typical efficacy (5–95%CI)	12 months typical efficacy (5–95%CI)
WOMAC pain				
6	−2.936 (−3.283~ −2.351)	−3.103 (−3.392~ −2.791)	−2.819 (−3.166~ −2.502)	−2.319 (−2.783~ −1.926)
10	−5.236 (−5.858~ −4.147)	−5.532 (−6.047~ −4.988)	−5.026 (−5.643~ −4.445)	−4.135 (−4.967~ −3.419)
16	−8.684 (−9.727~~ −6.924)	−9.176 (−10.025~ −8.264)	−8.336 (−9.352~ −7.367)	−6.859 (−8.250~ −5.700)
WOMAC stiffness				
2, BMI = 25	−0.896 (−1.078~ −0.575)	−0.956 (−1.127~ −0.763)	−0.839 (−1.054~ −0.653)	−0.642 (−0.943~ −0.433)
4, BMI = 25	−1.416 (−1.709~ −0.906)	−1.512 (−1.789~ −1.204)	−1.326 (−1.659~ −1.033)	−1.015 (−1.487~ −0.674)
6, BMI = 25	−2.239 (−2.699~ −1.456)	−2.390 (−2.803~ −1.898)	−2.097 (−2.624~ −1.630)	−1.605 (−2.350~ −1.083)
2, BMI = 30	−1.375 (−1.664~ −0.868)	−1.468 (−1.720~ −1.168)	−1.288 (−1.611~ −0.998)	−0.985 (−1.442~ −0.659)
4, BMI = 30	−2.174 (−2.615~ −1.422)	−2.320 (−2.739~ −1.841)	−2.036 (−2.556~ −1.577)	−1.558 (−2.258~ −1.050)
6, BMI = 30	−3.436 (−4.141~ −2.213)	−3.668 (−4.319~ −2.924)	−3.219 (−4.061~ −2.504)	−2.463 (−3.577~ −1.668)
WOMAC function				
/	−15.610 (−19.391~ −10.609)	−16.620 (−20.288~ −12.777)	−13.889 (−17.933~ −10.407)	−9.598 (−14.254~ −6.360)
VAS pain				
3	−1.246 (−1.488~ −0.932)	−1.443 (−1.665~ −1.211)	−1.297 (−1.531~ −1.080)	−1.030 (−1.303~ −0.809)
5	−1.986 (−2.371~ −1.510)	−2.300 (−2.647~ −1.919)	−2.068 (−2.432~ −1.731)	−1.641 (−2.062~ −1.287)
8	−3.995 (−4.790~ −3.020)	−4.627 (−5.317~ −3.859)	−4.160 (−4.902~ −3.463)	−3.302 (−4.123~ −2.589)

PRP, platelet rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

PRP treatment reached a peak at about 2–3 months and several factors, including age, BMI, K–L grade, OA duration, and baseline pain and stiffness scores were found to affect the efficacy of PRP.

To the best of our knowledge, this is the first study to compare PRP with HA for OA treatment by establishing pharmacodynamic models and PRP exhibited superior therapeutic effects on all outcomes, similar to our conventional meta-analysis. HA is the most widely used comparator in previous clinical trials compared to corticosteroid or saline injection[23]. In contrast to our findings, Migliorini *et al*. conducted a Bayesian network meta-analysis that included 30 RCTs (3463 participants) to compare PRP, placebo, corticosteroids, and HA at 3, 6, and 12 months follow-up. The results demonstrated no discrepancies among them for the WOMAC scores and VAS pain[24]. Additionally, novel HA-PRP conjugates are suggested to be a promising strategy for OA management mainly because they could not only increase joint lubrication but also promote chondrocyte proliferation[25,26]. However, our established model did not compare HA-PRP together with PRP due to insufficient numbers of studies, as such, future prospective studies could emphasize the HA-PRP combination as a possibly better option.

In this study, we established a pharmacodynamic model that could accurately estimate the time-effect of PRP injection efficacy with different baseline characteristics that were unclear previously[27]. Filardo *et al*.[28] conducted a meta-analysis showing no significant improvement of PRP injection for OA symptoms until 12 months, while Bennell *et al*.[5] summarized that PRP injection might safely provide symptomatic benefit for OA at least in 12 months. Our study reported that PRP treatment reached a peak efficacy at about 2–3 months, which was the first to provide a more explicit and accurate reference for the interval cycle of PRP injection in clinical practice.

The current MBMA has identified a significant impact of baseline WOMAC pain, stiffness, and VAS pain scores on the treatment efficacy across different time points. In other words, the model simulations suggested that treatment of PRP reduced symptoms to a greater degree in participants with more severe baseline symptoms. Thus, future PRP trials should consider including participants with higher baseline pain levels. We also found that participants whose BMI greater than or equal to 30 had greater efficacy of PRP treatment in WOMAC pain, WOMAC function, and VAS pain. Obese participants tend to secrete more inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha[29], which would aggravate OA symptoms. It was acknowledged that PRP injection could stimulate chondrocyte proliferation and release anti-inflammatory molecules[30,31]. Our assumption is that PRP could interfere with catabolic and inflammatory events caused by obesity, thereby enhancing chondrocyte proliferation.

We discovered some other practical predictors for the efficacy of PRP on WOMAC subscales and VAS pain in subgroup analyses. PRP injection therapy is quite expensive as the median cost of one injection is about $714 in the United States[32]. These results can help to identify the optimal population for PRP treatment and reduce unnecessary costs[33]. A prior trial showed PRP had better efficacy for participants at early or moderate stages of OA (K–L grade ≤ 2)[34], which was in line with our findings. In addition, we found that PRP treatment was more beneficial for patients with an OA duration of less than 6 months. Notably, our results also showed PRP had better efficacy in participants with higher baseline pain scores, which seems conflicting. However, one should bear in mind that symptoms of OA patients may not be positively correlated with their disease duration or K–L grades of the joints[35].

As for the necessity of activating PRP or not, our MBMA did not observe differences in WOMAC stiffness or VAS pain. Moreover, our MBMA did not manifest significant discrepancies of leukocyte removed or not for WOMAC subscales and VAS scores. Leukocyte-poor PRP may have an advantage over leukocyte-rich PRP for its anti-inflammatory effect, but another research argued that leukocyte-rich PRP contained more concentrated growth factors though it may have a proinflammatory role in OA[36]. Also, PRP injection frequency (once only or

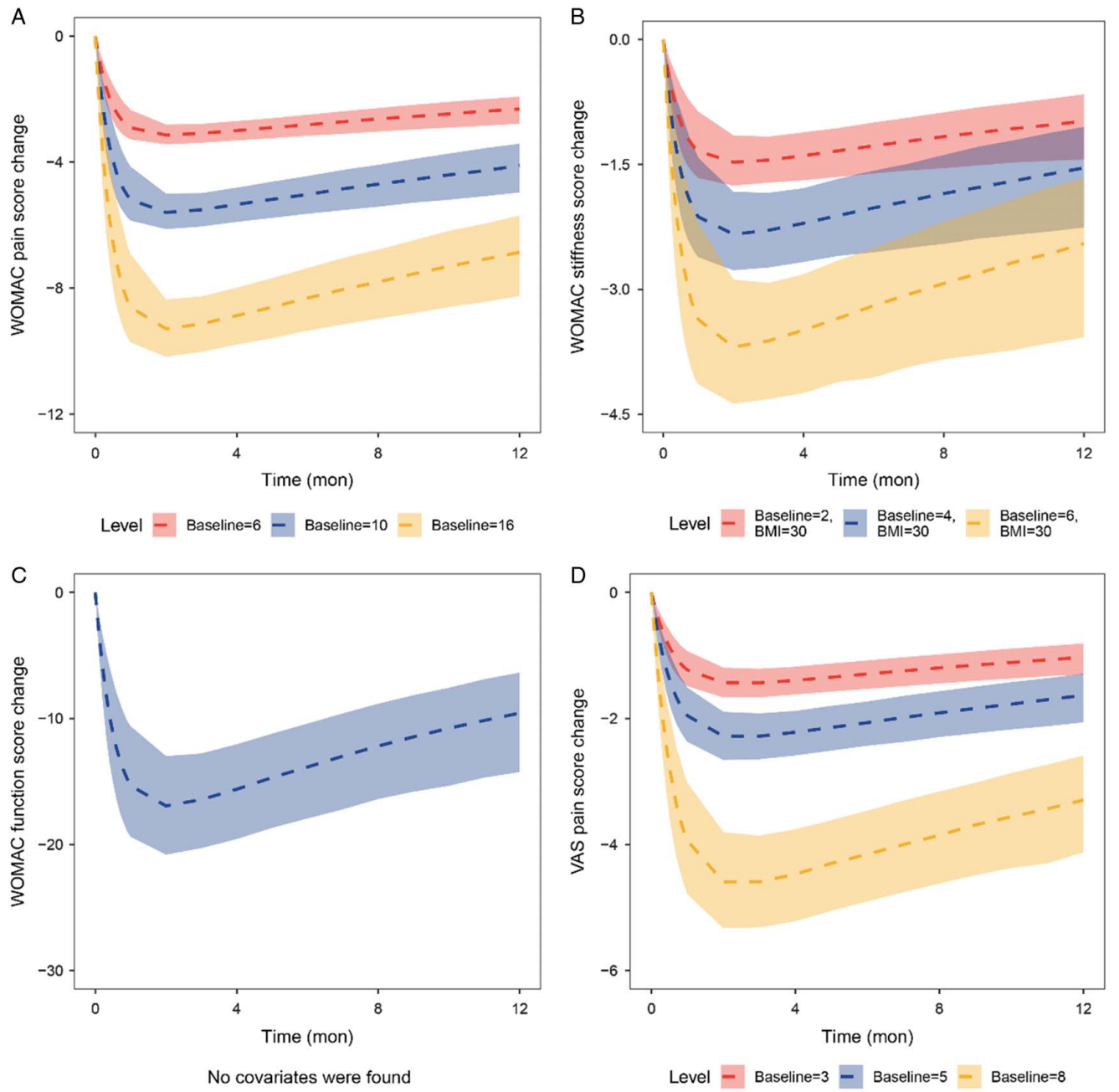

Figure 2. The typical PRP efficacy and 5~95% CIs of different WOMAC subscales and VAS under different baseline levels. PRP, platelet rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. (A) WOMAC pain score, (B) WOMAC stiffness score, (C) WOMAC function score, and (D) VAS pain score. *The dashed lines represent the median typical PRP efficacy estimated by model, the ribbons represent 5~95% CIs of typical efficacy, different colors represent different baseline levels.

once/week) was not a predictor of all outcomes in our MBMA analysis. Chou *et al.*[37] trial reported that increased injection time and longer follow-up could relieve pain and improve function more conspicuously. It is critical to point out that PRP preparation and administration protocols were not standardized among studies. Therefore, large RCTs using standardized approaches for PRP therapy are essential to define optimal PRP preparation and administration procedures.

The strengths of the current study include: quantitatively describing the time course of PRP treatment (such as the maximum drug effect and the onset time), identifying possible affecting factors of efficacy using the nonlinear models, eliminating trials' heterogeneity with covariate models, conforming to the physiological state better than conventional meta-analysis, and utilizing convincing outcome measures such as WOMAC and VAS.

This study also has potential limitations: First, the relatively small sample size may affect the power and the stability of the final model[38]. To ensure the stability and accuracy of the model, we had to fix some of the pharmacodynamic parameters or

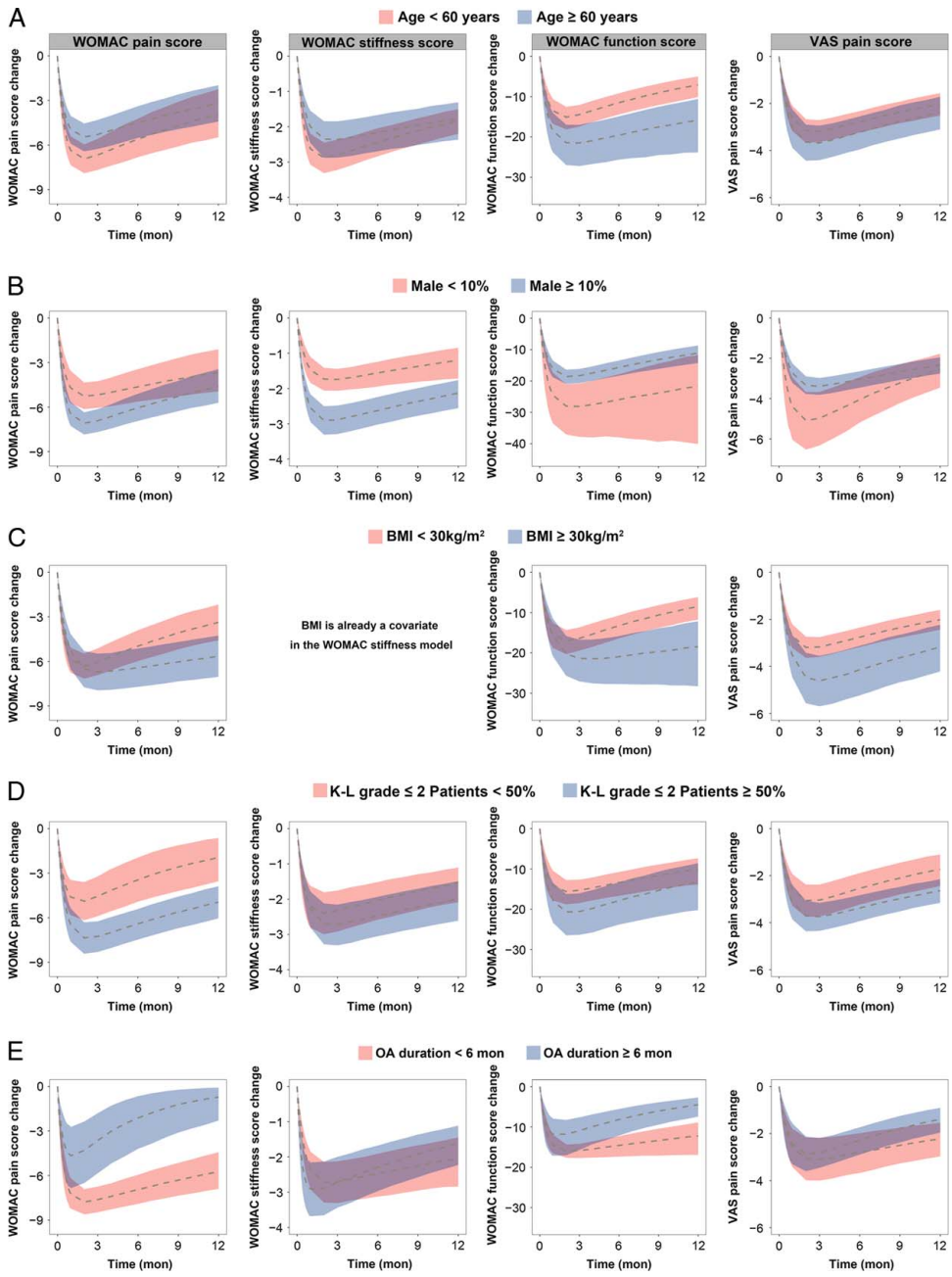

Figure 3. The results of subgroup analysis for PRP treatment. K–L, Kellgren–Lawrence; OA, osteoarthritis; PRP, platelet rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. (A) age subgroup; (B) male proportion subgroup; (C) BMI subgroup; (D) K–L grades subgroup, and (E) OA duration subgroup. *The dashed lines are the median of the summarized PRP efficacy estimated by model, ribbons are the 5~95% CIs of the summarized PRP efficacy, and different colors represent different subgroups. **#** Sample size for each subgroup (WOMAC pain, WOMAC stiffness, WOMAC function, and VAS pain): age less than 60 years (567, 518, 518, 944) , age greater than or equal to 60 years (346, 386, 386, 630), male proportion less than 10% (96, 96, 96, 116), male proportion greater than or equal to 10% (719, 710, 710, 1349), BMI less than 30 kg/m^2 (755, 746, 746, 1224), BMI greater than or equal to 30 kg/m^2 (107, 107, 107, 201), K–L grades less than or equal to 2 patients less than 50% (276, 276, 276, 532), K–L grades less than or equal to 2 patients greater than or equal to 50% (454, 445, 445, 801), OA duration less than 6 month (284, 284, 284, 439), OA duration greater than or equal to 6 month (212, 252, 252, 626). Number of trial arms in each subgroup (WOMAC pain, WOMAC stiffness, WOMAC function, VAS pain): age less than 60 years (17, 16, 16, 29), age greater than or equal to 60 years (12, 13, 13, 19) , male proportion less than 10% (4, 4, 4, 5), male proportion greater than or equal to 10% (22, 22, 22, 39), BMI less than 30 kg/m^2 (22, 22, 22, 34), BMI greater than or equal to 30 kg/m^2 (5, 5, 5, 8), K–L grades less than or equal to 2 patients less than 50% (10, 10, 10, 17), K–L grades less than or equal to 2 patients greater than or equal to 50% (13, 13, 13, 22), OA duration less than 6 month (7, 7, 8, 12), OA duration greater than or equal to 6 month (7, 8, 8, 17).

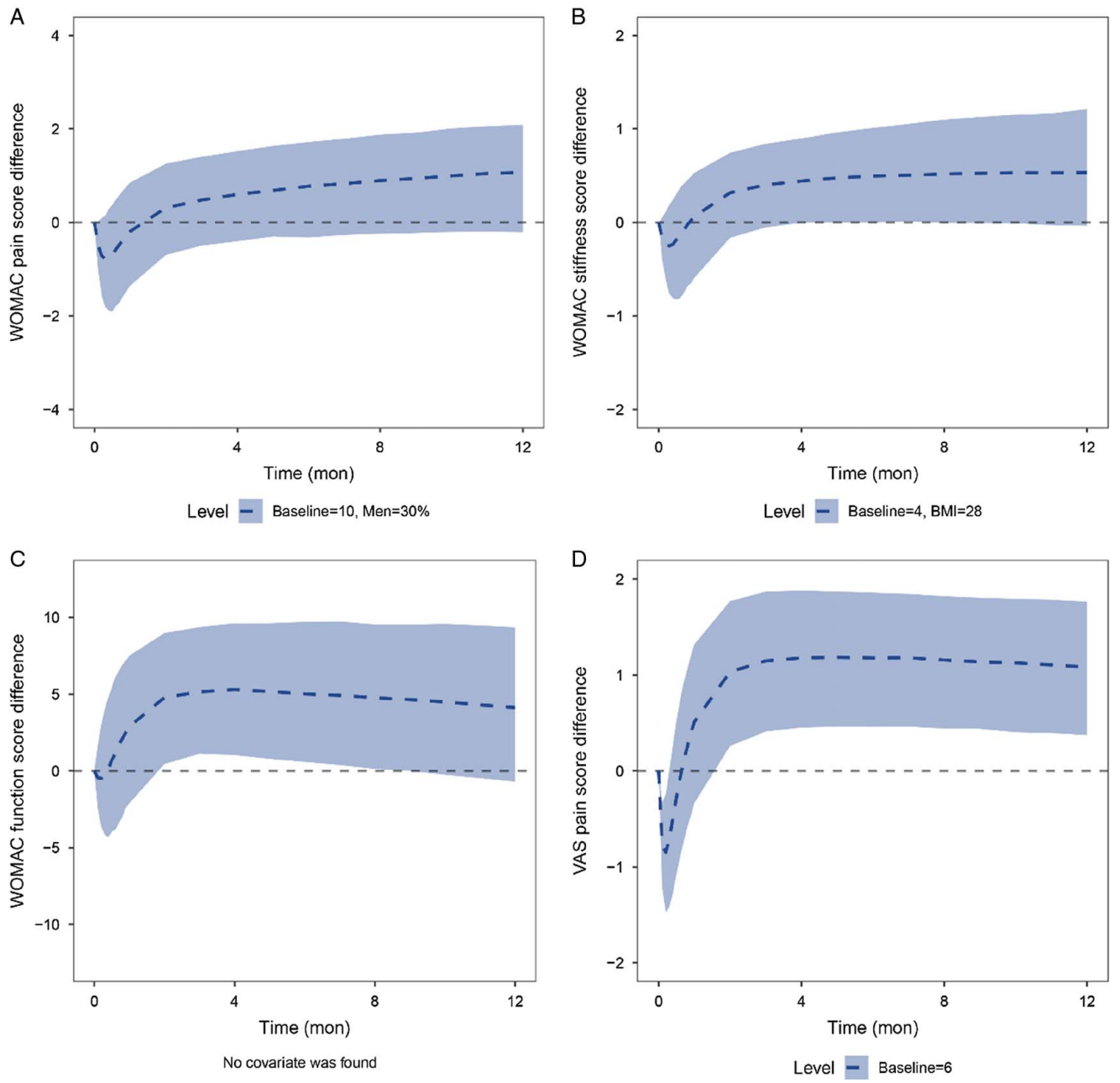

Figure 4. The relative effects between PRP and HA for different WOMAC subscales and VAS under a given baseline level. PRP, platelet rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. (A) WOMAC pain score difference, (B) WOMAC stiffness score difference, (C) WOMAC function score difference,and (D) VAS pain score difference. *The black dashed lines represent the typical efficacy difference estimated by the model, the ribbons represent 5~95% CIs of typical efficacy. **#** Sample size for PRP in each subgroup (WOMAC pain, WOMAC stiffness, WOMAC function, VAS pain): 918, 904, 904,1574; Sample size for HA in each subgroup (WOMAC pain, WOMAC stiffness, WOMAC function, VAS pain): 473,463,463,796. Number of PRP trial arms in each subgroup (WOMAC pain, WOMAC stiffness, WOMAC function, VAS pain): 29,29,29,49; Number of HA trial arms in each subgroup (WOMAC pain, WOMAC stiffness, WOMAC function, VAS pain):13,13,13,20.

use random effect models. Second, the missing data of some covariates in the pooled database, such as OA duration and PRP activation, may prevent us from determining whether they had potential influence by using the SCM method. Third, the included trials were heterogeneous in PRP preparation methods, and such heterogeneity was hard to be eliminated by the SCM method. Last, the quality of included studies was a 'moderate' risk of bias as 75% of studies were assessed as 'low risk of bias' or 'some concerns' (Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A201).

Conclusions

This study suggests that PRP treatment could significantly relieve pain and improve joint function, compared with HA treatment. Older ($\geq$60 years) obese (BMI $\geq$30) OA participants with K–L

grade less than or equal to 2, suffering OA for less than 6 months, and having more severe baseline symptoms could benefit most from PRP treatment. There was no significant association between PRP preparation or administration protocols and the outcomes. Further high-quality RCTs are required to confirm the optimal population of PRP treatment for OA.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Author contribution

Y.C., J.L., and S.H. served as co-first authors, with equal contributions to the manuscript. Z.Z., L.L., C.D.: conception and design; Y.C., J.L., S.H., T.F., M.Z., Z.L., X.W.: drafting of the manuscript; J.L., X.W., L.J., Y.P., D.H., L.L.: critical revision of the manuscript for important intellectual content; L.L., J.L., L.L.: statistical analysis; Z.Z., C.D.: obtained funding; Z.Z., L.L., D.H., C.D.: administrative, technical, or material support; Z.Z., L.L., W.H., L.L., S.N.F.: supervision. Acquisition, analysis, or interpretation of data is done by all authors.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Guarantor

Ying Cao, Jieren Luo, Lujin Li, and Zhaohua Zhu had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Data availability statement

All data generated and analyzed during this study are included in this published article. The data presented in the article may be requested by consulting the correspondence author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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