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Review

Efficacy of mesenchymal stem cells and platelet-rich plasma therapies on wound healing: A Systematic Review and meta-analysis

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ABSTRACT

Background: Wound healing is a complex physiological process essential for maintaining tissue integrity and function. This meta-analysis aims to evaluate the efficacy of mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP), and their combination in enhancing wound healing.
Methods: We conducted a systematic search of PubMed, Web of Science, and Scopus databases for studies published from 2010 to 2024. The inclusion criteria were randomized controlled trials (RCTs) and controlled clinical trials involving human subjects treated with MSCs, PRP, or both. The primary outcomes assessed were wound closure rates and mean healing times, while secondary outcomes included wound size reduction, pain management, infection rates, recurrence, adverse events, and cost-effectiveness. Data were pooled using STATA software version 17.0, with standardized mean differences (SMDs) and risk differences (RDs) calculated.
Results: A total of 34 studies involving 2458 patients were included. PRP and MSCs significantly reduced wound healing time (PRP: SMD = −1.08, 95 % CI: 1.75 to −0.42, $p < 0.001$; MSCs: SMD = −1.7195 %, CI: 2.44 to −0.99, $p < 0.001$). MSCs positively impacted new vessel development (overall SMD = 0.55, 95 % CI: 0.39 to 0.71, $p < 0.001$). PRP-treated groups had higher ulcer healing rates (72.4 % vs 52.5 %, RD = 0.21, 95 % CI: 0.16 to 0.26, $p < 0.001$). Infection rates showed no statistically significant difference between PRP and control groups (DR = −0.11, 95 % CI: 0.34 to 0.12, $p > 0.05$), while rest pain scores were significantly lower in PRP-treated patients (SMD = −4.69, 95 % CI: 0.87 to −0.62, $p = 0.02$). PRP-treated ulcers had lower recurrence rates (RD = −0.14, 95 % CI: 0.75 to 0.97, $p = 0.01$).
Conclusions: The findings from this meta-analysis underscore the promising potential of PRP and MSCs as effective therapeutic strategies for wound healing when used individually.

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1. Introduction

Wounds are characterized by disruptions or breaks in the normal anatomical structure and functional continuity of tissues [1]. Wound healing is a critical physiological response involving self-repair and regeneration following an injury, encompassing three sequential and overlapping stages: hemostasis/inflammation, proliferation, and remodeling [2]. Maintaining optimal wound healing is essential not only for physical recovery but also for preventing complications such as chronic wounds, infections, and scarring [3,4]. There is significant pressure on healthcare systems to develop cost-effective wound management practices. Despite advances in conventional wound care management, numerous shortcomings remain that may render treatments ineffective or even detrimental to patients [5]. Therefore, the development of effective, appropriate, and safe wound healing therapies is of paramount importance.

Mesenchymal stem cells (MSCs) have emerged as a promising alternative in tissue repair and wound healing due to their unique properties [6]. These cells can be harvested from various sources, including adipose tissue (ADMSC), bone marrow (BMMSC), and umbilical cord (UCMSC) [6,7]. MSCs are distinguished by their capacity for self-renewal, differentiate into various cell types, and exert immunomodulatory effects, all while demonstrating a robust proliferative capacity [8]. Furthermore, they can secrete cytokines through autocrine or paracrine mechanisms in pathological environments, promoting re-epithelialization and stimulating angiogenesis and blood vessel regeneration [9]. This orchestrated response supports an efficient wound healing process, highlighting the potential of MSC therapy to address the limitations of traditional wound care modalities.

In addition, platelet-rich plasma (PRP), an autologous blood product, presents another innovative solution for a variety of dermatological conditions. PRP is rich in platelets, cytokines, and growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF). These components can enhance stem cell proliferation, angiogenesis, and tissue remodeling [10]. Consequently, PRP has gained recognition in various clinical settings for its efficacy in treating acute and chronic wounds, surgical incisions, and soft tissue injuries [11,12]. By potentially accelerating the recovery time of ulcers, PRP may enhance patients' quality of life while alleviating the healthcare burden associated with wound management [13]. We hypothesize that the combination of MSCs and PRP could emerge as an innovative strategy that harnesses the strengths of both therapies. This synergistic approach seeks to enhance and optimize the wound healing process through the regenerative properties of MSCs and the growth factor-rich environment provided by PRP.

To date, the comparative efficacy of MSC, PRP and their combined application in wound healing has not yet been systematically evaluated. Therefore, this meta-analysis seeks to aggregate current evidence on MSCs and/or PRP for wound healing, aiming to determine the effectiveness of these interventions in clinical settings by assessing the proportion of healed wounds and the average wound-healing time. The finding may provide a clearer understanding of how these therapies operate independently and in concert, ultimately guiding clinical decision-making and facilitating future research initiatives in a timely manner.

2. Material and methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [14]. A filled PRISMA Checklist was documented in Supplementary S1.

2.1. Information sources and search strategy

The search strategy was used to search PubMed, Web of Sciences, Scopus, and Google Scholar (limited to peer-reviewed studies) on July 25, 2024 using the terms (("mesenchymal stem cells"[MeSH Terms] OR "mesenchymal stem cell"[Title/Abstract] OR “MSCs”[Title/Abstract] OR "mesenchymal stromal

cell"[Title/Abstract] OR "platelet rich plasma"[MeSH Terms] OR "platelet rich plasma"[Title/Abstract] OR “PRP"[Title/Abstract] OR "platelet rich fibrin"[Title/Abstract]) AND ("wound healing"[MeSH Terms] OR "wound healings"[Title/Abstract] OR "wound epithelialization"[Title/Abstract] OR "wound repair"[Title/Abstract]) AND ("Clinical trial"[Title/Abstract] OR "Randomized controlled trial"[Title/Abstract]). In addition, a manual search for references to relevant reviews and primary articles were conducted. The full search strategy is outlined in supplementary S2.

2.2. Eligibility criteria

The studies were eligible based on the “PICOS” approach as following.

- P (population): Adult patients with wounds;
- I (intervention): Mesenchymal stem cell (MSC) and/or platelet-rich plasma (PRP) treatment;
- C (comparison): Conventional therapy, normal saline, or placebo;
- O (outcome): Primary outcome: wound closure, healing rate, change in wound size; secondary outcomes: healing time, pain, infection, new vessel, adverse events, recurrence, and quality of life.
- S (study design): Publication in English language, full-text, randomized control trials (RCTs) and controlled clinical trials involving human subjects.

Review articles, non-comparative studies, comments, letters, editorials, protocols, guidelines, case-series, care reports, and articles that involved in vivo or in vitro study designs were excluded. Publications before 2010, studies with incomplete or unclear analytical data (e.g., missing key outcome measures such as wound closure rates, healing time, or infection rates), and studies that did not report the desired outcomes were excluded.

2.3. Study selection and data extraction

The retrieved literature was imported into Endnote X8 software to remove the duplicates, followed by screening by two independent researchers to decide whether to include the articles according to the inclusion and exclusion criteria. Excel software was used for the following data extraction: the last name of the first author, year of publication, country, study design, sample size, characteristics of participants, intervention type, intervention preparation, follow-up period, and the concluding remarks (Table 1). We extracted primary and secondary outcomes to evaluate the safety and efficacy of stem cell/PRP therapy on wounds.

2.4. Quality assessment

Two independent investigators carried out the assessment of methodological quality using the Cochrane Risk of Bias tool version 2 (RoB2) [15]. The results underwent a cross-verification process, and any discrepancies encountered were addressed through detailed discussions and resolved accordingly. The following potential bias were evaluated: (1) whether the random sequence generation method is accurate, (2) whether allocation concealment is maintained, (3) whether blinding methods are utilized for participants and implementers, (4) whether outcome assessors are blinded, (5) whether the data results are complete, (6) whether reporting is conducted selectively, and (7) other bias. Each article was classified as being at low risk of bias indicated by a plus (+), unclear risk of bias by a minus (−) or high risk of bias by cross (χ) according to the assessment details for risk of bias presented above.

2.5. Data synthesis and analysis

STATA software version 17.0 was used for statistical meta-analysis. Continuous data were expressed as standardized mean differences (SMD) with 95 % confidence intervals (CI); while dichotomous results were pooled as risk difference (RDs) with 95 % CI. Forest plots were constructed for graphically displaying the effect sizes and visual inspection analysis. Heterogeneity of the included studies was determined using the *I2* statistic and Cochran's Q test. In case of heterogeneity (*I2* $\geq$50 % and *P*-value<0.05), a random effect model was selected to decrease the impact of heterogeneity on the results. Otherwise, a fixed-effects model was used for the meta-analysis. Sensitivity analyses were conducted to investigate studies that contributed to heterogeneity. Subgroup analyses were performed to evaluate the effect of certain study characteristics on outcomes with high heterogeneity. Funnel plot asymmetry was confirmed to assess publication bias using Egger's test. All statistical significance was set at a *p*-value <0.05.

3. Results

3.1. Literature search results

A total of 1821 articles were identified through database searches, with 1372 remaining after removing duplicates. Then, 1251 studies were excluded after screening the titles and abstracts because they were not relevant to our study's objective. After preliminary screening and scanning of the full texts, 87 studies were excluded. The remaining 34 eligible publications released between 2010 and 2024 were included in the current meta-analysis [16–49]. The detailed literature screening process is illustrated in Fig. 1.

3.2. Study characteristics

A total of 34 studies [16–49], involving 2458 patients, were included in the meta-analysis. Of these, 31 were randomized controlled trials (RCTs) [16–19,21,22,25–49], 2 were controlled clinical studies [20,23], and 1 was a prospective study [24]. The studies were conducted in various locations, including China [33–35,42,48,49], Korea [27,30,38], Egypt [16,24,28,39,45], Iran [17,19,31,36,46], Italy [18,43], India [41], Spain [21], the United Kingdom [25,44], the United States [26], the Netherlands [37], Germany [32], Greece [22,29], Denmark [20], Turkey [47], the Czech Republic [23], and several centers across Europe and Israel [40]. Among the studies, 19 [16–18,20–22,24–26,28–31,33,34,39,41,46,48] evaluated the effect of platelet-rich plasma (PRP) therapy on wound healing, while 12 [19,23,27,32,35,37,38,40,42,45,47,49] focused on stem cell therapy. Additionally, 3 studies [36,43,44] assessed the combination of stem cell therapy and PRP. In the PRP intervention studies, 17 used PRP in the form of gel, dressing, or injection, while the other two studies applied platelet-rich fibrin (PRF) [41] and leukocyte-poor platelet-rich plasma (L-PRP) [20], respectively. Regarding stem cell applications, 6 studies used adipose-derived stem cells (ADSCs) [19,38,40,45,47,49], one utilized bone marrow-derived mesenchymal stem cells (BMMSCs) [37], and others used bone marrow-derived mononuclear cells (BMMNCs) [23], human umbilical cord mesenchymal stem cells (HUCMSCs) [42], and human processed lipoaspirate (PLA) cells [27]. In the other two studies, BMMNCs or bone marrow-enriched tissue repair cells (BMTRCs) [32] and BMMSCs or BMMNCs [35] were used. In terms of combination therapy, one study used ADSCs plus PRP [43], another administered ADSCs alone or with PRP [44], and another examined human placenta-derived mesenchymal stem cells (hPDMSCs) alone or with PRP gel [36]. The sample sizes of the included studies ranged from 11 to 212 patients. The follow-up periods

Table 1
Characteristics of the included studies.

Author, Year; Country	Study design	Wound type	Male/total participant I:C	Age (yr) I:C	Intervention strategy	Wound area (Mean ± SD) I:C	MSC isolation/PRP preparation	Follow up period	Main conclusion
Ahmed et al., 2016; Egypt [16]	RCT	DFU	I: 20/28 C: 18/28	I: 43.2 ± 18.2 C: 49.8 ± 15.4	PRP	I: 2−10.2 cm^2 C: 2.47−11.55 cm^2	Blood was centrifuged at 1500 rpm for 5 min to obtain plasma and then centrifuged at 3500 rpm for 5 min. Pellet was diluted in plasma to produce PRP, and then mixed with thrombin to form a PRP gel.	2−12 weeks	Autologous platelet gel outperforms local antiseptic dressings in both healing rate and infection prevention for clean diabetic ulcers.
Alamdari et al, 2021; Iran [17]	RCT	DFU	I: 26/43 C:30/47	I: 56.3 ± 7.1 C: 56.7 ± 7.2	PRP	NR	Blood was centrifuged twice (at 1500 and 3500 rpm for 5 min). Pellet as PRP was diluted in plasma. PRP gel was obtain by adding thrombin and CaCl2.	6 months	PRP can be efficiently accelerate the healing rate of foot ulcers.
Amato et al, 2019; Italy [18]	RCT	Mixed ulcer	I: 18/53 C: 16/47	68 ± 8	PRP	I: 26 ± 16 cm^2 C: 24 ± 9 cm^2	Blood was centrifuged duration 14 min, with the following program: 2 min at 2700 rpm, 4 min at 2400 rpm, 4 min at 2700 rpm, 3 min at 3000 rpm.	3 months	CGF (evolutined PRP) is useful for improving clinical outcomes in mixed ulcers of the legs, with lower pain and infection.
Behrangi et al., 2022; Iran [19]	RCT	Acne scar	I: NR/7 C: NR/7	18−70	ADSCs	I: 12.65 cm^2 C: 11.42 cm^2	Fat tissue digested with type I collagenase. Cells of the SVF were pelleted by 10 min centrifugation at 500g.	3 months	Applying SVF in acne scar treatment can greatly enhance dermal and epidermal thickness, and also improve scar volume, surface, and depth.
Capion et al, 2021; Denmark [20]	CCT	Surgery	I: 3/16 C: 8/17	I: 65.6 ± 8.5 C: 68.9 ± 7.1	L-PRP	I: 15.4 ± 2.9 cm C: 16.0 ± 3.5 cm	The blood was centrifuged at 270 g for 10 min. The upper layer; rich in platelets and leukocytes was centrifuged at 900 g for 12 min, yielding the final L-PRP product at the bottom.	1 month	A one-time local application of L-PRP during surgery enhanced epithelialization and wound healing in THA patients.
Cardenosa et al, 2017; Spain [21]	RCT	Venous ulcer	I: 15/55 C: 16/47	I: 64.09 C: 64.2	PRP	I: 13.69 ± 30 cm^2 C: 16.67 ± 23.87 cm^2	Autologous PRP was obtained by one single centrifuge of blood.	24 weeks	PRP application is a safe method to speed up healing and reduce pain in venous ulcers.
Dinaki et al, 2024; Greece [22]	RCT	Surgery	I: NR/15 C:NR/15	I: 45.47 ± 13.24 C: 52.20 ± 7.64	PRP	NR	PRP is produced by dual-speed centrifugation of peripheral blood(at 200 RCF for 12 min, at 1600 RCF for 8 min).	1/2/4/8/12 weeks	PRP enhances wound healing following sinus surgery due to its minimal invasiveness, lack of hazards or side effects, and favorable clinical results.
Dubsky et al, 2013; Czech Republic [23]	CCT	Diabetic foot disease and CLI	I: 15/17 C: 17/22	I: 60.7 ± 9.4 C: 63.3 ± 9.1	BMMNCs	I: 5.2 ± 1.6 cm^2 C:5.9 ± 2 cm^2	Bone marrow was taken from the iliac crest and BMMNC were separated by using a smart PReP2.	6 months	Compared to conservative therapy, BMMNC has superior benefit for treatment of CLI in patients with diabetic foot diseases.
Elbarbary et al, 2020; Egypt [24]	Pros-Pective	Chronic venous leg Ulcer	I: 26/30 C: 24/30	I: 45.4 ± 9.35 C: 41.80 ± 13.3	PRP	I: 16.5 ± 8.2 cm^2 17.8 ± 5.4 cm^2	Autologous venous blood was centrifuged (at 2500 rpm for 10 min, at 3500 rpm for 5 min). The PRP, situated in the bottom, was aspirated and activated by adding CaCl2.	3/6/12 months	PRP injections improve the healing of chronic venous ulcers more effectively than either PRP application or compression therapy alone.
			I: 22/30 C: 24/30	I: 43.4 ± 13 C: 41.80 ± 13.3	PRP	I: 15.7 ± 7.4 cm^2 C:17.8 ± 5.4 cm^2			
Game et al, 2018; UK [25]	RCT	DFU	I: 107/132 C: 110/134	I: 61·9 ± 11·4 C: 62 ± 11·9	PRP	I: 228·8 ± 207·43 mm^2 C: 240·8 ± 217.1 mm^2	LeucoPatch	6 months	The use of LeucoPatch in diabetic patients with foot ulcer is associated with significant enhancement of healing rate and reduction in healing time.
Gude et al, 2019; USA [26]	RCT	DFU	I: 51/66 C: 49/63	I: 64.7 C: 66.9	PRP	I: 4.1 cm^2 C: 5.6 cm^2	Aurix hematogel	>12 weeks	Aurix hematogel effectively Improves healing of chronic DFUs of all severities
Han et al., 2012; Korea [27]	RCT	DFU	I: 15/26 C: 14/26	I: 66.5 ± 7.5 C: 68.4 ± 8.7	PLA	I: 4.3 ± 2.1 cm^2 C: 4.0 ± 2.1 cm^2	Autogenous PLA cells were isolated from adipose tissue following washing, digestion and centrifugation at 300g for 10 min.	8 weeks	Uncultured PLA cell autografts is a simple, safe, and effective treatment for DFUs resulted in the acceleration of healing rate and reduction of healing time.

Helmy et al, 2021; Egypt [28]	RCT	Chronic leg ulcer	I: 26/40 C: 23/40	I: 48 ± 11 C: 44 ± 11.4	PRP	I: 16.7 ± 11 cm^2 C: 20.4 ± 18 cm^2	PRP was obtained by in a soft speed and then hard spin centrifugation of blood.	12 months	PRP injection is effective, safe, simple, and significant in promoting the wound healing process and decreasing the healing time, pain, adverse events, and recurrence in CLUs.
Hossam et al, 2022; Greece [29]	RCT	Non-ischemic diabetic foot ulcer	I: 28/40 C: 38/40	NR	PRP	I: 15.2 ± 5.6 cm^2 C: 14.5 ± 5.6 cm^2	Blood was centrifuged (1000 rpm for 10 min) and a second spin (1500 rpm for 10 min) in PRP extract and PPP supernatant.	12 weeks	PRP is a cost-beneficial treatment that can enhance wound healing and decrease the local infection rate in DFUs.
Jeong et al, 2010; Korea [30]	RCT	DFU	I: 27/52 C: 26/48	I: 64.5 ± 8.1 C: 63.8 ± 6.4	PRP	I: 5.7 ± 3.6 cm^2 C: 5.3 ± 2.2 cm^2	Blood bank platelet concentrates were centrifuged at 3000 g for 30 min. Plasma supernatants were discarded and the platelet precipitant was collected.	12 weeks	Blood bank platelet concentrate offers a simple and effective treatment for DFUs.
Karimi et al, 2016; Iran [31]	RCT	DFU	I: 20/25 C: 18/25	NR	PRP	I: 12.79 ± 4.86 mm^2 C: 14.17 ± 8.52 mm^2	Blood was centrifuged at 200 rpm for 10 min. The PRP accumulated on the upper surface placed in a sterile cotton gauze to prepare a PRP impregnated gauze.	3 weeks	PRP dressing significantly decreases the depth and surface area of DFUs in a three-week period.
Kirana et al, 2012; Germany [32]	RCT	Diabetic foot with CLI	I: 9/12 C: NR/6	I: 9.6 ± 4.2 cm^2 C: NR	BMMNCs	I: 68.5 ± 1.5 C: NR	Isolation of BMMNCs was achieved by a commercially system. Automated cells purification was performed for 75 min and 400 g, followed by two washing cycles.	4/8/12/20/28/36/44/52 weeks	The transplantation of BMMNCs as well as BMTRCs are safe and feasible, resulted in improvement of microcirculation and complete wound healing.
			I: 10/12 C: NR/6	I: 7.7 ± 2.7 cm^2 C: NR	BMTRCs	I: 70.9 ± 1.7 C: NR	BMTRCs were achieved after 12 days cultivation of BMMNCs inside a bioreactor.		
Liu et al, 2018; China [33]	RCT	Burn	I: 16/34 C: 17/34	34.2 ± 10.8	PRP	I: 15.3 ± 4.7 C: 17.5 ± 5.8 (% of body)	Blood was centrifuged twice (at 1500 and 3600 rpm,10 min). The sedimented PRP was mixed with CaCl2 + thrombin to prepare gel.	1 month	APG can significantly enhance recovery rates, accelerate healing time, decrease the need for dressing changes, reduce wound pain severity of patients with burn wounds.
Liu et al, 2021; China [34]	RCT	Pressure injury	I: 25/51 C: 27/51	I: 60.79 ± 6.38 C: 59.36 ± 6.21	PRP	NR	Blood was centrifuged twice (at 1500 rpm, 10 min). Then PRP, in the middle layer. Was mixed with calcium and thrombin and subsequently coagulated to create PRP gel.	3 weeks	PRP gel can speed up wound healing, alleviate wound pain, regulate the expression of certain proteins in granulation tissue, lower inflammatory factors levels, and improve the quality of life of patients.
Lu et al, 2011; China [35]	RCT	Diabetic critical limb ischemia and foot ulcer	I: 7/18 C: 15/37 I: 8/19 C: 15/37	I: 63 ± 8 C: 64 ± 9 I: 65 ± 10 C: 64 ± 9	BMMSCs BMMNCs	I: 4.2 ± 2.9 cm^2 C: 4.5 ± 2.3 cm^2 I: 4.3 ± 3.1 cm^2 C: 4.5 ± 2.3 cm^2	Bone marrow underwent Percoll density gradient centrifugation to harvest the mononuclear cell layer, then cultured in a-MEM with 10 % autologous serum, with medium changes to reach the desired number of expanded BMMSCs.	6 months	BMMSCs therapy might be more well-tolerated and effective than BMMNCs in enhancing lower limb blood flow and aiding foot ulcer healing in diabetic patients with CLI.
Meamar et al, 2021; Iran [36]	RCT	DFU	I: NR/11 C: NR/7	56 ± 10.5 and 68 ± 8.1	hPDMSCs	I: 11.1 cm^2 C: 8.6 cm^2	Placenta were washed and cut and cultured. After expansion and characterize of hPDMSCs, 10 6 cells/cm2 were seeded onto the nanofibers and incubated for 72 h.	12 weeks	DFUs patients in both the hPDMSCs and hPDMSCs + PRP gel groups showed enhanced wound healing and increased pain-free walking distance compared to the control group.
			I: NR/10 C: NR/7		hPDMSCs + PRP		Nanofibers loaded with hPDMSCs were prepared and used to treat ulcers after coating them with obtained PRP gel.		
Molendijk et al, 2015; Netherlands [37]	RCT	Crohn's disease	I: 4/5 C: 3/6	I: 40.4 C: 37.3 I: 40.4 C: 37.3 I: 33.4 C: 37.3	BMMSCs (1 × 107) BMMSCs (3 × 107) BMMSCs (9 × 107)	NR	Bone marrow was collected by aspiration from healthy donors and mononuclear cells were isolated by Ficoll techniques and expanded according to LUMC protocol.	24 weeks	Local administration of allogeneic MSCs is safe, and injection 3 × 107 cells appeared to promote healing of perianal fistulas.

(*continued on next page*)

Table 1 (*continued*)

Author, Year; Country	Study design	Wound type	Male/total participant I:C	Age (yr) I:C	Intervention strategy	Wound area (Mean ± SD) I:C	MSC isolation/PRP preparation	Follow up period	Main conclusion
Moon et al, 2019; Korea [38]	RCT	DFU	I: 14/22 C: 13/17	I: 59.9 ± 13.3 C: 68.4 ± 9.9	ADSCs	I: 2.0 ± 0.9 cm^2 C: 2.8 ± 2.0 cm^2	Adipose tissues were rinsed and digested (with collagenase I). Liquid portion was centrifuged at 300 g for 10 min. The SVF was seeded onto the hydrogel matrix to obtain 1 × 106 ASCs/ sheet.	12 weeks	Allogeneic ADSCs can enhance wound healing rate and might be effective and safe to treat DFUs.
Orban et al, 2022; Egypt [39]	RCT	DFU	I: 20/36 C: 21/36	I: 56.03 ± 8.39 C: 58.69 ± 6.68	PRP	I: 3.33 ± 1.31 C: 3.23 ± 1.20	Autologous PRP was obtained by double step centrifuge (at 1000 rpm and 3000 rpm, for 10 min) of blood. PRP was activated by adding calcium gluconate.	20 weeks	Compared with conventional wound care. The use of autologous PRP results in a higher rate of wound healing in less time in managing DFUs.
Panés et al, 2016; Seven European countries & Israel [40]	RCT	Crohn's disease	I: 60/107 C: 56/105	I: 39 C: 37.6	ADSCs	NR	Cells were isolated from the stromal vascular fraction from healthy adult donors by liposuction, then expanded according to classic cell culture.	24 weeks	Cx601 is a safe and effective therapy for patients with Crohn's disease who have not responded to standard and/ biological treatments.
Parwani et al, 2024; India [41]	Split-mouth RCT	Periodontitis	I: 6/13 C: 6/13	I: 29.5 C: 29.5	PRF	NR	Peripheral blood was centrifuged at 4000 rpm for 8 min. After that, PRF was collected from middle phase	6 weeks	PRF can accelerate healing and reduce the number of periodontal treatment sessions needed for pocket closure.
Qin et al, 2016; China [42]	RCT	DFU	I: 17/28 C: 15/25	I: 75 ± 3 C: 73 ± 5	UCMSCs	NR	Tissues were washed, cut into small pieces, and treated with collagenase IV and trypsin. Cells were filtered and cultured.	3 months	HUCMSC transplantation after angioplasty is a safe and effective that promote ulcer healing, and improve the quality of life of patients.
Raposio et al, 2016; Italy [43]	RCT	Mixed ulcer	I: 11/16 C: 10/24	I: 70.7 C: 74.5	ADSCs + PRP	I: 25.18 ± 5.6 cm^2 C: 11.24 ± 2.6 cm^2	Peripheral blood was centrifuged to obtain PRP. Abdominal subcutaneous adipose tissue was harvested to obtain ADSCs which were mixed with autologous PRP to create an enriched PRP (e-PRP).	18 months	ADSCs + PRP (e-PRP) significantly enhanced wound closure rates with a faster recovery without causing any serious complications.
Smith et al, 2020; UK [44]	RCT	DFU	I: 6/6 C: 4/6 I: 5/6 C: 4/6	I: 60.2 C: 55.2 I: 57.5 C: 55.2	ADSCs ADSCs + PRP	I: 3.1 ± 1.3 cm^2 C: 6.4 ± 5.9 cm^2 I: 1.3 ± 1.4 cm^2 C: 6.4 ± 5.9 cm^2	Whole blood was combined with ACD-A. PRP was produced using the Angel system and then combined with processed lipoaspirate.	12 weeks	Fat grafting alone or with PRP in DFU patients is feasible and safe.There was no difference between any of the groups in terms of clinical outcomes.
Tanios et al, 2021; Egypt [45]	RCT	Mixed chronic ulcer	I: 29/50 C: 24/50	I: 48.12 ± 14.58 C: 48.04 ± 10.56	ADSCs	I: 6.25 ± 0.9 cm^2 C: 5/63 ± 0.75 cm^2	Adipose tissue was harvested by liposuction. After washing, the samples underwent digestion and were centrifuged at 600 g for 10 min. The resulting pellets were resuspended in a buffer, and SVF was subsequently filtered.	6 months	Treatment of chronic ulcers using autologous ADSCs resulted in the acceleration of healing rates and enhancement re-epithelialization, angiogenesis, and inflammatory cells.
Tofigh et al., 2022; Iran [46]	RCT	DFU	I: 52/81 C: 45/80	I: 55.8 ± 5.6 C: 60.2 ± 5.2	PRP	I: 3.2 ± 0.5 C:3.3 ± 0.5	Becaplermin (Regranex) 0.01 % gel containing PDGF was used.	12 weeks	In the 6 week of the intervention, the wound area in PDGF dressing group was significantly smaller than the surgical group.
Uzun et al. 2021; Turkey [47]	RCT	DFU	I: NR/10 C: NR/10	I: 57.5 ± 8.4 C: 57.2 ± 4.5	ADSCs	I: 23.5 ± 5.6 cm^2 C: 25.8 ± 5.4 cm^2	The adipose tissue pieces were digested with collagenase II. After centrifugation at 350g for 5 min, cell pellet was cultured.	>3 months	Allogeneic ADSCs injection is safe and effective method to treat DFUs.
Yang et al, 2017; China [48]	RCT	Lower-extremity Ischemic ulcer	I: 17/38 C: 19/38	I: 40.1 ± 10.2 C: 43.7 ± 9.8	PRP	NR	Blood was centrifuged twice (at 1500 and 3600 bpm for 10 min). Then PRP was mixed with CaCl2+thrombin to prepare gel.	1 month	PRP gel lead to a higher wound healing rate, and lower VAS, and increase the growth factor levels in tissues of ulcers.
Zhou et al, 2020; China [49]	RCT	Crohn's disease	I: 11/11 C: 10/11	I: 24.4 ± 5.0 C: 24.9 ± 5.4	ADSCs	NR	Adipose tissue was washed, digested (with collagenase I), and centrifuged. The SVF was obtained by centrifuging the filtrate.	52 weeks	ADSC is a viable and effective treatment that alleviates pain, enables quick recovery, and enhances quality of life of patients with Crohn's disease.

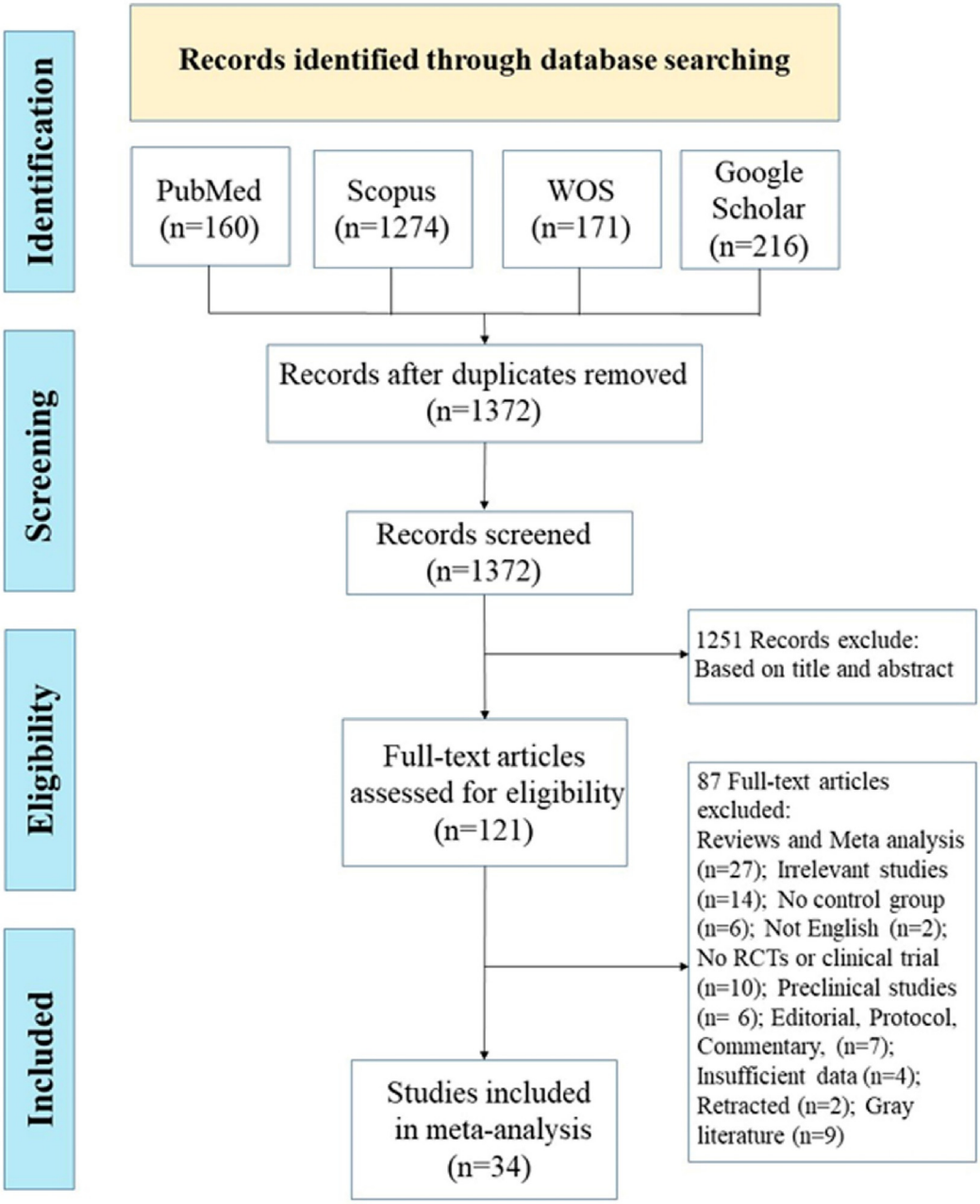

Fig. 1. Flow chart of study selection in the meta-analysis. WOS: Web of Science.

in studies on PRP interventions ranged from two to 48 weeks, while in studies on cell therapy, the follow-up durations spanned from one month to 18 months. The characteristics of the included studies are presented in Table 1.

3.3. Quality of included literature

The risk of bias assessment was conducted across multiple domains for the 34 studies included in the meta-analysis. The overall quality of these studies was moderate, with ratings ranging from low to high. Notably, 10 studies demonstrated a low risk of bias in all assessed categories, reflecting a high level of methodological rigor [16,17,25,27,29,31,37,40,45,46]. However, 9 studies were classified as having a high risk of bias [19,20,23,28,30,32,36,39,41]. This group included four RCTs that exhibited selective reporting bias, two studies that adequately detailed their methods for sequence generation, one RCT that did not specify the methods used to achieve blinding for participants and implementers, and two other studies that faced issues with allocation concealment or incomplete outcome data. Most included studies were considered to have a low risk of detection bias and attrition bias. Out of the 34 included studies, 15 were of some concern [18,21,22,24,26,33–35,38,42–44,47–49] (Fig. 2A and B).

3.4. Ulcer and wound healing rate

The ulcer healing rate refers to the proportion of patients achieving complete ulcer healing following treatment, calculated as

the ratio of patients with complete healing to the total number of participants in each group. In this meta-analysis, a total of 17 studies (18 groups) reported ulcer healing rate ranging from 36 % (9/25) to 100 % (30/30) within the PRP group. The findings demonstrated that the ulcer healing rate in the PRP-treated group was significantly higher than that in the control group, 585/808 (72.4 %) vs 423/804 (52.5), respectively (RD = 0.21, 95 % CI: 0.16 to 0.26, p < 0.001, Fig. 3A). The outcomes showed heterogeneity was minimal (Q-test = 27.7, P = 0.05, I^2 = 37 %).

In the context of cell therapy, 12 trials (15 groups) reported complete wound healing. A total of 309 patients received stem cell treatment, while 297 patients were assigned to the control group. As Fig. 3B illustrated, statistical analysis indicated a significant increase in the rate of complete wound healing associated with MSC therapy when compared to the control groups (211 vs 129; RD = 0.33, 95 % CI: 0.2 to 0.45, p < 0.001). The outcomes showed heterogeneity (Q-test: 43.4, P < 0.001, I^2 = 68.3 %). Subgroup analyses according to type of stem cells showed consistent results (Fig. 3C). Based on results, ADMSCs, BMMNCs, BMMSCs, and BMTRCs all demonstrate significant improvements in wound healing, with RD of 0.25, 0.38, 0.39, and 0.67, respectively, indicating increasing effectiveness, particularly for BMTRCs. In contrast, hPMSCs show the lowest RD of 0.20, suggesting they are beneficial but less effective than the other MSC types studied.

The findings from our meta-analysis indicate a modest overall risk difference of 0.06 for the combined use of PRP and MSCs in wound healing rate, which suggests that this combination treatment has a slight, non-significant effect on healing rates (p = 0.7, Fig. 3D). Raposio et al. [43] observed significant higher healing rate per day (in square centimeters) in ADSCs + PRP-treated group than control group (0.22 ± 0.06 vs 0.08 ± 0.01, respectively; p < 0.05). Smith et al. [44] revealed that the healing rates following combined ADSCs and PRP treatment were better than those in the control groups (33 % vs. 20 %). However, this difference was not statistically significant (p > 0.05).

The RD values 0.04 for Rapassio et al. [43] and 0.13 for Smith et al. [44], reflect varying efficacy, but both contribute to a combined RD that does not reach statistical significance (p = 0.6).

The confidence interval of −0.17 to 0.28 suggests that the true effect of the PRP and MSC combination could be negligible, implying that this treatment strategy may not be as beneficial as anticipated [21,24,28,29,31,46].

3.5. Wound size reduction

Six studies [21,24,28,29,31,46] compared changes in ulcer area before and after PRP treatment against conventional treatment. Our results indicated that patients in the PRP group experienced a greater reduction in ulcer size compared to the control group (SMD = −0.95, 95 % CI: 1.66 to −0.24, P = 0.01). Additionally, the pooled SMDs from three RCTs [19,38,45] showed a significant reduction in post-treatment wound size in the ADSCs group compared to the control groups (SMD = −0.4, 95 % CI: 2.48 to 1.67, P = 0.7), demonstrating better improvement in the stem cell group. The pooled results are presented in Fig. 4A and B.

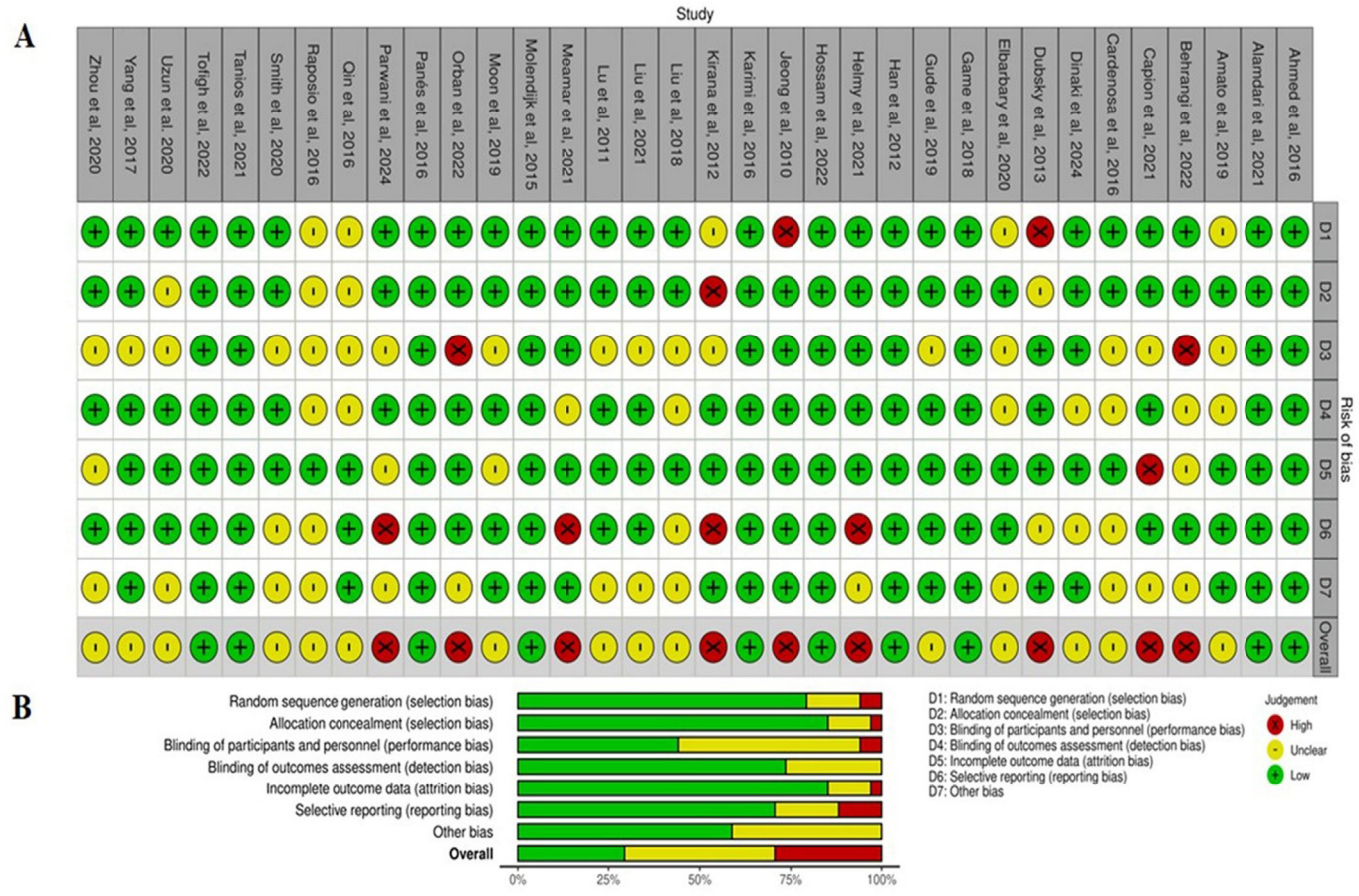

Fig. 2. Risk of bias graph (A). Summary of study risk bias analysis (B).

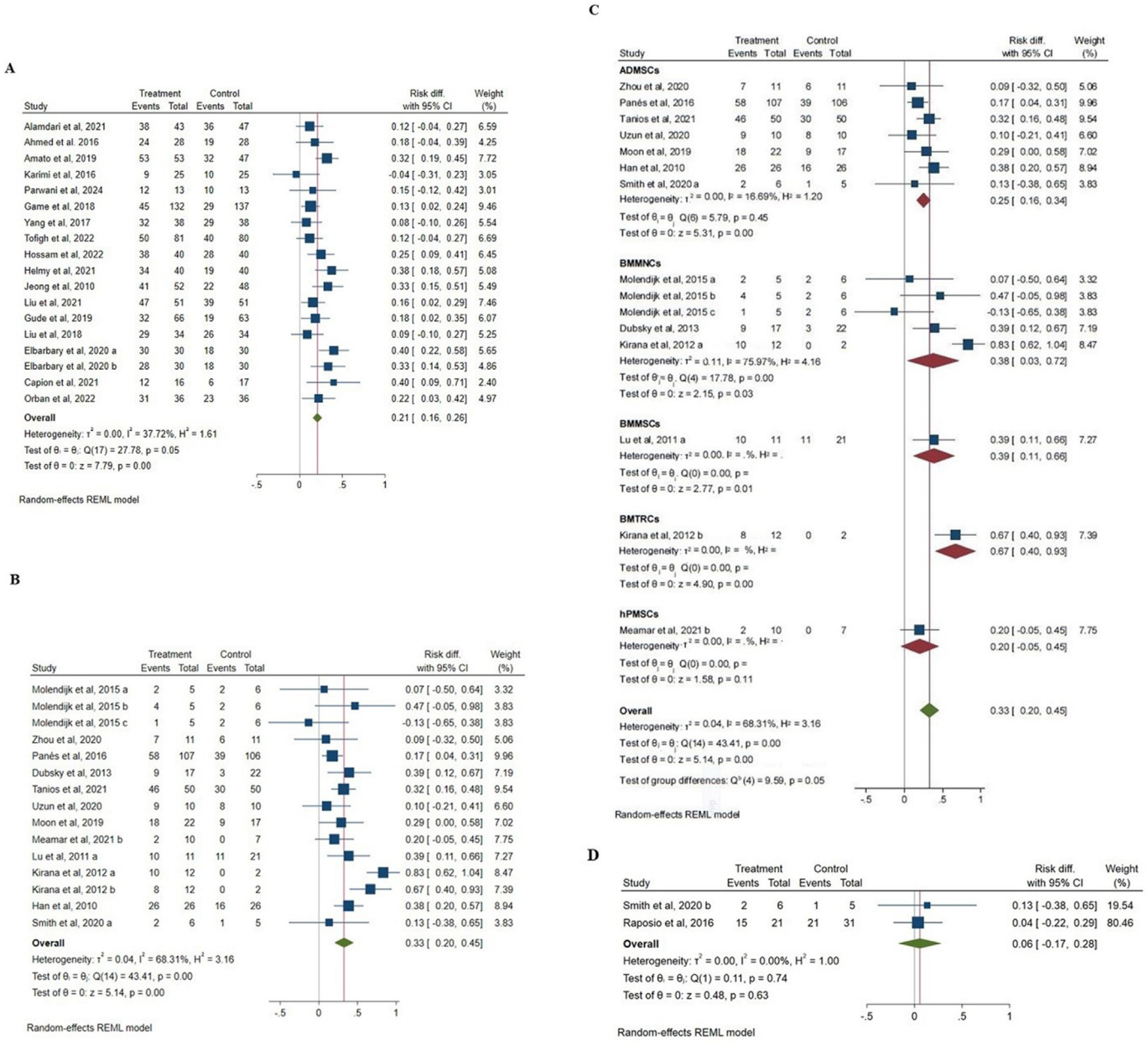

Fig. 3. Forest plot showing the effect of PRP (A), MSCs (B) therapy on ulcer healing rate. Forest plot of subgroup analysis of the effect of different MSC types on wound healing rate (C). Forest plot of the combination of PRP and MSCs on wound healing rate (D). Note: The square size corresponds to sample size or study weight. The green diamond represents the overall pooled effect size, while the red diamond indicates subgroup analyses.

3.6. Complete healing time

Four out of 12 MSCs-treated studies reported wound healing time. The SMD of these 4 trials [27,38,45,47] revealed a significant decrease (SMD = −1.71, 95 % CI: 2.44 to −0.99, P < 0.001, Fig. 5A) in the healing time of patients treated with ADSCs using a random effects model (P < 0.001, I^2 = 78 %, Fig. 5A), which confirmed that patients in the MSC group had a shorter mean time to complete wound closure. On the other hand, a total of 11 PRP-treated studies with 12 arms were conducted to compare wound healing time between PRP and conventional therapy. The meta-analysis results showed that PRP could significantly shorten the healing time compared with conventional therapy (SMD = −1.08, 95 % CI: 1.75 to −0.42, P < 0.001, Fig. 5B). The subgroup analyses based on wound healing duration (day, week, or month) showed similar results (Fig. 5C). The heterogeneity test results suggested that there was some heterogeneity among the included studies. MSCs showed a particularly strong effect in the week-long duration subgroup (SMD = −2.24). The combined effect size for MSCs was also substantial (SMD = −1.71), indicating their potential as a robust therapeutic option for wound healing.

In contrast, PRP exhibited significant effects over a longer duration (month-long), with an SMD of −1.56 (Fig. 5D). This suggests that PRP may be more effective when evaluated over extended periods.

3.7. New vessels development

Three studies [32,35,42] provided detailed information on the development of new blood vessels. The findings demonstrated a

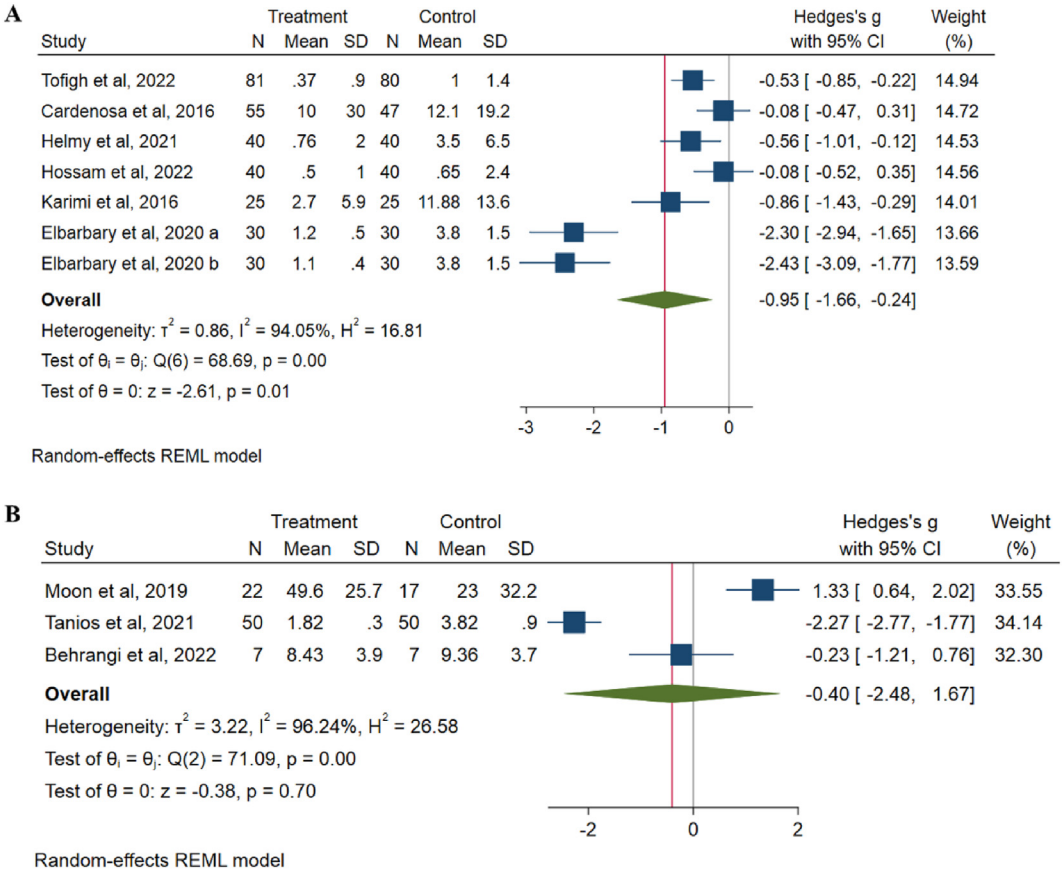

Fig. 4. Forest plot showing the effect of PRP (A) and MSCs (B) therapy on wound size reduction. Note: The square size corresponds to sample size or study weight. The green diamond represents the overall pooled effect size.

significantly positive effects and higher rate of angiogenesis in the stem cell treatment group compared to the control group ($P < 0.001$, Fig. 6A). The results presented in Fig. 6B demonstrated that BMMSCs had a higher impact (SMD = 0.83) compared to BMMNCs (SMD = 0.39). The overall effect size of 0.55 indicates that MSCs contribute substantially to new vessel formation, which is critical for effective wound healing.

These findings suggest that the angiogenic potential of MSCs can play a pivotal role in improving wound healing outcomes. The distinct effects observed between BMMNCs and BMMSCs highlight the importance of selecting the appropriate cell type for specific therapeutic goals.

3.8. Rate of infection

Among the included PRP-treated trials, six reported the incidence of infection in both PRP-treated and control wound areas. All of them observed more infection in control group than PRP group. Although the analysis revealed no significant difference in the risk of infection between the PRP group and the control group (DR = −0.11, 95 % CI: 0.34, 0.12, $p > 0.05$, Fig. 7A).

Two trials [42,45] compared the infection rates between the cell therapy group and the conventional treatment group. Tanios et al. [45] found a significant reduction in the infection rate among patients treated with ADSCs compared to the control group (6 % vs. 28 %, $p < 0.001$). They suggested that this difference may be attributable to the biological activity of the stem cells, which enhance vascularity through angiogenesis. In contrast, Qin et al. [42] reported an increased risk of infection in diabetic patients treated with UCMSCs compared to the control group. However, overall, the difference between treated and control group was not statistically significant. (DR = −0.11, 95 % CI: 0.34, 0.12, $p > 0.05$, Fig. 7B).

3.9. Wound rest pain

Six studies reported detailed pain scores after PRP treatment compared with the control group. The meta-analysis showed that the rest pain score for PRP-treated patients was lower than that of the conventional group (SMD = −4.69, 95 % CI: 0.87 to −0.62, P = 0.02, Fig. 8A). Three trials [35,47,49] reported rest pain scores for stem cell therapy in comparison to the control group (Fig. 8B). Lu et al. [35] and Zhou et al. [49] found that, compared to the control group, the rest pain score in the MSC group decreased more significantly after treatment. In contrast, the study by Uzun et al. [47] reported higher rest pain scores in the ADSCs group compared to the control group (Fig. 8C).

3.10. Ulcer recurrence and adverse events

Only two studies (with three arms) compared the incidence of recurrence between the PRP and control groups. Our results indicated that the recurrence rate in the control group was significantly higher than in the PRP-treated group (DR = −0.14, 95 % CI: 0.25, −0.03, P = 0.01, Fig. 9). The outcomes revealed no significant statistical heterogeneity (P = 0.1, I^2 = 47 %).

In their study on diabetic patients, Moon et al. [38] observed that ulcers recurred in two subjects in the ADSCs treatment group 6

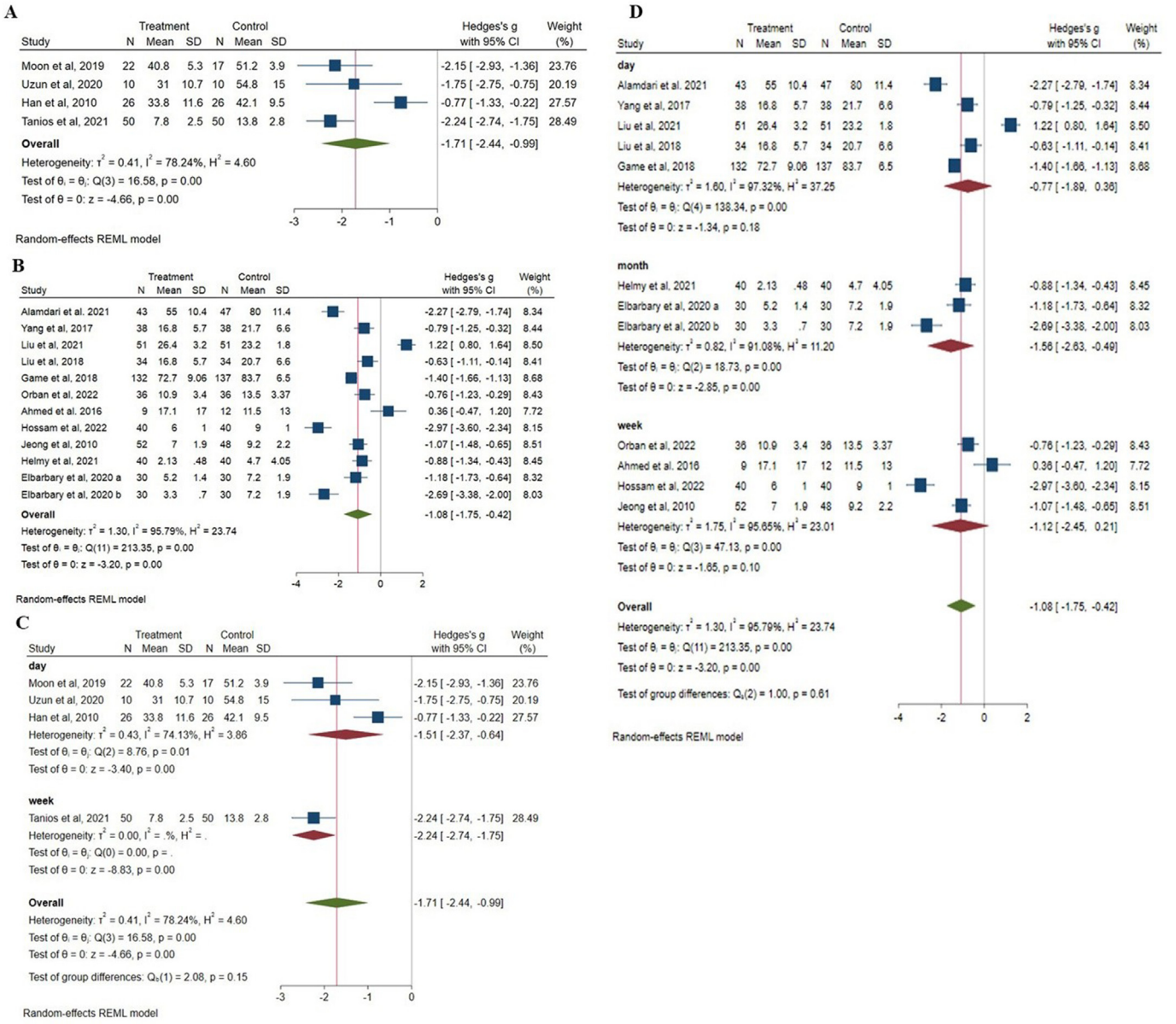

Fig. 5. Forest plot showing the effect of MSCs (A) and PRP (B) therapy on wound healing time. Forest plot of subgroup analysis MSCs (C) and PRP based on different time (D). Note: The square size corresponds to sample size or study weight. The green diamond represents the overall pooled effect size, while the red diamond indicates subgroup analyses.

months after the completion of the trial. As the ulcer locations were at the toe tip and on the plantar surface of the foot; areas susceptible to pressure, the authors concluded that the recurrence of ulcers might not have been related to the cell therapy. Furthermore, they did not observe any adverse reactions related to the treatment for two years following the completion of the study. The main remark of the studies judging adverse events are summarized in Table 2.

3.11. Cost of treatments

Four of studies [18,29,44,47] reported the comparison between costs of treatment. Evaluation of the costs associated with PRP and MSC therapies reveals significant insights into their economic viability compared to conventional treatments. The studies indicate that while initial costs may vary significantly, the overall financial implications often favor regenerative therapies due to their enhanced effectiveness and reduced need for subsequent interventions.

Ameto et al. [18] highlighted that the application of concentrated growth factor (CGF) as an adjunct treatment for lower limb ulcers entails a total procedure cost of €7.50. This study emphasizes that despite the higher unit cost of CGF dressings compared to standard dressings, the overall expenditure remains advantageous. This is primarily due to the reduction in the number of dressings required for complete healing, thereby offsetting the initial higher costs. Hossam et al. [29] confirmed the cost-effectiveness of PRP treatments, reporting a total treatment cost of $247.50 for the PRP group compared to $437.50 for the control group. This clear discrepancy illustrates that PRP not only offers therapeutic benefits but does so at a lower overall expense, which is crucial for both patients and healthcare systems. Orban et al. [39] provided additional insights, noting that the mean overall care cost for treating a single foot ulcer was approximately $504.58 when utilizing PRP,

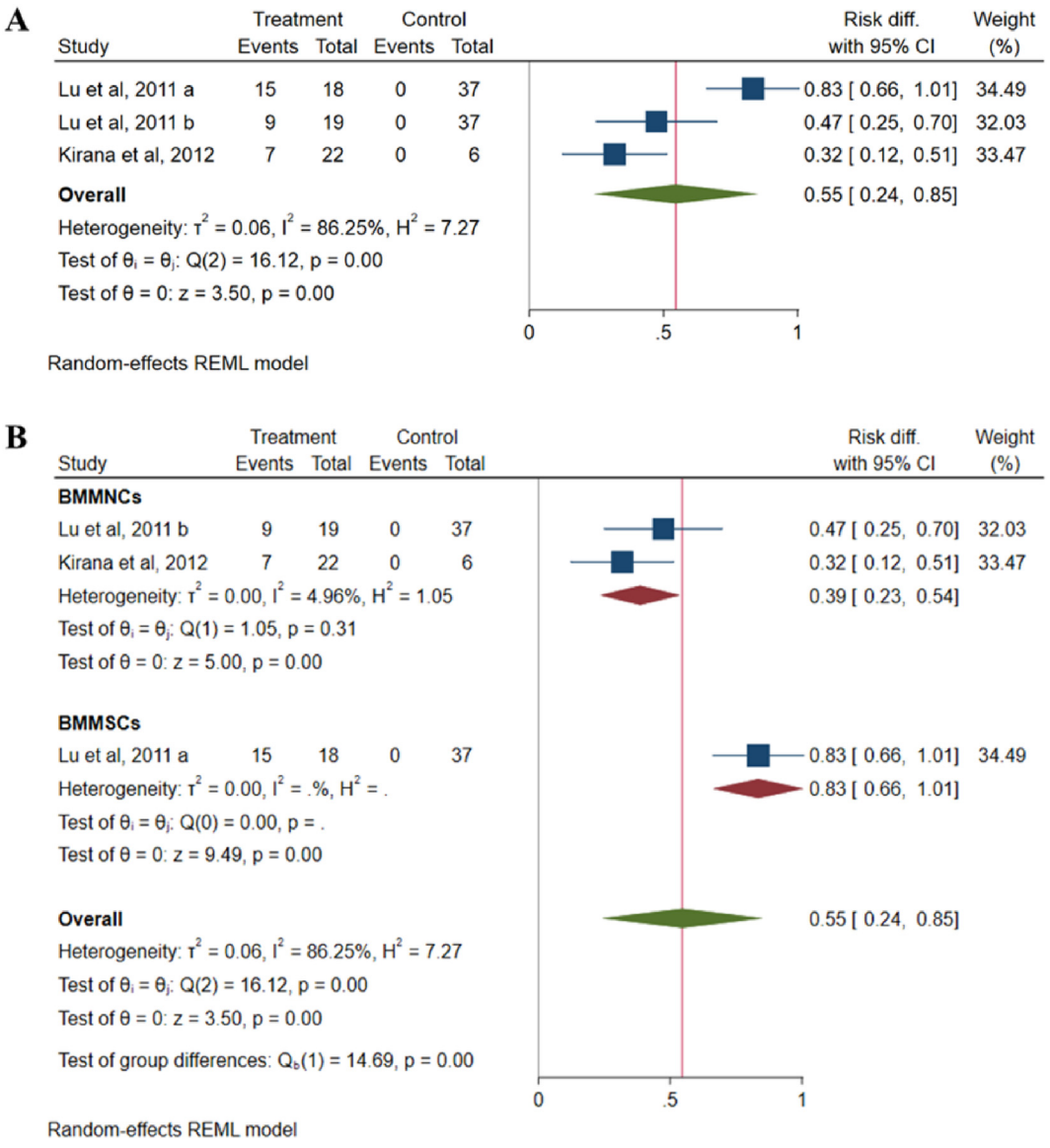

Fig. 6. Forest plot showing the effect of MSCs therapy on new vessel development (A). Forest plot of subgroup analysis (B). Note: The square size corresponds to sample size or study weight. The green diamond represents the overall pooled effect size, while the red diamond indicates subgroup analyses.

contrasted with $484.17 for conventional dressings. Though the initial cost of PRP appears higher, the treatment yields faster wound healing rates, which ultimately leads to reduced morbidity and potential cost savings from fewer complications and hospital visits.

Smith et al. [44] conducted a comparative analysis of dressing costs among different treatment groups, revealing that the average expenditure per patient on dressings was control £15.01; Fat grafting £8.09; ADSC + PRP £13.45. Despite the variations, there was no significant difference in dressing costs within or across any of the groups over time ($P > 0.05$). This finding indicates that while PRP and cell therapies may have different initial costs, the cost of ongoing treatment does not significantly differ. Finally, Uzun et al. [47] presented a more detailed cost analysis specific to diabetic foot ulcers, showing that the mean cost for the ADMSCs group was significantly higher at $6695.30 compared to $4082.00 for the control group ($p = 0.001$). While this higher cost reflects the complexity and tailored nature of cell therapies, the long-term benefits associated with improved healing and reduced recurrence rates may justify the initial investment. Costs of treatments has been summarized in Table 3.

3.12. Publication bias and sensitivity analysis

Publication bias was assessed using Egger's test. Fig. 10 A and B present largely symmetrical funnel plots of the effect of PRP and MSCs therapy on wound healing rate, indicating that there was no significant evidence of publication bias ($p = 0.71$ and 0.18, respectively). Additionally, a sensitivity analysis was conducted by sequentially removing each included study, and the results demonstrated that none of the studies altered the overall findings qualitatively.

4. Discussion

This meta-analysis investigated the effects of MSCs, PRP, alone and in combination on wound healing by analyzing 34 studies involving 2458 patients. The findings from this study provide robust evidence for the efficacy of these therapies in promoting wound healing and minimizing complications. Our results reveal that both PRP and MSC therapies significantly improved ulcer healing rates compared to conventional treatments. The PRP-

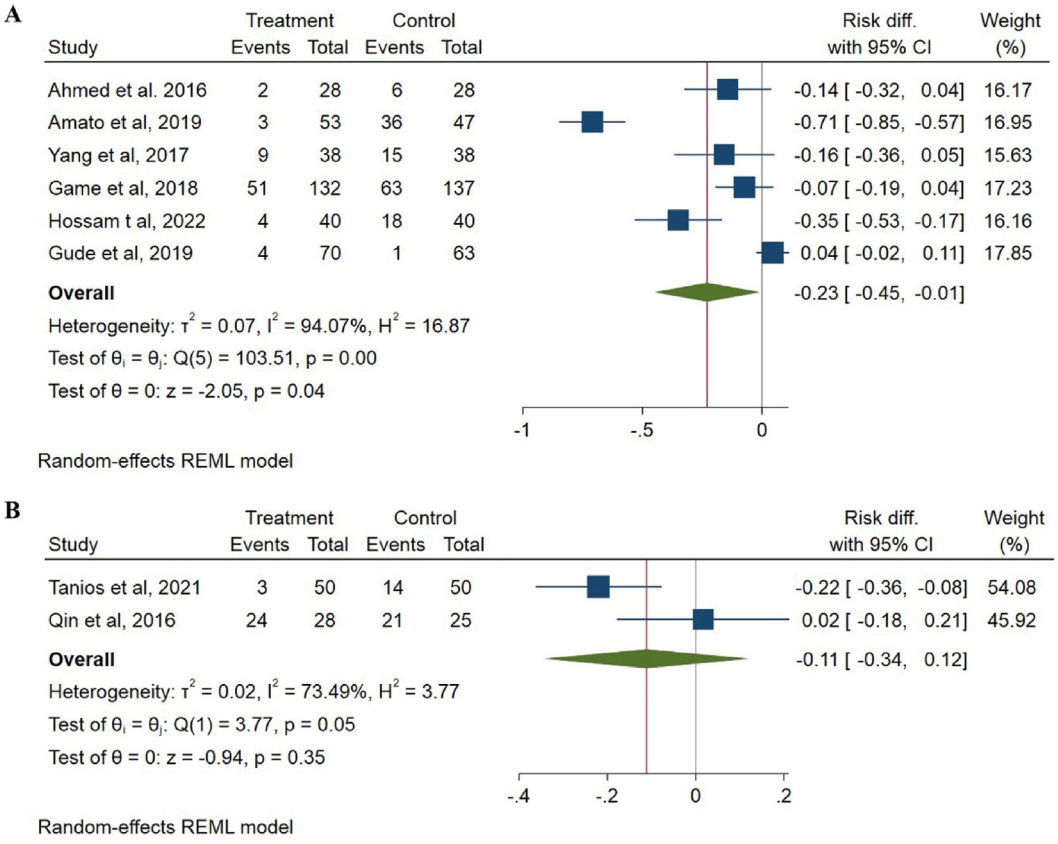

Fig. 7. Forest plot showing the effect of PRP (A) and MSCs (B) therapy on rate of infection. Note: The square size corresponds to sample size or study weight. The green diamond represents the overall pooled effect size.

treated group exhibited a healing rate of 585 out of 808 patients, while the control group recorded 423 out of 804. Likewise, MSC therapy demonstrated a significant increase in complete wound healing rates, with 211 successful outcomes compared to 129 in the control group (RD = 0.33, P < 0.001). These results highlight the potential of regenerative therapies to enhance wound healing outcomes. The subgroup analysis results highlight that the type of MSCs administered significantly influences the effectiveness of wound healing therapies. Notably, the RD of 0.67 for BMTRCs is particularly striking, suggesting that BMTRCs are associated with a remarkable 67 % increase in successful wound healing outcomes. This finding implies that BMTRCs, closely followed by BMMSCs and BMMNCs, not only accelerate the wound healing process but also enhance the quality of the healed tissue compared to other MSC types evaluated. However, while BMTRCs demonstrated the highest risk difference, these results should be interpreted cautiously due to the limited number of studies directly comparing different MSC types. Further research is warranted to validate these findings and to elucidate the underlying mechanisms driving these differences.

Whereas some studies suggest a potential synergy between PRP and MSCs, others did not show significant improvements. This inconsistency may be due to differences in cell types, PRP concentration, or administration methods. For example, Raposio et al. [43] used ADSCs combined with PRP and observed significant improvements, while Smith et al. [44] found no significant difference. These discrepancies highlight the need for standardized protocols in future research.

Current meta-analysis demonstrated a significant reduction in healing time for both MSC and PRP therapies, supporting their role in accelerating recovery. PRP, in particular, was shown to significantly reduce healing time compared to conventional therapies. The overall SMD of −1.08 highlights the effectiveness of PRP in expediting wound healing. Furthermore, the studies consistently reported substantial reductions in wound size for both treatment groups, indicating that these therapies not only expedite healing but also facilitate more effective wound closure. Moreover, the combination of MSCs and PRP showed promising results as well. Studies indicated higher healing rates and reduced wound sizes when these therapies were used together compared to control groups, suggesting potential synergistic effects. However, while some studies found significant improvements, others reported no statistical significance, emphasizing the need for further research to identify optimal treatment protocols.

A critical mechanism driving the effectiveness of MSC and PRP therapies is their ability to stimulate angiogenesis. Research by Liu et al. [34] and Yang et al. [48] noted elevated levels of growth factors, including transforming growth factor (TGF)-β, insulin-like growth factor 1 (IGF-1), Platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) in wound tissues of patients treated with PRP compared to controls. The studies evaluating MSCs revealed significant positive effects on new vessel development, a critical factor in effective wound healing. BMMSCs were particularly effective (SMD = 0.83), compared to BMMNCs (SMD = 0.39), with an overall effect size of 0.55. This underscores the angiogenic potential of MSCs in promoting vascularization; therefore, facilitate improved oxygen and nutrient delivery to the affected areas and enhancing the wound healing process.

Pain management outcomes were also assessed as part of the treatment efficacy. Our meta-analysis demonstrated that PRP treatment was associated with lower rest pain scores compared to

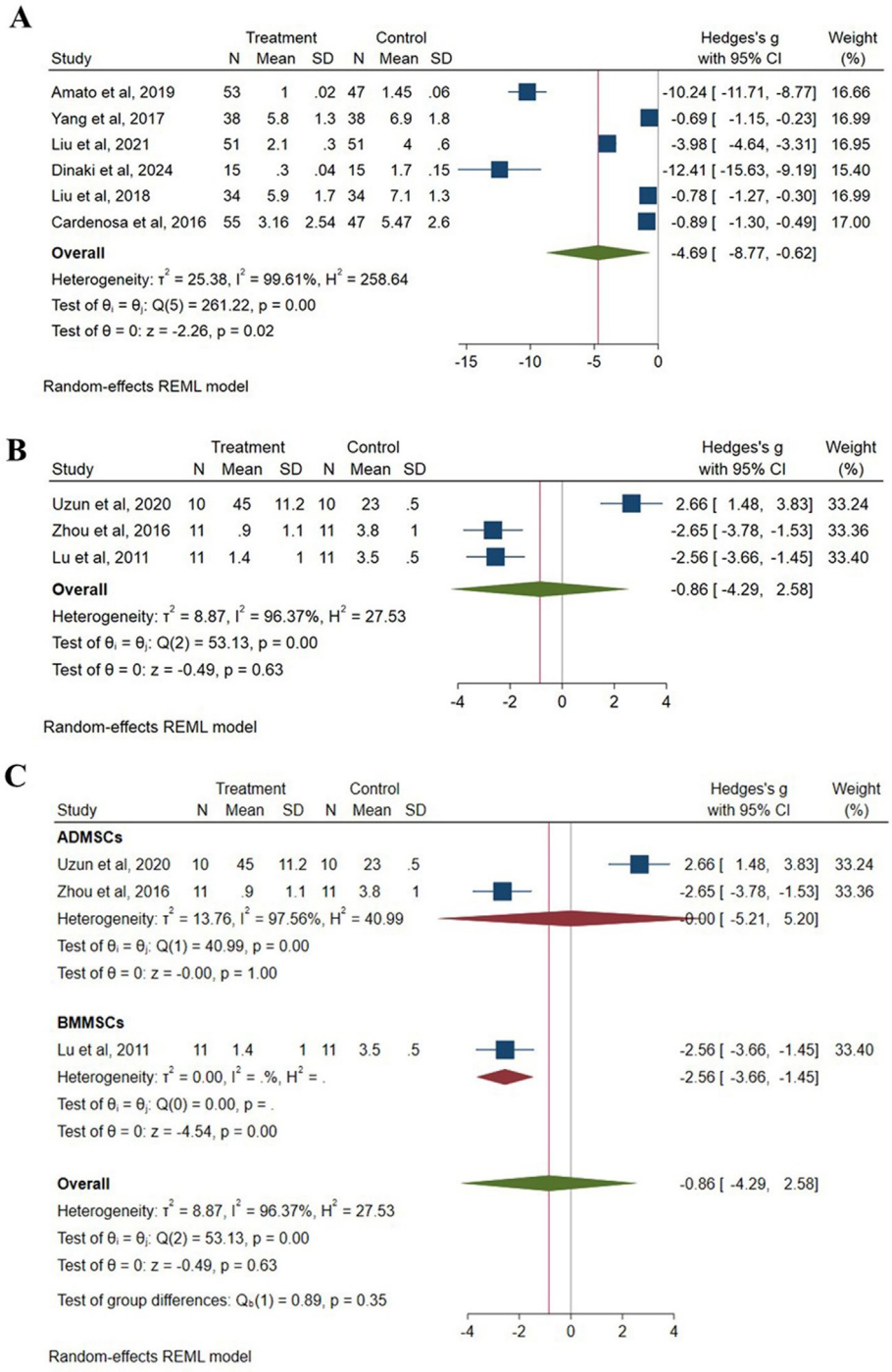

Fig. 8. Forest plot showing the effect of PRP (A) and MSCs (B) therapy on wound rest pain. Forest plot of subgroup analysis (C). Note: The square size corresponds to sample size or study weight. The green diamond represents the overall pooled effect size, while the red diamond indicates subgroup analyses.

the control group. Most studies reported improved pain outcomes, contributing to overall patient satisfaction and enhancing quality of life during the healing process. For example, Jeong et al. [30] found that patients in the PRP group reported greater satisfaction compared to those in the control group (mean scores of 7.6 ± 1.6 vs. 5.3 ± 1.4, respectively; $p < 0.05$). For MSC therapy, results varied, with some studies reporting significant pain reduction, while others reported higher pain scores.

The safety profile of MSC and PRP therapies appears favorable based on our analysis, which revealed no major adverse events associated with stem cell therapy. Notably, the incidence of ulcer recurrence was significantly lower in the PRP group than in the controls, demonstrating the potential for long-term benefits of PRP therapy. However, observed inconsistencies in infection rates across studies highlight the need for careful evaluation and monitoring in future clinical applications.

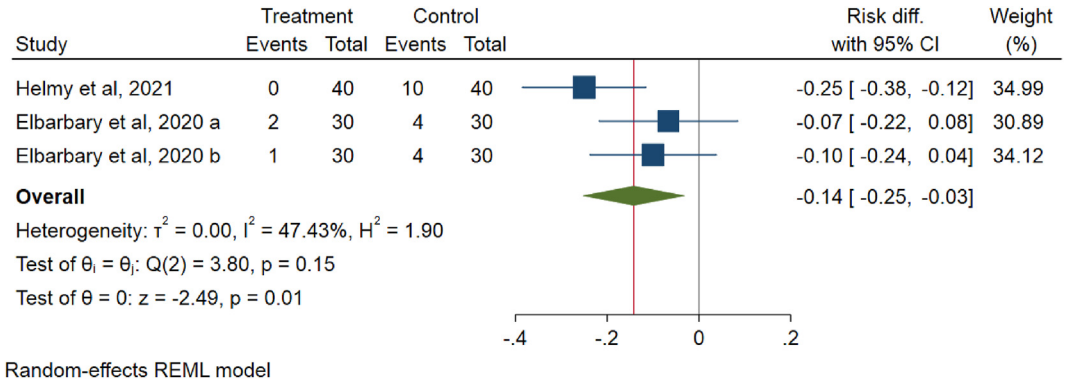

Fig. 9. Forest plot showing the effect of PRP therapy on recurrence rate.

Table 2
Main conclusion of the studies assessing adverse events.

Author, Year	Main remark
Cardenosa et al., 2017 [21]	No adverse events recorded in either of the two PRP and control groups.
Dubsky et al., 2013 [23]	No serious adverse events were observed following stem cell therapy, except leg edema which improved over time.
Game et al., 2018 [25]	No statistically significant difference found between the PRP and the control groups
Han et al., 2012 [27]	No adverse events related to the study treatment recorded
Helmy et al., 2021 [28]	No adverse events recorded
Jeong et al., 2010 [30]	No adverse events related to the study treatment recorded
Kirana et al., 2012 [32]	No adverse events regarding bone marrow aspirations And stem cells applications recorded
Liu et al, 2018 [33]	No statistically significant difference in adverse reactions between the PRP and the control groups
Liu et al, 2021 [34]	No serious adverse reactions or complications observed
Lu et al, 2011 [35]	No serious adverse events related to treatment
Molendijk et al, 2015 [37]	No adverse events related to MSC therapy recorded
Moon et al., 2019 [38]	No serious adverse events related to allogeneic ADSCs therapy recorded
Panés et al., 2016 [40]	Adverse events in 17 % of MSC group and 29 % of placebo group, commonly anal abscess and proctalgia
Smith et al., 2020 [44]	Five non serious adverse events (infection, chest sepsis, antibiotics allergic reaction, cardiac failure, and the necrotic toe) recorded
Uzun et al., 2021 [47]	No adverse events related to MSC therapy recorded
Yang et al., 2017 [48]	No statistically significant difference between the PRP and the control groups
Zhou et al., 2020 [49]	No adverse events associated with cell therapy recorded

Table 3
Costs of treatments.

Study	Treatment Group	Control Group	Cost of Treatment (PRP/MSC)	Cost of Control Treatment	Cost-Effectiveness Notes
Amato et al. (2019) [18]	PRP (CGF)	Standard dressings	€7.50 per procedure	Not specified	Higher unit cost of CGF dressings offset by fewer dressings needed for complete healing.
Hossam et al. (2022) [29]	PRP	Conventional treatment	$247.50 total	$437.50 total	PRP treatment was more cost-effective due to faster healing and fewer complications.
Orban et al. (2022) [39]	PRP	Conventional dressings	$504.58 mean cost	$484.17 mean cost	PRP had higher initial costs but led to faster healing, reducing long-term healthcare costs.
Smith et al. (2020) [44]	ADSCs + PRP	Control (standard care)	£13.45 per patient	£15.01 per patient	No significant difference in dressing costs between groups over time ($p > 0.05$).
Uzun et al. (2021) [47]	ADSCs	Control (standard care)	$6695.30 mean cost	$4082.00 mean cost	Higher initial cost of ADSCs justified by improved healing and reduced recurrence rates.

Our cost analysis reveals that, despite the higher initial expenses, PRP and MSC treatments are economically favorable in the long run. These therapies, with their reduced healing times, fewer complications, and diminished need for subsequent interventions, position PRP and MSC as cost-effective options in wound management. As healthcare providers search for effective and economical treatment strategies, adopting these regenerative therapies could lead to substantial long-term savings. Further research is essential to quantify long-term cost benefits and to integrate these therapies into standard care protocols, thereby realizing their potential cost-benefit advantages in clinical settings.

The heterogeneity observed in the meta-analysis may be attributed to variations in PRP preparation methods, MSC sources, and patient populations. For example, PRP preparation protocols varied significantly across studies, with some using single centrifugation and others using double centrifugation. Similarly, MSC sources ranged from adipose tissue to bone marrow and umbilical cord, which may have influenced the outcomes. Future studies

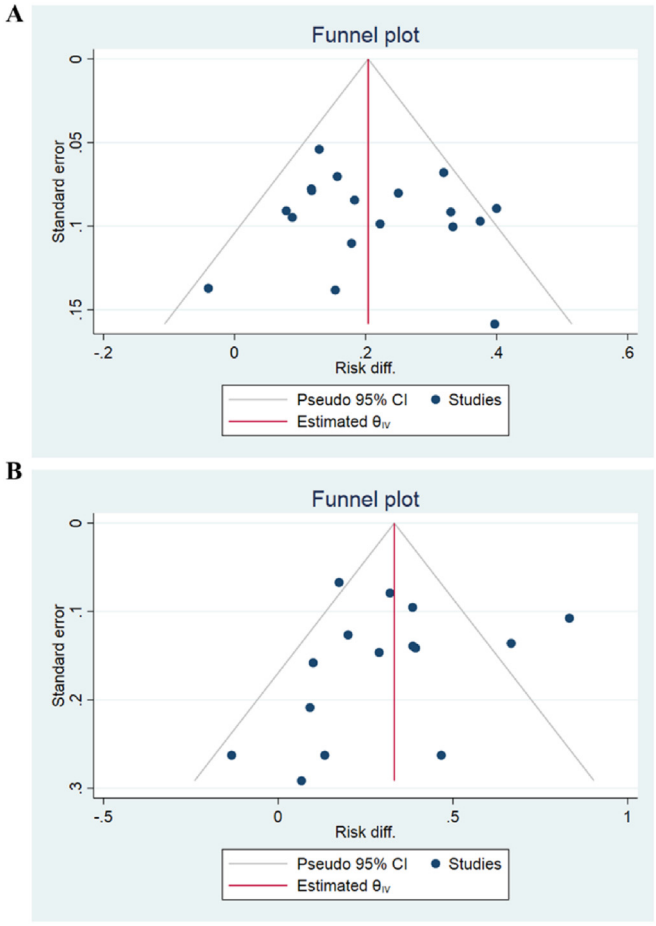

Fig. 10. Publication bias related to the effect of PRP (A) and MSCs (B) therapy on wound healing rate.

should aim to standardize these protocols to reduce heterogeneity and improve comparability.

5. Limitations and considerations

Despite these promising findings, this meta-analysis is not without limitations. Variability in study designs, types of MSCs utilized, forms of PRP application, the frequency of treatments, dose of cells, and assessment methodologies for outcomes may introduce biases that could affect the generalizability of the results. Additionally, while funnel plot analysis did not indicate significant publication bias, the possibility of unpublished studies with negative results cannot be ruled out. Egger's test showed no significant evidence of publication bias, but it is important to acknowledge that this test has limited power in small sample sizes. Future meta-analyses should consider including unpublished data to reduce the risk of bias. The quality of the included studies varied, with several displaying a moderate risk of bias. To accurately evaluate the efficacy of MSC and PRP therapies, future investigations should prioritize high-quality clinical trials with standardized protocols to validate and refine these findings. Key elements requiring standardization include PRP preparation methods, platelet concentration in PRP, MSC dosage, the number of MSCs administered, and consistent outcome measures. Establishing these standardized parameters will enhance the reliability and comparability of results across studies, ultimately advancing the clinical application of these therapies.

6. Conclusion and future directions

In summary, this meta-analysis underscores the beneficial effects of MSCs and PRP on wound healing, demonstrating significant improvements in healing rates, reductions in wound size, and better pain management outcomes. Given the favorable safety profile and potential to enhance wound healing, further studies are recommended to optimize treatment protocols, explore long-term outcomes, and deepen our understanding of the underlying mechanisms of action. As the field evolves, integrating MSC and PRP therapies into clinical practice may represent a significant advancement in the management of complex wounds and the enhancement of patient outcomes.

Consent to participate declaration

Not Applicable.

Ethical approval

Not Applicable.

Human ethics and consent to participate declaration

Not applicable.

Clinical trial number

Not applicable.

Author contributions

Conception and design of the study: Ming Zhu, Yunqing Sun, Lianmei Qiu. Acquisition of data: Ming Zhu, Yunqing Sun. Analysis and interpretation of data: Yunqing Sun, Lianmei Qiu. Drafting or revising the manuscript: Ming Zhu, Yunqing Sun, Lianmei Qiu. All authors have approved the final article.

Data availability statement

Data available on request from the authors.

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None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2025.04.010.

References

[1] Chhabra S, Chhabra N, Kaur A, Gupta N. Wound healing concepts in clinical practice of OMFS. J Maxillofac Oral Surg 2017;16:403–23.
[2] Stone II R, Natesan S, Kowalczewski CJ, Mangum LH, Clay NE, Clohessy RM, et al. Advancements in regenerative strategies through the continuum of burn care. Front Pharmacol 2018;9:672.
[3] Basu S, Shukla V. Complications of wound healing. In: Measurements in wound healing. Science and Practice; 2013. p. 109–44.

[4] Wang Y, Beekman J, Hew J, Jackson S, Issler-Fisher AC, Parungao R, et al. Burn injury: challenges and advances in burn wound healing, infection, pain and scarring. Adv Drug Deliv Rev 2018;123:3–17.
[5] Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care 2015;4(9):560–82.
[6] Maxson S, Lopez EA, Yoo D, Danilkovitch-Miagkova A, LeRoux MA. Concise review: role of mesenchymal stem cells in wound repair. Stem Cells Trans Med 2012;1:142–9.
[7] Mazini L, Rochette L, Admou B, Amal S, Malka G. Hopes and limits of adipose-derived stem cells (ADSCs) and mesenchymal stem cells (MSCs) in wound healing. Int J Mol Sci 2020;21:1306.
[8] Dabrowska S, Andrzejewska A, Janowski M, Lukomska B. Immunomodulatory and regenerative effects of mesenchymal stem cells and extracellular vesicles: therapeutic outlook for inflammatory and degenerative diseases. Front Immunol 2021;11:591065.
[9] Bian D, Wu Y, Song G, Azizi R, Zamani A. The application of mesenchymal stromal cells (MSCs) and their derivative exosome in skin wound healing: a comprehensive review. Stem Cell Res Ther 2022;13:24.
[10] Manole CG, Soare C, Ceafalan LC, Voiculescu VM. Platelet-rich plasma in dermatology: new insights on the cellular mechanism of skin repair and regeneration. Life 2023;14:40.
[11] Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immun Ageing 2013;10:1–10.
[12] Etulain J. Platelets in wound healing and regenerative medicine. Platelets 2018;29:556–68.
[13] Chicharro-Alcántara D, Rubio-Zaragoza M, Damiá-Giménez E, Carrillo-Poveda JM, Cuervo-Serrato B, Peláez-Gorrea P, et al. Platelet rich plasma: new insights for cutaneous wound healing management. J Funct Biomater 2018;9:10.
[14] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 2021;372.
[15] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011:343.
[16] Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. Ann Vasc Surg 2017;38:206–11.
[17] Alamdari NM, Shafiee A, Mirmohseni A, Besharat S. Evaluation of the efficacy of platelet-rich plasma on healing of clean diabetic foot ulcers: a randomized clinical trial in Tehran, Iran. Diabetes Metabol Syndr: Clin Res Rev 2021;15:621–6.
[18] Amato B, Farina MA, Campisi S, Ciliberti M, Donna VD, Florio A, et al. CGF treatment of leg ulcers: a randomized controlled trial. Open Med 2019;14:959–67.
[19] Behrangi E, Moradi S, Ghassemi M, Goodarzi A, Hanifnia A, Zare S, et al. The investigation of the efficacy and safety of stromal vascular fraction in the treatment of nanofat-treated acne scar: a randomized blinded controlled clinical trial. Stem Cell Res Ther 2022;13:298.
[20] Capion SC, Jørgensen HB, Ågren MS, Daugaard H, Ribel-Madsen S, Marando D, et al. The wound healing effect of local leukocyte platelet-rich plasma after total hip arthroplasty: a randomized controlled trial. Wound Repair Regen 2021;29:988–95.
[21] Cardenosa ME, Domínguez-Maldonado G, Córdoba-Fernández A. Efficacy and safety of the use of platelet-rich plasma to manage venous ulcers. J Tissue Viability 2017;26:138–43.
[22] Dinaki K, Grigoriadis N, Vizirianakis IS, Constantinidis J, Triaridis S, Karkos P. The impact of submucosal PRP injection on wound healing after endoscopic sinus surgery: a randomized clinical trial. Eur Arch Otorhinolaryngol 2024:1–13.
[23] Dubsky M, Jirkovska A, Bem R, Fejfarova V, Pagacova L, Sixta B, et al. Both autologous bone marrow mononuclear cell and peripheral blood progenitor cell therapies similarly improve ischaemia in patients with diabetic foot in comparison with control treatment. Diabetes/Metabolism Res Rev 2013;29:369–76.
[24] Elbarbary AH, Hassan HA, Elbendak EA. Autologous platelet-rich plasma injection enhances healing of chronic venous leg ulcer: a prospective randomised study. Int Wound J 2020;17:992–1001.
[25] Game F, Jeffcoate W, Tarnow L, Jacobsen JL, Whitham DJ, Harrison EF, et al. LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. Lancet Diabetes Endocrinol 2018;6:870–8.
[26] Gude W, Hagan D, Abood F, Clausen P. Aurix gel is an effective intervention for chronic diabetic foot ulcers: a pragmatic randomized controlled trial. Adv Skin Wound Care 2019;32:416–26.
[27] Han SK, Kim HR, Kim WK. The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. Wound Repair Regen 2010;18:342–8.
[28] Helmy Y, Farouk N, Ali Dahy A, Abu-Elsoud A, Fouad khattab R, Elshahat Mohammed S, et al. Objective assessment of Platelet-Rich Plasma (PRP) potentiality in the treatment of Chronic leg Ulcer: RCT on 80 patients with Venous ulcer. J Cosmet Dermatol 2021;20:3257–63.
[29] Hossam EM, Alserr AHK, Antonopoulos CN, Zaki A, Eldaly W. Autologous platelet rich plasma promotes the healing of non-ischemic diabetic foot ulcers. A randomized controlled trial. Ann Vasc Surg 2022;82:165–71.
[30] Jeong S-H, Han S-K, Kim W-K. Treatment of diabetic foot ulcers using a blood bank platelet concentrate. Plast Reconstr Surg 2010;125:944–52.
[31] Karimi R, Afshar M, Salimian M, Sharif A, Hidariyan M. The effect of platelet rich plasma dressing on healing diabetic foot ulcers. Nurs Midwifery Stud 2016;5:e30314.
[32] Kirana S, Stratmann B, Prante C, Prohaska W, Koerperich H, Lammers D, et al. Autologous stem cell therapy in the treatment of limb ischaemia induced chronic tissue ulcers of diabetic foot patients. Int J Clin Pract 2012;66:384–93.
[33] Liu J, Qu W, Li R, Zheng C, Zhang L. Efficacy of autologous platelet-rich gel in the treatment of deep grade II burn wounds. Int J Clin Exp Med 2018;11:2654–9.
[34] Liu Q, Zhang N, Li Z, He H. Efficacy of autologous platelet-rich plasma gel in the treatment of refractory pressure injuries and its effect on wound healing time and patient quality of life. Clinics 2021;76:e2355.
[35] Lu D, Chen B, Liang Z, Deng W, Jiang Y, Li S, et al. Comparison of bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for treatment of diabetic critical limb ischemia and foot ulcer: a double-blind, randomized, controlled trial. Diabetes Res Clin Pract 2011;92:26–36.
[36] Meamar R, Ghasemi-Mobarakeh L, Norouzi M-R, Siavash M, Hamblin MR, Fesharaki M. Improved wound healing of diabetic foot ulcers using human placenta-derived mesenchymal stem cells in gelatin electrospun nanofibrous scaffolds plus a platelet-rich plasma gel: a randomized clinical trial. Int Immunopharmacol 2021;101:108282.
[37] Molendijk I, Bonsing BA, Roelofs H, Peeters KC, Wasser MN, Dijkstra G, et al. Allogeneic bone marrow–derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease. Gastroenterology 2015;149:918–927. e6.
[38] Moon K-C, Suh H-S, Kim K-B, Han S-K, Young K-W, Lee J-W, et al. Potential of allogeneic adipose-derived stem cell–hydrogel complex for treating diabetic foot ulcers. Diabetes 2019;68:837–46.
[39] Orban YA, Soliman MA, Hegab YH, Alkilany MM. Autologous platelet-rich plasma vs conventional dressing in the management of chronic diabetic foot ulcers. Wounds: A Compe Clini Res Pract 2022;33:36–42.
[40] Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet 2016;388:1281–90.
[41] Parwani SR, Thakare KS, Kawadkar KP, Soni NJ, Parwani R, Dadlani H, et al. Platelet-rich fibrin in non-surgical periodontal therapy: a split-mouth randomized controlled clinical trial. Dent J 2024;12:135.
[42] Qin H, Zhu X, Zhang B, Zhou L, Wang W. Clinical evaluation of human umbilical cord mesenchymal stem cell transplantation after angioplasty for diabetic foot. Exp Clin Endocrinol Diabetes 2016;124:497–503.
[43] Raposio E, Bertozzi N, Bonomini S, Bernuzzi G, Formentini A, Grignaffini E, et al. Adipose-derived stem cells added to platelet-rich plasma for chronic skin ulcer therapy. Wounds: A compe Clinic Res Pract 2016;28:126–31.
[44] Smith OJ, Leigh R, Kanapathy M, Macneal P, Jell G, Hachach-Haram N, et al. Fat grafting and platelet-rich plasma for the treatment of diabetic foot ulcers: a feasibility-randomised controlled trial. Int Wound J 2020;17:1578–94.
[45] Tanios E, Ahmed TM, Shafik EA, Sherif MF, Sayed D, Gaber N, et al. Efficacy of adipose-derived stromal vascular fraction cells in the management of chronic ulcers: a randomized clinical trial. Regen Med 2021;16:975–88.
[46] Tofigh AM, Tajik M. Comparing the standard surgical dressing with dehydrated amnion and platelet-derived growth factor dressings in the healing rate of diabetic foot ulcer: a randomized clinical trial. Diabetes Res Clin Pract 2022;185:109775.
[47] Uzun E, Güney A, Gönen ZB, Özkul Y, Kafadar İH, Günay M, et al. Intralesional allogeneic adipose-derived stem cells application in chronic diabetic foot ulcer: phase I/2 safety study. Foot Ankle Surg 2021;27:636–42.
[48] Yang L, Gao L, Lv Y, Wang J. Autologous platelet-rich gel for lower-extremity ischemic ulcers in patients with type 2 diabetes. Int J Clin Exp Med 2017;10:13796–801.
[49] Zhou C, Li M, Zhang Y, Ni M, Wang Y, Xu D, et al. Autologous adipose-derived stem cells for the treatment of Crohn's fistula-in-ano: an open-label, controlled trial. Stem Cell Res Ther 2020;11:1–13.