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SYSTEMATIC REVIEW

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Efficacy and safety of autologous platelet-rich plasma for diabetic foot ulcer healing: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background The occurrence of a diabetic foot ulcer (DFU) is a significant complication of diabetes that often precedes the need for amputation. Autologous platelet-rich plasma (Au-PRP), a substance abundant in various growth factors and cytokines, is increasingly being recognized as a promising method for promoting ulcer healing due to its potential similarities to the physiological wound healing process.

Methods The databases Medline, EMBASE, PubMed, and the Cochrane Library were systematically accessed on January 26, 2023, without any consideration for the date of publication. The selection and assessment of research studies were conducted autonomously, based on predetermined criteria and methodological standards. Two researchers gathered data and evaluated the potential for bias separately. We utilize the Stata 17.0 software to conduct data analysis and generate relevant visual representations.

Results The results of the meta-analysis indicate that autologous PRP has a significant positive effect on the healing rate (RR = 1.42, 95% CI 1.30–1.56, $P < 0.001$), reduces the healing time (MD = − 3.13, 95% CI − 5.86 to − 0.39, $P < 0.001$), accelerates the reduction of ulcer area (MD = 1.02, 95% CI 0.51–1.53, $P < 0.001$), decreases the rate of amputation (RR = 0.35, 95% CI 0.15–0.83, $P < 0.001$), and does not increase the incidence of adverse events (RR = 0.96, 95% CI 0.57–1.61, $P > 0.05$) when compared to conventional therapy.

Conclusions Au-PRP therapy has been shown to facilitate the process of wound healing and represents a viable and secure therapeutic alternative for individuals with DFU.

Keywords Platelet-rich plasma, Diabetic foot ulcer, Randomized controlled trials, Meta-analysis

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia [1]. As per the findings of the research, the global prevalence of DM was estimated to be approximately 436 million individuals in the year 2019. It is projected that the number of individuals affected by DM worldwide will escalate to 700 million by the year 2045 [2]. The incidence of DM and its associated complications has not only significantly diminished patients' quality of life, but also posed a substantial threat to their survival, thereby presenting significant economic and healthcare obstacles. Diabetic foot ulcer (DFU) is a prevalent complication of DM. Research indicates that the global annual incidence

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of DFU is approximately 6.3% [3]. DFU can be attributed to several factors such as inadequate management of blood glucose levels, structural abnormalities of the foot, neurological impairments, compromised circulation, and physical injury [4, 5]. Once the DFU is formed, it is easy to develop into a chronic refractory wound, which eventually leads to amputation or even death. In addition, due to the persistence of ulcer formation factors, even if the wound heals successfully, ulcers are still easy to recur in a short period of time [4]. The cost of DFU in the USA increased fivefold from 2005 to 2010, spending more than $1 billion a year on DFU care [6, 7]. As of 2017, the expenditure for prevention and treatment of DM amounted to approximately $237 billion, with a significant portion of almost 33% allocated towards DFU. This proportion is comparable to the expenses incurred for prevalent types of cancer [8]. The efficacy of traditional therapeutic interventions, including glycemic control, neural nourishment, anti-infective measures, localized decompression, comprehensive debridement and dressing modifications, sufficient drainage, enhanced microcirculation, and vascular restructuring, is suboptimal in facilitating the healing of diabetic foot ulcers [9–11].

PRP is a concentrated plasma preparation that contains a high concentration of platelets. It is derived from either autologous or allogeneic whole blood of patients [12]. Based on the origin of the blood, platelet-rich plasma (PRP) can be classified into two categories: autologous PRP (Au-PRP) and allogeneic PRP (Al-PRP). Due to its autologous nature, Au-PRP is not susceptible to immune rejection, thus making it the predominant form of PRP utilized in clinical settings. The therapeutic mechanism of Au-PRP in the treatment of DFU is attributed to its rich composition of growth factors, white blood cells, antimicrobial peptides, fibrin, and diverse cytokines. These constituents work in tandem to regulate the inflammatory response, expedite the formation of extracellular matrix, promote angiogenesis, and facilitate re-epithelialization, ultimately leading to the healing of the ulcer. The utilization of Au-PRP as a potential treatment for DFU may prove advantageous based on the pathophysiological mechanisms of wound healing in diabetes. Nevertheless, the current body of evidence is insufficient to substantiate this hypothesis [13]. The utilization of Au-PRP has been suggested as a potential treatment option for DFU that have failed to heal despite standard therapy [14].

The objective of this study is to investigate, assess, and synthesize scientific data pertaining to the safety and therapeutic effectiveness of Au-PRP in the management of DFU in comparison with conventional treatment or any other substitute therapy.

Materials and methods

During the systematic review process and subsequent reporting of our results, we maintained adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Since the information utilized in this article was sourced from published materials, there was no need for informed consent or ethical approval. Two researchers conducted a systematic search of pertinent studies, independently determined their eligibility, extracted data, and evaluated the quality of the research. The two researchers were required to reach a consensus and resolve any points of disagreement.

Search strategy

The electronic databases of Medline, EMBASE, PubMed, and the Cochrane Library were searched on January 26, 2023. The vocabulary and grammar were adjusted in accordance with the database through specific modifications. The study utilized the search phrases "platelet-rich plasma" in conjunction with "foot ulcer" or "diabetic foot." There were no restrictions on language or timeframe. The PubMed search strategy is shown below: (("Platelet Rich Plasma"[MeSH Terms] OR "Plasma, Platelet-Rich"[MeSH Terms] OR "Platelet-rich Plasma Gel"[MeSH Terms] OR "PRP"[MeSH Terms] OR "Platelet-Rich Plasma"[MeSH Terms])) AND ("Diabetic Foot"[MeSH Terms] OR "Foot Ulcer, Diabetic"[MeSH Terms] OR "Feet, Diabetic"[MeSH Terms] OR "Diabetic foot ulcer wounds"[MeSH Terms] OR "Diabetic Feet"[MeSH Terms] OR "Diabetic foot ulcer"[MeSH Terms] OR "Diabetic foot Wound"[MeSH Terms]) AND ("Randomized Controlled Trial"[Publication Type] OR "Randomized"[MeSH Terms] OR "Placebo"[MeSH Terms]). In order to conduct a comprehensive systematic search, the reference lists of all relevant articles were scrutinized to identify any additional studies that met the established inclusion criteria.

Inclusion criteria and exclusion criteria

The following requirements required to be met by studies to be included in the systematic review: (1) Design: randomized controlled trials (RCTs). (2) Population aged between 18 and 65 years who have DFU. (3) Intervention: any product containing a supraphysiologic concentration of autologous platelets. (4) Comparator: conventional therapy, no intervention, and alternative treatment for foot ulcers. (5) Outcome measures: proportion of DFU that is completely healed, total epithelialized area (cm2), ulcer volume decrease (cm3), duration to complete wound healing, wound complications, adverse events, amputation rate.

The exclusion criteria were as follows: (1) repeatedly published literature; (2) studies with incomplete or

unclear analytical data and inconsistent outcome indicators; (3) studies with poor quality and lack of original data.

Data extraction

Two reviewers were required to independently scrutinize the literature and extract the pertinent data. The results obtained required a process of cross-verification, and in case of any inconsistencies, they were subject to thorough discussion and resolution. During the literature screening process, the researchers initially review the title and abstract of the articles. Subsequently, they scrutinize the complete text to ascertain its inclusion in the study, while eliminating any overtly irrelevant content. The standardized Excel files contain extracted and recorded requisite data, which includes the surname of the first author, publication year, country, study design, demographic information of participants, treatment strategy, ulcer classification, PRP preparation, and PRP application. In instances where the published report lacked pertinent data, the investigators of the original study were contacted via email to request access to the unpublished data.

Quality assessment

The quality of the included studies was assessed by the Cochrane Collaboration's risk of bias tool [16]. Two reviewers independently evaluated the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was judged as having a low, unclear, or high risk of bias. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer, if necessary.

Statistical analyses

The heterogeneity between studies was assessed using Chi-square statistics and quantified by the size of I^2. The heterogeneity of the included studies was assessed using the I^2 statistic. I^2 values greater than 50% indicated significant heterogeneity, whereas values of 0% signified no observable heterogeneity. When I^2 was greater than 50%, the random effect model was chosen; when I^2 was less than 50%, the fixed-effect model was employed. To assess the robustness of our results and identify any potential influence of individual studies on the overall effect size, we conducted a sensitivity analysis. This analysis involved sequentially removing each study from the meta-analysis and recalculating the overall effect size, examining whether the point estimates of the overall effect remained within the 95% confidence interval of the initial combined effect. The assessment of publication bias was conducted through the utilization of Egger's test and funnel plots. Statistical significance was determined by considering a two-sided P value of less than 0.05 in all analyses. The Stata version 17 (StataCorp, College Station, TX, USA) was utilized to analyze data from randomized controlled trials (RCTs) that satisfied the inclusion criteria. The certainty of the synthesized evidence was evaluated using the GRADEprofiler grading system following the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach [17].

Results

Search results and study selection

The initial query of the electronic databases yielded a total of 1765 research studies. Following the elimination of redundant literature, careful examination of titles and abstracts, and rigorous adherence to the established inclusion and exclusion criteria, a total of 56 relevant pieces of literature were procured, while 34 were deemed unsuitable for further analysis. Ultimately, a total of 22 articles were included [18–39]. The literature screening process and results are shown in Fig. 1.

Study characteristics

The selected trials encompassed a total of 1559 individuals who presented with wounds resulting from diabetic foot ulcers. Of these participants, 785 were subjected to treatment with platelet-rich plasma, while the remaining 774 were assigned to a control group. At the onset of the study, the quantity of individuals involved varied between 13 and 200. Table 1 presents a concise overview of the key characteristics of the studies that were incorporated. All the publications were released in the English language and spanned the years between 1992 and 2022. Each study analyzed data pertaining to a solitary ulcer per participant. Nineteen research studies were conducted to compare the effectiveness of PRP in combination with standard care versus standard care alone. One study was conducted to evaluate the efficacy of PRP in conjunction with standard care as opposed to platelet-poor plasma in conjunction with standard care [23]. One study was conducted to evaluate the efficacy of PRP in conjunction with standard care against oxidized regenerated cellulose/collagen biomaterial in conjunction with standard care [21]. Another study conducted a comparison between the administration of PRP in conjunction with standard care and the application of Saline gel in conjunction with standard care [20].

Results of quality assessment

The evaluation of bias risk was conducted across multiple domains in the 22 studies that were included. Seven studies demonstrated a low risk of bias in all categories,

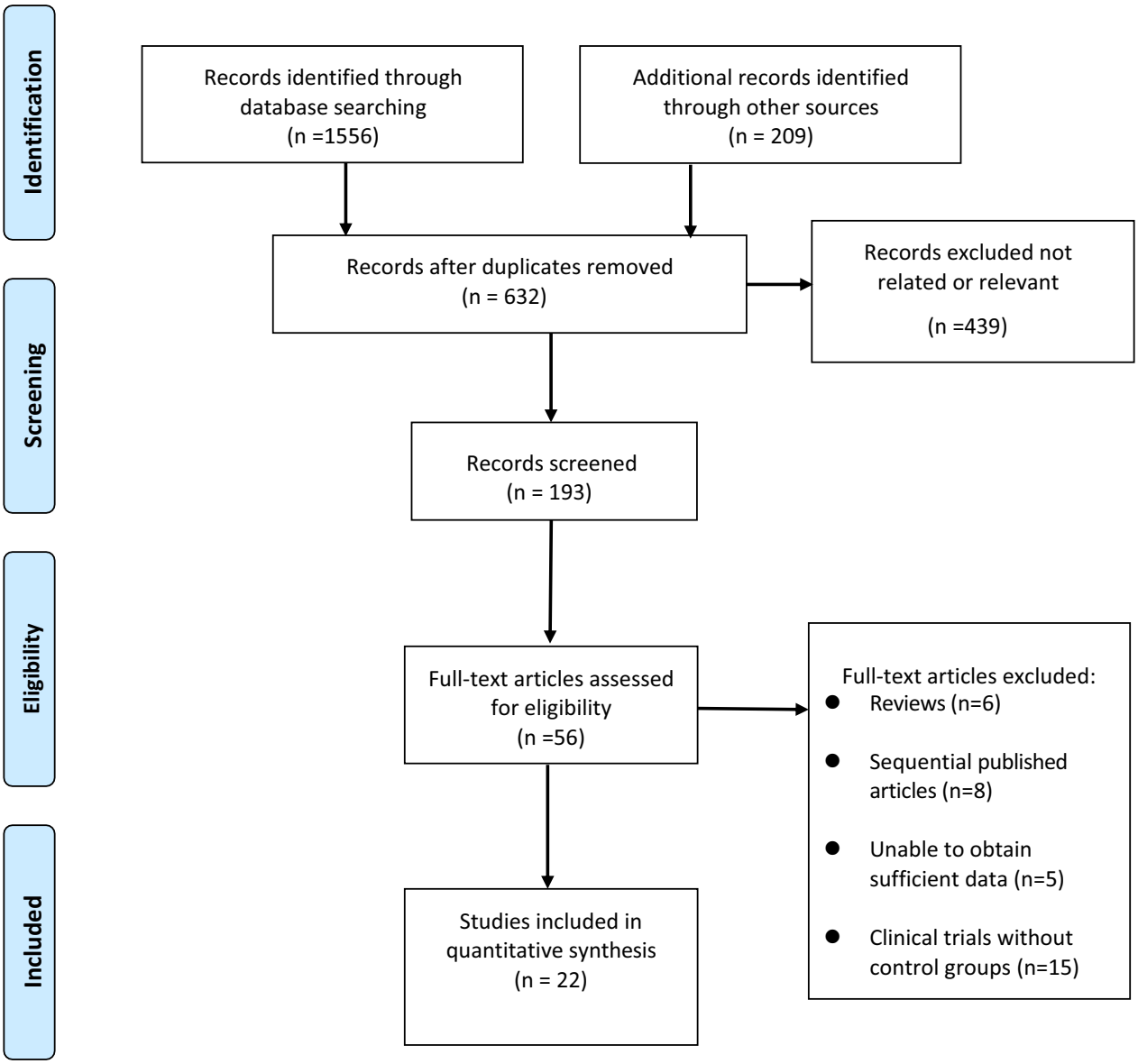

Fig. 1 Selection process of included studies

indicating a high level of methodological rigor. However, 20% of the studies were found to have a high risk of bias in the domain of blinding of participants and personnel. This suggests that the potential for performance bias might have influenced the outcomes in these studies. Furthermore, in 21% of the included randomized controlled trials, a high risk of selective reporting bias was observed. This indicates that the possibility of incomplete or selective outcome reporting may have affected the overall results of these studies (Fig. 2).

Overall healing rate of DFU

In the literature, 22 studies have documented the healing rate of Au-PRP compared to conventional treatment for DFU. The ulcer healing rate for the Au-PRP group varied between 12.5% (2/16) and 100% (29/29). The results of the control treatment group indicated that the conventional treatment did not result in any ulcer healing, as evidenced by the lowest healing rate of 0%. However, the highest healing rate of 92.3% (24/26) was observed in this group. The findings of the meta-analysis indicate that the use of Au-PRP is associated with a notable enhancement

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Study design	Country	Total/PRP	Treatment strategy	Treatment strategy	Ulcer classification	PRP preparation	PRP application
Tofigh	2022	RCT	Iran	161/81	PRP"	Control"	Wagner classification: I, II, III, IV, V	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcer with Vaseline gauze, few layers of sterile gauze, and non-compressible bandage. This was repeated twice weekly
Meamar	2021	RCT	Iran	17/10	PRP + SC	SC	Texas classification: IA, IIA, IC, IIC	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcers after irrigation with 0.9% saline twice weekly covered with non-absorbing dressing
Helmy	2021	RCT	Egypt	80/40	PRP + SC	SC	Wagner classification: I-IV	NC	PRP gel applied on ulcers covered with two pieces of dry sterile gauzes. PRP dressing was performed only once at the beginning of study
Hossam	2021	RCT	Iran	160/80	PRP + SC	SC	Wagner classification: I, II, III, IV, V	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcers covered with two pieces of dry sterile gauzes. PRP dressing was performed only once at the beginning of study
Alamdari	2021	RCT	Iran	90/43	PRP + SC	SC	Ulcers that had exposed bone or bone, involvement were excluded	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcers covered with Vaseline gauze and then a dressing. This was repeated twice weekly
Habeeb	2020	RCT	Egypt	44/22	PRP + SC	SC	Wagner classification: I, II, III, IV, V	Peripheral blood was centrifuged at 2000 rpm A for 10 min	PRP gel applied on ulcers covered with vapor-permeable film (Tegaderm, 3 M)
Liao	2020	RCT	China	200/100	PRP + SC	SC	NC	1. Peripheral blood was centrifuged for 1.5 min. 2. It was delivered by autologel system	PRP gel applied on ulcers covered with vapor-permeable film (Tegaderm, 3 M)
Elsaid	2020	RCT	Egypt	24/12	PRP + SC	SC	Wagner classification: I-IV	1. Peripheral blood was centrifuged at 3600 rpm. 2. A second centrifugation at 2400 rpm	PRP gel applied on ulcer with Vaseline gauze, few layers of sterile gauze, and non-compressible bandage. This was repeated twice weekly
Rainys	2019	RCT	Lithuania	69/35	PRP + SC	SC	NC	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcer with contact layer dressing covered with non-absorbent foam dressing changed every 3–4 d

Table 1 (continued)

Author	Year	Study design	Country	Total/PRP	Treatment strategy	Treatment strategy	Ulcer classification	PRP preparation	PRP application
Singh	2018	RCT	India	55/29	PRP + SC	SC	Ulcers that had exposed bone or bone, involvement were excluded	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	An appropriate amount of the PRP (approximately 3–4 ml of PRP for a 5 × 10 cm ulcer) was injected at various points along the wound edges once a week
Ahmed	2017	RCT	Egypt	56/28	PRP + SC	SC	Texas classification: IA, IIA, IC, IIC	1. Peripheral blood was centrifuged at 1500 rpm for 5 min. 2. A second centrifugation at 3500 rpm for 5 min	PRP gel applied on ulcers after irrigation with 0.9% saline twice weekly covered with non-absorbing dressing
Karimi	2016	RCT	Iran	50/25	PRP + SC	SC	Wagner classification: I, II	Peripheral blood was centrifuged at 2000 rpm A for 10 min	PRP gel applied on ulcers covered with two pieces of dry sterile gauzes. PRP dressing was performed only once at the beginning of study
Li	2015	RCT	China	103/48	PRP + SC	SC	Wagner classification: I, IV	1. Peripheral blood was centrifuged for 1.5 min. 2. It was delivered by autologel System	Weekly topical application of PRP gel with covered with standard dressing changed weekly
Li	2012	RCT	China	117/59	PRP + SC	SC	Wagner classification: I, II, III, IV, V	1. Peripheral blood was centrifuged at 313 × g for 4 min 2. A second centrifugation at 1252 × g for 6 min	PRP gel applied on ulcers covered with two pieces of dry sterile gauzes. PRP dressing was performed only once at the beginning of study
Saad Setta	2011	RCT	Egypt	24/12	PRP + SC	SC	Ulcers that had exposed tendons, ligaments or bone were excluded	1. Peripheral blood was centrifuged at 1007 × g. 2. A second centrifugation at 477.5 × g	PRP gel applied on ulcers covered with Vaseline gauze and then a dressing. This was repeated twice weekly
Jeong	2010	RCT	Korea	100/52	PRP + SC	PPP + SC	Texas classification: IA, IIA, IC, IIC	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcers covered with two pieces of dry sterile gauzes. PRP dressing was performed only once at the beginning of study
Friese	2007	RCT	Netherlands	42/21	PRP + SC	SC	Wagner classification: I, II, III	It was delivered by Harvest System (Harvest Technologies, Plymouth, MA)	PRP gel applied on ulcer every two weeks
Kakagia	2007	RCT	Greece	32/16	PRP + SC	SC	NC	It was delivered by Gravitational Platelet Separation System (GPS, Biomet)	PRP gel applied on ulcers covered with vapor-permeable film (Tegaderm, 3 M)

Table 1 (continued)

Author	Year	Study design	Country	Total/PRP	Treatment strategy	Treatment strategy	Ulcer classification	PRP preparation	PRP application
Driver	2006	RCT	USA	72/40	PRP + ORC/CB + SC	ORC/CB + SC	Texas classification: IA	1. Peripheral blood was centrifuged for 1.5 min. 2. It was delivered by autologel System(AutoloGel, Cytomedix, Gaithersburg, MD	Weekly topical application of PRP gel with covered with standard dressing changed weekly
Saldalamacchia	2004	RCT	Italy	14/7	PRP + SC	Saline gel + SC	Wagner classification: II, III	NC	Weekly topical application of PRP gel with covered with standard dressing changed weekly
Steed	1996	RCT	USA	36/18	PRP + SC	SC	Wagner classification: I, II, III	Delivered by Gravitational Platelet Separation System (GPS, Biomet)	PRP gel applied on ulcers covered with Vaseline gauze and then a dressing. This was repeated twice weekly
Steed	1992	RCT	USA	13/7	PRP + SC	SC	NC	Peripheral blood centrifuge at a rate of 2000–3200 rpm for 10–15 min	PRP gel applied on ulcer every two weeks

NC, not clear; ORC/CB, oxidized regenerated cellulose/collagen biomaterial; PPP, platelet-poor plasma; SC, standard care

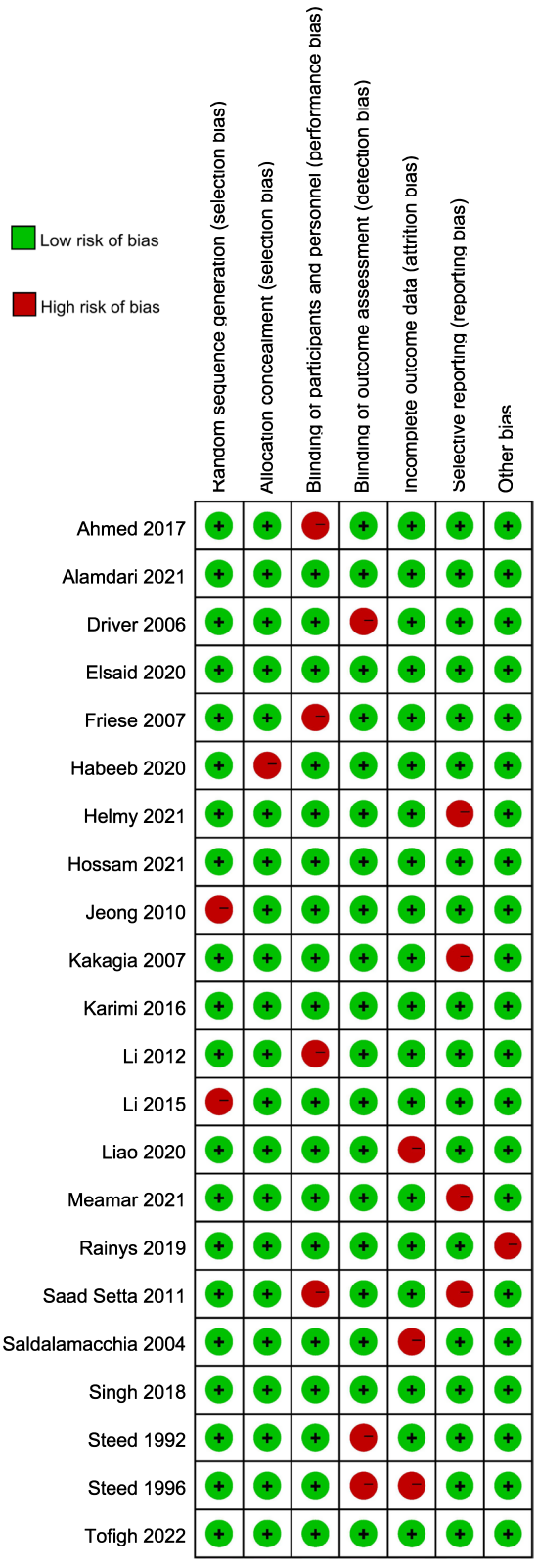

Fig. 2 Risk of bias summary graph for the included studies

in the healing rate of DFU when compared to conventional treatment. This difference is statistically significant (RR = 1.42, 95% CI 1.30–1.56, $P < 0.001$; Fig. 3). The outcomes of the heterogeneity test ($P < 0.001$ and $I^2 = 54.8\%$) indicated the presence of heterogeneity among the studies that were incorporated in the analysis.

Time to complete wound healing

A total of 3 studies [20, 32, 36] were conducted to compare the healing time of DFU between Au-PRP and conventional therapy alone. The results of meta-analysis showed that Au-PRP could significantly shorten the healing time of DFU compared with conventional therapy, and the difference was statistically significant (MD = −3.13, 95% CI −5.86 to −0.39, $P < 0.001$; Fig. 4). The results of heterogeneity test ($P < 0.0001$, and $I^2 = 97.5\%$) suggested that there was some heterogeneity among the included studies.

Ulcer volume reduction

Three studies [25, 26, 39] reported the changes of ulcer area before and after treatment in the two groups. The results of meta-analysis showed that Au-PRP could significantly accelerate the reduction of DFU area compared with conventional therapy, and the difference was statistically significant (MD = 1.02, 95% CI 0.51–1.53, $P < 0.001$; Fig. 4). The results of heterogeneity test ($P = 0.210$, and $I^2 = 36\%$) suggested that there was not heterogeneity among the included studies.

Amputation rate

A total of 3 studies [32, 36, 37] reported amputation rates in two groups of patients. The results of meta-analysis showed that Au-PRP could significantly reduce the rate of amputation compared with conventional therapy, and the difference was statistically significant (RR = 0.35, 95% CI 0.15–0.83, $P < 0.001$; Fig. 5). The results of heterogeneity test ($P = 0.615$, and $I^2 = 0.0\%$) suggested that there was not heterogeneity among the included studies.

Adverse events

A total of 4 studies [20, 26, 36, 37] reported the occurrence of adverse reactions including local fever, local itching, tingling, ant sensation, local infection, dermatitis, etc. The results of meta-analysis showed that Au-PRP could not increase the incidence of adverse events compared with conventional therapy (RR = 0.96, 95% CI 0.57–1.61, $P > 0.05$; Fig. 5). The results of heterogeneity test ($P = 0.203$, and $I^2 = 34.9\%$) suggested that there was not heterogeneity among the included studies.

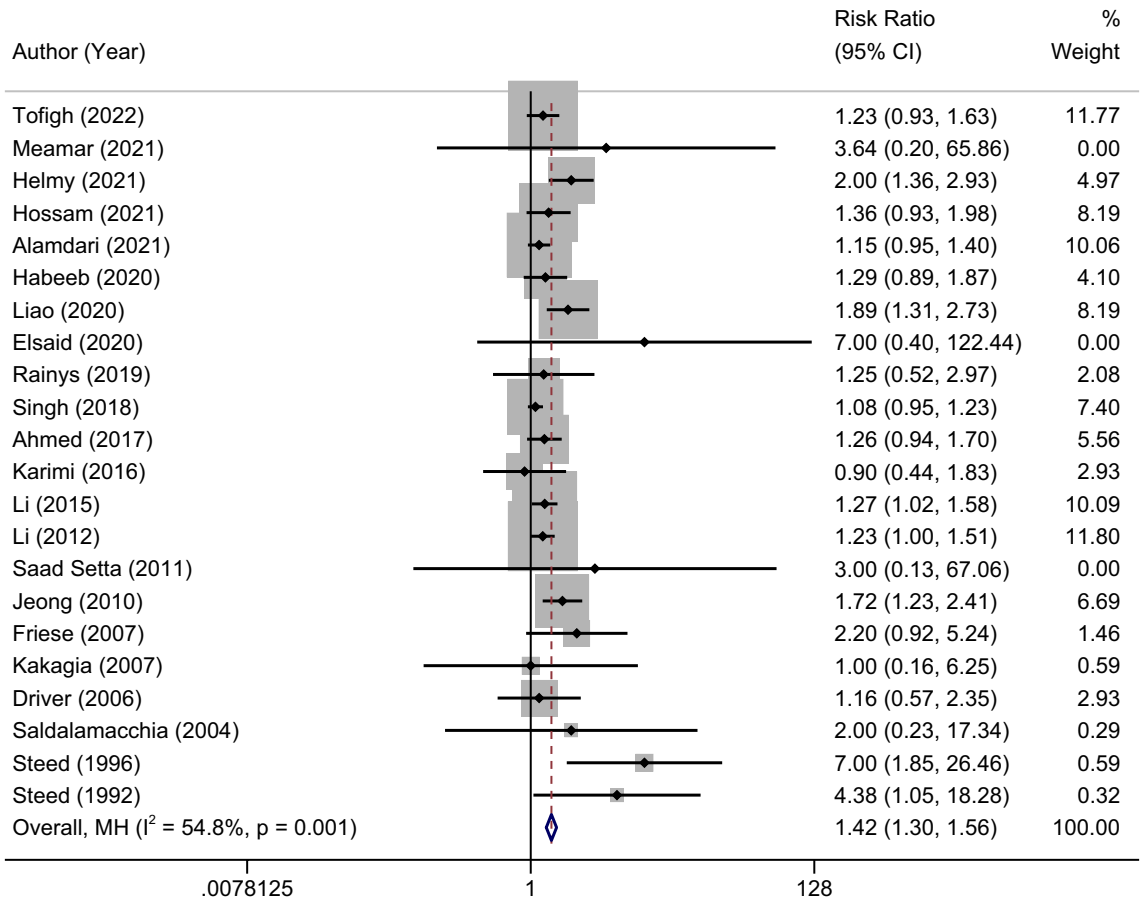

Fig. 3 Forest plot comparing the efficacy of autologous platelet-rich plasma against control on the healing of diabetic foot ulcers

Publication bias

The funnel plots constructed with the observed study showed symmetry, and no significant publication bias was detected in funnel plots (Fig. 6).

Sensitivity analysis

Overall healing rate of DFU: The sensitivity analysis revealed that our results were robust and not unduly influenced by any single study. After sequentially excluding each study and recalculating the overall effect size, the point estimates consistently fell within the 95% confidence interval of the initial combined effect. This finding indicates that the conclusions drawn from our meta-analysis remain stable and reliable, even when considering potential variations across individual studies (Fig. 7A).

Time to complete wound healing: Our second sensitivity analysis, which involved sequentially removing each of the three studies and recalculating the overall effect size, revealed that the point estimates consistently fell outside the 95% confidence interval of the initial combined effect. This finding suggests that there is considerable variability among the individual studies, and the overall effect size might be influenced by one or more of the included studies (Fig. 7B).

Certainty of evidence

The certainty of the evidence for each outcome was assessed using the GRADEprofiler grading system based on the GRADE approach. The evaluation considered the risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence for each outcome was classified as high, moderate, low, or very low. A detailed summary of the certainty of evidence assessment for each outcome is provided in Table 2.

Discussion

The high incidence of DFU, challenges in wound healing, frequent ulcer relapse, and increased amputation rates are the primary contributors to disability, hospitalization, and mortality among individuals with diabetes. The scientific basis underpinning the utilization of PRP is the deficiency of growth factors in chronic wounds. PRP aims to address biological factors that impede the healing process by providing a physiologic pool of cytokines

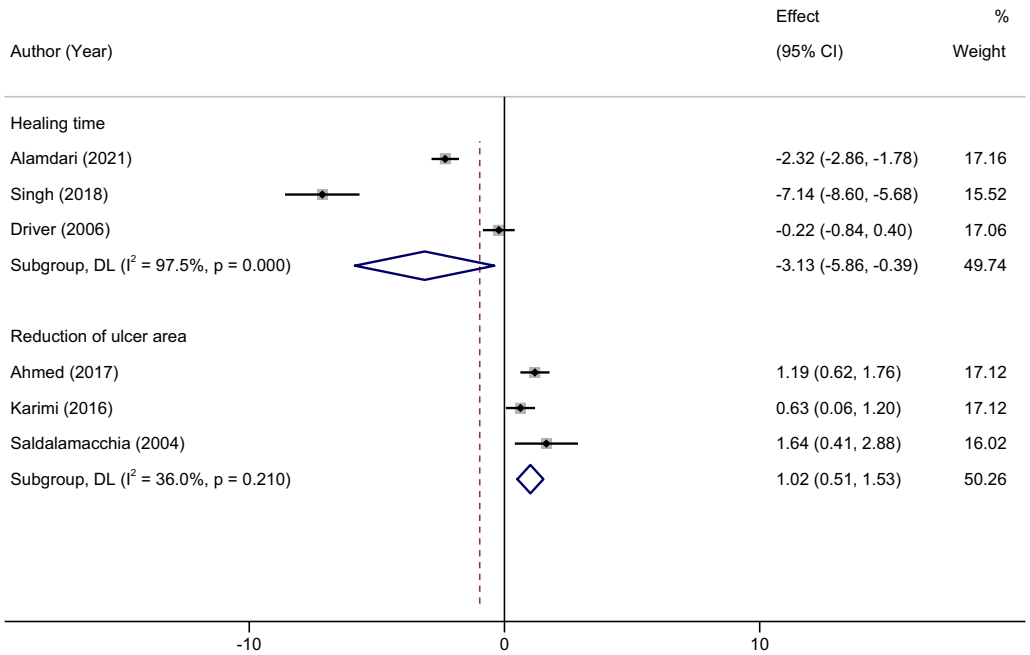

Fig. 4 Forest plot comparing the efficacy of autologous platelet-rich plasma against control on the healing time and reduction of ulcer area of diabetic foot ulcers

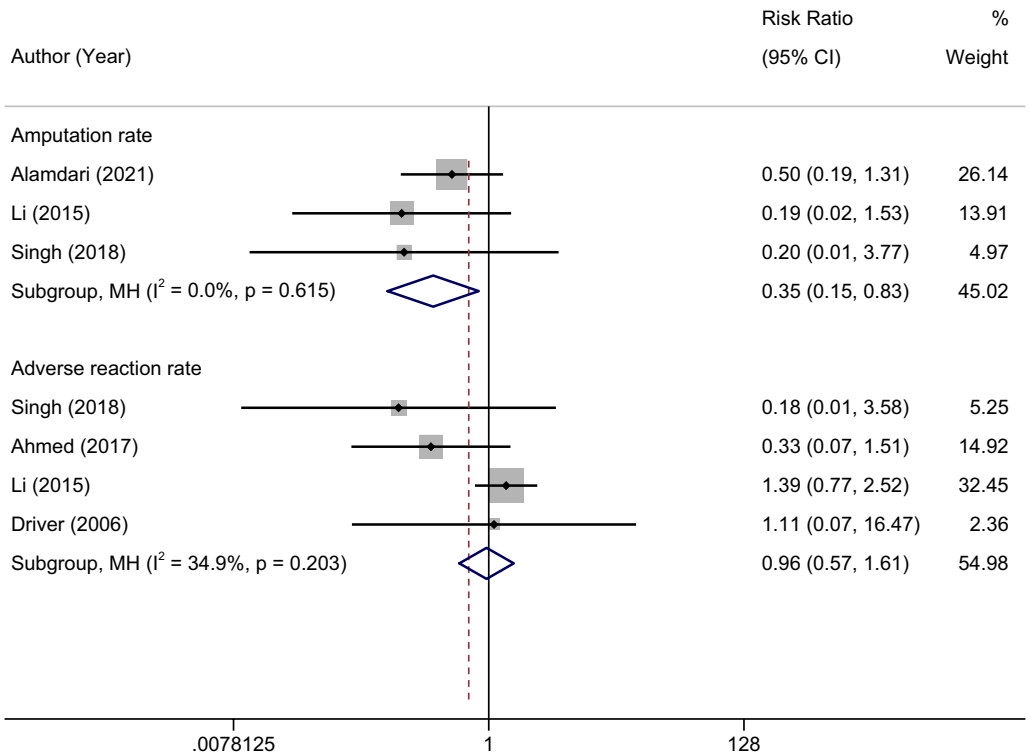

Fig. 5 Forest plot comparing the efficacy of autologous platelet-rich plasma against control on the amputation rate and adverse reaction rate

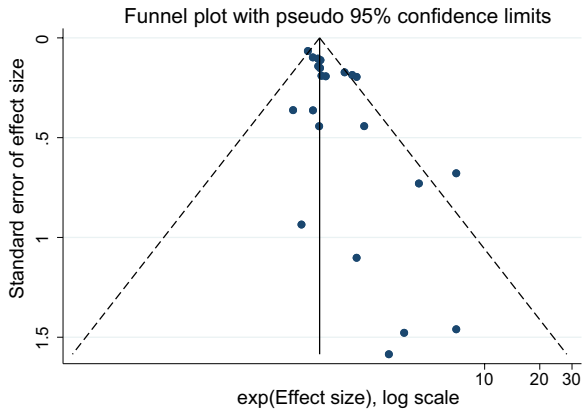

Fig. 6 Funnel chart of the correlation between vitamin D level in children and dental caries risk

that possess therapeutic efficacy [40]. Au-PRP possesses distinctive biological benefits in the facilitation of wound healing, albeit its precise mechanism remains incompletely elucidated. The potential mechanisms for enhancing wound healing are commonly accepted to be: (1) platelet-rich plasma (PRP) is rich in growth factors that are analogous to those found in the human body. These include transforming growth factor (TGF- β), platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), Hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF) [41]. (2) Au-PRP can inhibit excessive inflammatory reaction of wound, regulate the balance of matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP), and reduce the degradation of wound growth factor and ECM [42]. (3) leukocytes, antimicrobial peptides and platelets in Au-PRP can inhibit the growth of many kinds of bacteria and reduce wound infection [43]. (4) The fibrin present in Au-PRP serves as a scaffold to support various cells involved in the process of wound healing and contributes to wound contraction. In contemporary times, an increasing number of academics hold the belief that Au-PRP exhibits promising potential in the management of DFU owing to its distinctive biological impacts [44].

The rate of healing is a crucial metric for evaluating the efficacy of a medication or intervention on diabetic foot ulcers. The findings of this meta-analysis indicate that the use of Au-PRP can lead to a noteworthy enhancement in the healing rate of DFU in comparison with conventional treatment. The findings are comparable to those of a previous meta-analysis comprising 8 randomized controlled trials and 2 prospective studies, which reported a prevalence of 65.3 vs. 45.5% [45], but it should be noted that certain interventions featured in the meta-analysis comprised of Al-PRP or PDGF. Conversely, the interventions incorporated in this meta-analysis, in accordance with the PICO principle, solely consisted of Au-PRP, thereby rendering the findings more compelling. The ultimate closure of a wound is contingent upon the proliferation of epidermal cells during the wound healing process. In the process of tissue remodeling, various growth factors such as PDGF, KGF, and TGF-β have the potential to stimulate the differentiation of fibroblasts into myofibroblasts. This, in turn, can expedite the contraction of the collagen matrix [46, 47]. Simultaneously, various growth factors such as EGF, IGF, KGF, HGF, among others, have the ability to stimulate the division and proliferation of epithelial cells, thereby expediting the process of wound contraction and re-epithelialization [48, 49]. Moreover, high levels of fibrin present in Au-PRP serve as a scaffold for diverse wound repair cells and facilitate wound contraction. The findings of this meta-analysis indicate that the use of Au-PRP can expedite the pace of wound reduction in comparison with conventional treatment, with a statistically significant difference ($P<0.0001$). The statistical analysis revealed a significant reduction in ulcer healing time ($P<0.00001$) concomitant with an increase in the rate of ulcer healing. Patients with DFU are at a significantly elevated risk of amputation, which represents a major contributing factor to disability in this population [6]. The findings of this meta-analysis indicate that the application of Au-PRP can lead to a statistically significant reduction in the amputation rate among patients with DFU when compared to conventional treatment. The presence of multiple active constituents in PRP speeds up wound healing, thereby diminishing the likelihood of wound infection or the propagation of infectious agents. Simultaneously, PRP presents a noteworthy benefit in comparison with traditional therapy by enhancing the healing process of chronic refractory DFU, thereby diminishing the possibility of amputation in DFU patients.

The preparation of Au-PRP is derived from the patient's peripheral venous blood, thereby minimizing the risk of immune-mediated rejection. The procedure requires a relatively small amount of patient blood (approximately 30–50 ml per instance) and can be performed within the ward, which contributes to a less invasive process overall, reducing potential patient discomfort and stress. However, the variability in sample volume and preparation protocols utilized in the included studies may impact the reproducibility and comparability of the results. Therefore, we recommend adopting a universal standardized conventional preparation method, such as the one proposed by Muthu et al. [50]. This method does not require the expense of commercial kits, making it more accessible to a wider range of clinical settings. Several studies

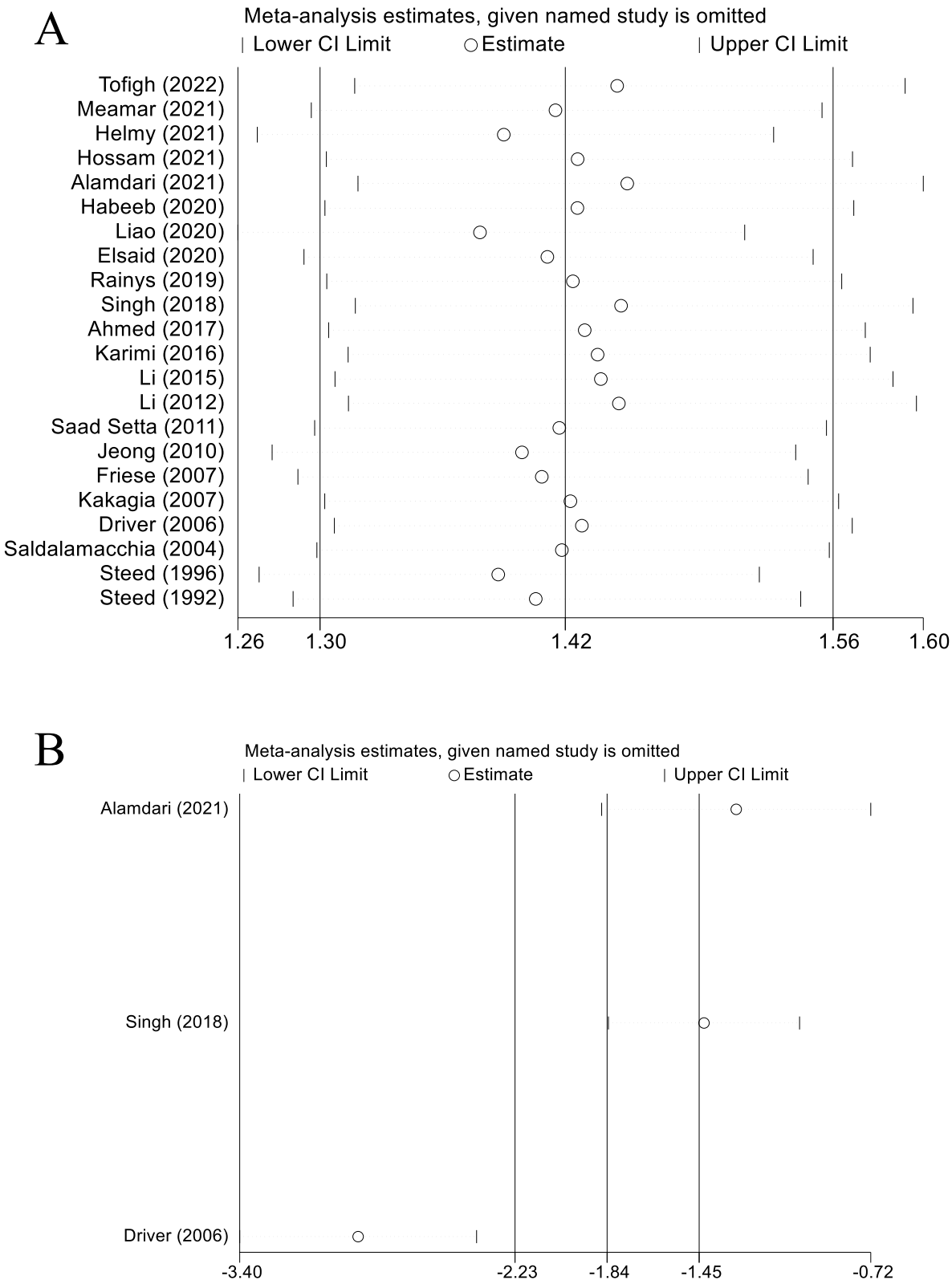

Fig. 7 Sensitivity analysis for "overall healing rate of DFU" (**A**) and "time to complete wound healing" (**B**)

Table 2 Summary of Certainty of Evidence Assessment for Each Outcome Using the PROfiler Grading System

Outcome	Certainty of Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias
Overall Healing Rate of DFU	High	Low	Moderate	Low	Low	Low
Time to Complete Wound Healing	Moderate	Moderate	High	Low	Moderate	Low
Ulcer Volume Reduction	High	Low	Low	Low	Low	Low
Amputation Rate	Moderate	Low	Low	Moderate	Low	Low
Adverse Events	Low	Moderate	Moderate	High	Moderate	Moderate

[20, 37] have investigated the impact of treatment on hemoglobin, platelet, and coagulation function by conducting re-examinations. The findings indicate that the indices did not exhibit any statistically significant alterations in comparison with their pretreatment levels and did not have any detrimental impact on the patients' blood. The present meta-analysis indicates that there was no statistically significant disparity in the occurrence of unfavorable reactions related to diabetic foot ulcer between the two cohorts. Thus, it is imperative to adhere to the indications and contraindications of Au-PRP during the treatment process to avoid any potential systemic or wound-related adverse reactions. This method of DFU treatment is considered safe.

Our study has several limitations: Initially, it should be noted that certain literatures included in the analysis may exhibit suboptimal quality, as their experimental design may lack rigor. This may potentially compromise the persuasiveness of certain meta-analysis outcomes. The cost of treatment is a crucial consideration for patients with DFU when selecting a treatment option. However, it is noteworthy that only a single study in this research has presented a comparison of treatment costs between the two groups, which precludes a quantitative analysis. Ultimately, the aggregate quantity of investigations and subjects was limited, indicating that more expansive cohort studies are requisite to furnish more precise data.

Conclusions

The findings of this systematic review and meta-analysis indicate that the use of Au-PRP therapy is a viable and secure therapeutic approach for DFU, as it effectively enhances wound healing. Therefore, it can be concluded that Au-PRP is a viable biological adjuvant therapy option for addressing non-healing DFU.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-023-03854-x.

Additional file 1. Medline and EMBASE Search Strategies.

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Author contributions

ZHM contributed to the conception of the study; DJ and YM contributed significantly to literature search, data extraction, quality assessment, data analyses and manuscript preparation; ZXY contributed improving the article for language and style and protocol preparation; DJ helped to perform the analysis with constructive discussions; ZHM revised the manuscript and approved the final version. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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