Received: 3 November 2023 | Accepted: 14 December 2023

DOI: 10.1111/iwj.14622

REVIEW ARTICLE

IWJ WILEY

Clinical efficacy of blood derivatives on wound healing: A systematic review and network meta-analysis

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Funding information
General Hospital of Southern Theatre Command, Grant/Award Number: 2022NZB002

Abstract

This study aims to evaluate the clinical effects of different blood derivatives on wound healing using network meta-analysis. PubMed, Embase, OVID, Web of Science, SCOPUS and Cochrane Central were searched to obtain studies about blood derivatives on wound healing until October 2023. R 4.2.0 and Stata 15.0 softwares were used for data analysis. Forty-four studies comprising 5164 patients were included. The results of network meta-analysis showed that the healing area from high to low was GF + ORCCB, ORCCB, GF, PRF, Unnas paste dressing, APG, PRP injection, PRP, PRP + thrombin gel, PPP, HPL, CT. The healing time from low to high was PRP + thrombin gel, GF, PRP, PC + K, PC, APG, PRF, CT, Silver sulfadiazine ointment. The number of patients cured from high to low was APG, PRP injection, PRP, Aurix, PRF, Leucopatch, HPL, Antimicrobial Ointment Dressing, CT, 60 μg/cm^2 repifermin, 120 μg/cm^2 repifermin, AFG, PPP. The order of analgesic effect from high to low was AFG, Aminogam gel, PRF, PRP, Oxidised oil, APG, GF, CT. The order of the number of wound infection cases from low to high is APG, 20 μg/cm^2 repifermin, 60 μg/cm^2 repifermin, PRP, LeucoPatch, CT, PPP, Antiseptic ointment dressing. Healing area: GF + ORCCB had the best effect; Healing time: PRP + thrombin gel took the shortest time. The number of cured patients and the reduction of wound infection: APG has the best effect. Analgesic effect: AFG has the best effect. More studies with large sample sizes are needed to confirm the above findings.

Abbreviations: AFG, autologous fibrin gel; APG, autologous platelet gel; APL, autologous platelet lysate; Aurix, aurix gel; CT, conventional treatment; GF, growth factor; HPL, autologous platelet lysate; MCMC, Markov chain Monte Carlo; MD, mean difference; NOS, Newcastle Ottawa scale; OR, odds ratio; ORCCB, oxidised regenerated cellulose and collagen biomaterial; Ozonated oil, ozone gas dissolved in olive oil; PC + K, keratinocytes suspended in platelet concentrate; PC, platelet concentrate; PG, platelet gel; PPP, platelet-poor plasma; PRF injection, injectable platelet-rich fibrin; PRF, platelet-rich fibrin; PRG, platelet rich gel; PRP, platelet-rich plasma; PSRF, potential scale reduction factor; RCT, randomised controlled trial.

KEYWORDS
blood derivatives, clinical effect, network meta-analysis, wound healing

Key Messages

- Healing area: GF + ORCCB had the best effect on wound healing.
- Healing time: PRP + thrombin gel taken the shortest time on wound healing.
- The number of cured patients and the reduction of wound infection: APG has the best effect on wound healing.
- Analgesic effect: AFG has the best effect on wound healing.

1 | INTRODUCTION

With the acceleration of China's aging population, the number of patients with acute and chronic trauma caused by burns, surgery, diabetes, ulcers and other reasons is increasing. The increasing types and refractory coefficients of wounds have brought unprecedented challenges to clinical researchers.[1] The long-standing wounds not only affect the quality of life of patients and increase the difficulty of nursing, but also may lead to a variety of complications (pain, electrolyte disorders, osteomyelitis, cancer, etc.), and the serious ones may face amputation or even life-threatening risks.

Wound healing is a complex biological process that is highly regulated by a variety of growth factors, cytokines, cells and cell matrix.[2] It involves four stages (haemostasis, inflammation, proliferation and remodelling) that occur gradually and overlap with each other.[3] In addition to surgical repair, exogenous growth factors are also one of the effective ways to promote wound healing. Plasma derivatives are rich in high concentrations of platelets, which produce a large number of growth factors after activation. The main products of plasma derivatives in the clinic are platelet-rich plasma (PRP), platelet-gel (PG), platelet rich gel (PRG), platelet-rich fibrin (PRF), growth factor rich plasma (GF), autologous platelet lysate (APL), platelet concentrate (PC), autologous platelet gel (APG) and autologous fibrin gel (AFG), etc. There are many kinds of blood derivatives for the treatment of wound healing, and there is a lack of efficacy comparison between them, which is not conducive to clinical promotion and the selection of the best scheme. This study intends to use a network meta-analysis to compare the clinical efficacy of different plasma derivatives in the treatment of wound healing, to provide references and evidence for the selection of clinical drugs.

2 | MATERIALS AND METHODS

2.1 | Literature search

We searched PubMed, EMBASE, OVID, Web of Science, SCOPUS, and Cochrane Central, and manually included references of the retrieved literature as supplements. The retrieval time was from the establishment of each database to October 2023. The search was performed by combining subject words and free words. The retrieval strategy were as follows ('blood product' OR 'plasma derivatives' OR 'platelet-rich plasma' OR 'PRP' OR 'platelet-rich in growth factors' OR 'GF' OR 'platelet rich fabric' OR 'PRF' OR 'concentrated growth factor' OR 'CGF') AND ('healing of wound' OR 'wound healing' OR 'wound' OR 'surgery' OR 'burn').

2.2 | Document selection criteria

2.2.1 | Inclusion criteria

(1) The types of studies were RCT and cohort study; (2) The language is limited to English; (3) The study subjects were wounds caused by ulcers, burns, surgery, tooth extraction and other reasons, without limiting the age and gender of patients; (4) The intervention type was that the experimental group was mostly treated with blood derivatives alone or combined with other measures, without limiting the intervention time, and the control group was mostly treated with conventional/standard nursing. The experimental group and the control group should be consistent except for the inconsistent intervention measures.

2.2.2 | Exclusion criteria

(1) Repeatedly published literature, reviews, meta-analyses, treatises and conferences; (2) Literature on

relevant outcomes could not be extracted; (3) Literature with errors; (4) The literature with ≤5 patients in the treatment group or the control group.

2.3 | Literature quality evaluation

2.3.1 | Cochrane risk of bias assessment

The Cochrane bias risk assessment tool was used for evaluation,[4] including random allocation method, allocation scheme concealment, whether the research object and scheme implementer were blinded, whether the outcome evaluator was blinded, data integrity, selective reporting and other sources of bias. Each RCT included was evaluated as 'low-risk', 'unclear' and 'high-risk' from the above seven aspects.

2.3.2 | Newcastle Ottawa scale bias risk assessment

Cohort study: the Newcastle Ottawa scale (NOS)[5] was used to evaluate the quality of the five included cohort studies, including patient selection (four items, full score 4), comparability between groups (one item, full score 2) and exposure factors (three items, full score 3). A total score of ≥6 points was considered to be of high quality. Two researchers independently evaluated the literature. In case of disagreement, the third researcher ruled.

2.4 | Literature screening and data extraction

Two researchers independently screened the literature according to the inclusion and exclusion criteria, extracted the data and cross-checked them. According to the included literature, the corresponding data were extracted, mainly including the basic information of the study (research title, first author, publication time, country), the information needed for Cochrane and NOS risk of bias assessment, the characteristics of the study subjects (type of trauma, age, gender), grouping, intervention measures, follow-up time and various outcome indicators: ① healing area; ② wound healing time; ③ number of wound healing cases; ④ pain score; ⑤ number of wound infection cases. In case of different opinions, discuss with each other to reach an agreement. If no consensus can be reached, the third investigator will be consulted.

2.5 | Statistical analysis

Review Manager (version 5.3) was used to draw the risk bias chart, and the graph package of R (version 4.03) software was used to draw the network evidence chart of intervention measures. Dichotomous variables were expressed by odds ratio (OR); Mean difference (MD) was used for continuous variables. If heterogeneity was low ($I^2 < 50\%$), the fixed-effects model was used. Otherwise, the random-effects model was employed. The gemtc package of R 4.1.0 software was used for Bayesian network analysis, and the probability ranking of the interventions was performed. Markov chain Monte Carlo (MCMC) random/fixed effects model was used for analysis, and the parameters were set; The initial value is set to 2.5, and the number of simulated annealing and iteration for four chains is 20 000 and 50 000. Evaluate the potential scale reduction factor (PSRF). When the PSRF is close to 1 (1.00–1.05), it indicates that the convergence of the iteration is good. Otherwise, it needs to increase the number of simulations and re-evaluate. Finally, the comparison correction funnel plot was drawn with Stata SE (version 15.0) software to identify whether there was a small sample effect and publication bias in the results.

3 | RESULTS

3.1 | Results of literature search

The computer system searched PubMed ($n = 120$), Embase ($n = 6561$), OVID ($n = 2232$), Web of science ($n = 5184$), SCOPUS ($n = 3011$) and Cochrane CENTRAL ($n = 2142$) databases. After removing duplicates, 12 025 records remained. Twenty-six references were retrieved from the references as supplements. According to the inclusion and exclusion criteria, 11 898 records were preliminarily excluded by browsing the titles and abstracts, and 153 records were obtained. After reading the full text, 42 records were finally screened, as shown in Figure 1.

3.2 | Basic characteristics of the included literature

Among the 42 records, 38 were RCTs and four were cohort studies, including 5164 patients. In two studies, 55 patients were randomly treated with PRF or PRP on one side and conventional treatment on the remaining side. Among them, seven were from Italy, five each from Egypt and the United States, four from China, three each

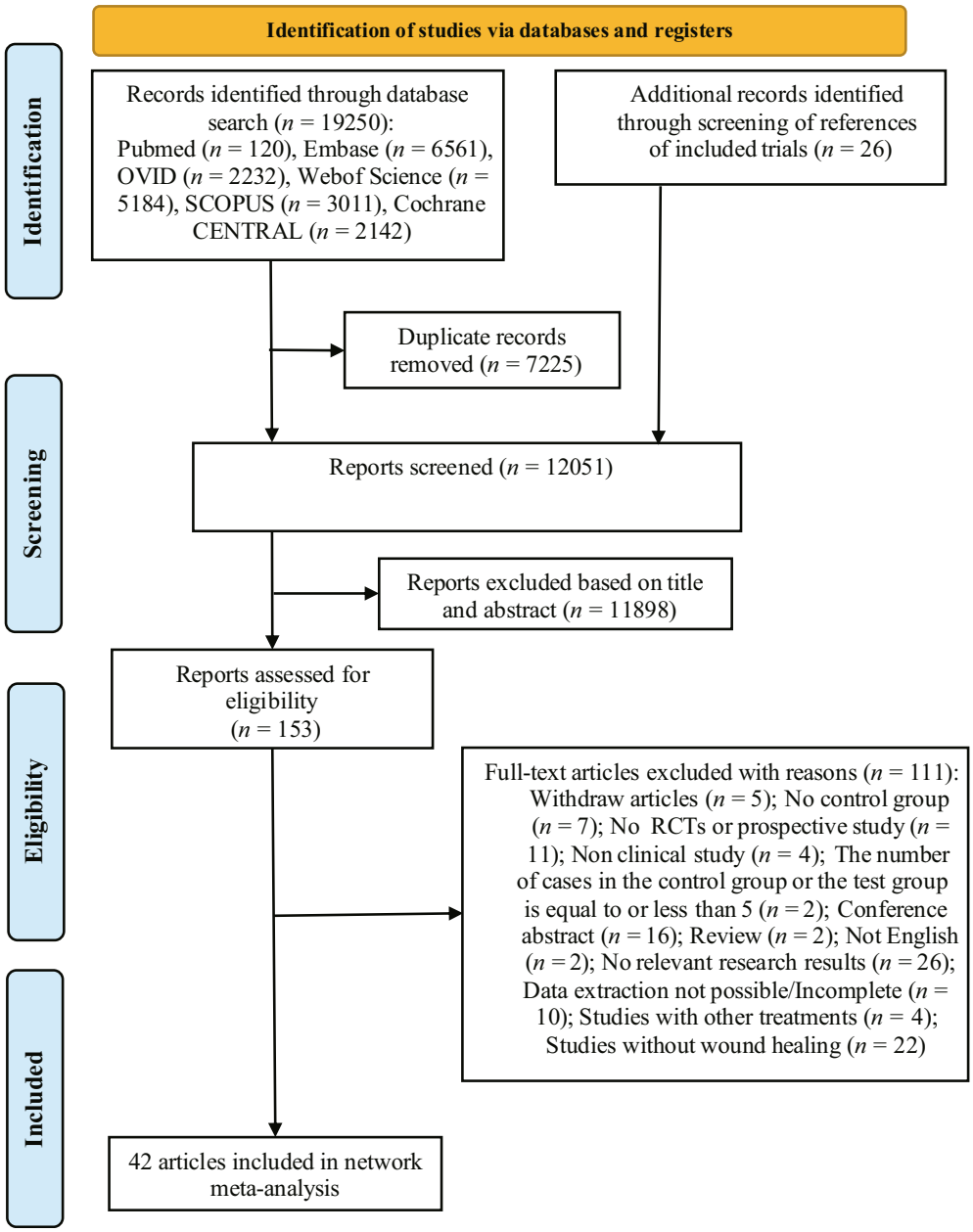

FIGURE 1 Flow chart of records search.

from Iran, India, and Spain, two from Turkey and one each from the remaining countries (Denmark, Czech Republic, Korea, Lithuania, United Kingdom, France, Germany, Switzerland, Greece and Australia), as shown in Table 1.

3.3 | Quality evaluation of literature

A total of 38 RCTs were included. One literature[27] used the date of birth for numbering and grouping, and one[20] indicated nonrandom grouping, rated as 'high risk of bias'. Nineteen records[8,10,12,14–16,21,25,26,29–31,33,37,43–47] only mentioned the use of random grouping, but did not specify the method of random grouping, and was rated as 'unclear risk of bias'. Seventeen records[6,7,9,11,13,18,19,22,23,28,32,34,35,38,40–42] mentioned specific methods of randomisation, such as computer-generated random table or number generators, which were rated as 'low risk of bias'. Nine records[6,7,9,11,13,18,19,22,23,28,32,34,35,38,40–42] explicitly mentioned the use of envelope concealment, which was rated as 'low risk of bias', and 29[8,12–16,18–20,23,25–34,37,38,40–45,47] did not mention whether it was hidden, which was rated as 'unclear risk of bias'. Ten records[6,9,18,23,38,42,43,45–47] were blinded to subjects and researchers, rated as 'low risk of bias', 17 records[6,9,18,23,38,42,43,45–47] did not mention whether to use blinding to subjects and researchers, rated as 'unclear risk of bias', and 11 records[6,9,18,23,38,42,43,45–47] were open-label, rated as 'high risk of bias'. Five records[7,9,13,22,23]

TABLE 1 Basic characteristics of literature.

Study	Year	Study type	Country	The type of disease	Case (T/C)	Case (Male/female)	Median age/years	Intervention measures T	Intervention measures C	Follow up (day)
Amse[6]	2021	RCT	Egypt	Palatal wound healing	13/13/13	NA	18–60	T1: PRF, T2: ozonated oil	CT	28
Capion[7]	2021	RCT	Denmark	Total hip arthroplasty	16/17	22/11	T: 65.6 ± 8.5; C: 68.9 ± 7.1	PRP	CT	28
Malekpour Alamdari[8]	2021	RCT	Iran	Diabetic foot ulcers	43/47	56/34	T: 56.3 ± 7.1; C: 56.7 ± 7.2	PRP	Silver sulfadiazine ointment	180
Vaheb[9]	2021	RCT	Iran	Burn injury	33/33	17/16	33.10 ± 2.60	PRF	CT	15
Elbarbary[10]	2020	RCT	Egypt	Chronic venous leg ulcer	30/30/30	72/18	T1: 45.4 ± 9.35 (22–60); T2: 43.4 ± 13 (25–61); C: 41.80 ± 13.3 (23–66)	T1: PRP, T2: PRP injections	CT	365
Elsaid[11]	2020	RCT	Egypt	Non-healing diabetic foot ulcers	12/12	14/10	T: 54.7 ± 6.6; C: 55.6 ± 6.5	PRP	CT	140
Kiziltoprak[12]	2020	RCT	Turkey	Palatal wound healing	12/12/12	9/27	T1: 28.92 ± 9.66; T2: 33.25 ± 10.97; C: 32.08 ± 9.46	T1: PRF, T2: AFG	CT	90
Lektemur Alpan[13]	2020	RCT	Turkey	Subepithelial connective tissue wound healing	20/20	19/21	T: 30.6 ± 6.45; C: 30.89 ± 6.92	PRF	CT	7
Slaninka[14]	2020	RCT	Czech Republic	Trophic (vascular, diabetes) 17; Trauma 3; Burn injury 1	20/20	9/15	Male: 60.44 (18–91), Female: 70.13 (55–84)	PRP	CT	33
Xie[15]	2020	RCT	China	Diabetic sinus tract wounds	25/23	27/21	T: 60.50 ± 8.27 (49–81); C: 61.10 ± 7.90 (48–80)	APG	CT	56
Yuvasri[16]	2020	RCT	India	Chronic venous leg ulcers	10/10	NA	NA	PRF	Unna's paste dressing	28
De Angelis[17]	2019	Prospective study	Italy	Chronic ulcers	182/182	NA	20–89	PRP	CT	120
Goda[18]	2019	RCT	Egypt	Diabetic foot ulcers	25/25	30/20	T: 56.88; C: 55.8	PRP	PPP	140
Gude[19]	2019	RCT	US	Chronic diabetic foot ulcers	66/63	100/29	T: 64.7; C: 66.9	Aurix	CT	84

(Continues)

TABLE 1 (Continued)

Study	Year	Study type	Country	The type of disease	Case (T/C)	Case (Male/female)	Median age/years	Intervention measures T	Intervention measures C	Follow up (day)
Jeong[20]	2019	RCT	Korea	Ulcers	7/7	12/2	T: 72.57 ± 7.74; C: 71.57 ± 5.41	PRP	CT	28
Rainys[21]	2019	RCT	Lithuania	Leg ulcers	35/34	35/34	T: 62.23 ± 14.72; C: 68.01 ± 14.89	PRP	CT	56
Game[22]	2018	RCT	UK	Diabetic foot ulcers	137/132	217/52	T: 61.9 ± 11.4; C: 62.0 ± 11.9	LeucoPatch	CT	140
Guazzo[23]	2018	RCT	Italy	Wound healing after mandibular third molar extraction	62/66	46/82	T: 46.9 ± 6.4; C: 48.5 ± 6.1	Aminogam gel	CT	14
Singh[24]	2018	Prospective study	India	Diabetic foot ulcers	29/26	34/21	T: 53.76 ± 10.38 (30–82); C: 55.69 ± 10.35 (35–75)	PRP	CT	28
Yeung[25]	2018	RCT	China	Burn injury	15/12	18/9	T: 45.27 ± 15.82; C: 46.00 ± 14.03	PRP	CT	21
Ahmed[26]	2017	RCT	Egypt	Diabetic foot ulcers	28/28	38/28	T: 43.2 ± 18.2; C: 49.8 ± 15.4	PRP	Antiseptic ointment dressing	90
Escamilla Cardenosa[27]	2017	RCT	Spain	Venous ulcers	55/47	31/71	T: 64.09 ± 13.72; C: 64.20 ± 16.26	GF	CT	168
Hersant[28]	2017	RCT	France	Necrotizing soft tissue infections	14/13	13/14	T: 54.8 ± 19.8; C: 57.7 ± 15.8	PRP + thrombin gel	CT	8
Samani[29]	2017	RCT	Iran	Free gingival graft's donor site wound healing	10/10	NA	20–45	PRP	CT	42
Somani[30]	2017	RCT	India	Chronic venous leg ulcers	9/6	NA	NA	PRF	CT	28
Volpe[31]	2017	RCT	Italy	Diabetic foot ulcers	10/10	13/7	T: 72.8 ± 8.7; C: 72.5 ± 10.3	APG	CT	30
Yang[32]	2017	RCT	China	Lower-extremity ischemic ulcers	38/38	36/40	T: 40.1 ± 10.2; C: 43.7 ± 9.8	APG	CT	30
Raposio[33]	2016	RCT	Italy	Chronic skin ulcer	16/21	21/19	T: 74.5; C: 70.75	PRP	CT	540
Aguirre Anda[34]	2015	RCT	Spain	Venous ulcers	12/11	9/14	T: 68.7 ± 8.9; C: 74.3 ± 9.3	GF	CT	56

TABLE 1 (Continued)

Study	Year	Study type	Country	The type of disease	Case (T/C)	Case (Male/female)	Median age/years	Intervention measures T	Intervention measures C	Follow up (day)
Li[35]	2015	RCT	China	Cutaneous ulcers	59/58	75/42	T: 61.4 ± 13.1; C: 64.1 ± 9.4	PRF	CT	84
Serraino[36]	2015	Prospective study	Italy	Sternotomy wound	422/671	694/399	NA	PRP	CT	365
Dorge[37]	2013	RCT	Germany	Deep sternal wound	97/99	142/54	T: 68 ± 8.6; C: 67 ± 9.5	PRP	CT	30
Guerid[38]	2013	RCT	Switzerland	Trauma 13, burn 12, ulcer 6, cutaneous tumours 4, others 10	15/15/15	25/20	T1: 46.9 ± 5.3; T2: 45.5 ± 3.9; C: 42.5 ± 3.1	T1: PC + K; T2: PC	CT	20
Serra[39]	2013	Prospective study	Italy	Transmetatarsal amputation	26/32	46/12	T: 6 7.5 (43–85); C: 6 3.5 (41–79)	APG	CT	30
Anitua[40]	2008	RCT	Spain	Chronic cutaneous ulcers	8/7	8/7	T: 45 ± 20; C: 61 ± 16	GF	PPP	56
Kakagia[41]	2007	RCT	Greece	Diabetic foot ulcers	17/17/17		T1: 57 ± 12; T2: 61 ± 9; C: 58 ± 10	T1: GF + ORCCB; T2: ORCCB	GF	56
Driver[42]	2006	RCT	US	Diabetic foot ulcers	40/32	59/13	T: 56.4 ± 10.2; C: 57.5 ± 9.1	PRP	CT	84
Robson[43]	2004	RCT	US	Chronic venous ulcers	123/112/117	216/136	T1: 60.9 ± 13.7; T2: 61.8 ± 15.6; C: 61.0 ± 15.4	T1: 60 μg/cm^2 repifermin; T1: 120 μg/cm^2 repifermin	CT	182
Saldalamacchia[44]	2004	RCT	Italy	Diabetic foot ulcers	7/7	6/8	T: 61.1 ± 9.4; C: 58.14 ± 7.8	APG	CT	35
Robson[45]	2001	RCT	US	Venous ulcers	31/32/31	61/33	T1: 61 ± 13 (39–86); T2: 59 ± 14 (33–83); C: 59 ± 13 (35–91)	T1: 20 mg/cm^2 repifermin; T2: 60 mg/cm^2 repifermin	CT	84
Stacey[46]	2000	RCT	Australia	Venous ulcer	44/42	36/50	T: 72 (35–90); C: 70 (26–92)	HPL	CT	140
Steed[47]	1992	RCT	US	Chronic cutaneous ulcers	7/6	9/4	T: 58.7 ± 12.4; C: 54.2 ± 12.9	HPL	CT	140

Abbreviations: AFG, autologous fibrin gel; APG, autologous platelet gel; Aurix, aurix gel; C, control group; CT, conventional treatment; GF, growth factor; HPL, autologous platelet lysate; NA, not applicable; ORCCB, oxidised regenerated cellulose and collagen biomaterial; PC, platelet concentrate; PC + K, keratinocytes suspended in platelet concentrate; PPP, platelet-poor plasma; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; RCT, randomised controlled trial; T, treatment group.

clearly adopted the blind method for the evaluation results, and were rated as 'low risk of bias'. Thirty-three records[6,8,10–12,14–16,18–21,25–35,37,38,40–47] did not indicate whether the results were evaluated in a blinded manner, and were rated as 'unclear risk of bias'. Twenty-eight records[6,8–14,16,18–20,25,26,28–32,34,37,38,40,41,44–47] with no data loss were rated as 'low risk of bias', and 10 records[7,15,21–23,27,33,35,42,43] with data loss were rated as 'high risk of bias'. None of the 38 records[7,15,21–23,27,33,35,42,43] had selective reports and were rated as 'low risk of bias'. None of the 38 records[7,15,21–23,27,33,35,42,43] indicated whether there were other biases and were rated as 'unclear risk of bias', as shown in Figure 2A,B.

The quality of four cohort studies was evaluated by the NOS scoring standard, including 1 with 8 points,[17] 2 with 7 points,[24,36] and 1 with 6 points.[39] The quality of these four records is relatively good, indicating that the risk of bias is small, as shown in Table S1.

3.4 | Healing area

3.4.1 | Evidence network

A total of 21 records reported the area of healing, involving 1077 patients, involving 12 dosing regimens, and the network evidence is shown in Figure 3A. The line between the two points represents the evidence of direct comparison between the two drugs, and no line indicates that there is no direct comparison, and the results can be obtained through indirect comparison. The thickness of the line indicates the number of studies using the two drugs in all included studies, and the size of the dot indicates the sample size of the included cases using the drug. The results showed that three closed loops were formed. CT had the largest sample size ($n = 447$), while PRP and CT had the largest number of studies ($n = 8$).

3.4.2 | Results of network meta-analysis

A total of 21 studies reported on the healing area, involving 12 intervention measures, forming a total of 14 pairwise comparisons. The inconsistency test and node splitting method showed good consistency ($I^2 < 50\%$), and there was no heterogeneity between studies ($p > 0.05$).

The results of the network meta-analysis showed that APG, GF, GF + Oxidised regenerated cellulose and collagen biomaterial (ORCCB), ORCCB, PRF and PRP significantly increased the area of wound healing compared to the CT group. GF + ORCCB was significantly larger than Autologous Platelet Lysate (HPL), Platelet-poor Plasma (PPP), PRP, PRP injection and Unnas paste dressing. GF was significantly higher than HPL, PPP, PRP and PRP injection. ORCCB was significantly greater than PPP, PRP and PRP injection. PRF is significantly greater than PRP. PRP + thrombin gel was significantly smaller than GF, GF + ORCCB and ORCCB. APG was significantly smaller than GF, GF + ORCCB and ORCCB. HPL was significantly smaller than ORCCB and PRF, and there was no statistically significant difference ($p > 0.05$) compared to other intervention measures, as shown in Table 2.

3.4.3 | Ranking of intervention efficacy

The order of healing area from high to low is GF + ORCCB > ORCCB > GF > PRF > Unnas paste dressing > APG > PRP injection > PRP > PRP + thrombin gel > PPP > HPL > CT, see Table S2.

3.4.4 | Publication bias assessment

The area of healing was assessed for publication bias. The funnel plot suggested that all studies were roughly symmetrically distributed on both sides of the vertical line with $x = 0$, indicating that there was less possibility of significant publication bias. Not all the dots are located inside the triangle, indicating that there may be a small sample effect, as shown in Figure S1.

3.5 | Wound healing time

3.5.1 | Evidence network

A total of ten records have reported the healing time of patients, a total of 481 patients, involving nine dosing regimens. The network evidence is shown in Figure 3B. The results showed that a closed loop was formed. CT had the largest sample size ($n = 185$), while PRP and CT had the largest number of studies ($n = 4$).

3.5.2 | Results of network meta-analysis

Ten records reported patient healing times involving nine interventions, forming a total of nine pairwise comparisons. The results of the inconsistency test and node splitting method showed good consistency ($I^2 < 50\%$), with no heterogeneity among the studies ($p > 0.05$). The results of the network meta-analysis showed that there was no statistical difference among all interventions ($p > 0.05$), as shown in Table 3.

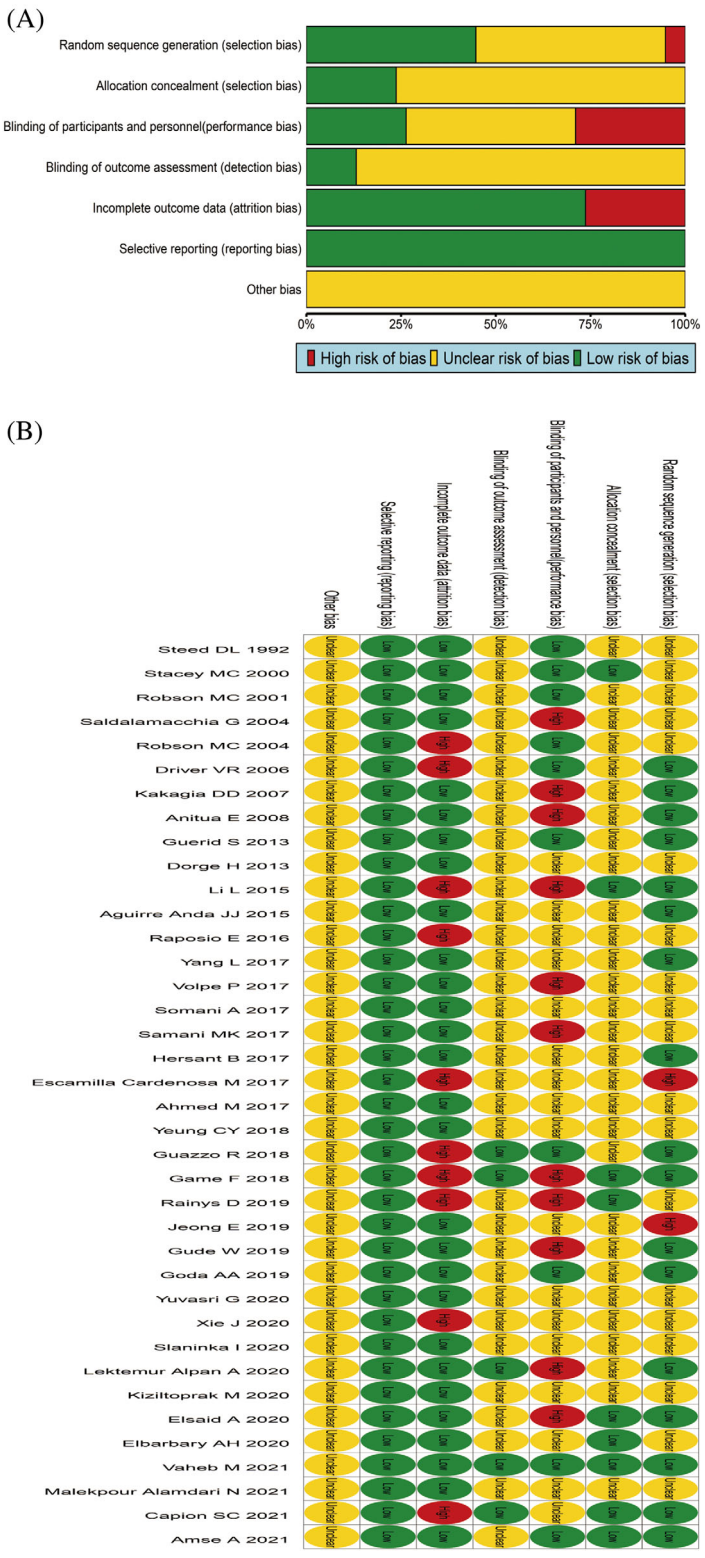

FIGURE 2 Quality assessment results of the literature included. (A) Risk of bias graph; (B) Risk of bias summary.

3.5.3 | Ranking of intervention efficacy

The order of healing time from low to high is PRP + thrombin gel <GF < PRP < Keratinocytes Suspended in Platelet Concentrate (PC + K) < PC < APG < PRF < CT < Silver sulfadiazine ointment, as shown in Table S3.

3.5.4 | Publication bias assessment

Evaluate publication bias on healing time and use Stata SE15.0 for comparison correction funnel plot. The funnel plot shows that all records are roughly symmetrically distributed on both sides of the $x = 0$ vertical line, indicating

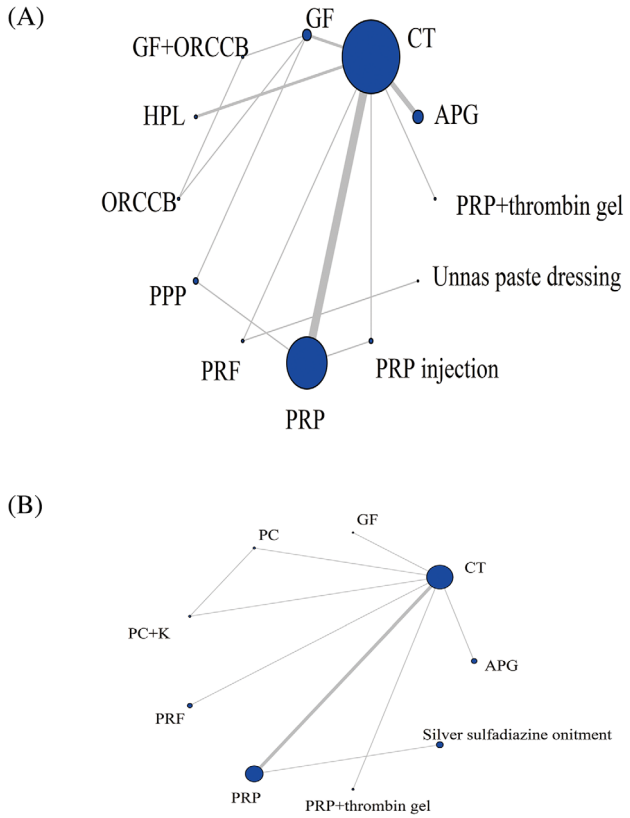

FIGURE 3 Evidence network charts of healing area (A) and healing time (B). APG, autologous platelet gel; CT, conventional treatment; GF, growth factor rich plasma; HPL, autologous platelet lysate; ORCCB, oxidised regenerated cellulose and collagen biomaterial; PPP, platelet-poor plasma; PRF, platelet-rich fibrin; PRP, platelet-rich plasma.

a small possibility of significant publication bias. Some dots are scattered outside the triangle, indicating a possible small sample effect, as shown in Figure S1.

3.6 | Number of wound healing cases

3.6.1 | Evidence network

A total of 15 records have reported the number of patients who have fully recovered, with a total of 1553 patients involved in 13 medication regimens. The network evidence is shown in Figure 4A. The results showed the formation of three closed loops. CT had the largest sample size ($n = 650$), while PRP and CT had the largest number of studies ($n = 5$).

3.6.2 | Results of network meta-analysis

Fifteen records have reported the number of patients who have recovered, involving 13 intervention measures, forming a total of 15 pairwise comparisons. The inconsistency test and node splitting method showed good consistency ($I^2 < 50\%$), and there was no heterogeneity between studies ($p > 0.05$). The results of the network meta-analysis showed that the therapeutic effect of APG was significantly greater than that of 120 μg/cm^2 replifermin and CT, and the PRP was significantly greater than that of CT ($p < 0.05$). There was no statistically significant difference between other intervention measures ($p > 0.05$), as shown in Table 4.

3.6.3 | Ranking of intervention efficacy

The order of number of wound healing cases from high to low is APG > PRP injection > PRP > Aurix > PRF > LeucoPatch > HPL > Antiseptic Ointment Dressing > CT > 60 μg/cm^2 replifermin > 120 μg/cm^2 replifermin > AFG > PPP, as shown in Table S4.

3.6.4 | Publication bias assessment

Evaluate publication bias and small sample effects on the number of recovered cases, and use Stata SE 15.0 for comparison correction funnel plots. The funnel plot indicates that all studies are roughly symmetrically distributed on both sides of the $x = 0$ vertical line, indicating a small possibility of significant publication bias. All the dots are inside the triangle, indicating that there cannot be a small sample effect, as shown in Figure S1.

3.7 | Pain score

3.7.1 | Evidence network

There are a total of nine articles reporting VAS pain scores, with a total of 457 patients involved in eight medication regimens. The network evidence is shown in Figure 4B. The results show the formation of two closed loops. CT has the largest sample size ($n = 211$), while PRF and CT have the highest number of studies ($n = 4$).

3.7.2 | Results of network meta-analysis

Nine records reported pain scores involving eight intervention measures, resulting in a total of nine pairwise comparisons. The inconsistency test and node splitting method showed good consistency

TABLE 2 Results of network meta-analysis of healing area.

Intervention measure	PRP + thrombin gel	APG	GF	GF + ORCCB	HPL	ORCCB	PPP	PRF	PRP	PRP injection	Unnas paste dressing	CT
PRP + thrombin gel	0											
APG	−4.32 (−30.75, 19.85)	0										
GF	−48.13 (−75.4, −21.56)	−43.77 (−62.26, −23.98)	0									
GF + ORCCB	−67.62 (−102.5, −33.55)	−63.33 (−91.61, −33.73)	−19.48 (−41.23, 2.25)	0								
HPL	10.68 (−16.06, 37.29)	14.93 (−2.54, 35.03)	58.78 (38.18, 80.13)	78.29 (48.54, 108.9)	0							
ORCCB	−52.43 (−87.27, −18.72)	−48.14 (−76.06, −18.87)	−4.34 (−25.67, 16.9)	15.17 (−6.82, 37.21)	−63.07 (−93.4, −33.81)	0						
PPP	2.54 (−26.89, 30.97)	6.82 (−14.36, 29.45)	50.61 (30.56, 70.68)	70.11 (40.54, 99.68)	−8.16 (−32.09, 14.92)	54.94 (25.88, 84.12)	0					
PRF	−29.85 (−65.83, 5.97)	−25.5 (−55.27, 6.01)	18.25 (−13.51, 50.56)	37.74 (−0.49, 76.58)	−40.56 (−72.4, −8.78)	22.5 (−15.44, 61.37)	−32.37 (−65.69, 1.69)	0				
PRP	0.32 (−24.05, 23.63)	4.66 (−9.11, 19.67)	48.43 (31.93, 64.76)	67.97 (40.57, 95.02)	−10.29 (−27.62, 5.89)	52.81 (25.93, 79.57)	−2.16 (−19.77, 15.2)	30.19 (0.32, 59.33)	0			
PRP injection	−0.58 (−29.93, 27.97)	3.7 (−17.33, 26.44)	47.48 (24.13, 71.07)	66.99 (35.27, 98.95)	−11.26 (−34.99, 11.77)	51.82 (20.48, 83.63)	−3.15 (−27.96, 22.03)	29.27 (−4.7, 62.65)	−0.96 (−19.05, 17.59)	0		
Unnas paste dressing	−15.76 (−62.29, 31.06)	−11.31 (−53.18, 31.97)	32.42 (−10.92, 76.37)	51.93 (3.6, 100.92)	−26.41 (−69.82, 16.99)	36.68 (−11.06, 85.67)	−18.22 (−62.68, 26.99)	14.12 (−15.3, 43.93)	−16.03 (−57.39, 26.06)	−15.11 (−59.72, 29.82)	0	
CT	12.84 (−9.57, 35.2)	17.13 (6.38, 30.31)	60.93 (46.35, 76.51)	80.44 (54.47, 107.34)	2.14 (−12.34, 16.8)	65.25 (39.77, 91.89)	10.3 (−7.65, 29.22)	42.72 (14.51, 70.96)	12.48 (4.68, 21.41)	13.41 (−4.57, 32.27)	28.58 (−12.36, 69.38)	CT

Abbreviations: APG, autologous platelet gel; CT, conventional treatment; GF, growth factor; HPL, autologous platelet lysate; ORCCB, oxidised regenerated cellulose and collagen biomaterial; PC, platelet concentrate; PPP, platelet-poor plasma; PRF, platelet-rich fibrin; PRF injection, injectable platelet-rich fibrin; PRP, platelet-rich plasma.

TABLE 3 Results of network meta-analysis of healing time.

Intervention measures	APG	GF	PC	PC + K	PRF	PRP	PRP + thrombin gel	Silver sulfadiazine onitment	CT
APG	0								
GF	9.16 (−41.29, 59.18)	0							
PC	1.78 (−48.31, 52.08)	−7.41 (−57.18, 42.96)	0						
PC + K	3.35 (−46.63, 53.33)	−5.84 (−55.81, 44.45)	1.51 (−34.03, 37.09)	0					
PRF	−0.43 (−50.31, 49.9)	−9.54 (−59.46, 40.9)	−2.15 (−52.66, 47.96)	−3.63 (−53.99, 46.4)	0				
PRP	4.44 (−35.6, 43.56)	−4.74 (−44.72, 34.95)	2.67 (−37.57, 42.33)	1.16 (−39.09, 40.51)	4.8 (−34.98, 44.23)	0			
PRP + thrombin gel	30.42 (−25.66, 87.2)	21.23 (−34.74, 77.93)	28.62 (−27.86, 85.38)	27.06 (−29.47, 83.9)	30.8 (−25.75, 87.13)	26.09 (−21.4, 73.99)	0		
Silver sulfadiazine onitment	−20.56 (−74.2, 32.66)	−29.67 (−83.46, 23.59)	−22.29 (−76.14, 30.83)	−23.78 (−77.54, 28.94)	−20.18 (−73.78, 32.98)	−24.98 (−60.47, 10.64)	−50.96 (−110.1, 7.91)	0	
CT	−4.9 (−40.38, 30.47)	−14.06 (−49.41, 21.38)	−6.64 (−42.27, 28.79)	−8.19 (−43.74, 27.22)	−4.53 (−39.89, 30.86)	−9.34 (−26.93, 8.94)	−35.32 (−79.81, 8.89)	15.63 (−23.88, 55.66)	0

Abbreviations: APG, autologous platelet gel; CT, conventional treatment; GF, growth factor; PC, platelet concentrate; PC + K, keratinocytes suspended in platelet concentrate; PRF, platelet-rich fibrin; PRP, platelet-rich plasma.

($I^2 < 50\%$), and there was no heterogeneity between studies ($p > 0.05$). The results of the network meta-analysis showed that the AFG score was significantly lower than that of CT ($p < 0.05$), and there was no statistically significant difference ($p > 0.05$) compared to other intervention measures, as shown in Table 5.

3.7.3 | Ranking of intervention efficacy

The order of pain scores from low to high is AFG < Aminogem gel < PRF < PRP < Ozoned oil < APG < GF < CT (Table S5).

3.7.4 | Publication bias assessment

The pain score was evaluated using Stata SE 15.0 for publication bias and small sample effects. The funnel plot indicates that all studies are roughly symmetrically distributed on both sides of the $x = 0$ vertical line, indicating a small possibility of significant publication bias. The two dots are scattered outside the triangle, indicating a possible small sample effect, as shown in Figure S1.

3.8 | Number of wound infection cases

3.8.1 | Evidence network

There are a total of eight records reports on the number of wound infection cases during treatment, with a total of 1818 patients involved in eight medication regimens. The network evidence is shown in Figure 4C. The results show the formation of a closed loop. CT has the largest sample size ($n = 983$), while PRP and CT have the largest number of studies ($n = 4$).

3.8.2 | Results of network meta-analysis

Eight records have reported the number of wound infection cases, involving eight intervention measures, forming a total of eight pairwise comparisons. The inconsistency test and node splitting method showed good consistency ($I^2 < 50\%$), and there was no heterogeneity between studies ($p > 0.05$). The results of the network meta-analysis showed that APG had the fewest number of infection cases and was significantly lower than other intervention measures ($p < 0.05$). There was no statistically significant difference ($p > 0.05$) between other intervention measures, as shown in Table 6.

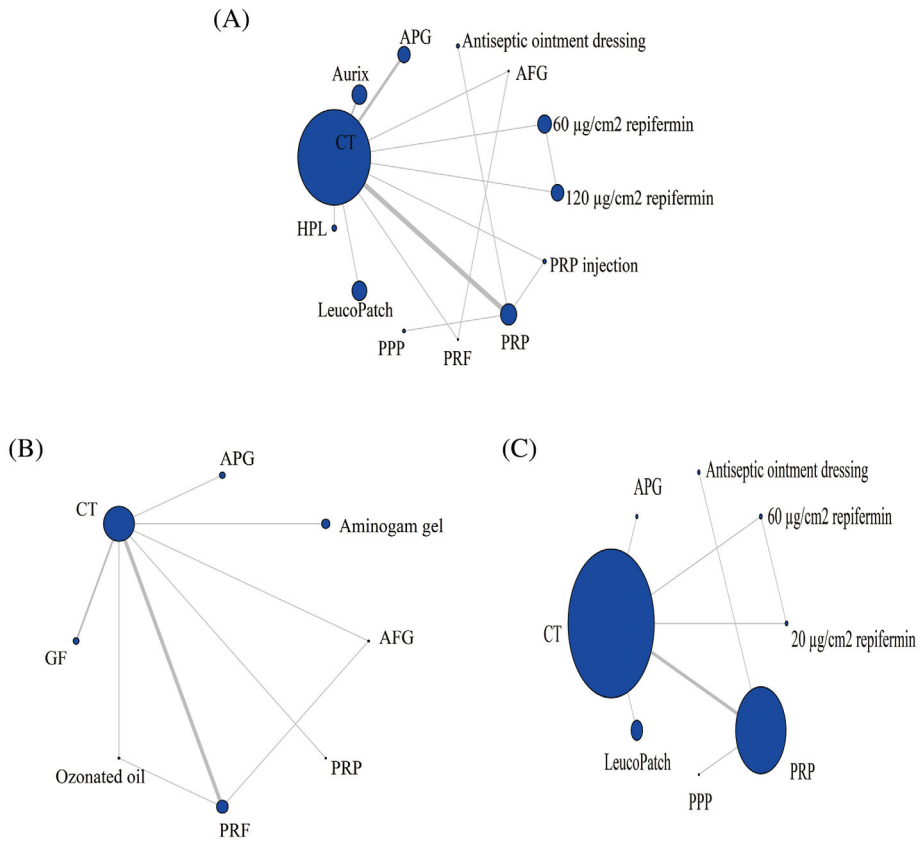

FIGURE 4 Evidence network charts of wound healing cases (A), pain score cases (B) and wound infection cases (C). AFG, autologous fibrin gel; APG, autologous platelet gel; CT, conventional treatment; GF, growth factor rich plasma; HPL, autologous platelet lysate; PPP, platelet-poor plasma; PRF, platelet-rich fibrin; PRP, platelet-rich plasma.

TABLE 4 Results of network meta-analysis of wound healing cases.

Intervention measures	120 μg/cm² repifermin	60 μg/cm² repifermin	AFG	Antiseptic ointment dressing	APG	Aurix	HPL	LeucoPatch	PPP	PRF	PRP	PRP injection	CT
120 μg/cm² repifermin	0												
60 μg/cm² repifermin	−0.29 (−2.13, 1.52)	0											
AFG	16.22 (−40.08, 73.89)	16.52 (−39.73, 74.2)	0										
Antiseptic ointment dressing	−0.34 (−3.41, 2.53)	−0.05 (−3.12, 2.86)	−16.57 (−74.3, 39.73)	0									
APG	−2.08 (−4.85, −0.19)	−1.78 (−4.55, 0.1)	−18.42 (−76.18, 37.89)	−1.76 (−4.79, 0.73)	0								
Aurix	−1.16 (−3.39, 1.1)	−0.86 (−3.1, 1.39)	−17.31 (−75, 38.83)	−0.81 (−3.46, 1.97)	0.93 (−0.63, 3.31)	0							
HPL	−0.46 (−3.14, 2.24)	−0.17 (−2.82, 2.53)	−16.65 (−74.32, 39.63)	−0.11 (−3.13, 3.08)	1.64 (−0.43, 4.5)	0.7 (−1.66, 3.08)	0						
LeucoPatch	−1.04 (−3.61, 1.55)	−0.75 (−3.29, 1.83)	−17.22 (−74.9, 39)	−0.68 (−3.58, 2.38)	1.05 (−0.83, 3.8)	0.13 (−2.12, 2.37)	−0.57 (−3.26, 2.09)	0					
PPP	0.23 (−2.85, 3.11)	0.52 (−2.54, 3.42)	−16.04 (−73.78, 40.37)	0.57 (−2.47, 3.61)	2.34 (−0.16, 5.39)	1.39 (−1.43, 4.03)	0.69 (−2.51, 3.69)	1.27 (−1.8, 4.16)	0				
PRF	−6.44 (−70.84, 49.94)	−6.14 (−70.53, 50.2)	−21.91 (−116.97, 72.28)	−6.07 (−70.63, 50.22)	−4.18 (−68.55, 52.1)	−5.29 (−69.71, 50.9)	−6.03 (−70.44, 50.22)	−5.42 (−69.81, 50.89)	−6.68 (−71.18, 49.71)	0			
PRP	−1.44 (−3.66, 0.5)	−1.15 (−3.36, 0.82)	−17.69 (−75.41, 38.5)	−1.11 (−3.29, 1)	0.66 (−0.86, 2.67)	−0.29 (−2.07, 1.24)	−0.98 (−3.33, 1.11)	−0.4 (−2.63, 1.52)	−1.67 (−3.88, 0.44)	4.98 (−51.24, 69.38)	0		
PRP injection	−2.07 (−4.74, 0.47)	−1.76 (−4.42, 0.76)	−18.28 (−75.93, 38)	−1.71 (−4.55, 1.13)	0.05 (−2.07, 2.7)	−0.9 (−3.25, 1.3)	−1.59 (−4.41, 1.03)	−1.02 (−3.69, 1.49)	−2.28 (−5.16, 0.58)	4.33 (−51.83, 68.64)	−0.6 (−2.45, 1.3)	0	
CT	−0.37 (−2.19, 1.45)	−0.08 (−1.89, 1.77)	−16.56 (−74.2, 39.64)	−0.02 (−2.34, 2.42)	1.73 (0.61, 3.6)	0.79 (−0.53, 2.12)	0.09 (−1.87, 2.05)	0.66 (−1.14, 2.48)	−0.6 (−2.92, 1.87)	6.11 (−50.12, 70.46)	1.08 (0.17, 2.21)	1.69 (−0.09, 3.64)	0

Abbreviations: AFG, autologous fibrin gel; APG, autologous platelet gel; Aurix, aurix gel; CT, conventional treatment; GF, growth factor; HPL, autologous platelet lysate; PPP, platelet-poor plasma; PRF, platelet-rich fibrin; PRF injection, injectable platelet-rich fibrin; PRP, platelet-rich plasma.

TABLE 5 Results of network meta-analysis of pain score.

Intervention measures	AFG	Aminogam_gel	APG	GF	Ozonated oil	PRF	PRP	CT
AFG	0							
Aminogam gel	−2.35 (−21.73, 15.57)	0						
APG	−11.42 (−30.89, 6.49)	−9.08 (−27.94, 9.72)	0					
GF	−11.68 (−28.47, 3.76)	−9.3 (−25.78, 7.07)	−0.2 (−16.43, 16.01)	0				
Ozonated oil	−9.28 (−26.52, 7.1)	−6.97 (−24.58, 11.34)	2.1 (−15.37, 20.16)	2.33 (−12.54, 17.85)	0			
PRF	−6.83 (−19.83, 5.82)	−4.5 (−19.03, 11.16)	4.55 (−9.76, 20.25)	4.78 (−6.28, 17.17)	2.44 (−9.16, 14.72)	0		
PRP	−9.34 (−28.52, 8.5)	−6.99 (−25.64, 11.79)	2.09 (−16.49, 20.83)	2.3 (−13.85, 18.57)	−0.02 (−18.21, 17.39)	−2.46 (−18.02, 11.77)	0	
CT	−12.56 (−26.42, −0.14)	−10.17 (−23.61, 3.14)	−1.11 (−14.27, 12.13)	−0.88 (−10.36, 8.55)	−3.22 (−15.51, 8.37)	−5.69 (−13.26, 0.61)	−3.18 (−16.45, 9.94)	0

Abbreviations: AFG, autologous fibrin gel; APG, autologous platelet gel; CT, conventional treatment; GF, growth factor; ozonated oil, ozone gas dissolved in olive oil; PG, platelet gel; PRF, platelet-rich fibrin; PRG, platelet-rich gel; PRP, platelet-rich plasma.

TABLE 6 Results of network meta-analysis of wound infection cases.

Intervention measures	20 μg/cm^2 repifermin	60 μg/cm^2 repifermin	Antiseptic ointment dressing	APG	LeucoPatch	PPP	PRP	CT
20 μg/cm^2 repifermin	0							
60 μg/cm^2 repifermin	−0.85 (−5.5, 3.71)	0						
Antiseptic ointment dressing	−2.71 (−9.7, 4.04)	−1.86 (−8.78, 4.84)	0					
APG	32.59 (2.42, 77.68)	33.5 (3.31, 78.54)	35.44 (5.03, 80.43)	0				
LeucoPatch	−1.5 (−7.71, 4.71)	−0.63 (−6.77, 5.4)	1.21 (−5.4, 8.02)	−34.18 (−79.14, −3.98)	0			
PPP	−2.34 (−9.81, 4.7)	−1.48 (−8.86, 5.51)	0.38 (−6.52, 7.12)	−35.09 (−80.19, −4.5)	−0.82 (−8.13, 6.08)	0		
PRP	−1.27 (−6.59, 3.82)	−0.41 (−5.61, 4.55)	1.43 (−3.04, 5.99)	−33.98 (−78.85, −4.04)	0.23 (−4.8, 5.1)	1.03 (−3.91, 6.34)	0	
CT	−1.8 (−6.4, 2.66)	−0.95 (−5.38, 3.42)	0.91 (−4.19, 6.19)	−34.53 (−79.24, −4.68)	−0.3 (−4.55, 3.9)	0.52 (−4.98, 6.43)	−0.53 (−3.02, 2.08)	0

Abbreviations: APG, autologous platelet gel; CT, conventional treatment; PPP, platelet-poor plasma; PRP, platelet-rich plasma.

3.8.3 | Ranking of intervention efficacy

The order of the number of wound infection cases from low to high is APG < 20 μg/cm^2 replifermin < 60 μg/cm^2 replifermin < PR < LeucoPatc < CT < PPP < Antiseptic Ointment Dressing, as shown in Table S6.

3.8.4 | Publication bias assessment

Evaluate publication bias and small sample effects on wound infections. The funnel plot indicates that all studies are roughly symmetrically distributed on both sides of the $x = 0$ vertical line, indicating a small possibility of significant publication bias. All the dots are inside the triangle, indicating that there cannot be a small sample effect, as shown in Figure S1.

4 | DISCUSSION

Plasma derivatives are substances prepared from healthy blood using separation and purification techniques such as chromatography and centrifugation. The mechanisms by which plasma derivatives promote wound healing are as follows: ① Platelets in plasma derivatives are activated to release powerful cell/growth factors (TGF-β, PDGF, IGF-1 and EGF, etc.), which act on a variety of target cells to promote cell proliferation, matrix synthesis, collagen deposition, and ultimately achieving tissue repair.[48] ② The anti-inflammatory cytokines in plasma derivatives can regulate the process of inflammatory response.[49] ③ Adhesion factors (fibrin, fibronectin and hyalonin) in plasma derivatives construct a three-dimensional structure locally (required for tissue repair), repairing cell movement and facilitating wound repair.[50] ④ Plasma derivatives induce the release of local growth factors, cytokines, or microRNAs through autocrine and paracrine pathways, promoting wound healing.[51] ⑤ Platelet activation in plasma derivatives releases bioactive substances (chemokines, histamines and adenosine) that directly induce platelet aggregation, alleviate pain and indirectly chemotactic leukocytes to exert bactericidal effects.[52] In recent years, with the rapid development of regenerative medicine, the use of plasma derivatives for wound treatment has achieved remarkable results,[53] but the lack of direct or indirect comparison of efficacy among derivatives is not conducive to clinical promotion and the selection of the best program. In this study, network meta-analysis was used to analyse the healing area, healing time, healing number, late infection number and analgesia score, in order to provide evidence for the selection of clinical drugs.

The healing area shows that GF + ORCCB has the largest healing area, and the combination of wound environment regulator (ORCCB) and GF can significantly accelerate the healing area of the wound. This may be due to: ① ORCCB can change the external environment of the wound by binding and inactivating proteases and gelatinases that seep out of the wound, creating a protective environment for growth factor healing.[54] ② ORCCB can physically bind proteases. When the proteases are fully controlled, this material has the ability to bind and protect growth factors, and can send 70% of the growth factors back to the wound surface, which is beneficial for wound healing.[55] Zhang et al.[56] confirmed through meta-analysis that ORCCB is beneficial in improving the wound healing rate and relative percentage reduction compared to other traditional nursing materials (non-MMP, inhibitory biomaterials and modern excipients).

PRP + thrombobin gel has the shortest healing time. PRP increases the rate of wound healing by increasing haemostasis, releasing growth factors, re-epithelialization, inducing fibroblast proliferation of extracellular matrix and promoting angiogenesis. Thrombin is another important component of wound healing.[57] The combination of the two can convert fibrin in PRP into a network structure, embed platelets, white blood cells, and growth factors, and produce a certain adhesive effect, retaining the sample at the delivery site and stimulating the release of growth factors, accelerating wound healing time.[58]

APG has the best effect on healing and reducing post-infection. APG can accelerate wound healing and promote tissue regeneration by increasing the production of extracellular matrix and granulation tissue,[59] which is consistent with the results of this analysis. The activated platelets in APG contain a series of microbicidal proteins with antibacterial activity, which exert strong antibacterial effects mainly by altering the permeability of cell membranes and inhibiting the synthesis of large molecules.[60] This may be a key factor in reducing the number of infections in the later stages of surgery.

Postoperative pain assessment is an important component of wound healing and plays a decisive role in wound healing. Segal et al.[61] found through a randomised trial that there was no significant difference in the analgesic effect of AFG compared to not using AFG ($p = 0.988$). Contrary to Segal N's research, this article found that AFG has a significantly higher postoperative analgesic effect than CT, which may be due to the release of mediators such as histamine, 5-hydroxytryptamine and dopamine from concentrated platelets, thereby reducing the occurrence of pain.[12] This indicates that there are relatively few included literature on some blood derivatives with low quality, and more high-quality

studies with larger sample sizes are needed to confirm them in the later stage.

Limitations of this study: ① Most of the 38 RCT studies included were of low quality, and the vast majority did not indicate specific randomised, hidden, or blind methods, which poses a certain risk of bias and affects the authenticity and reliability of the results.② Some studies include a small sample size, which may reduce the credibility of the results.③ The inclusion of research implemented in multiple countries around the world has a certain impact on the results due to differences in medical standards and standard protocols. ④ Inconsistent inclusion of causes of trauma (surgical wounds, ulcers, burns, etc.) may affect the accuracy of the results. ⑤ The lack of direct comparison between different blood derivatives affects the credibility of the results. ⑥ This study included four retrospective cohort studies, which may have a certain impact on the results. Given the above limitations, clinical practice should maintain a rigorous and cautious attitude, conduct more multi-centre, large-sample clinical studies and provide more sources of evidence for further verifying its efficacy.

5 | CONCLUSIONS

GF + ORCCB is the best in reducing wounds, and PRP + thrombin gel has the shortest treatment time. The number of people who have recovered from APG and the reduction of wound infections are the most prominent, and the analgesic effect of APG is the best. Clinical medical staff can choose appropriate treatment plans based on the needs of patients.

ACKNOWLEDGEMENTS

The authors thank all the participants of this work.

FUNDING INFORMATION

This research was supported by the Yucai Foundation of General Hospital of Southern Theater Command (Grant No. 2022NZB002).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data used in this network meta-analysis are available to the authors upon reasonable request.

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REFERENCES

1. Huang Y, Fu X. The establishment and development of wound repair discipline in China. *Front Surg*. 2022;9:1046494.
2. Chester D, Brown AC. The role of biophysical properties of provisional matrix proteins in wound repair. *Matrix Biol*. 2017; 60-61:124-140.
3. El Mohtadi M, Whitehead K, Dempsey-Hibbert N, Belboul A, Ashworth J. Estrogen deficiency-a central paradigm in age-related impaired healing? *EXCLI J*. 2021;20:99-116.
4. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
5. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol*. 2014;14:45.
6. Amse A, Nfh B. Clinical and cytological assessment of platelet-rich fibrin versus topical ozonated oil in palatal wound healing after free gingival graft harvesting: randomized controlled trial. *J Oral Maxillofac Surg Med Pathol*. 2021;34:343-351.
7. Capion SC, Jorgensen HBL, Agren MS, 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(6):988-995.
8. Malekpour Alamdari N, 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 Metab Syndr*. 2021;15(2):621-626.
9. Vaheb M, Karrabi M, Khajeh M, Asadi A, Shahrestanaki E, Sahebkar M. Evaluation of the effect of platelet-rich fibrin on wound healing at Split-thickness skin graft donor sites: a randomized, placebo-controlled, triple-blind study. *Int J Low Extrem Wounds*. 2021;20(1):29-36.
10. 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(4): 992-1001.
11. Elsaid A, El-Said M, Emile S, Youssef M, Khafagy W, Elshobaky A. Randomized controlled trial on autologous platelet-rich plasma versus saline dressing in treatment of non-healing diabetic foot ulcers. *World J Surg*. 2020;44(4):1294-1301.
12. Kiziltoprak M, Uslu MO. Comparison of the effects of injectable platelet-rich fibrin and autologous fibrin glue applications on palatal wound healing: a randomized controlled clinical trial. *Clin Oral Investig*. 2020;24(12):4549-4561.
13. Lektemur Alpan A, Torumtay Cin G. PRF improves wound healing and postoperative discomfort after harvesting subepithelial connective tissue graft from palate: a randomized controlled trial. *Clin Oral Investig*. 2020;24(1):425-436.
14. Slaninka I, Fibir A, Kaska M, Paral J. Use of autologous platelet-rich plasma in healing skin graft donor sites. *J Wound Care*. 2020;29(1):36-41.
15. Xie J, Fang Y, Zhao Y, Cao D, Lv Y. Autologous platelet-rich gel for the treatment of diabetic sinus tract wounds: a clinical study. *J Surg Res*. 2020;247:271-279.
16. Yuvasri G, Rai R. Comparison of efficacy of autologous platelet-rich fibrin versus Unna's paste dressing in chronic venous leg ulcers: a comparative study. *Indian Dermatol Online J*. 2020;11(1):58-61.

17. De Angelis B, D'Autilio M, Orlandi F, et al. Gentile P:wound healing: in vitro and in vivo evaluation of a bio-functionalized scaffold based on hyaluronic acid and platelet-rich plasma in chronic ulcers. *J Clin Med*. 2019;8(9):1486.
18. Goda AA, Ewada A, Ewees H, Hamza M. Platelet-rich plasma for the treatment of diabetic foot ulcer: a randomized, double-blind study. *Egypt J Surg*. 2019;37:178.
19. 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(9): 416-426.
20. Jeong E, Yoo IK, Cakir OO, et al. Effectiveness of autologous platelet-rich plasma for the healing of ulcers after endoscopic submucosal dissection. *Clin Endosc*. 2019;52(5):472-478.
21. Rainys D, Cepas A, Dambrauskaite K, Nedzelskiene I, Rimdeika R. Effectiveness of autologous platelet-rich plasma gel in the treatment of hard-to-heal leg ulcers: a randomised control trial. *J Wound Care*. 2019;28(10):658-667.
22. Game F, Jeffcoate W, Tarnow L, et al. LeucoPatch IItt: 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(11):870-878.
23. Guazzo R, Perissinotto E, Mazzoleni S, Ricci S, Penarrocha-Oltra D, Sivolella S. Effect on wound healing of a topical gel containing amino acid and sodium hyaluronate applied to the alveolar socket after mandibular third molar extraction: a double-blind randomized controlled trial. *Quintessence Int*. 2018;49(10):831-840.
24. Singh SP, Kumar V, Pandey A, Pandey P, Gupta V, Verma R. Role of platelet-rich plasma in healing diabetic foot ulcers: a prospective study. *J Wound Care*. 2018;27(9):550-556.
25. Yeung CY, Hsieh PS, Wei LG, et al. Efficacy of lyophilised platelet-rich plasma powder on healing rate in patients with deep second degree burn injury: a prospective double-blind randomized clinical trial. *Ann Plast Surg*. 2018;80(2S Suppl 1): S66-S69.
26. Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg*. 2017;38:206-211.
27. Escamilla Cardenosa M, Dominguez-Maldonado G, Cordoba-Fernandez A. Efficacy and safety of the use of platelet-rich plasma to manage venous ulcers. *J Tissue Viability*. 2017;26(2): 138-143.
28. Hersant B, SidAhmed-Mezi M, Bosc R, Meningaud JP. Autologous platelet-rich plasma/thrombin gel combined with split-thickness skin graft to manage postinfectious skin defects: a randomized controlled study. *Adv Skin Wound Care*. 2017; 30(11):502-508.
29. Samani MK, Saberi BV, Ali Tabatabaei SM, Moghadam MG. The clinical evaluation of platelet-rich plasma on free gingival graft's donor site wound healing. *Eur J Dent*. 2017;11(4): 447-454.
30. Somani A, Rai R. Comparison of efficacy of autologous platelet-rich fibrin versus saline dressing in chronic venous leg ulcers: a randomised controlled trial. *J Cutan Aesthet Surg*. 2017;10(1):8-12.
31. Volpe P, Marcuccio D, Stilo G, et al. Efficacy of cord blood platelet gel application for enhancing diabetic foot ulcer healing after lower limb revascularization. *Semin Vasc Surg*. 2017;30(4):106-112.
32. Yang L, Gao L, Lv Y, JJIJoC W. Medicine E: autologous platelet-rich gel for lower-extremity ischemic ulcers in patients with type 2 diabetes. *Int J Clin Exp Med*. 2017;10(9):13796-13801.
33. Raposio E, Bertozzi N, Bonomini S, et al. Adipose-derived stem cells added to platelet-rich plasma for chronic skin ulcer therapy. *Wounds*. 2016;28(4):126-131.
34. Aguirre Anda JJ, Anitua E, Francisco S, Cabezas A, Orive G, Algorta J. Efficacy and safety of plasma rich in growth factors in the treatment of venous ulcers: a randomized clinical trial controlled with conventional treatment. *Clin Dermatol*. 2015;3: 13-20.
35. Li L, Chen D, Wang C, et al. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: a prospective, randomized clinical trial. *Wound Repair Regen*. 2015;23(4):495-505.
36. Serraino GF, Dominijanni A, Jiritano F, et al. Platelet-rich plasma inside the sternotomy wound reduces the incidence of sternal wound infections. *Int Wound J*. 2015;12(3):260-264.
37. Dorge H, Sellin C, Bury MC, et al. Incidence of deep sternal wound infection is not reduced with autologous platelet rich plasma in high-risk cardiac surgery patients. *Thorac Cardiovasc Surg*. 2013;61(3):180-184.
38. Guerid S, Darwiche SE, Berger MM, Applegate LA, Benathan M, Raffoul W. Autologous keratinocyte suspension in platelet concentrate accelerates and enhances wound healing—a prospective randomized clinical trial on skin graft donor sites: platelet concentrate and keratinocytes on donor sites. *Fibrogenesis Tissue Repair*. 2013;6(1):8.
39. Serra R, Buffone G, Dominijanni A, Molinari V, Montemurro R, de Franciscis S. Application of platelet-rich gel to enhance healing of transmetatarsal amputations in diabetic dysvascular patients. *Int Wound J*. 2013;10(5):612-615.
40. Anitua E, Aguirre JJ, Algorta J, et al. Effectiveness of autologous preparation rich in growth factors for the treatment of chronic cutaneous ulcers. *J Biomed Mater Res B Appl Biomater*. 2008;84(2):415-421.
41. Kakagia DD, Kazakos KJ, Xarchas KC, et al. Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. *J Diabetes Complications*. 2007;21(6):387-391.
42. Driver VR, Hanft J, Fylling CP, Beriou JM. Autologel Diabetic Foot Ulcer Study G: a prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage*. 2006;52(6):68-70. 72, 74 passim.
43. Robson MC, Hanfnt J, Garner W, Jenson J. Cooper DMJTJoAR: healing of chronic venous ulcers is not enhanced by the addition of topical repifermin (KGF2) to standardized care. *J Appl Res*. 2004;4(2):302-311.
44. Saldalamacchia G, Lapice E, Cuomo V, et al. A controlled study of the use of autologous platelet gel for the treatment of diabetic foot ulcers. *Nutr Metab Cardiovasc Dis*. 2004;14(6): 395-396.
45. Robson MC, Phillips TJ, Falanga V, et al. Randomized trial of topically applied repifermin (recombinant human keratinocyte growth factor-2) to accelerate wound healing in venous ulcers. *Wound Repair Regen*. 2001;9(5):347-352.

46. Stacey MC, Mata SD, Trengove NJ, Mather CA. Randomised double-blind placebo controlled trial of topical autologous platelet lysate in venous ulcer healing. *Eur J Vasc Endovasc Surg*. 2000;20(3):296-301.
47. Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. *Diabet Care*. 1992;15(11):1598-1604.
48. Picard F, Hersant B, Bosc R, Meningaud JP. The growing evidence for the use of platelet-rich plasma on diabetic chronic wounds: a review and a proposal for a new standard care. *Wound Repair Regen*. 2015;23(5):638-643.
49. Papait A, Cancedda R, Mastrogiacomo M, Poggi A. Allogeneic platelet-rich plasma affects monocyte differentiation to dendritic cells causing an anti-inflammatory microenvironment, putatively fostering wound healing. *J Tissue Eng Regen Med*. 2018;12(1):30-43.
50. Miron RJ, Fujioka-Kobayashi M, Bishara M, Zhang Y, Hernandez M, Choukroun J. Platelet-rich fibrin and soft tissue wound healing: a systematic review. *Tissue Eng Part B Rev*. 2017;23(1):83-99.
51. De Pascale MR, Sommese L, Casamassimi A, Napoli C. Platelet derivatives in regenerative medicine: an update. *Transfus Med Rev*. 2015;29(1):52-61.
52. Edelblute CM, Donate AL, Hargrave BY, Heller LC. Human platelet gel supernatant inactivates opportunistic wound pathogens on skin. *Platelets*. 2015;26(1):13-16.
53. Fu X. Wound care in China: from repair to regeneration. *Int J Low Extrem Wounds*. 2012;11(3):143-145.
54. Smeets R, Ulrich D, Unglaub F, Woltje M, Pallua N. Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. *Int Wound J*. 2008;5(2):195-203.
55. Cullen B, Watt PW, Lundqvist C, et al. The role of oxidised regenerated cellulose/collagen in chronic wound repair and its potential mechanism of action. *Int J Biochem Cell Biol*. 2002;34(12):1544-1556.
56. Zhang L, Wang S, Tan M, Zhou H, Tang Y, Zou Y. Efficacy of oxidized regenerated cellulose/collagen dressing for management of skin wounds: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2021;2021:1058671.
57. Pradnyandari NKPD. Natasha RRJISM: the role of platelet-rich plasma (PRP) in burn wound healing: a literature-review. *Intisari Sains Medis*. 2022;13(2):507-510.
58. Matuska AM, Klimovich ML, Anz AW, Podesta L, Chapman JR. Autologous thrombin preparations: biocompatibility and growth factor release. *Wound Repair Regen*. 2021;29(1):144-152.
59. Whitlow J, Shackelford A, Sievert A, Sistino J. Barriers to the acceptance and use of autologous platelet gel. *Perfusion*. 2008;23(5):283-289.
60. Tang YQ, Yeaman MR, Selsted ME. Antimicrobial peptides from human platelets. *Infect Immun*. 2002;70(12):6524-6533.
61. Segal N, Puterman M, Rotem E, et al. A prospective randomized double-blind trial of fibrin glue for reducing pain and bleeding after tonsillectomy. *Int J Pediatr Otorhinolaryngol*. 2008;72(4):469-473.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wu Y, Peng G, Wang Y, et al. Clinical efficacy of blood derivatives on wound healing: A systematic review and network meta-analysis. *Int Wound J*. 2024;21(4):e14622. doi:10.1111/iwj.14622