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# Effectiveness and safety of dermal matrix used for diabetic foot ulcer: a systematic review and meta-analysis of randomized controlled trials

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## Abstract

**Background** Diabetic foot ulcers (DFUs) have become a global health concern, which can lead to diabetic foot infection (DFI), lower leg amputation, and even mortality. Though the standard of care (SOC) practices have been recognized as the “gold standard” for DFU care, SOC alone may not be adequate to heal all DFUs and prevent their recurrence. The use of dermal matrix has emerged as an adjuvant treatment to enhance DFU healing. The current study aimed to evaluate the effectiveness and safety of dermal matrix application as an adjuvant treatment to the SOC.

**Methods** The databases of PubMed, Embase and CENTRAL were independently searched by two authors, with the following key terms: “diabetic foot ulcer”, “acellular dermal matrix”, “wound healing”, and so on. Randomized controlled trials (RCTs) evaluated the efficacy and safety of dermal matrix in the treatment of DFUs were eligible for inclusion. The primary outcomes analyzed included time to complete healing and complete healing rate at the final follow-up, while secondary outcomes included wound area, ulcer recurrence rate, amputation risk and complication risk. Meta-analyses were performed using random-effect or fixed-effect models, based on the heterogeneity test.

**Results** This study included a total of 15 RCTs with a total of 1524 subjects. Of these, 689 patients were treated with SOC alone, while 835 patients received SOC plus dermal matrix. Compared to the SOC group, significantly shorter time (MD = 2.84, 95%CI: 1.37 ~ 4.32,  $p < 0.001^{***}$ ) was required to achieve complete healing in dermal matrix group. Significantly higher complete healing rate (OR = 0.40, 95%CI: 0.33 ~ 0.49,  $p < 0.001^{***}$ ) and lower overall (RR = 1.83, 95%CI: 1.15 ~ 2.93,  $p = 0.011^*$ ) and major (RR = 2.64, 95%CI: 1.30 ~ 5.36,  $p = 0.007^{**}$ ) amputation risks were achieved in dermal matrix group compared to SOC group. No significant difference was found in the wound area, ulcer recurrence rate, and complication risk between the two groups.

**Conclusions** The application of dermal matrix as an adjuvant therapy in conjunction with SOC effectively improved the healing process of DFUs and reduced the amputation risk when compared to SOC alone. Furthermore, dermal matrix application was well tolerated by the subjects with no added complication risk.

**Keywords** Dermal matrix, Diabetic foot ulceration, Wound healing, Meta-analysis

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## Introduction

Diabetic foot ulcers (DFUs) have become a global health concern, with an estimated incidence of 19 to 35% in patients with diabetes mellitus [1]. It has been reported by the International Diabetes Federation that there will be 9.1–26.1 million patients develop DFUs annually [1]. Patients with DFUs are related with decreased quality of life (QoF) and increased risk of depression [2, 3]. Furthermore, diabetic foot infection (DFI) is more frequent in the DFU patients due to the incomplete skin and exposed bone, which may result in increased amputation risk to as high as 92% [4, 5]. It was reported that approximately 1 in 6 DFU patients will suffer from amputation, causing a mortality rate of about 47% within 5 years and a recurrence risk as high as 66% [6, 7].

DFUs treatment is associated with about 1/3 of the total diabetic care cost [8]. The primary goal of DFU treatment is to promote the re-epithelialisation of wound to reduce the complications risk associated with ulceration and to improve the patient's QoF to a 'pre-ulceration' status. Besides glycemic control and revascularization, standard of care (SOC) treatment has been commonly selected as the conventional application for DFU wound management, which usually consists of the surgical sharp debridement, wound moist dressing, application of removable or irremovable off-loading device, and infection control [7, 9, 10]. The review of Everett et al. [11] summarized a total of 7 critical SOC practices, including surgical debridement, dressings promoting a moist wound environment, wound off-loading, vascular assessment, treatment of active infection, glycemic control, and multidisciplinary care. Although these SOC practices are considered the "gold standard" for DFU care, the 20-week healing rate of DFU after SOC was less than 30% [12], and 40 and 65% of healed DFUs will recur within 1 year and 5 years, respectively [1]. Therefore, current SOC alone may not be sufficient to heal all DFUs and prevent their recurrence [13].

In recent years, a broad spectrum of novel treatments have been developed to improve diabetic wound healing. In a review by Snyder et al. [14], they identified a total of 76 commercially available skin substitutes used to treat chronic wounds. The majority of these substitutes do not contain cells and are derived from human placental membrane (the placenta's inner layer), animal tissue, or donated human dermis allograft. These skin substitutes, whether allogeneic or xenogeneic graft, could provide the essential structure of extracellular matrix, signals for cellular migration, proliferation, angiogenesis, and endogenous matrix production and biochemical functions for enhancing wound healing [15, 16]. Many studies have demonstrated that these dermal matrices are effective when applied as adjuvant treatment to enhance DFUs

healing [17–19]. However, high-level evidence to comprehensively illustrate the effectiveness and safety of SOC plus dermal matrix over SOC alone is still scarce.

Thus, the current systematic review will be conducted with the aim of evaluating the effectiveness and safety of dermal matrix application as an adjuvant treatment of SOC, basing on the available evidence from randomized controlled trials (RCTs).

## Materials and methods

This study was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [20], and the checklist is presented in Supplementary Appendix 1.

### Data sources

The following three databases were independently searched by two authors: PubMed, Embase and CENTRAL. The searching was completed using a method of combination of subject and free terms, with the following key terms: "diabetic foot ulcer", "acellular dermal matrix", "cellular dermal matrix", "wound healing", and so on. No restriction on the publication countries/ regions and publication date, while the publication language was restricted on English. Additionally, the references lists of the included studies were reviewed, and the potential related studies were hand searched and screened for eligibility.

### Inclusion and exclusion criteria

The retrieved records from the three databases were screened according to the following inclusion criteria: (1) patients: diagnosed with DFU; (2) intervention: biogenic skin substitutes for enhancing DFU healing, whether allogeneic or xenogeneic dermal matrix graft; (3) comparison: between SOC and dermal matrix; (4) outcomes: treatment outcomes of DFU, including ulcer healing rate, healing time, wound area, ulcer recurrence, amputation risk and complication risk; (5) studies: only prospectively designed RCTs were eligible.

Studies were excluded according to the following criteria: (1) patients with ulcers on foot caused by reasons other than diabetes, or patients with ulcers caused by diabetes on the lower leg; (2) patients treated with methods other than dermal matrix or SOC; (3) no available data on the effectiveness and safety outcomes; (4) studies designed as case series, cohort study, retrospective case-control study, systematic review/ meta analysis, literature review, and so on.

### Study screening and data extracting

Two authors independently screened all electronic records retrieved from the databases, according to the

inclusion and exclusion criteria to select eligible studies. At the beginning, the records were imported into the EndNote software version X9 to eliminate the duplicates. Then, the two authors reviewed the titles/ abstracts of the remaining non-duplicates, to remove clearly irrelevant studies. After then, the full-text of the remained studies was downloaded and reviewed to evaluate the eligibility for inclusion.

The data extraction process was also completed by two authors independently, to obtain the following items: (1) study characteristics: the first author's name, publication year, corresponding country/ region, study period, and follow-up time; (2) subjects characteristics: patients number, dropped patients number, male percentage, mean age, mean BMI, diabetes type (type I or type II), length of diabetes history, glycosylated hemoglobin percentage (HbA1c%), ankle-brachial index (ABI), patients with diabetic polyneuropathy (DPN), DFU grade according to Wagner or other classifications, DFU site (planta, dorsal, or other sites), DFU size, and DFU age; (3) treatment details: treatment regimens in screening phase and treatment phase, screening criterion for randomization in screening phase, and dermal matrix product; (4) outcome evaluations: ulcer healing rate, healing time, wound area, ulcer recurrence, amputation risk and complication risk.

#### Quality assessment

The quality of the included RCTs was assessed using the Cochrane Collaboration tool for risk of bias assessment [21], which evaluates a total of 7 kinds of biases for RCTs as follows: (1) randomization sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other bias.

#### Statistical analysis

When results of per-protocol (PP) and intention-to-treat (ITT) analyses were both reported, the ITT principle was followed in the analyses process. Comparisons of continuous outcomes (including time to complete heal and wound area, at final follow-up) between SOC and dermal matrix groups, were expressed as mean difference (MD) and 95% confidence interval (95% CI). Single-rate meta analysis was performed to calculate the pooled healing rate and ulceration recurrence rate of dermal matrix group at the final follow-up. Comparisons of dichotomous outcomes between SOC and dermal matrix groups, were expressed as odds ratio (OR, complete healing rate) and risk ratio (RR, ulcer recurrence

rate, amputation risk and complication risk) as well as their 95% CIs. Heterogeneity among studies was estimated by  $I^2$  statistics. If  $I^2 \geq 50\%$ , it indicates significant heterogeneity and random-effect model was applied. Otherwise, a fixed-effect model was used in case of non-significant heterogeneity.

If significant heterogeneity was detected, sensitivity analysis was performed by omitting each individual study sequentially to assess the impact of each study on the results. For outcomes reported in more than 5 studies, funnel plot was plotted, and publication bias was assessed using Egger's and Begg's tests ( $p < 0.100$  and  $p < 0.050$  were considered to indicate significant publication bias respectively). If significant publication bias was detected, non-parametric trim-and-filling method was used to adjust the publication bias. Data analyses were performed using the R language version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided and  $P$  value of less than 0.05 was considered significant.

## Results

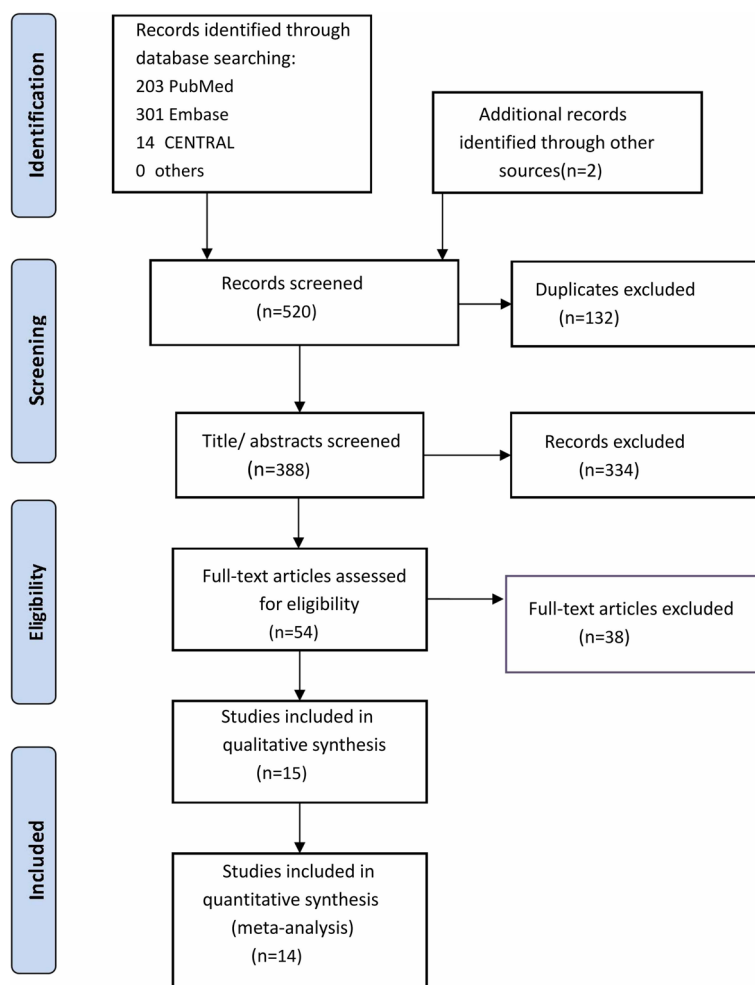
### Study selecting

The flow chart of studies screening is shown in Fig. 1. From the initial search, 520 studies were identified, of which 132 were duplicates that were immediately excluded. A further 334 records were excluded after screening the titles/ abstracts, leaving 54 articles for full-text review. As a result, a total of 15 [22–36] and 14 [22, 23, 25–36] RCTs were included in the qualitative and quantitative synthesis (meta-analysis), respectively.

### Summary of the included studies

Table 1 summarizes the characteristics of the included studies. A total of 15 trials involving 1524 subjects were included in the analysis. The studies randomized a total of 689 patients to receive SOC alone and 835 patients to receive SOC plus dermal matrix. The male percentages were reported in 13 of the studies, ranging from 34.6 to 100.0%. The mean age was reported in 14 studies, ranging from 55.2 to 66.6 years. The mean BMI was available in 10 studies, ranging from 28.5 to 36.5 kg/m<sup>2</sup>. The follow-up periods were 4, 6, 12, 16, 21, 24, 28, and 42 weeks in 1 [22], 1 [36], 5 [25, 29–31, 34], 4 [23, 24, 27, 35], 1 [32], 1 [26], 1 [28] and 1 [33] studies, respectively. At the final follow-up, a total of 147 and 155 patients dropped out for follow-up.

Table 2 summarizes the basic information about the status of diabetes mellitus and DFUs at randomization. HbA1c% levels were reported in 12 studies, with a range of 7.11 to 10.2%. The mean ABI was reported in



**Fig. 1** Flowchart of study searching and screening

4 studies, with a range of 0.7 to 1.2. A total of 12 studies reported the mean DFU size, with a range of 1.3 to 32.1 cm<sup>2</sup>. The treatment details of the included studies are listed in Table 3. Before the treatment phase, 8 studies [23–25, 27, 28, 31, 32, 34] included screening phase and applied SOC treatment (surgical debridement, wound dressings, wound off-loading, and infection management) to the enrolled patients lasting for 1 or 2 weeks. At the end of the screening phase, the including criterion for randomization was set as less than 20% [25, 27], 30% [23, 31, 32] or 40% [28] reduction of wound area in the ulcer site. Many different dermal matrix products were applied for wound repair, with the GraftJacket matrix (Wright Medical Technology, Inc., Arlington, TN, USA) being the most commonly researched product in 4 RCTs [22, 26, 29, 35].

Figure 2 shows the results of the quality assessment of the included RCTs. Due to the obviously different treatment process, the blinding of the patients was difficult. As a result, there is a high risk of bias in the item of “blinding of participants and personnel”. The item “blinding of outcome assessment” was also presented with high risk of bias in 4 of the studies. The other items were of relatively low risk of bias.

**Effectiveness of the dermal matrix in DFU**

The comparison of mean time to complete healing between SOC and dermal matrix is presented in Fig. 3. Six primary trials were pooled with random-effect model ( $I^2 = 97%$ ), and significantly shorter time was required to achieve complete healing in dermal matrix group compared to the SOC group (see the forest plot in Fig. 3A,

**Table 1** Characteristics of the included studies

Study ID	Study period	Country	Interventions	No. of patients	Male%	Mean age-years	Mean BMI	Diabetes type	Length of diabetes	Follow-up time	Dropped patients
Brigido, 2004 [22]	2003.4–2003.6	USA	SOC GraftJacket tissue matrix	20 20	77.5	Median: 58 (range: 43–70)	NA NA	NA NA	NA NA	weekly for 4 weeks	0 0
Driver, 2015 [23]	2010.4–2013.11	USA	SOC SOC + IDRT	153 154	74.5 76.6	57.3 ± 9.7 55.8 ± 10.6	34.1 ± 8.4 34.0 ± 7.2	NA NA	NA NA	up to 16 weeks or until 100% wound closure	71 48
Cazzell, 2019 [24]	NA	USA	SOC + ADM allograft	61	75.4	55.2 ± 11.8	32.9 ± 7.4	I: 4.9%; II: 90.2%; Pre-D: 4.9%	NA	weekly for 16 weeks	14
Zelen, 2016 [25]	2014.12–2015.11	USA	SOC SOC + human reticular CDM	20 20	600 800	57.1 ± 10.7 61.5 ± 10.9	32.3 ± 6.9 33.9 ± 8.7	NA NA	NA NA	weekly for 12 weeks	3 1
Cazzell, 2017 [26]	NA	USA	SOC D-ADM GJ-ADM	69 71 28	73.9 80.3 71.4	56.9 ± 10.9 59.1 ± 12.8 58.5 ± 9.8	32.8 ± 6.9 32.6 ± 8.3 31.4 ± 5.1	I: 2.9%; II: 97.1% I: 5.6%; II: 90.1% I: 7.1%; II: 92.9%	NA NA NA	24 weeks with major endpoints at weeks 12, 16, and 24	13 18 5
Zelen, 2018 [27]	2014.12–2017.3	USA	SOC SOC + human reticular CDM	40 40	700 600	59.0 ± 12.0 62.0 ± 13.0	35.0 ± 7.9 34.0 ± 8.8	NA NA	NA NA	weekly for 16 weeks or until 100% wound closure	0 0
Tchanque-Fossuo, 2019 [28]	2011.10–2016.8	USA	SOC SOC + cellular Dermagraft SOC + acellular Oasis	29 29 31	89.5 100.0 94.7	63.3 ± 9.1 62.8 ± 9.0 61.9 ± 8.6	36.5 ± 6.6 32.4 ± 5.3 36.5 ± 11.6	NA NA NA	NA NA NA	28w: 8-week treatment phase + 4-week maintenance phase + 4 monthly visits	8 7 9
Reyzelman, 2009 [29]	NA	USA	SOC ADM	39 47	NA NA	58.9 ± 11.6 55.4 ± 9.6	34.6 ± 8.5 34.6 ± 6.7	I: 5.1%; II: 94.9% I: 10.9%; II: 89.1%	NA NA	up to 12 weeks or until 100% wound closure	2 5
Hu, 2016 [30]	2010.9–2013.11	China	SOC + STSG SOC + STSG + human ADM	26 26	346 423	61.7 ± 12.1 66.6 ± 12.7	NA NA	II: 100% II: 100%	11.8 ± 7.8y 15.0 ± 8.7y	for 12 months after grafting surgery	2 1
Lantis, 2021 [31]	NA	USA	SOC Graftskin	104 103	806 769	58.5 ± 11.9 57.6 ± 11.5	32.2 ± 7.6 33.3 ± 7.6	I: 6.7%; II: 93.3% I: 10.7%; II: 89.3%	NA NA	weekly for 12 weeks or until 100% wound closure	22 24
Veves, 2001 [32]	NA	USA	SOC (saline-moistened gauze) Graftskin	96 112	77.2 79.2	56.0 ± 10.0 58.0 ± 10.0	33.1 ± 7.7 30.9 ± 6.5	NA NA	NA NA	efficacy evaluation for 12 weeks + safety evaluation for another 3 months	22 22

**Table 1** (continued)

Study ID	Study period	Country	Interventions	No. of patients	Male%	Mean age-years	Mean BMI	Diabetes type	Length of diabetes	Follow-up time	Dropped patients
Hahn, 2021 [33]	2016.4–2016.12	Korea	SOC (NPWT)	15	71.4	59.9±13.4	NA	NA	16.3±10.3y	every other day for 6 months or until 100% wound closure	0
			NPWT + micro-nized dermal matrix	15	73.3	63.5±12.9	NA	NA	22.5±14.7y		1
Cazzell, 2015 [34]	2013.5–2014.7	USA	SOC	41	73.0	56.6±10.8	NA	NA	NA	up to 12 weeks or until 100% wound closure	4
			tri-layer porcine SIS	41	78.0	57.1±10.9	NA	NA	NA		0
Brigido, 2006 [35]	NA	USA	SOC (sharp debridement)	14	NA	66.2±4.4	NA	NA	NA	up to 16 weeks	0
			SOC + Graftjacket tissue matrix	14	NA	61.4±7.2	NA	NA	NA		0
Campitello, 2017 [36]	NA	Italy	SOC (wet dressing)	23	56.5	62.1±7.7	28.9±2.7	NA	NA	weekly for 6 weeks or until 100% wound closure	0
			Integra Flowable Wound Matrix	23	65.2	64.0±8.9	28.5±2.5	NA	NA		0

SOC standard of care, IDRT Integra Dermal Regeneration Template, NA not available, ADM acellular dermal matrix, CDM cellular dermal matrix, D-ADM DermACELL acellular dermal matrix, GJ-ADM GraftJacket acellular dermal matrix, Pre-D prediabetes, STSG split-thickness skin grafting, NPWT negative-pressure wound therapy, SIS small intestine submucosa, BMI body mass index

**Table 2** Baseline information about the statuses of diabetes mellitus and diabetic foot ulceration (DFU)

Study ID	Interventions	No. of patients	HbA1c%	ABI	DPN%	DFU grade	Site of DFU	DFU size (cm <sup>2</sup> )	DFU age
Brigido, 2004 [22]	SOC	20	NA	NA	NA	NA	NA	NA	Mean: 25w
	GraftJacket tissue matrix	20							Mean: 27w
Driver, 2015 [23]	SOC	153	8.2±1.9	NA	NA	Wagner 2:116 (75.8%)	Dorsal: 127(83.6%); Plantar: 25(16.5%)	3.7±2.7	303±418d
	SOC+IDRT	154	8.0±1.8			Wagner 2: 109 (70.8%)	Dorsal: 126(81.8%); Plantar: 28(18.2%)	3.5±2.5	308±491d
Cazzell, 2019 [24]	SOC+ADM allograft	61	NA	NA	42.6%	Wagner 3: 59 (96.7%); Wagner 4: 2 (3.3%)	Ankle: 1(1.6%); Dorsal: 33(54.1%); Plantar: 26(42.6%); Plantar/dorsal: 1(1.6%)	29.0±21.0	3.8±3.4 m
Zelen, 2016 [25]	SOC	20	7.8±1.8	NA	NA	NA	Toe: 7(35.0%); Forefoot: 7(35.0%); Midfoot: 2(10.0%); Ankle/hindfoot: 4(20.0%)	2.7±2.3	NA
	SOC+human reticular CDM	20	7.9±1.6				Toe: 6(30.0%); Forefoot: 5(25.0%); Midfoot: 7(35.0%); Ankle/hindfoot: 2(10.0%)	4.7±5.2	
Cazzell, 2017 [26]	SOC	69	8.4±1.9	NA	NA	Wagner 1: 14 (20.3%); Wagner 2: 55 (79.7%)	Dorsal: 15(21.7%); Plantar: 52(75.4%); Other: 2(2.9%)	3.6±3.6	36.4±36.4w
	D-ADM	71	8.5±1.8			Wagner 1: 12 (16.9%); Wagner 2: 59 (83.1%)	Dorsal: 12(16.9%); Plantar: 56(78.9%); Other: 3(4.2%)	3.9±4.2	40.0±36.4w
	GJ-ADM	28	7.6±1.4			Wagner 1: 5 (17.9%); Wagner 2: 23 (82.1%)	Dorsal: 6(21.4%); Plantar: 21(75.0%); Other: 1(3.6%)	3.3±2.7	36.8±53.6w
Zelen, 2018 [27]	SOC	40	7.8±1.5	NA	100%	NA	Toe: 11 (28%); Forefoot: 18 (45%); Midfoot: 8 (20%); Ankle/hindfoot: 3 (7%)	3.2±4.0	>=4w
	SOC+human reticular CDM	40	7.6±1.4				Toe: 13 (33%); Forefoot: 13 (33%); Midfoot: 6 (15%); Ankle/hindfoot: 8 (20%)	2.7±2.4	

**Table 2** (continued)

Study ID	Interventions	No. of patients	HbA1c%	ABI	DPN%	DFU grade	Site of DFU	DFU size (cm <sup>2</sup> )	DFU age
Tchanque-Fossuo, 2019 [28]	SOC	29	8.6±1.7	1.07±0.14	NA	NA	Dorsal: 3 (15.8%); Plantar: 15 (79.0%); Lateral: 1 (5.3%)	1.3±0.9	21.7±36.1w
	SOC+cellular Dermagraft	29	7.6±1.5	1.22±0.17			Dorsal: 1 (5.9%); Plantar: 13 (76.5%); Lateral: 2 (11.8%); Medial: 1 (5.9%)	1.6±1.8	37.6±96.1w
	SOC+acellular Oasis	31	7.7±1.5	1.10±0.12			Dorsal: 3 (15.8%); Plantar: 15 (79.0%); Lateral: 1 (5.3%)	3.1±3.8	10.9±7.6w
Reyzelman, 2009 [29]	SOC	39	7.6±1.6	ranging from 0.7 to 1.2	NA	University of Texas (UT) grade 1 or 2	Toe: 5(12.8%); Foot: 17(43.6%); Heel: 8(20.5%); Other: 3(7.7%)	5.1±4.8	22.9±29.8w
	ADM	47	8.2±2.0				Toe: 15(32.6%); Foot: 15(32.6%); Heel: 4(8.7%); Other: 5(10.9%)	3.6±4.3	23.3±22.4w
Hu, 2016 [30]	SOC+STSG	26	10.2±1.1	0.9±0.2	NA	Wagner grade 2 or 3	Ankle: 4 (15.4%); Dorsal: 6 (23.1%); Plantar: 7 (26.9%); Forefoot: 5 (19.2%); Heel: 4 (15.4%)	28.6±25.2	25.0±33.9w
	SOC+STSG + human ADM	26	9.8±1.5	1.0±0.2			Ankle: 6 (23.1%); Dorsal: 7 (26.9%); Plantar: 7 (26.9%); Forefoot: 2 (7.7%); Heel: 4 (15.4%)	32.1±22.2	29.4±41.7w
Lantis, 2021 [31]	SOC	104	8.3±1.8	NA	59.6%	NA	Dorsal: 24 (23.1%); Plantar: 80 (76.9%)	3.8±2.8	233.1±312.9d
	Graftskin	103	8.1±1.9		50.5%		Dorsal: 25 (24.2%); Plantar: 78 (75.8%)	3.6±2.5	263.9±514.5d
Veves, 2001 [32]	SOC (saline-moistened gauze)	96	8.6±1.4	0.65–0.80: 10 (10.4%); 0.80–1.00: 29 (30.2%); > 1.00: 54 (56.3%)	100%	NA	Plantar: 100%	2.8±2.5	11.1±12.5m
	Graftskin	112	8.6±1.5	0.65–0.80: 10 (8.9%); 0.80–1.00: 50 (35.7%); > 1.00: 59 (52.7%)				3.0±3.1	11.5±13.3m



**Table 2** (continued)

Study ID	Interventions	No. of patients	HbA1c%	ABI	DPN%	DFU grade	Site of DFU	DFU size (cm <sup>2</sup> )	DFU age
Hahn, 2021 [33]	SOC (NPWT)	15	8.2±2.4	0.8±0.7	50.0%	Wagner grade 2 or higher	Ankle: 2(14.3%); Dorsal: 4 (28.6%); Plantar: 2 (14.3%); Forefoot: 3 (21.4%); Heel: 3 (21.4%)	13.1±22.2	1–3 m: 5; 3–6 m: 7; >6 m: 2
	NPWT + micro-nized dermal matrix	15	7.1±1.8	0.7±0.6	60.0%		Ankle: 3 (20.0%); Dorsal: 2 (13.3%); Plantar: 3 (20.0%); Forefoot: 4 (26.7%); Heel: 3 (20.0%)	16.3±10.3	1–3 m: 4; 3–6 m: 8; >6 m: 3
Cazzell, 2015 [34]	SOC	41	NA	NA	100%	NA	Plantar: 100%	2.6±7.5	22.2±13.5w
	tri-layer porcine SIS	41	NA	NA	NA	NA		2.1±2.3	21.3±12.3w
Brigido, 2006 [35]	SOC (sharp debridement)	14	7.9±0.6	NA	NA	Wagner grade 2	Plantar: 4(28.6%); Dorsal: 3(21.4%); Medial: 2(14.3%); Lateral: 3(21.4%); Other: 2(14.3%)	NA	NA
	SOC + Graft-jacket tissue matrix	14	8.1±1.0	NA	NA	Wagner grade 2	Plantar: 5(35.7%); Dorsal: 3(21.4%); Medial: 5(35.7%); Other: 1(7.1%)	NA	NA
Campitiello, 2017 [36]	SOC (wet dressing)	23	7.8±0.8	Right: 0.94±0.1; Left: 0.93±0.1	NA	Wagner grade 3	Abscesses foot: 16 (69.6%); Heel: 2 (8.7%); Metatarsal head: 5 (21.7%)	NA	39.5±9.9w
	Integra Flowable Wound Matrix	23	7.9±0.8	Right: 0.92±0.1 Left: 0.92±0.1	NA	Wagner grade 3	Abscesses foot: 18 (78.3%); Heel: 1 (4.4%); Metatarsal head: 4 (17.4%)	NA	38.56±12.6w

SOC standard of care, IDRT Integra Dermal Regeneration Template, NA not available, ADM acellular dermal matrix, CDM cellular dermal matrix, D-ADM DermACELL acellular dermal matrix, GJ-ADM GraftJacket acellular dermal matrix, STSG split-thickness skin grafting, NPWT negative-pressure wound therapy, SIS small intestine submucosa, ABI ankle-brachial index, DPN diabetic polyneuropathy

MD=2.84, 95%CI: 1.37~4.32,  $p < 0.001^{***}$ ). The funnel plot (Fig. 3B), Egger's test ( $p=0.143$ ) and Begg's test ( $p=0.573$ ) indicate that there is no significant publication bias. The forest plot of sensitivity analysis (Fig. 3C) showed there was no single study that significantly influenced the pooling result.

The pooling result for complete healing rate of dermal matrix group at final follow-up is shown in Fig. 4. Thirteen studies and 16 arms were pooled with random effects model ( $I^2=86\%$ ), and the pooled healing rate of dermal matrix group was 0.70 (95CI: 0.61~0.78) (see the forest plot in Fig. 4A). The forest plot of sensitivity analysis (Fig. 4D) revealed that none of the studies had a significant impact on the pooled result.. However, the funnel plot (Fig. 4B), Egger's test ( $p=0.012$ ) and Begg's test ( $p=0.529$ ) indicated the presence of significant publication bias. Therefore, a trim and filling funnel plot was generated, which resulted in an adjusted healing rate

of 0.56 (95CI: 0.47~0.66) for the dermal matrix group (Fig. 4C).

The comparison of the complete healing rate between SOC and dermal matrix is presented in Fig. 5. Thirteen studies and 16 arms were pooled with fixed-effect model ( $I^2=33\%$ ), resulting in a significantly higher complete healing rate in dermal matrix group compared to the SOC group (see the forest plot in Fig. 5A, OR=0.40, 95%CI: 0.33~0.49,  $p < 0.001^{***}$ ). The funnel plot (Fig. 5B), Egger's test ( $p=0.224$ ) and Begg's test ( $p=0.242$ ) did not show any significant publication bias. Sensitivity analysis was not conducted as there was no significant heterogeneity.

Figure 6 shows the comparison of wound area between SOC and dermal matrix, which pooled the data from three studies and four arms using random effects model ( $I^2=98\%$ ). No significant difference between two groups was found (Fig. 6A, MD=0.29, 95%CI: -0.32~0.91,

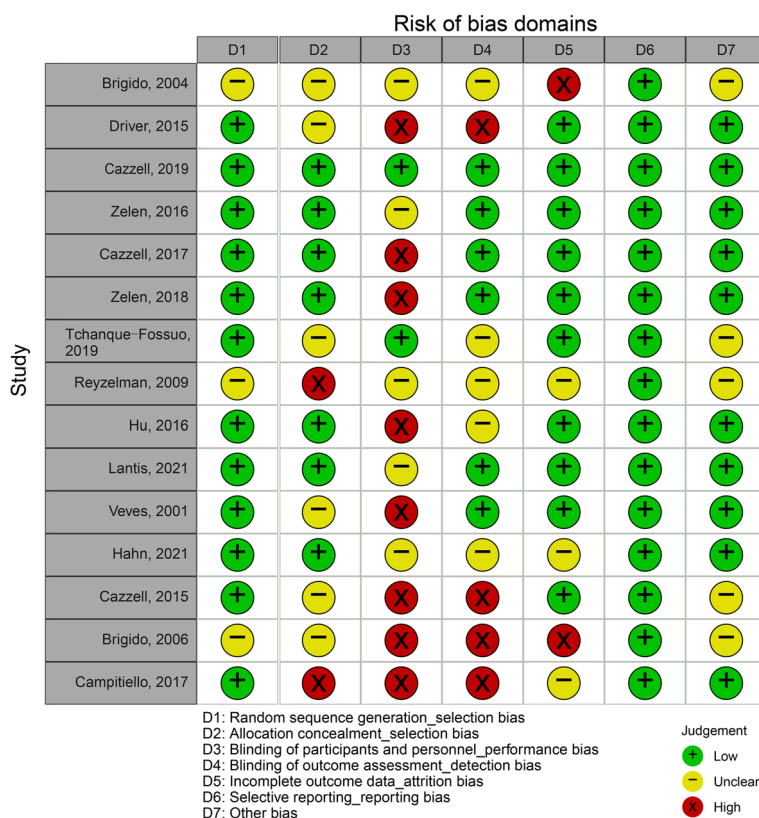
**Table 3** Treatment details of the included studies

Study ID	Interventions		Screening phase		Treatment phase		Dermal matrix product
	Interventions	Treatment regimen	screening criterion	Intervention regimen	Dermal matrix product		
Brigido, 2004 [22]	SOC GraftJacket tissue matrix	No screening phase		sharp debridement, wound gel with gauze dressings, offloading surgical application of scaffold at day 0	CraftJacket tissue matrix (Wright Medical Technology, Inc., Arlington, Tenn)		
Driver, 2015 [23]	SOC SOC + iDRT	1) period: 2w; 2) treatment: infection and exudate management, sharp debridement, moist wound therapy, offloading device	≤30% reduction in ulcer site	sharp debridement, moist wound therapy, offloading iDRT was applied to the debrided wound, trimmed to size and secured with sutures or staples	Integra Dermal Regeneration Template (iDRT; marketed as Omni-graft Dermal Regeneration Matrix)		
Cazzell, 2019 [24]	SOC + ADM allograft	1) period: 1w; 2) treatment: surgical debridement, offloading device, NPWT	none	surgical debridement, offloading, NPWT, Meshed 4*4cm and 5*7 cm D-ADM were attached onto wound	DermACELL (D-ADM; LifeNet Health, Virginia Beach, Virginia)		
Zelen, 2016 [25]	SOC SOC + human reticular CDM	1) period: 2w; 2) treatment: surgical debridement, wound dressing, offloading device	≤20% reduction in ulcer site	surgical debridement, offloading, wound dressing HR-ADM provided in size-specific grafts as small as 1.5*1.5 cm	AlloPatch® Pliable™ (Musculoskeletal Transplant Foundation, Edison, NJ, USA)		
Cazzell, 2017 [26]	SOC D-ADM GJ-ADM	No screening phase		sharp debridement, moist wound treatment, off-loading meshed 4×4-cm (thickness: 0.5–1.0 mm) D-ADM meshed 4×4-cm (thickness: 0.38–1.02 mm) GJ-ADM	– DermACELL; LifeNet Health, Virginia Beach, VA GraftJacket; Wright Medical Technology, Memphis, TN		
Zelen, 2018 [27]	SOC SOC + human reticular CDM	1) period: 2w; 2) treatment: sharp debridement, wound dressing, offloading device	≤20% reduction in ulcer site	wound dressing, offloading provided in sizes as small as 1.5×1.5 cm to optimize donor tissue	AlloPatch Pliable (MTF; Musculoskeletal Transplant Foundation, Edison, New Jersey)		
Tchanque-Fossuo, 2019 [28]	SOC SOC + cellular Dermagraft	1) period: 2w; 2) treatment: debridement, SOC dressing, offloading device, infection management	≤40% reduction in ulcer site	SOC wound dressing NA	– Dermagraft (bioengineered ECM containing living fibroblasts)		
Reyzelman, 2009 [29]	SOC + acellular Oasis SOC ADM	No screening phase		moist-wound therapy, debridement, offloading application of a human ADM (4*4 cm)	Oasis (ECM devoid of living cells) GraftJacket Regenerative Tissue Matrix – Ulcer Repair; Wright Medical Technology, Inc., Arlington, TN		

**Table 3** (continued)

Study ID	Interventions		Screening phase		Treatment phase	
	Treatment regimen	screening criterion	Treatment regimen	Intervention regimen	Dermal matrix product	
Hu, 2016 [30]	SOC + STSG	No screening phase	No screening phase	patient education, glucose control, off-loading, wound moist treatment, debridement, infection control	human allograft; ADM purchased from Jie-Ya Life Tissue Engineering (Beijing, China)	
Lantis, 2021 [31]	SOC + STSG + human ADM		1) period: 2w; 2) treatment: sharp debridement, infection elimination, moist wound dressing, offloading device, infection management	ADM was implanted onto the debrided wounds as a scaffold and covering		
	SOC	≤30% reduction in ulcer site		sharp debridement, infection elimination, moist wound dressing, offloading device, infection management	fetal bovine dermis (FBADM) (PriMatrix, Integra LifeSciences, Princeton, US)	
	Graftskin			meshed 4 × 4-cm graft placed in direct contact with a freshly debrided wound		
Veves, 2001 [32]	SOC (saline-moistened gauze)	≤30% reduction in ulcer site	1) period: 1w; 2) treatment: aggressive debridement, saline-moistened gauze	moist-wound therapy, off-loading	Graftskin (Apligraf, Organogenesis, Canton, MA, and Novartis Pharmaceuticals, East Hanover, NJ)	
	Graftskin			Graftskin was placed directly over the ulcer site		
Hahn, 2021 [33]	SOC (NPWT)	No screening phase	No screening phase	surgical debridement, NPWT	MHADDM (CG-PASTE; CGBio Co Ltd)	
	NPWT + micronized dermal matrix			MHADDM was molded to fit three-dimensional shape of wound		
Cazzell, 2015 [34]	SOC	1) period: 1w; 2) treatment: debridement, callus resection, offloading device	1) period: 1w; 2) treatment: debridement, callus resection, offloading device	wound care/dressings	tri-layer porcine SIS (OASISUltra; Cook Biotech, Inc., West Lafayette, IN; exclusively marketed by Smith and Nephew, Inc., Fort Worth, TX)	
	tri-layer porcine SIS	none		SIS was applied once each week to ulcers. The matrix was cut so that there was an approximate 1/8 in. overlap on the wound edge		
Brigido, 2006 [35]	SOC (sharp debridement)	No screening phase	No screening phase	sharp debridement, off-loading, wound dressing	Graftjacket (Wright Medical Technology, Inc., Arlington, TN, USA)	
	SOC + Graftjacket tissue matrix			Graftjacket was prepared for implantation		
Campitello, 2017 [36]	SOC (wet dressing)	No screening phase	No screening phase	sharp debridement, removable off-loading, wound dressing	Integra Flowable Wound Matrix, Integra LifeScience Corp, Plainsboro, NJ, USA	
	Integra Flowable Wound Matrix			the matrix Integra TM Flowable Wound Matrix was applied to the lesion, using the flexible injector		

SOC standard of care, IDRT Integra Dermal Regeneration Template, MA not available, ADM acellular dermal matrix, CDM cellular dermal matrix, D-ADM DermACELL acellular dermal matrix, G-I-ADM GraftJacket acellular dermal matrix, STSG split-thickness skin grafting, NPWT negative-pressure wound therapy, SIS small intestine submucosa



**Fig. 2** The light bulb diagram for quality assessment of the included studies

$p=0.352$ ). The forest plot of sensitivity analysis (Fig. 6B) showed there was no arm caused significant influence on the pooling result.

**Safety of the dermal matrix in DFU**

The ulcer recurrence rate comparison between SOC and dermal matrix is presented in Fig. 7A-B. Five studies were pooled with fixed-effect model ( $I^2=32%$ ), and no significant difference in ulcer recurrence rate was observed between the two groups (Fig. 7A,  $RR=1.32$ ,  $95\%CI: 0.92 \sim 1.89$ ,  $p=0.138$ ). The funnel plot (Fig. 7B), Egger’s test ( $p=0.827$ ) and Begg’s test ( $p=1.000$ ) did not show any significant publication bias. Sensitivity analysis was not conducted as there was no significant heterogeneity.

The pooling result for ulcer recurrence rate of dermal matrix group at final follow-up is shown in Fig. 7C-E. Five studies were pooled with random-effect model ( $I^2=64%$ ), resulting in a pooled ulcer recurrence rate of 0.11 ( $95\%CI: 0.05 \sim 0.17$ ) for the dermal matrix group (see the forest plot in Fig. 7C). The forest plot of sensitivity analysis (Fig. 7E) showed that no study had a

significant influence on the pooled result. The funnel plot (Fig. 7D), Egger’s test ( $p=0.738$ ) and Begg’s test ( $p=1.000$ ) did not indicate the presence of significant publication bias.

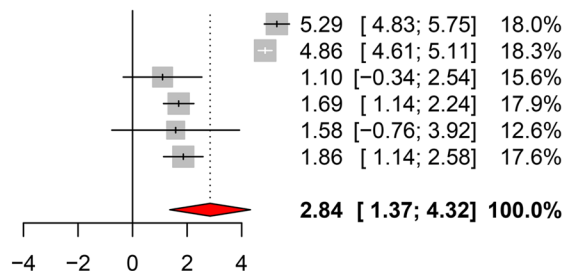
Figure 8A shows the forest plot comparing the overall amputation risk between SOC and dermal matrix groups using fixed-effect model ( $I^2=0%$ ), demonstrating that dermal matrix application could significantly lower the overall amputation risk ( $RR=1.83$ ,  $95\%CI: 1.15 \sim 2.93$ ,  $p=0.011^*$ ). After then, subgroup analyses were conducted for both major (Fig. 8B) and minor (Fig. 8C) amputation risks, showing that dermal matrix application could significantly lower the major amputation risk ( $RR=2.64$ ,  $95\%CI: 1.30 \sim 5.36$ ,  $p=0.007^{**}$ ), but had no significant impact on the minor amputation risk ( $RR=1.02$ ,  $95\%CI: 0.49 \sim 2.12$ ,  $p=0.959$ ). Publication bias test and sensitivity analysis were not performed.

The comparison of complication rate between SOC and dermal matrix is presented in Fig. 9. Thirteen studies and 15 arms were pooled with fixed-effect model ( $I^2=0%$ ), and no significantly different complication rate was observed between two groups (Fig. 9A,  $RR=1.06$ ,

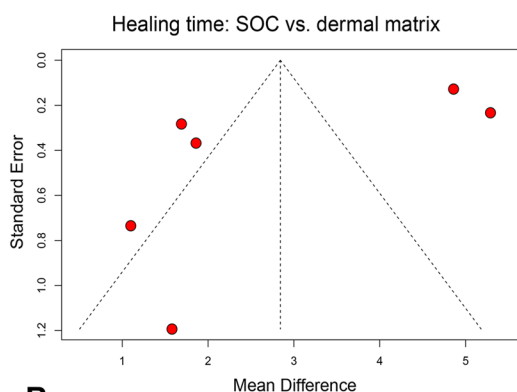
### Healing time: SOC vs. dermal matrix

Study	SOC			Dermal matrix			Mean Difference	MD	95%-CI	Weight
	Total	Mean	SD	Total	Mean	SD				
Zelen--2016	20	11.00	0.5100	20	5.71	0.9100		5.29	[ 4.83; 5.75]	18.0%
Zelen--2018	40	10.29	0.4700	40	5.43	0.6600		4.86	[ 4.61; 5.11]	18.3%
Reyzelman--2009	39	6.80	3.3000	47	5.70	3.5000		1.10	[ -0.34; 2.54]	15.6%
Lantis--2021	104	8.06	2.0500	103	6.37	2.0200		1.69	[ 1.14; 2.24]	17.9%
Brigido--2006	14	13.50	3.4200	14	11.92	2.8700		1.58	[ -0.76; 3.92]	12.6%
Campitiello--2017	23	6.11	1.1700	23	4.25	1.3200		1.86	[ 1.14; 2.58]	17.6%
<b>Random effects model</b>	<b>240</b>			<b>247</b>				<b>2.84</b>	<b>[ 1.37; 4.32]</b>	<b>100.0%</b>

Heterogeneity:  $I^2 = 97\%$ ,  $\tau^2 = 3.0925$ ,  $p < 0.01$

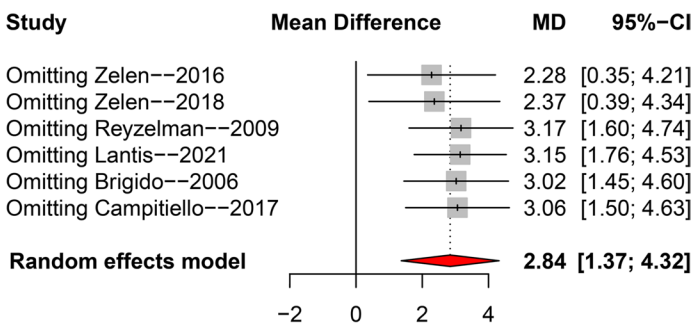


**A**



**B**

Sensitivity analysis: healing time between SOC and dermal matrix



**C**

**Fig. 3** The pooling result for complete healing time compared between SOC and dermal matrix groups at final follow-up. **A** forest plot; **B** funnel plot; **C** forest plot for sensitivity analysis

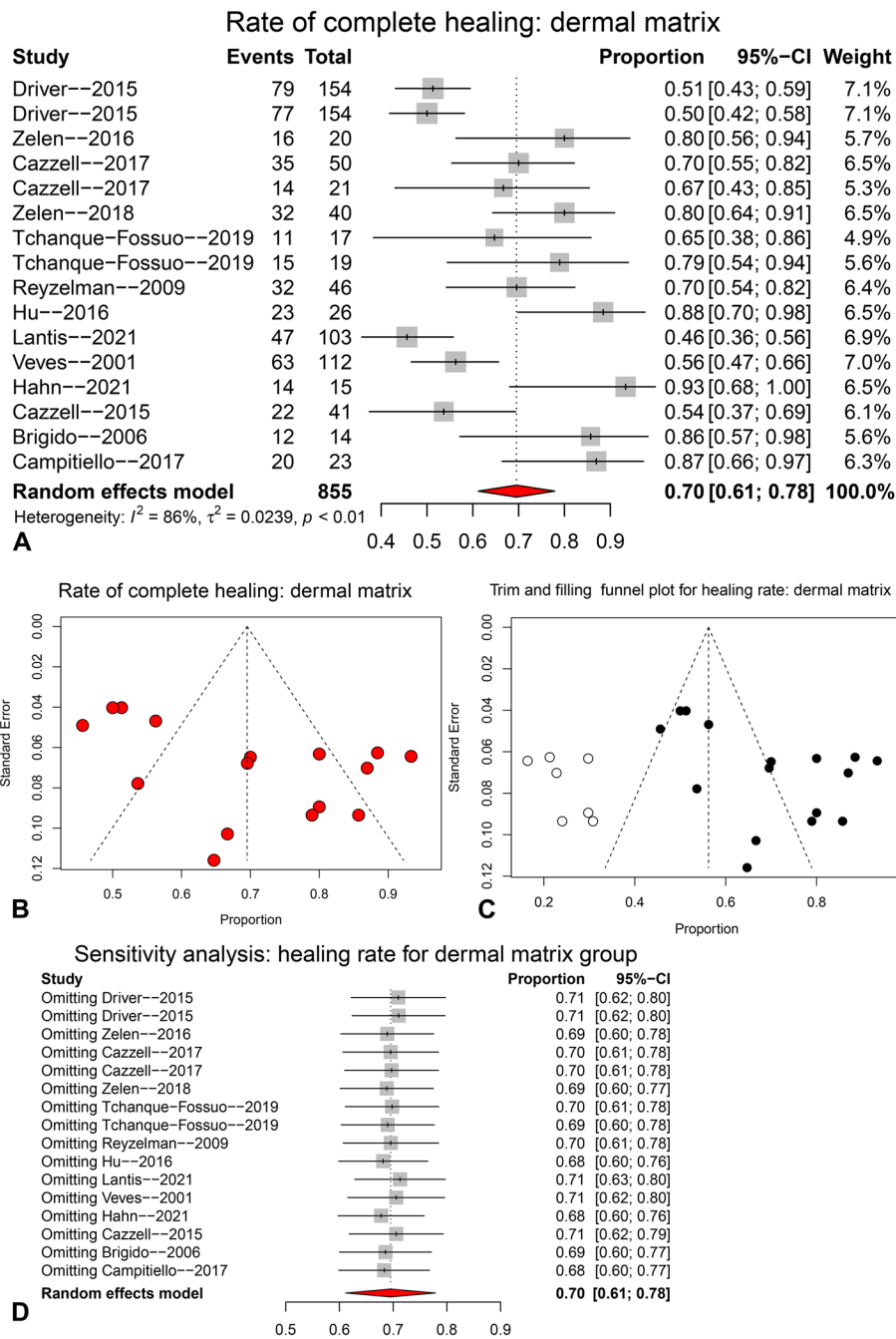
95%CI: 0.93~1.20,  $p=0.409$ ). The funnel plot (Fig. 9B), Egger’s test ( $p=0.494$ ) and Begg’s test ( $p=0.622$ ) did not indicate the presence of significant publication bias. Sensitivity analysis was not conducted as there was no significant heterogeneity.

### Discussion

In this study, we performed a systematic review and meta-analysis based on high-level evidence from RCTs, and found that application of dermal matrix was associated with significantly shorter time to complete healing, increased healing rate, and reduced amputation risk, compared to SOC alone. However, there was no significant difference in wound area, ulcer recurrence and complication risk, between the two groups.

DFUs are always characterized by chronicity and recurrence, making them difficult to fully heal and potentially leading to minor or major limb amputations. The clinical challenges related with DFUs treatment have spawned multiple adjuvant techniques to improve the wound healing. Usually, an ulcer continued

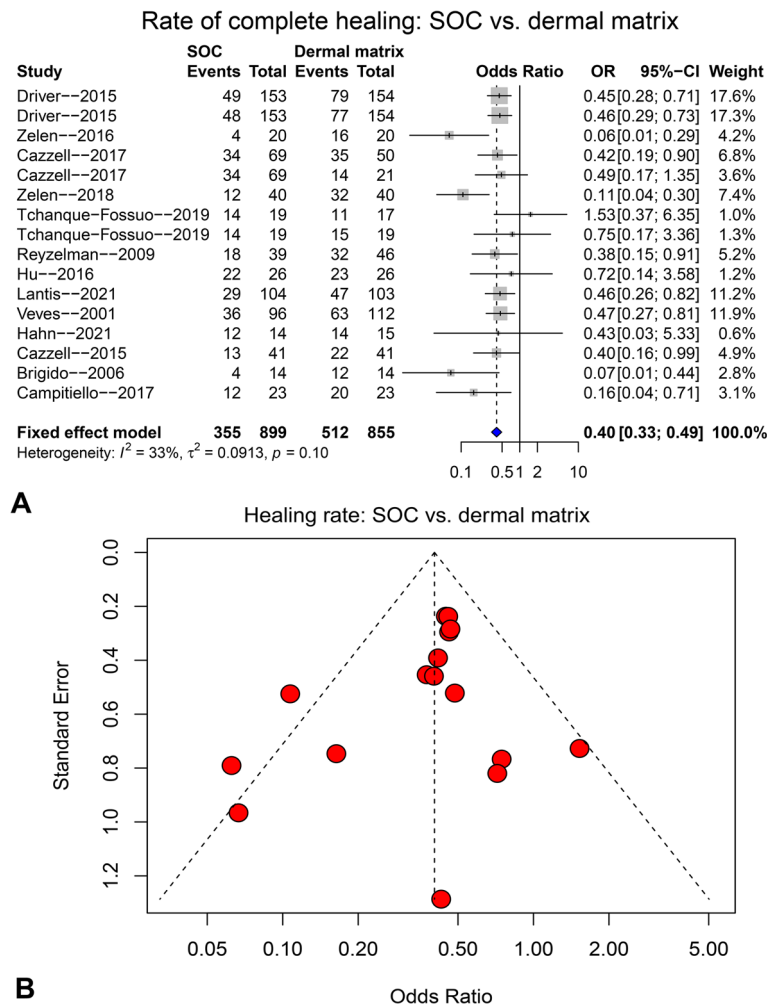
for more than 4 weeks is qualified as chronic wound, which can present additional challenges to complete the wound healing because of infection, biofilm formation, and underlying tissue desiccation that cause exacerbated conditions and disturbed healing process. Multiple biologic dressings have been applied in clinical researches in the setting of DFUs, showing promise treatment outcomes. Martin et al. [37] evaluated the outcomes of 17 consecutive patients with neuropathic diabetic foot wounds treated with an acellular matrix, which showed a 20-week healing rate of 82.4% with an average healing time of  $8.9 \pm 2.7$  weeks. Lee et al. [38] compared the efficacy of applying a paste formulation of acellular dermal matrix (ADM) with conventional foam dressing in treating DFUs, reporting an increased healing rate (56.52% vs. 23.08%), increased ratio of healed area ( $74.17\% \pm 30.84\%$  vs.  $51.87\% \pm 32.81\%$ ) and decreased length of time to heal ( $13.54 \pm 9.18$  vs.  $21.5 \pm 11.98$  days) in ADM group, at the 60-day primary outcome mark. Zelen et al. [25] compared the clinical outcomes of human reticular acellular dermis matrix



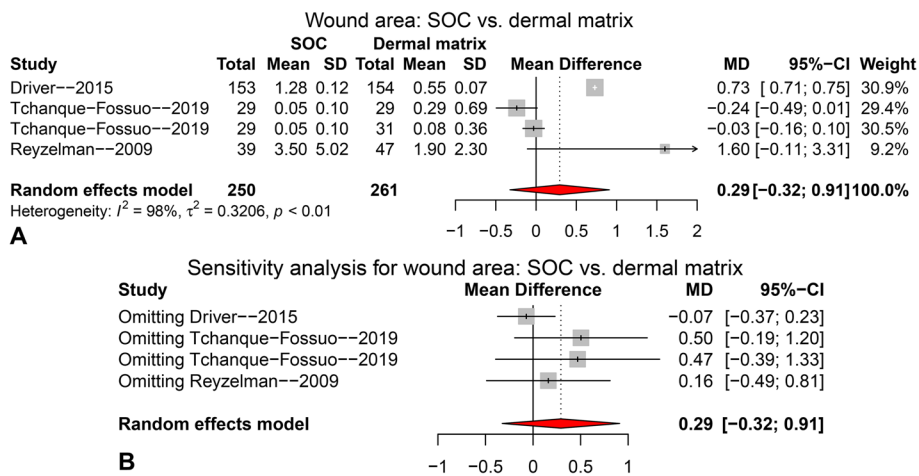
**Fig. 4** The pooling result for complete healing rate of dermal matrix group at final follow-up. **A** forest plot; **B** funnel plot; **C** trim and filling funnel plot; **D** forest plot for sensitivity analysis

(HR-ADM) versus SOC to facilitate wound closure in non-healing DFUs. At the final follow-up (12 weeks), DFUs of HR-ADM and SOC groups healed in 80 and 20% of the patients, with a mean healing time of 40 days and 77 days, respectively. There was no significantly

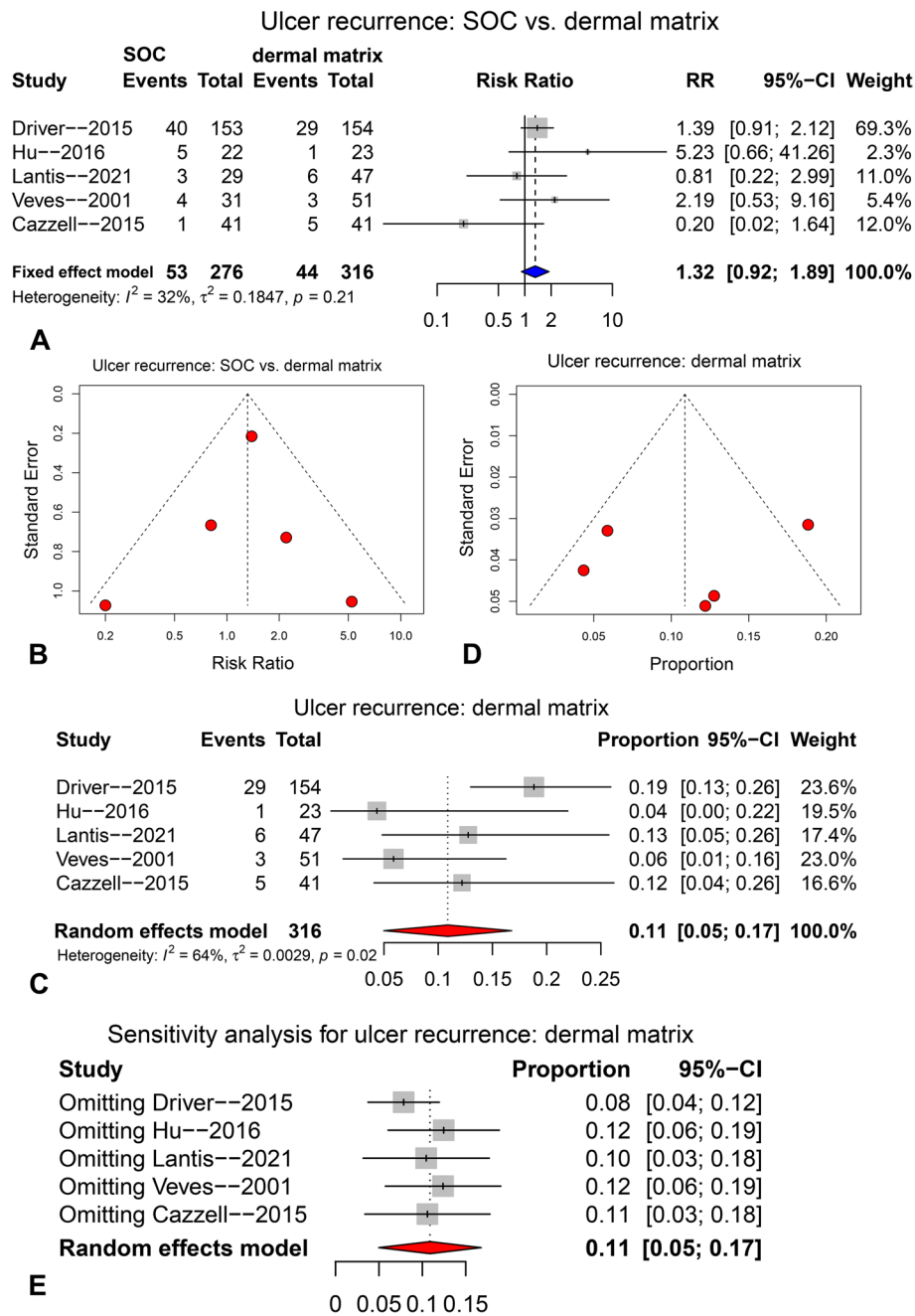
increased adverse or serious adverse events between the two groups or any adverse events related to the graft. In another RCT by Hahn et al. [33], the clinical outcomes of a micronized dermal matrix (MDM) was compared with conventional negative-pressure wound



**Fig. 5** The pooling result for complete healing rate compared between SOC and dermal matrix groups at final follow-up. **A** forest plot; **B** funnel plot



**Fig. 6** The pooling result for wound area compared between SOC and dermal matrix groups at final follow-up. **A** forest plot; **B** forest plot for sensitivity analysis

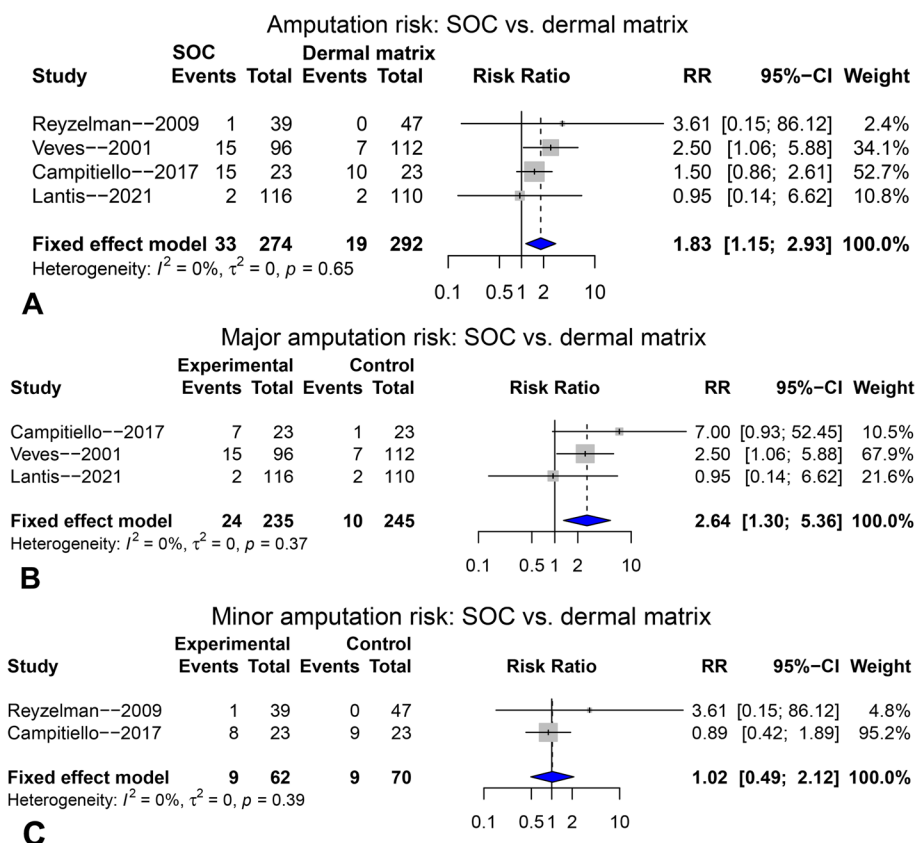


**Fig. 7** The pooling results for ulcer recurrence rate compared between SOC and dermal matrix groups (A and B), and for ulcer recurrence rate of dermal matrix group (C-E), at final follow-up. A & C. forest plot; B & D. funnel plot; E forest plot for sensitivity analysis

therapy (NPWT) in the treatment of DFUs. As a result, all wounds treated with MDM showed healthy granulation tissue without noticeable complications during follow-up. The MDM group showed a higher healing rate compared to NPWT group, at 42 and 120 days,

while similar healing rates were achieved between two groups at 6-month follow-up period. In 2017, a systematic review and meta-analysis conducted by Guo et al. [39] compared the efficacy and safety of ADM in DFU treatment, which showed that compared with the





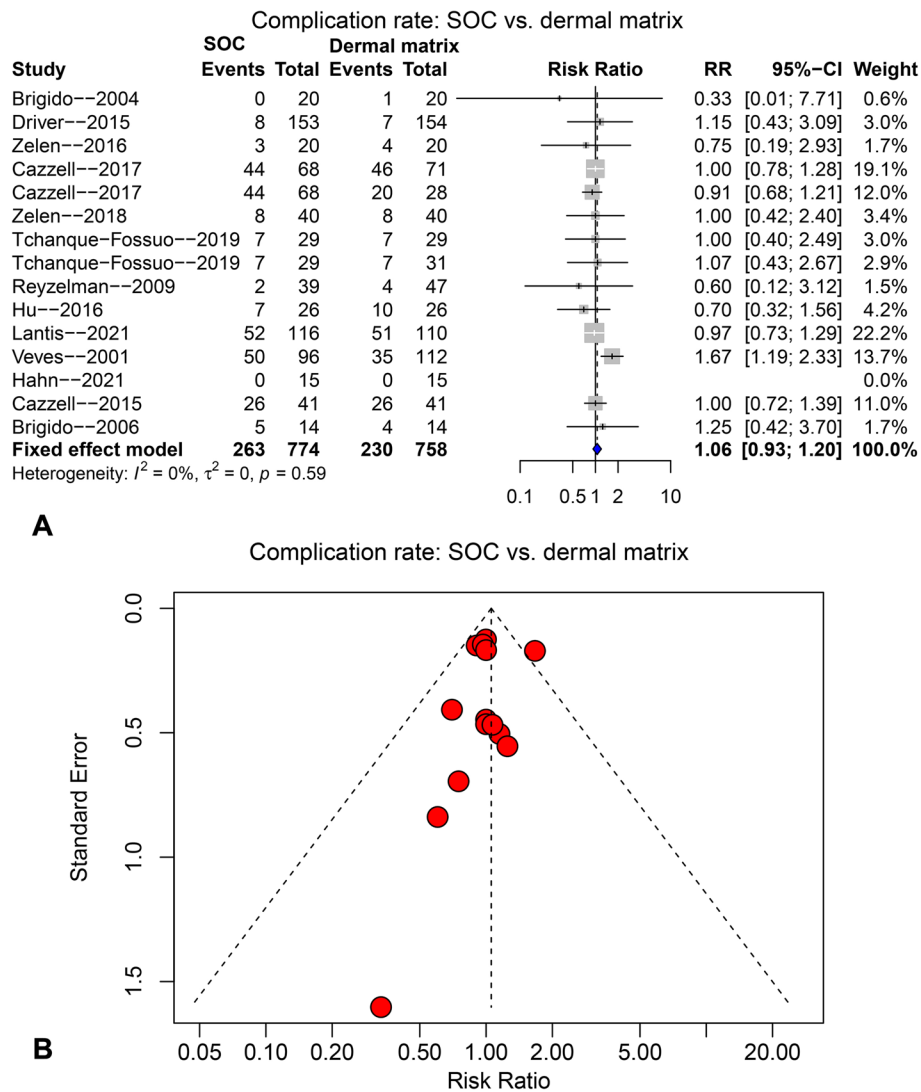
**Fig. 8** The pooling results for overall amputation risk (A) major amputation risk (B) and minor amputation risk (C) compared between SOC and dermal matrix groups, at final follow-up

SOC alone, the ADM group was associated with higher complete healing rates at 12 and 16 weeks, and shorter mean time to complete wound healing. The adverse event rates in both groups were similar, indicating that the use of ADM did not increase the risk of adverse events.

In the current study, we included 15 RCTs involving 1524 patients, and demonstrated that dermal matrix is an effective and safe treatment option for enhancing DFU healing. The results of this study support previous studies documenting the successful application of dermal matrix therapy. Dermal matrix acts as a sterile tissue graft which can be applied directly to wound beds of DFUs and integrate with the surrounding host tissues to actively stimulate cell migration, angiogenesis, and epithelialization, resulting in accelerated wound healing [40]. Although the final follow-up wound area was similar between two treatment groups, the percentage area reduction (PAR) was demonstrated to be significantly increased in several studies [23, 26, 27, 31, 34]. However, the PAR was

not pooled by meta-analysis due to the non-availability of the primary data (mean value and standard deviation of PAR).

This study, nevertheless, has several limitations that should be pointed out. Firstly, the dermal matrix products used in the studies varied among different manufacturers, which may introduce potential risk of bias. Secondly, due to the inconcealability of the treatment process with dermal matrix in the primary trials, an additional risk of bias may be caused by the unblinded application of dermal matrix to patients. Additionally, the studies reported outcomes at different follow-up times, making it difficult to pool the data. In this study, we selected the data at the final follow-up to conduct the analyses. Finally, most of the current available RCTs have relatively small sample sizes and short-term follow-up periods, which indicates that some more trials with larger sample size and longer follow-up period are required to provide some more convincing evidence.



**Fig. 9** The pooling result for complication risk compared between SOC and dermal matrix groups, at final follow-up. **A** forest plot; **B** funnel plot

**Conclusions**

The results of the current meta-analysis demonstrated that the application of dermal matrix as an adjuvant therapy to SOC can effectively enhance the healing process of DFUs and reduce the amputation risk when compared to SOC alone. Additionally, dermal matrix application was well tolerated by the subjects without added complication risk. However, some further well-designed prospective trials with larger sample sizes and longer follow-up periods are required to provide more convincing evidence.

**Abbreviations**

SOC Standard of care  
 IDRT Integra dermal regeneration template  
 NA Not available  
 ADM Acellular dermal matrix

CDM Cellular dermal matrix  
 D-ADM DermACELL acellular dermal matrix  
 GJ-ADM GraftJacket acellular dermal matrix  
 Pre-D Prediabetes  
 STSG Split-thickness skin grafting  
 NPWT Negative-pressure wound therapy  
 SIS Small intestine submucosa  
 BMI Body mass index  
 DFU Diabetic foot ulcer  
 DFI Diabetic foot infection  
 RCTs Randomized controlled trials  
 MD Mean difference  
 OR Odds ratio  
 RR Risk ratio  
 QoF Quality of life  
 PRISMA Preferred reporting items for systematic reviews and meta-analyses  
 DPN Diabetic polyneuropathy  
 PP Per-protocol  
 ITT Intention-to-treat  
 95% CI 95% Confidence interval

HR-ADM Human reticular acellular dermis matrix  
MDM Micronized dermal matrix

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12902-024-01550-3>.

**Additional file 1.** Checklist of the PRISMA for network meta-analysis.

## Acknowledgements

Not applicable.

## Authors' contributions

Lei Sui and Qiang Xie: methodology, validation, formal analysis, investigation, data curation, writing-original draft, writing-reviewing and editing, and project administration. Lei Sui, Qiang Xie, and Hong-tao Jiang: investigation, and data processing. Lei Sui: validation, writing-reviewing and editing. Xiao-dong Li: project administration. All authors read and approved the final manuscript.

## Funding

This work was supported by grant from the Hebei Province Medical Science Research Project (No. 20241445). The sponsor or funder had no involvement in any part of this study. All authors confirmed the independence of researchers from funding sources.

## Availability of data and materials

The datasets used and/or analyzed during the current 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 no competing interests.

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Received: 10 May 2023 Accepted: 5 February 2024

Published online: 20 February 2024

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