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REVIEW ARTICLE

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Influencing factors for the recurrence of diabetic foot ulcers: A meta-analysis

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Abstract

This study aims to systematically review and identify the related influencing factors for the recurrence of diabetic foot ulcers (DFUs)in diabetic patients. We searched PUBMED, EMBASE, Web of Science, Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang and VIP databases to identify eligible studies published before March 31, 2022 to collect case–control studies or cohort studies on the related influencing factors for the recurrence of DFUs. Two reviewers independently screened the literature, and extracted data. Also, they assessed the risk of bias of the included studies using the Newcastle-Ottawa Scale. A meta-analysis was performed using RevMan5.4.1 software. 20 studies were included; 4238 patients were enrolled, in which 1567 were in the DFU recurrence group and 2671 were in the non-recurrent DFU group. Risk factors for the recurrence of DFUs included diabetic peripheral neuropathy (odds ratio [OR] = 4.05, 95% CI, 2.50-6.58, $P < 0.00001$), peripheral vascular disease (OR = 3.94, 95% CI, 2.65-5.84, $P < 0.00001$), poor blood glucose control (OR = 3.27, 95% confidence interval [CI], 2.79-3.84, $P < 0.00001$), plantar ulcer (OR = 3.66, 95% CI, 2.06-6.50, $P < 0.00001$), osteomyelitis (OR = 7.17, 95% CI, 2.29-22.47, $P = 0.0007$), smoking (OR = 1.98, 95% CI, 1.65-2.38, $P < 0.00001$), history of amputation (OR = 11.96, 95%CI, 4.60-31.14, $P <$ 00001), multidrug-resistant bacterial infection (OR = 3.61, 95%CI, 3.13-4.17, $P < 0.00001$), callus (OR = 5.70, 95%CI, 1.36-23.89, $P = 0.02$), previous diabetic foot ulcer (OR = 4.10, 95% CI, 2.58-6.50, $P < 0.00001$), duration of previous diabetic foot ulcer >60d (OR = 1.02, 95% CI, 1.00-1.03, $P = 0.004$), history of vascular intervention (OR = 3.20, 95% CI, 2.13-4.81, $P < 0.00001$) and Wagner grade III/IV (OR = 4.40, 95% CI, 2.21-8.78, $P < 0.0001$). However, no significant differences were found in age, duration of diabetes, body mass index, total cholesterol or foot deformity. Recurrence of diabetic foot ulcers is affected by a variety of factors. Thus, we should focus on high-risk groups and take targeted interventions as soon as possible to reduce the recurrence rate of DFUs, because of the

limited quality and quantity of the included studies, more rigorous studies with adequate sample sizes are needed to verify the conclusion.

KEYWORDS

diabetic foot ulcer, meta-analysis, recurrence, risk factor

Key Messages

- This study evaluated the related risk factors influencing the recurrence of DFUs among diabetic patients.
- Poor blood glucose control, plantar ulcer, diabetic peripheral neuropathy; peripheral vascular disease, smoking, osteomyelitis, amputation, the duration of previous diabetic foot ulcers >60d, history of vascular intervention, Wagner grade III/IV, multidrug-resistant bacterial infection, callus and previous history of diabetic foot ulcer were associated with the recurrence of DFUs.
- The recurrence of DFUs is affected by many factors. We should focus on high-risk groups and take targeted intervention measures as soon as possible to reduce the recurrence rate of DFUs.

1 | INTRODUCTION

Diabetes is often accompanied by a variety of complications. According to study,[1] the overall prevalence of chronic complications was 73.2%. Diabetic foot ulcer (DFU) is one of the most serious complications of diabetes, and about 30% of diabetic patients will develop into a foot ulcer in their lifetime.[2] Recurrent foot ulcer refers to the new foot ulcer in a person who has a history of foot ulceration, regardless of previous foot ulcer location and the time of previous foot ulceration.[3] Diabetic foot ulcers have a long course of disease, are prone to infection, and are not easy to heal. Even after the ulcer heals, it still maintains a high recurrence rate. Research survey[4] showed that the recurrence rate of diabetic foot ulcers within 1 year after healing was 40%, the recurrence rate was 60% within 3 years and 65% within 5 years. In China, the 1-year recurrence rate of diabetic foot ulcers was as high as 31.6%, and the annual mortality rate was 14.4%.[5] Treatment become more difficult and the prognosis is poor after the recurrence of DFU. Diabetic foot has become a major public health problem that increases the burden on patients, families and society.[6] At present, there is a big diversity between the results of the current research on the influencing factors of DFU recurrence differ. Therefore, this study adopted a systematic review method to clarify the influencing factors of diabetic foot ulcer recurrence and attempted to provide evidence for its prevention. This meta-analysis has been registered with PROSPERO; the registration number: CRD42022300410.

2 | MATERIALS AND METHODS

2.1 | Literature search strategy

PUBMED, EMBASE, Web of Science, Cochrane Library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang and VIP databases were searched to collect case–control studies or cohort studies on the related influencing factors for recurrence of DFUs published before March31, 2022 by using the following search terms: diabetic foot, diabetic feet, diabetic foot ulcer, DF, DFU; recurrence, recrudescence, relapse, return; risk factors, relevant factors, predictors, predicted factors, associate factors, influence factors and incidence. In addition, all references to the retrieved studies were checked to ensure that the eligible studies were included. The entire process was independently completed by two researchers. PubMed is an example. (See Box 1 for details).

2.2 | Study inclusion and exclusion criteria

2.2.1 | Type of study

case–control study or cohort study.

2.2.2 | Study population

patients diagnosed with DFUs.

BOX 1

#1 "Diabetic Foot"[Mesh].
#2 ((((Diabetic Foot[Title/Abstract]) OR (diabetic feet[Title/Abstract])) OR.
(diabetic foot ulcer[Title/Abstract])) OR
(DF[Title/Abstract])) OR (DFU[Title/Abstract])
#3 #1 OR #2.
#4 "Recurrence"[Mesh].
#5 (((recurrence[Title/Abstract]) OR (recrudescence[Title/Abstract])) OR.
(relapse[Title/Abstract])) OR (return[Title/Abstract])
#6 #4 OR #5.
#7 "Risk Factors"[Mesh].
#8 ((((((risk factor*[Title/Abstract]) OR (relevant factor*[Title/Abstract])) OR.
(predictor*[Title/Abstract])) OR (predicted factor*[Title/Abstract])) OR.
(associate factor*[Title/Abstract])) OR
(influence factor*[Title/Abstract])) OR.
incidence*[Title/Abstract]).
#9 #7 OR #8.
#10 #3 AND #6 AND #9.
#10 #3 AND #6 AND #9.

2.2.3 | Exposure factors

Factors that may contribute to the recurrence of DFUs; and data on the risk factors for recurrence of DFUs reported as odds ratios (ORs) with 95% confidence intervals (95% CI), or can be calculated with sufficient information.

2.2.4 | Outcome indicator

Recurrence of diabetic foot ulcer.

2.2.5 | Language

English or Chinese article.

2.2.6 | Exclusion criteria

(a) reviews, systematic reviews, conference literature and case studies; (b) repeated literature; (c) incomplete or unavailable literature; (d) low-quality research of Newcastle-Ottawa scale (NOS) score ≤5.

2.3 | Data abstraction and quality appraisal

Two researchers independently screened the literature, performed the quality assessment on the included studies. Also, they extracted data and cross-checked. We contacted the authors about unclear or missing information when necessary. When screening the literature, the two researchers firstly read the title and abstract and then read the full text to determine whether to include or not. The NOS scale was used to evaluate the quality of the selected literatures to ensure the quality of included studies, The content of data extraction includes: first author, year of publication, type of study design, location of study, population size (recurrence/non-recurrence), sample ages, follow-up time, recurrence rate, influencing factors and other relevant data. The entire process was independently completed by two researchers, and the disagreements were negotiated and resolved with a third researcher.

2.4 | Statistical analysis

All statistical analyses were performed using the Review Manager Software (RevMan5.4.1). Compared with univariate analysis, the outcome data adjusted by the confounding factors such as gender and smoking were preferred in our study. If two or more studies reported the same risk factor, pooled OR estimates with corresponding 95% CIs were calculated. If the OR was not reported, for discontinuous outcomes, it was calculated from the original data. If data could not be synthesised, or risk factors were identified in only one study, the results were presented in a descriptive manner. Heterogeneity among studies was assessed by using the χ^2 and I^2 tests. A fixed-effects model was adopted when there was no statistically significant heterogeneity among the studies ($P > 0.10$ and $I^2 < 50\%$); otherwise, the source of heterogeneity was further analysed; and meta-analysis was performed using a random-effects model after significant clinical heterogeneity was excluded. For clinical heterogeneity, we used methods such as subgroup analysis or sensitivity analysis, or only descriptive analysis.

3 | RESULTS

3.1 | Search process

A total of 1495 relevant studies were retrieved through the search of literature. Including 294 in PubMed, 199 in

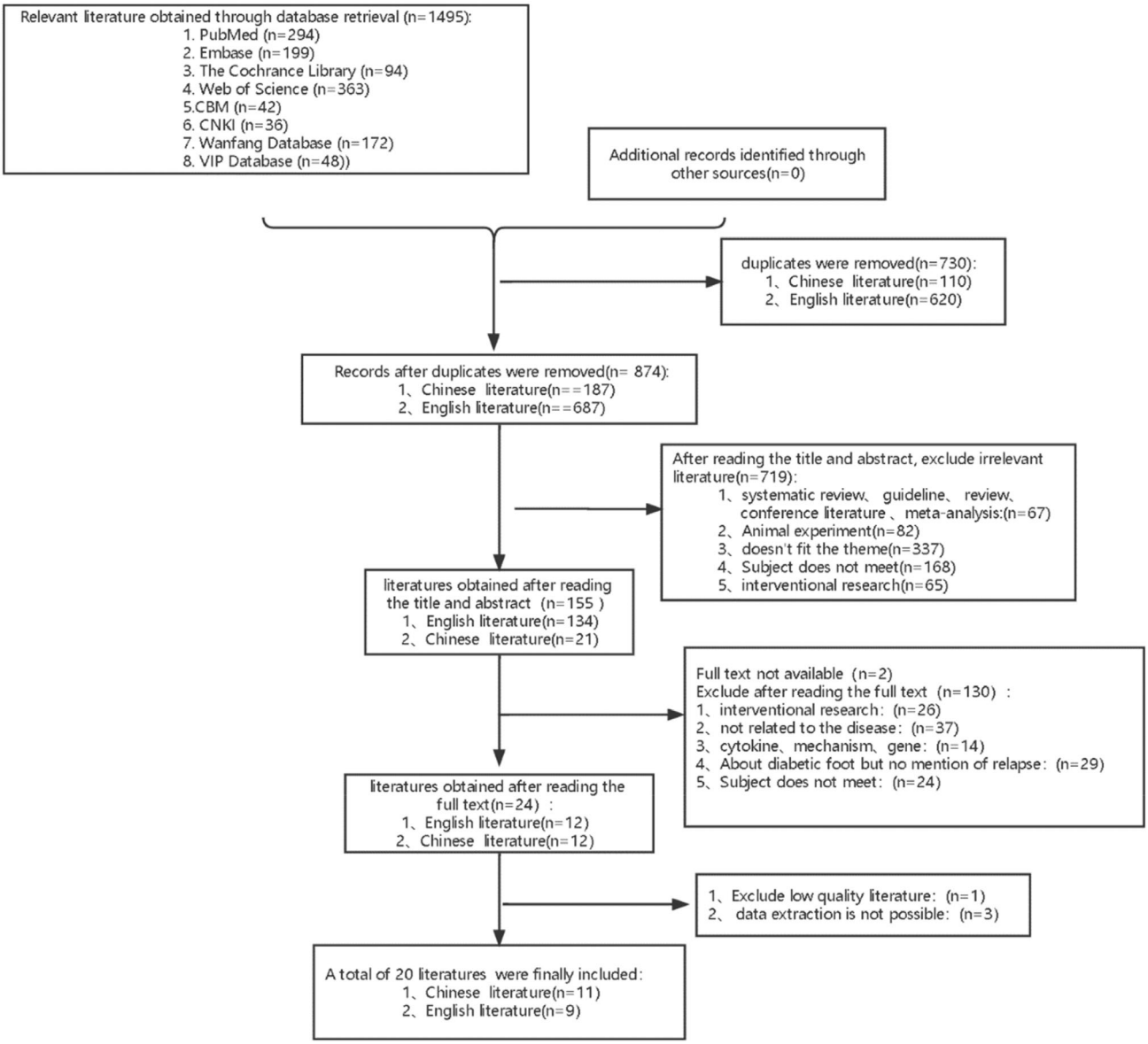

FIGURE 1 Flow diagram of the literature search

Embase, 363 in Web of Science, 94 in Cochrane Library, 42 in CBM, 36 in CNKI, 172 in Wang Fang, and 48 in VIP database. After layer-by-layer screening, 20 papers were finally included, of which 11 were Chinese and 9 were English. The literature screening process was shown in Figure 1.

3.2 | Characteristics of the included studies

Finally, after screening, 20 studies in total were included in this Meta-analysis, published between 2007 and 2022, including two case–control studies and 18 cohort studies. A total of 4238 patients were involved, including 1567 patients with DFU recurrence. In addition, 42 recurrence-related risk factors were involved, such as poor blood glucose control, plantar ulcer, diabetic peripheral neuropathy, peripheral vascular disease, smoking, osteomyelitis, amputation and the duration of previous DFU > 60d, history of vascular intervention, Wagner grade III/IV, and multidrug-resistant bacterial infection. The basic characteristics of the included studies are listed in the Table 1. The NOS scale score was between 6 and 9 points, and the results of the literature quality assessment were shown in Table 2.

3.3 | Synthesis of the results

Among the 20 studies included in this meta-analysis, there were 24 factors (external triggers, gender, surgical

TABLE 1 Characteristics of the included studies

Author/year	Nation	Study design	Sample (T/C)	T rate	Age (years)	Follow up (months)	Influencing factors
Qianhongjie, 2013[7]	China	R	33/108	23.4%	68 ± 10	12	⑤ ⑬
Huxiling, 2014[8]	China	R	57/174	24.7%	58 ± 10.2	36	③ ⑤ ⑥ ⑦ ⑫ ⑩
Changxiaoxia2017[9]	China	R	97/253	27.7%	65.25 ± 11.49	37.14 ± 17.60	⑤ ⑥ ⑫ ⑱ ⑲ ⑳ ㉑
Xiechaoyun, 2018[10]	China	R	51/114	30.91%	72.6 ± 8.0	24	② ③ ⑨ ⑪ ⑯ ㉒
Mozewei, 2018[11]	China	R	85/104	45.0%	66.6 ± 9.80	44.83 ± 16.69	① ② ④ ⑥
Chengyuxia, 2019[12]	China	NR	102/279	26.8%	61.2 ± 11.4	0	⑧ ⑭ ㉓
Xiexiaoling, 2020[13]	China	R	43/104	29.25%	45 to 85	10	① ② ③ ④ ⑪ ㉔
Shenjinfu, 2020[14]	China	R	87/98	47.0%	56 to 84	36	① ⑥ ㉕ ㉖ ㉗
Wangmeijun, 2021[15]	China	R	208/84	71.2%	63.8 ± 11.1	60	② ③ ⑥ ⑦ ㉘ ㉙ ㉚
Wuyihua, 2021[16]	China	R	25/110	22.73%	68.51 ± 6.98	24	① ② ⑪ ⑯ ㉛
Lvjing, 2022[17]	China	R	67/189	26.9%	65.8 ± 12.2	12	① ⑨ ⑰ ㉜ ㉝
Peters, 2007[18]	Netherlands	R	49/32	26.8%	NO	27.1 ± 9.2	② ④
Dubsky, 2013[19]	Czech	R	42/31	57.5%	NO	36	③ ④ ⑦ ㉞
Waaijman, 2014[20]	Netherlands	R	71/100	41.5%	63.3(10.1)	18	⑩ ㉟ ㊱
Khalifa, 2018[21]	Egypt	R	57/36	61.3%	51.73 ± 9.45	24	① ② ③ ④ ⑤ ⑨ ⑬ ㊲ ⑮ ㊳ ㊴
Tabanjeh, 2020[22]	Jordan	R	76/54	58.5%	59.9 ± 11.5	24	⑦ ⑮
Yu Xia Cheng, 2021[23]	China	NR	178/395	31.1%	53 to 70	0	⑤ ⑧ ⑭ ⑰
Roy Raoul, 2021[24]	Philippines	R	31/65	32.3%	55.8 ± 9.9	12	① ④ ㊵
Cynthia, 2021[25]	Canada	R	36/49	54.5%	63.39 ± 11.82	12	⑧ ㊶
Carmine, 2021[26]	Italy	R	172/292	37.1%	71.1 ± 8.8	42.8 ± 23.3	② ㊶ ㊷

Note: NO: no report; R: cohort study; NR: case–control study; T: recurrence; C: non-recurrence. Influencing factors: ① Diabetic peripheral neuropathy; ② Peripheral artery disease; ③ Poor blood glucose control; ④ Plantar ulcers; ⑤ Duration of diabetes; ⑥ Age; ⑦ Osteomyelitis; ⑧ Previous amputation; ⑨ Smoking; ⑩ Duration of past diabetic foot ulcers; ⑪ Multidrug-resistant bacterial infection; ⑫ BMI; ⑬ Total cholesterol; ⑭ History of vascular intervention; ⑮ Foot deformity; ⑯ Diabetic foot Wagner grade III/IV; ⑰ Callus; ⑱ External incentives; ⑲ Gender; ⑳ Operation treatment; ㉑ Discharge to follow-up interval; ㉒ Plasma viscosity ≥1.5 mPa·s; ㉓ No socks for outdoor activities; ㉔ Nutritional status; ㉕ Total bilirubin; ㉖ Albumin; ㉗ Walking disorder; ㉘ Foot care behaviour; ㉙ Response of caregiver; ㉚ End-stage renal disease stage 5; ㉛ Incomplete debridement; ㉜ Abnormal skin colour on the feet; ㉝ Coronary heart disease; ㉞ CRP>5 mg/L; ㉟ Minor lesion; ㊱ Change in daily steps; ㊲ Foot dryness; ㊳ Proper foot care; ㊴Wear appropriate shoes; ㊵ More than one foot ulcer; ㊶ Previous history of diabetic foot ulcer; ㊷ Cardiovascular disease.

treatment, nutritional status, etc.) but only mentioned in one literature. Thus, more research is needed to confirm the result, and no meta-analysis was performed here. This study conducted meta-analysis on 18 possible influencing factors, of which 13 items were statistically significant (DPN, PAD, poor blood glucose control, plantar ulcers, osteomyelitis, smoking, history of amputation, MDROS infection, callus, previous DFU, duration of previous DFU > 60d, history of vascular intervention and Wagner grade III/IV). Five factors (age, duration of diabetes, BMI, TC and foot deformity.) were not observed to be statistically significant, The analysis results are shown in Table 3 and Figures 1 to 18.

TABLE 2 Summary of the results of Newcastle–Ottawa scale (NOS) quality appraisal.

Study design	Author/year	Selection of population				Comparability	Evaluation of exposure or outcome			Total
R	Mozewei, 2018[11]	*	*	*	*	**	*	*	*	9*
R	Wangmeijun, 2021[15]	*	*	*	*	**	*	*	*	9*
R	Xiechaoyun, 2018[10]	*	*	*	*	**	*	*	*	9*
R	Huxiling, 2014[8]	*	*	*	*	*	*	*	*	8*
R	Xiexiaoling, 2020[13]	*	*	*	*	*	*	0	*	7*
R	Qianhongjie, 2013[7]	*	*	0	*	*	*	0	*	6*
NR	Chengyuxia, 2019[12]	0	*	*	*	**	*	*	*	8*
R	Changxiaoxia, 2017[9]	*	*	*	*	**	*	*	*	9*
R	Shenjinfu, 2020[14]	*	*	*	*	*	*	*	*	9*
R	Wuyihua, 2021[16]	*	*	*	*	*	*	*	*	9*
R	Lvjing, 2022[17]	*	*	0	*	**	*	*	*	8*
R	Peters, 2007[18]	*	*	0	*	**	*	*	*	8*
R	Michal Dubsky, 2013[19]	*	*	*	*	**	*	*	*	9*
R	Waaijman, 2014[20]	*	0	*	*	**	*	*	*	8*
R	Khalifa, 2018[21]	*	*	*	*	**	*	*	*	9*
R	Tabanjeh, 2020[22]	*	*	*	0	*	*	*	*	7*
NR	Yu Xia Cheng, 2021[23]	*	*	*	*	**	*	*	*	9*
R	Roy Raoul, 2021[24]	*	*	*	*	**	*	*	0	8*
R	Cynthia, 2021[25]	*	*	*	0	**	*	0	0	6*
R	Carmine, 2021[26]	*	*	*	0	**	*	*	0	7*

Note: R: cohort study; NR: case–control study.

3.3.1 | Results of meta-analysis

Four studies[8,9,11,14,15] reported the relationship between age and the risk of DFU recurrence. However, obvious heterogeneity was found in the included four studies ($I^2 = 89\%$, $P < 0.00001$), This may be due to the different criteria for age stratification between included studies. Using random-effects analysis, we found no significance in the estimate of the study effect size (OR = 1.06, 95%CI, 0.85-1.31, $P = 0.61$) (Figure 2).

Three studies[10,17,21] mentioned the association between smoking and DFU recurrence. There was no heterogeneity between the three included studies ($I^2 = 0\%$, P = 0.74) and a fixed-effects model was applied. The results showed that smoking is associated with an increased incidence of DFU recurrence (OR = 1.98, 95% CI, 1.65-2.38, $P < 0.00001$) (Figure 3).

Two studies[8,9] discussed the association between BMI and DFU recurrence. However, obvious heterogeneity was found in the two included studies ($I^2 = 86\%$, $P = 0.008$). A random-effects model was used for analysis. The result showed that there is no statistically significant association between BMI and recurrence of DFUs (OR = 0.83, 95%CI, 0.56-1.23, $P = 0.36$) (Figure 4).

Five studies[7-9,21,23] reported the relationship between the duration of diabetes and the risk of DFU recurrence. Significant heterogeneity was found in the five included studies ($I^2 = 71\%$, $P = 0.008$), a random-effects model was used for analysis. The results showed that there is no statistically significant relationship between the duration of diabetes and the recurrence of DFUs (1.02, 95%CI, 0.97-1.07, $P = 0.47$) (Figure 5).

Six studies[8,10,13,15,19,21] reported that poor blood glucose control is a risk factor for the recurrence of DFU. In our study, glycated haemoglobin was divided into glycated haemoglobin <7.5% group and glycated haemoglobin≥7.5% group. However, obvious heterogeneity was found among the included six studies ($I^2 = 95\%$, $P = 0.00001$). This may be due to the mistakes made by Hu xiling et al[8] in inputting the factor blood glucose. After excluding the study of Huxiling et al[8] heterogeneity was reduced to 0%, the fixed-effects model was applied to analyse the pooled OR with an outcome of (OR = 3.27, 95%CI [2.79,3.84], $P < 0.00001$). The results showed that

TABLE 3 Meta-analysis of the pooled Influencing factors for the recurrence of DFU

Risk factors	Number	Sample	Heterogeneity test (P, I^2)	Model	Combined OR(95%CI)	P
Age	5[8,9,11,14,15]	1247	$P < 0.00001$; $I^2 = 89\%$	Random	1.06[0.85,1.31]	$P = 0.61$*
Duration of diabetes	5[7-9,21,23]	1388	$P = 0.008$; $I^2 = 71\%$	Random	1.02[0.97,1.07]	$P = 0.47$*
Poor blood glucose control	6[8,10,13,15,19,21]	769	$P = 0.69$; $I^2 = 0\%$	Fixed	3.27[2.79,3.84]	$P < 0.00001$
plantar location of ulcer	6[11,13,18,19,21,24]	679	$P = 0.003$; $I^2 = 72\%$	Random	3.66[2.06,6.50]	$P < 0.00001$
DPN	7[11,13,14,16,17,21,24]	1101	$P < 0.00001$; $I^2 = 84\%$	Random	4.05[2.50,6.58]	$P < 0.00001$
PAD	7[10,11,15,16,18,21,26]	1419	$P = 0.03$; $I^2 = 57\%$	Random	3.94[2.65,5.84]	$P < 0.00001$
Smoking	3[10,17,21]	514	$P = 0.74$; $I^2 = 0\%$	Fixed	1.98[1.65,2.38]	$P < 0.00001$
Osteomyelitis	4[8,15,19,22]	726	$P = 0.01$; $I^2 = 72\%$	Random	7.17[2.29,22.47]	$P = 0.0007$
Previous amputation	3[9,23,25]	1039	$P = 0.04$; $I^2 = 68\%$	Random	11.96[4.60,31.14]	$P < 00001$
BMI	2[8,9]	581	$P = 0.008$; $I^2 = 86\%$	Random	0.83[0.56,1.23]	$P = 0.36$*
TC	2[7,21]	234	$P = 0.05$; $I^2 = 75\%$	Random	1.33[0.57,3.11]	$P = 0.52$*
vascular intervention	2[12,23]	954	$P = 0.25$; $I^2 = 25\%$	Fixed	3.20[2.13,4.81]	$P < 0.00001$
Foot deformity	2[21,22]	223	$P = 0.12$; $I^2 = 60\%$	Random	3.29[0.83,13.00]	$P = 0.09$*
Wagner grade III/IV	2[10,16]	300	$P = 0.99$; $I^2 = 0\%$	Fixed	4.40[2.21,8.78]	$P < 0.0001$
MDROS infection	3[10,13,16]	447	$P = 0.85$; $I^2 = 0\%$	Fixed	3.61[3.13,4.17]	$P < 0.00001$
callus	2[17,23]	829	$P < 0.0001$; $I^2 = 94\%$	Random	5.70[1.36,23.89]	$P = 0.02$
Duration of DFU > 60d	2[9,20]	251	$P = 0.30$; $I^2 = 7\%$	Fixed	1.02[1.00,1.03]	$P = 0.004$
Previous DFU	2[24,25]	549	$P = 0.19$; $I^2 = 42\%$	Fixed	4.10[2.58,6.50]	$P < 0.00001$

Abbreviations: BMI, body mass index; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; MDROS, Multi-drug resistant bacteria; PVD, diabetic peripheral vascular disease; TC, total cholesterol.
*The difference is not statistically significant.

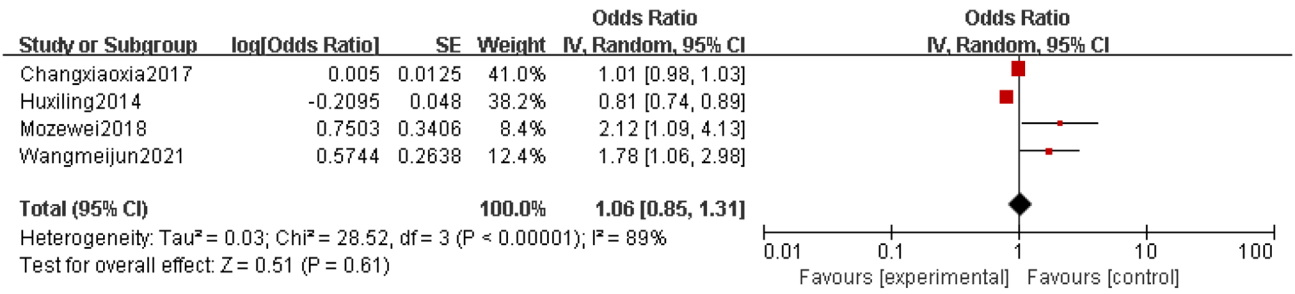

FIGURE 2 Forest plot: effect of age on diabetic foot ulcer recurrence

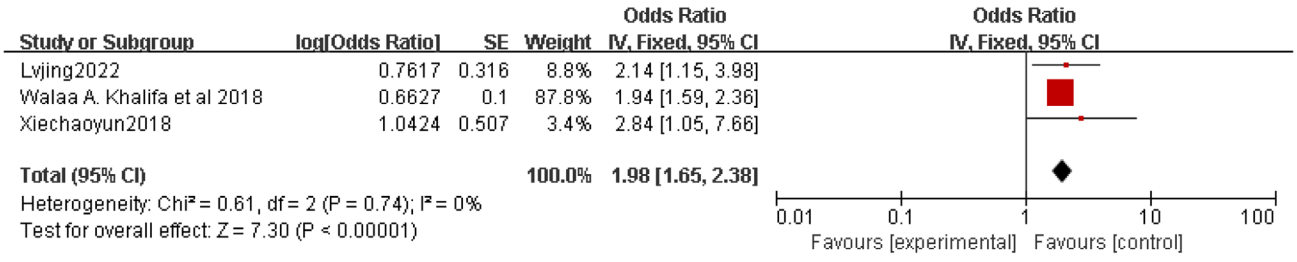

FIGURE 3 Forest plot: effect of smoking on diabetic foot ulcer recurrence

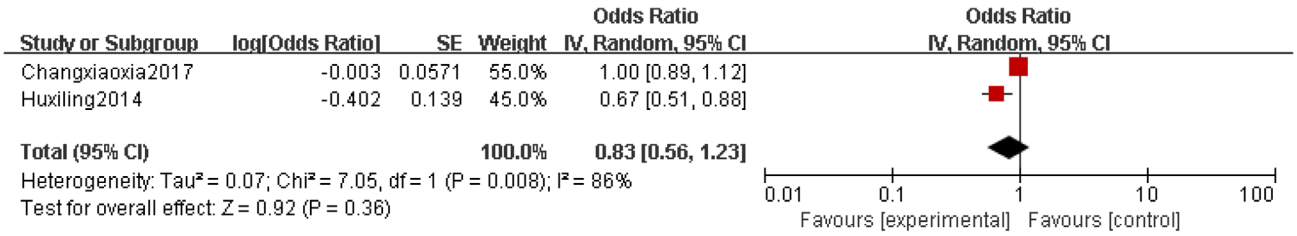

FIGURE 4 Forest plot: effect of BMI on diabetic foot ulcer recurrence

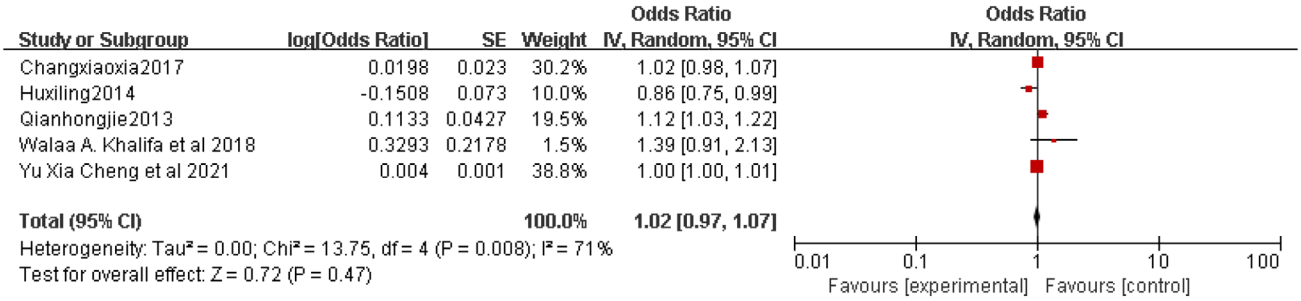

FIGURE 5 Forest plot effect of duration of diabetes on diabetic foot ulcer recurrence

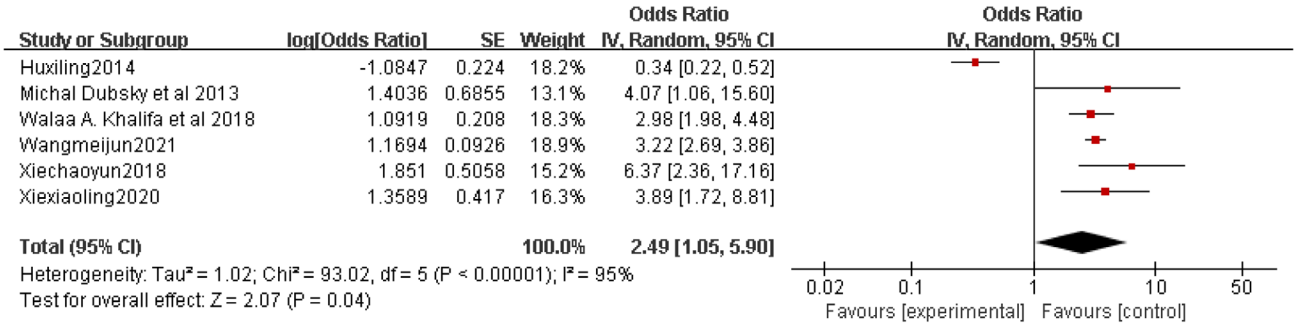

FIGURE 6 Forest plot effect of poor blood glucose control on diabetic foot ulcer recurrence

poor blood glucose control is associated with an increased incidence of DFU recurrence (Figure 6).

Six studies[11,13,18,19,21,24] reported the effect of plantar ulcers on the recurrence of DFU. Moderate heterogeneity was found among the six included studies ($I^2 = 72\%$, $P = 0.003$). The random-effects model was used for analysis. The results showed that patients with plantar ulcers are at a higher risk of ulcer relapse (OR = 3.66, 95%CI [2.06,6.50], $P < 0.00001$). After excluding the study of Roy Raoul Felipe et al,[24] the heterogeneity between the five included studies decreased to 36%. It may be due to the population heterogeneity made by the study of Roy Raoul Felipe et al.[24] The fixed-effects model was used for analysis and the results showed that plantar ulcers was associated with an increased incidence of DFU recurrence (OR = 2.58, 95%CI [2.02,3.30], $P < 0.00001$). The results of the two analyses are consistent, indicating that the stability of results is good (Figure 7).

Seven studies[11,13,14,16,17,21,24] reported that DPN is a risk factor for the recurrence of DFU. Significant heterogeneity was found among the seven included studies ($I^2 = 94\%$, $P < 0.0001$). This may be related to the different diagnostic criteria for DPN. The random-effects model was used for analysis, and the results showed the DPN is a risk factor for the recurrence of DFU (OR = 4.05, 95%CI [2.50,6.58], $P < 0.00001$) (Figure 8).

Four studies[8,15,19,22] reported the relationship between Osteomyelitis and the risk of DFU recurrence. However, obvious heterogeneity was found among the included four studies ($I^2 = 72\%$, $P = 0.01$). The random-effects model was used for analysis, and the results showed that the association between the history of osteomyelitis and the recurrence of DFU was of statistical significance (OR = 7.17, 95%CI [2.29,22.47], $P = 0.007$). After excluding the study of WangMeijun et al,[15] the heterogeneity between the studies decreased to 35%. This may be due to

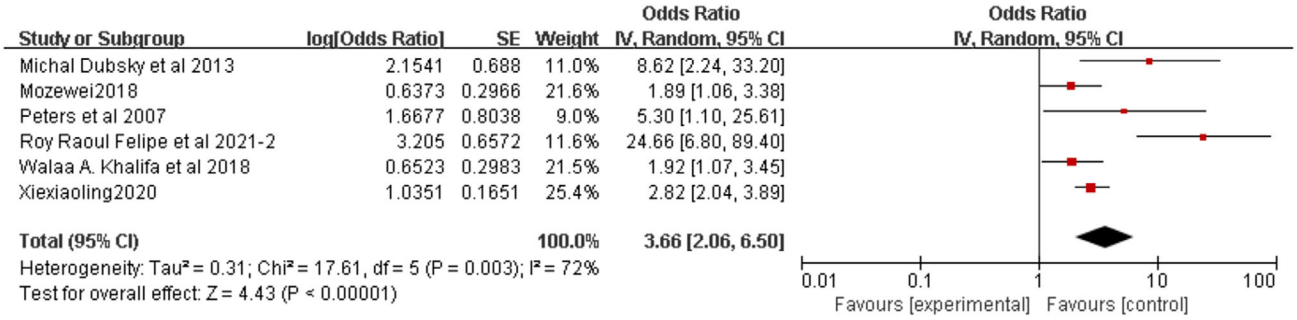

FIGURE 7 Forest plot effect of plantar ulcer on diabetic foot ulcer recurrence

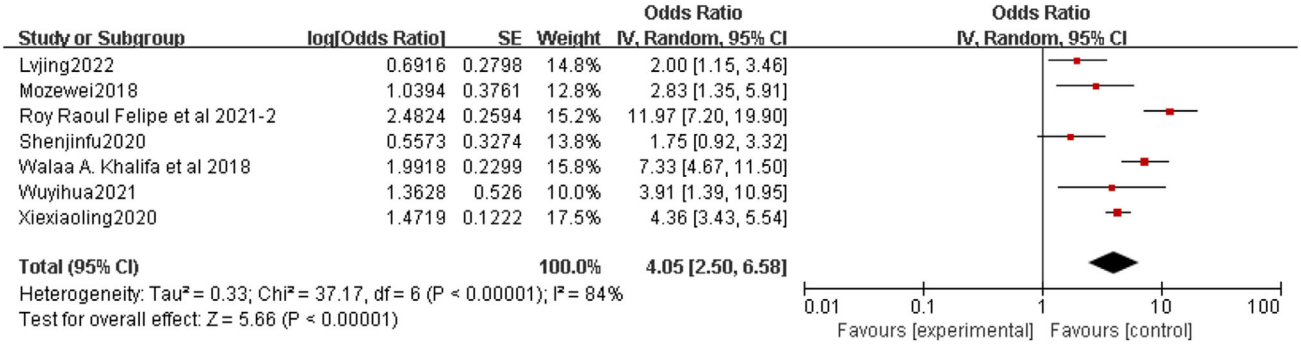

FIGURE 8 Forest plot effect of DPN on diabetic foot ulcer recurrence

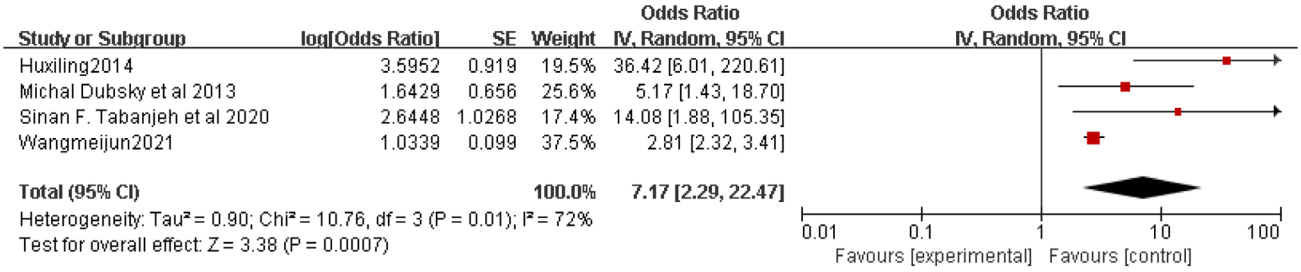

FIGURE 9 Forest plot effect of Osteomyelitis on diabetic foot ulcer recurrence

differences in the criteria for judging osteomyelitis between studies. Besides, the fixed-effects model was used for analysis, and the results showed that osteomyelitis is an independent risk factor for DFU recurrence (OR = 10.75, 95% CI [4.25,27.20], $P < 0.00001$). The results of the two analyses are consistent, indicating that the stability of the results is good (Figure 9).

Seven studies[10,11,15,16,18,21,26] mentioned the effect of PAD on the recurrence of DFU. Consider that heterogeneity of the seven included studies was moderate ($I^2 = 57\%$, $P = 0.003$), the random-effects model was used for analysis. The results showed that patients with PAD are at a higher risk of DFU recurrence (OR = 3.94, 95% CI [2.65,5.84], $P < 0.00001$). After excluding the study of Carmine et al,[26] the heterogeneity decreased to 37%. It may be related to population heterogeneity. In addition, the fixed-effects model was also used for analysis (OR = 4.37, 95%CI [3.32,5.75], $P < 0.00001$), and the two results are consistent, indicating that the stability of the results is good (Figure 10).

Two studies[9,20] reported the effect of the duration of previous DFU on the recurrence of DFU. Consider that heterogeneity of the two included studies was small, the fixed-effects model was used for analysis ($I^2 = 7\%$, $P = 0.30$). The results showed that patients with duration of past DFUs >60d are at a higher risk of DFU recurrence (OR = 1.02, 95% CI, 1.00-1.03, $P = 0.004$) (Figure 11).

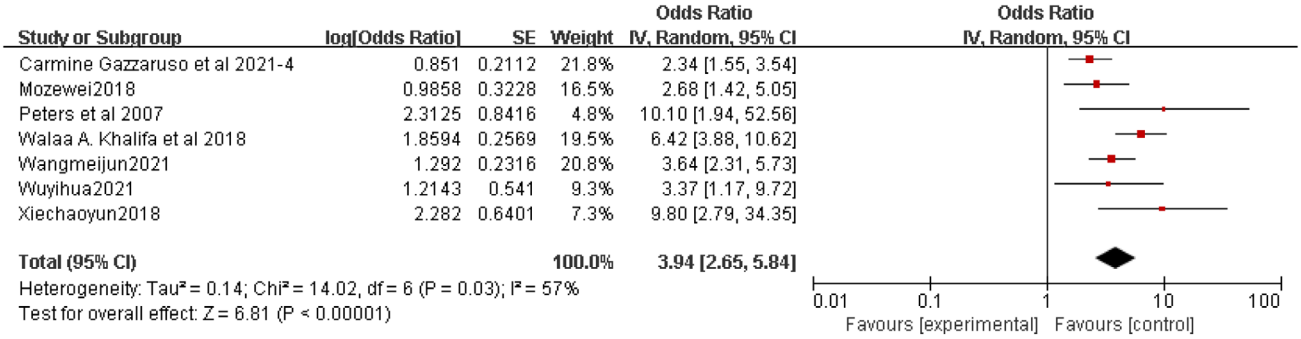

FIGURE 10 Forest plot: effect of PAD on diabetic foot ulcer recurrence

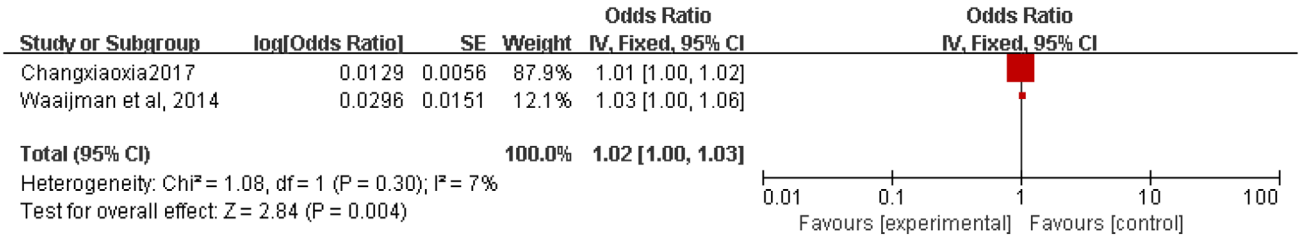

FIGURE 11 Forest plot: effect of the duration of DFUs >60d on DFU recurrence

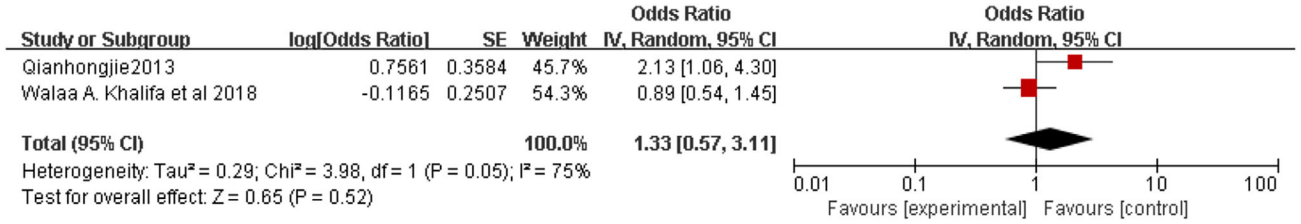

FIGURE 12 Forest plot: effect of TC on diabetic foot ulcer recurrence

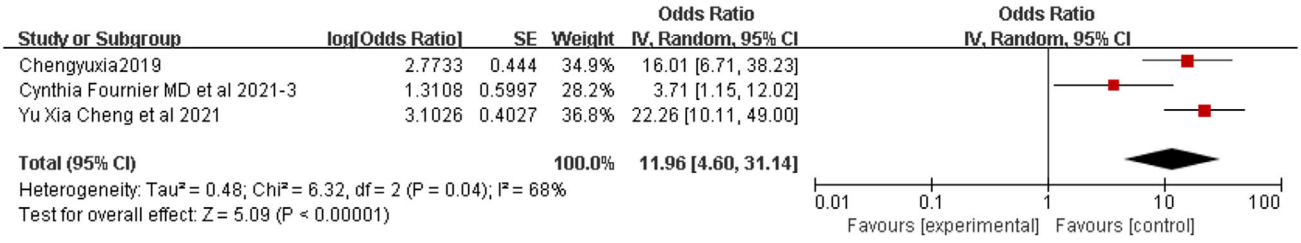

FIGURE 13 Forest plot effect of amputation on diabetic foot ulcer recurrence

Two studies[7,21] reported the effect of TC on the recurrence of DFU. Distinct heterogeneity was found among the included two studies ($I^2 = 75\%$, $P = 0.05$). The random-effects model was used for analysis. The results showed that there is no statistically significant association between TC and the recurrence of DFU (OR = 1.33, 95%CI, 0.57-3.11, $P = 0.52$) (Figure 12).

Three studies[9,23,25] mentioned the effect of toe or extremity amputation on the recurrence of DFU. Moderate heterogeneity was found among the three included studies ($I^2 = 68\%$, $P = 0.04$). The random-effects model was used for analysis. The results showed that patients with amputation were at a significant risk of DFU recurrence (OR = 11.96, 95%CI [4.60,31.14], $P < 0.00001$).

After excluding the study of Cynthia Fournier et al,[25] the heterogeneity between remained studies was eliminated. This may be related to population heterogeneity .The fixed-effects model was used for the analysis, the results showed that amputation was a risk for DFU recurrence (OR = 19.18, 95%CI [10.69,34.42], $P < 0.00001$). The conclusions of the two analyses are consistent, indicating that the stability of the results is relatively good (Figure 13).

Three studies[10,13,16] mentioned the effect of the multidrug-resistant bacterial infection on the recurrence of DFU. There was no heterogeneity between the three included studies ($I^2 = 0\%$, $P = 0.85$). The fixed-effects model was used for analysis. The results showed that multidrug-resistant bacterial infection is a risk factor for the recurrence of DFU (OR = 3.61, 95%CI [3.13, 4.17], $P < 0.00001$) (Figure 14).

Two studies[10,16] reported the effect of Wagner grading on the recurrence of DFU. There was no heterogeneity between the included two studies ($I^2 = 0\%$, $P = 0.74$). The fixed-effects model was used for analysis. The results show that in the Wagner grading of diabetic foot, Wanger grade III/IV is a risk factor for the recurrence of DFU (OR = 4.40, 95%CI [2.21, 8.78], $P < 0.0001$) (Figure 15).

Two studies[12,23] reported the effect of history of vascular intervention on the recurrence of DFU. The heterogeneity between the two included studies was small ($I^2 = 25\%$, $P = 0.25$). The fixed-effects model was used for analysis. The results showed that history of vascular intervention is a risk factor for the recurrence of DFU (OR = 3.20, 95%CI [2.13, 4.81], $P < 0.00001$) (Figure 16).

Two studies[21,22] reported the effect of foot deformity on the recurrence of DFU. Moderate heterogeneity was found in the two included studies ($I^2 = 60\%$, $P = 0.12$). The random effects model was used for analysis. The results showed that there is no statistically significant association between foot deformity and the recurrence of

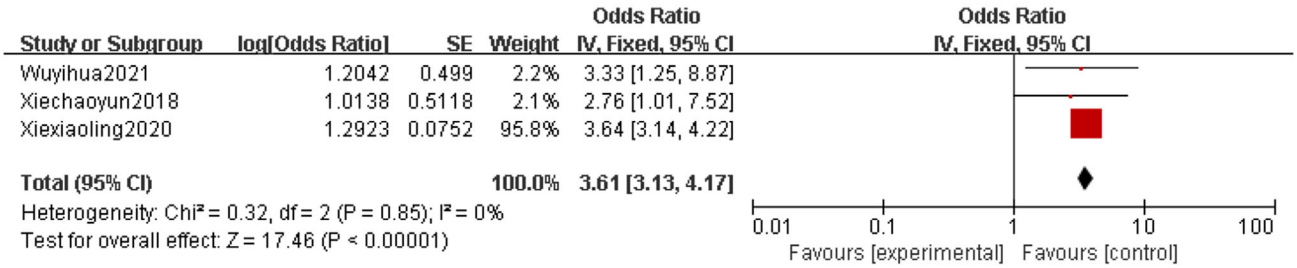

FIGURE 14 Forest plot effect of multidrug-resistant bacterial infection on diabetic foot ulcer recurrence

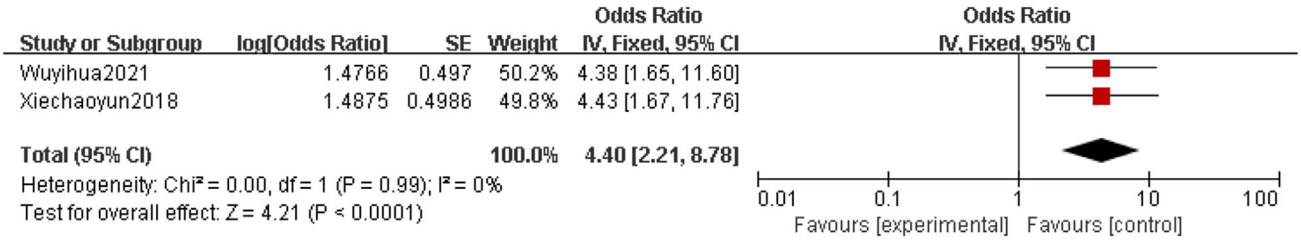

FIGURE 15 Forest plot effect of Wagner grade (III/IV) on diabetic foot ulcer recurrence

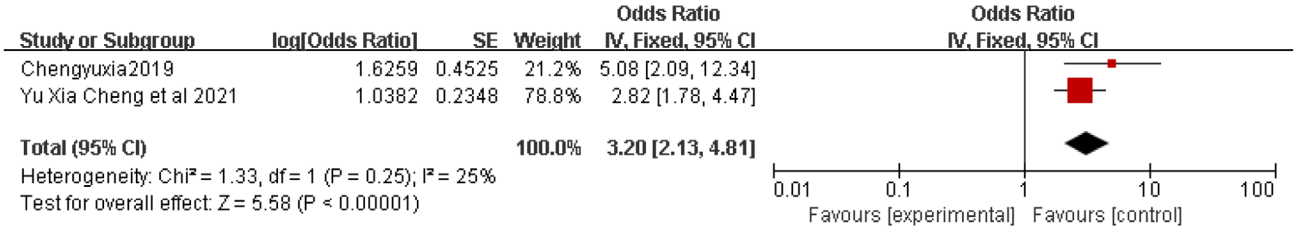

FIGURE 16 Forest plot effect of history of vascular intervention on diabetic foot ulcer recurrence

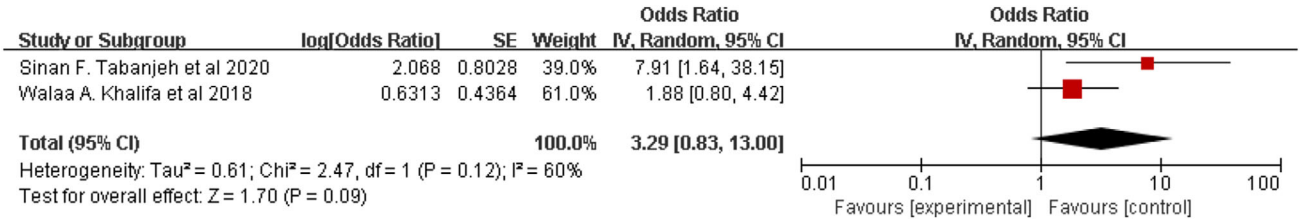

FIGURE 17 Forest plot effect of foot deformity on diabetic foot ulcer recurrence

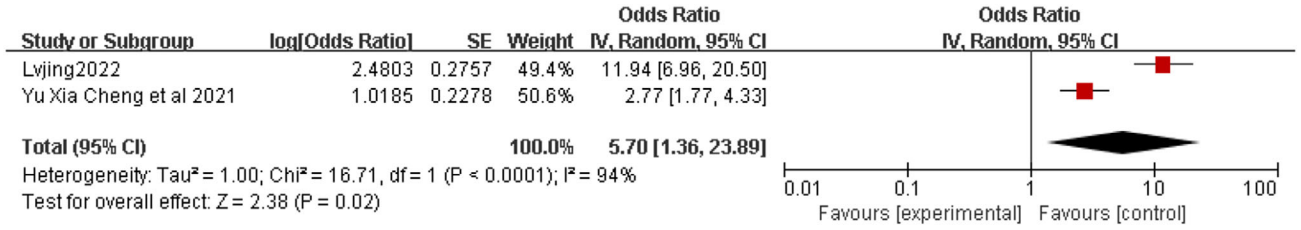

FIGURE 18 Forest plot effect of callus on diabetic foot ulcer recurrence

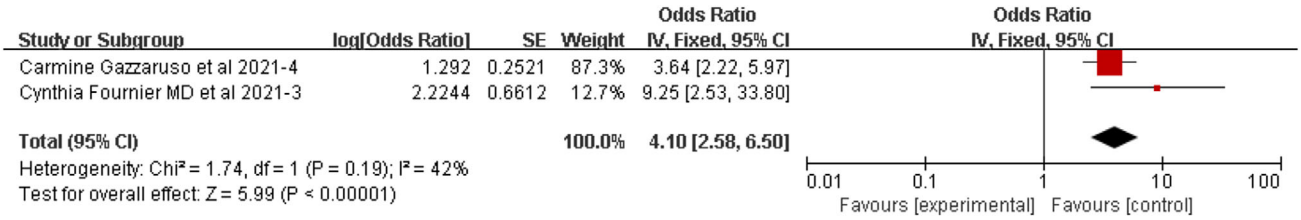

FIGURE 19 Forest plot effect of previous DFUs on diabetic foot ulcer recurrence

DFU (OR = 3.29, 95%CI [0.83, 13.00], $P = 0.09$) (Figure 17).

Two studies[17,23] reported the relationship between callus and the risk of DFU recurrence. However, distinct heterogeneity was found in the two included studies ($I^2 = 94\%$, $P < 0.0001$). A random-effects model was used for analysis. The results showed that callus is a risk factor for the recurrence of DFU, (OR = 5.70, 95%CI [1.36, 23.89], $P = 0.02$). (Figure 18).

Two studies[24,25] mentioned the effect of history of ulcer on the recurrence of DFU. The heterogeneity of the two included studies was small ($I^2 = 42\%$, $P = 0.19$). Fixed-effects model was used for analysis, and the results showed that history of ulcer is a risk factor for the recurrence of DFU (OR = 4.10, 95% CI [2.58, 6.50], $P < 0.00001$) (Figure 19).

4 | DISCUSSION

While most patients with DFUs heal within 1 year after receiving correct and adequate treatment, the recurrence rate of diabetic foot ulcers remains high.[4,5] Therefore, it may make more sense to define an individual with a closed wound on DFU as a state of remission. As diabetic foot ulcer has a high risk of infection, hospitalisation and amputation,[27,28] the prevention of ulcer recurrence is an important topic in the management of patients with diabetic foot healing. Moreover, we need to have a better understanding of ulcer recurrence prediction factors in order to develop better strategies to prevent ulcer recurrence.

Through certain data integration, this study found that: DPN, PAD, poor blood glucose control, plantar ulcers, osteomyelitis, smoking, history of amputation, MDROS infection, callus, previous DFU, duration of previous DFU > 60d, history of vascular intervention and Wagner grade III/IV were risk factors for the recurrence of DFUs; no significant differences were found in age, duration of diabetes, BMI, TC and foot deformity.

Our study included 11 more articles than the meta-analysis of Ze-Hao Huang et al.[29] In our study, gender was not included in the results of the extracted multivariate analysis. However, the study of Ze-Hao Huang et al[29]

showed that gender was a risk factor for the recurrence of DFUs. Thus, a large number of high-quality studies are needed to improve the reliability of the results in the future. In addition, the results of Ze-Hao Huang et al[29] showed that the duration of diabetes was also a risk factor for the recurrence of DFUs. Consequently, our study included two more articles on the duration of diabetes on the basis of the study of Ze-Hao Huang et al,[29] and found that there was no statistical significance between the duration of diabetes and the recurrence of DFUs.

Our meta-analysis reaffirmed some of the research results of Ze-Hao Huang et al.[29] For example, DPN, PAD, plantar ulcer, smoking and duration of previous diabetic foot ulcer >60d are risk factors for DFU recurrence, and the correlation between age, BMI, TC and the recurrence of DFUs is of no statistical significance. Besides, we also found seven new risk factors for foot ulcer recurrence (such as poor blood glucose control, osteomyelitis, history of vascular intervention, previous diabetic foot ulcer, Wagner grade III/IV and multidrug-resistant bacterial infection). Furthermore, relationship between foot deformity and DFU recurrence in our study is of no statistical significance due to the limited available analysis data. As this conclusion was made based on only two studies, more research is necessary to further examine the influence of foot deformity on the recurrence of DFU.

According to the review, recurrent foot ulcer is the result of a combination of multiple factors. However, because of the limited quantity and quality of the included studies, the research evidence of risk factors for DFU recurrence is still insufficient. Some conclusions in our study may be biased, and more studies are needed to verify the correlation between the above risk factors and DFU recurrence.

5 | INNOVATION

This study is of certain innovation, and the results of this meta-analysis are of great significance for clinical practice. First of all, the lifetime incidence of DFU is very high, ranging from 19% ∼ 34%. Also, the high recurrence rate, high disability rate and high mortality of DFUs underscore the importance of preventing DFUs.[30,31] Secondly, a total of 20 high-quality studies were included in our study, and the extracted risk factors in this study were all obtained from the data of the multivariate analyses in other studies. Therefore, we could draw more reliable conclusions. Third, we newly discovered seven risk factors for DFU recurrence, which provides a new perspective for preventing the recurrence of DFUs. In addition, we also found that the included studies were mostly focused on analysing risk factors with clinical characteristics, and that most risk factors are irreversible. Therefore, in the future, more high-quality studies should focus more on changeable risk factors, such as behavioural risk factors, so as to make more contribution to the prevention of the recurrence of DFUs.

6 | LIMITATION

Finally, this study also has certain limitations: First of all, as the included studies were case–control and cohort studies, the evidence for causal reasoning was relatively weak. Secondly, our study only performed meta-analyses on relatively high-profile risk factors in the original literature, Thus, to avoid bias, the data used in this paper were all data of multivariate logistics analysis adjusted by confounding factors such as gender and age. Some risk factors were not included due to a lack of data or insufficient literature, which may have a certain impact on the comprehensiveness and reliability of the studies; Furthermore, eight risk factors (previous diabetic foot ulcer, history of vascular intervention, Wagner grade III/IV, callus, duration of diabetic foot disease >60d, BMI, TC and foot deformity) were identified in only two studies, and the studies may have publication bias. Thus, the results were not convincing. Moreover, because of limitations of the included data, we did not conduct subgroup analysis and funnel plots analysis. Some of our results show significant heterogeneity, which may account for the difficulty to identify heterogeneity. These affect the confidence of the results to some extent. Hence, further research should be conducted to validate our conclusion.

7 | CONCLUSION

The recurrence of DFUs is the result of a combination of factors. Health-care providers can focus on identified risk factors and take effective measures to prevent recurrence of DFUs and change the patient's final clinical outcome. Besides, evidence-based risk factors of DFU recurrence can be used to formulate an overall strategy for the prevention and management of foot ulcer recurrence.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

This statement will be published alongside your manuscript

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