Original Article

Risk factors for multidrug-resistant bacterial infections in patients with diabetic foot ulcers: a systematic review and meta-analysis

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Background: Diabetic foot ulcer (DFU) is one of the main causes of disability and death in diabetic patients, along with the continuous development of relevant research. The purpose of this paper is to study the risk factors of multidrug resistant organisms (MDROs) infection in patients with DFUs by meta-analysis.

Methods: We searched the PubMed, EMBASE, Cochrane library, and Web of Science databases for literature related to the risk factors of MDRO infection in patients with DFUs from the date of establishment of the database to September 2021. Duplicate studies were excluded using Endnote X9 software. Stata 15.1 software was used to meta-analyze the data. Random or fixed effects models were used to combine and analyze the odds ratio (OR) and 95% confidence interval (CI) of the included risk factors. Heterogeneity was analyzed by the Q and I2 tests. Egger's linear regression method was used to evaluate the publication bias of the included articles. Sensitivity analysis was used to analyze the source of heterogeneity.

Results: A total of 13 articles were included in the study. Meta-analysis was performed on 15 risk factors. Among them, hospital records before admission (OR =5.18, 95% CI: 1.45–18.51, P=0.011), antibiotic use before admission (OR =2.17, 95% CI: 1.24–3.79, P=0.006), diabetes type (OR =2.44, 95% CI: 1.29–4.64, P=0.006), ulcer type (OR =2.17, 95% CI: 1.06–4.41, P=0.033), ulcer size (OR =2.56, 95% CI: 1.53–4.28, P<0.001), osteomyelitis (OR =3.50, 95% CI: 2.37–5.16, P<0.001), vascular disease (OR =2.37, 95% CI: 1.41–3.99, P=0.001), surgical treatment (OR =4.80, 95% CI: 2.95–7.83, P<0.001), and these meta-analysis results were statistically different and could be considered as risk factors for MDRO infection.

Conclusions: The risk factors of MDRO infection in DFU patients include hospitalization records before admission, antibiotic use before admission, type of diabetes, type of ulcer, size of ulcer, osteomyelitis, vascular lesions, and surgical treatment. This study contributes to the ability of the population of DFU patients infected with MDROs to receive timely treatment at an early stage and delay disease development.

Keywords: Diabetes; foot ulcer; multidrug-resistant bacteria; risk factors; meta-analysis

Submitted Oct 20, 2021. Accepted for publication Dec 14, 2021.
doi: 10.21037/apm-21-3406
View this article at: https://dx.doi.org/10.21037/apm-21-3406

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Introduction

Diabetic foot is one of the most serious complications of diabetes, with an incidence of 25%, of which 50% is combined with bacterial infections. Diabetic foot ulcers (DFUs) are ulcers of the foot and destruction of deep tissues in diabetic patients due to vascular and neuropathic lesions of the lower extremities (1). The incidence of multidrug-resistant organism (MDRO) infection remains high in DFU patients (2). Studies (3,4) have shown that 40–80% of DFU patients have some degree of infection, which has now become the most important factor for hospitalization and amputation in DFU patients. At present, most patients with severe DFU need to be treated with antibiotics, and due to the frequent use of antibiotics, multiple resistant bacteria lead to slow wound recovery and have a great impact on people's quality of life.

MDROs are defined as pathogens with simultaneous resistance to three or more classes of antimicrobial agents in clinical practice (5). At present, common multidrug-resistant bacteria include methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), extended-spectrum β-lactamase (EsBLs)-producing bacteria, multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA), and carbapenem-resistant *Enterobacteriaceae* (CRE) (6). Considering that the risk rate of MDRO infection is increasing every year, combined with the complex and variable drug resistance of strains, leads to difficulty in controlling infection and high medical costs, as well as increased amputation and mortality rates, which greatly reduces the effect of treatment and the quality of life of patients (3,7).

In order to reduce the occurrence of infections caused by drug-resistant bacteria and improve patient outcomes, numerous studies (8-20) have reported risk factors for MDRO infection. In recent years, with the increased research related to MDRO infection in DFU patients, more attention has been paid to the risk factors involved, but due to the interference of some factors such as sample size, study subjects, or region, the conclusions drawn are not consistent, and are even conflicting in some cases, resulting in a decrease in the strength of the research. Similar studies have been conducted before, and this study incorporating the latest studies and with view to a comprehensive investigation and meta-analysis of the previously published literature, so as to gain insight into the relationship between MDRO infection and DFU patients. We sought to identify the risk factors associated with MDRO infection in DFU patients, and to provide a relevant theoretical basis for disease observation and prevention. We present the following article in accordance with the MOOSE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3406).

Methods

Literature search strategy

Because the relevant foreign research is more perfect, our study was only included in foreign journals for research. We conducted a search of major foreign journal literature databases, including PubMed, Embase, Cochrane library, and Web of Science. The search period was from the date of establishment of the database to September 2021. Medical Subject Headings (MeSH) terms combined with free words were used for the search, and the English language was searched with ('diabetic foot' or 'diabetic foot ulcer') and ('drug resistance' or 'risk factors' or 'multiple' or 'mdros') and ('cohort studies' or 'prospective studies').

Literature screening

Inclusion criteria: (I) the study subjects were DFU patients with MDRO infection; (II) the study type was a selection cohort study, cross-sectional study, or case-control study; (III) there was a definite diagnosis of MDRO infection; and (IV) the relevant risk factors were clearly mentioned.

Exclusion criteria: (I) basic research such as animal experiments; (II) literature such as reviews or meta-analyses; (III) repeated publications and studies with the same data; (IV) articles for which data could not be obtained; and (V) outcome measures unrelated to the purpose of this study.

Risk of bias evaluation and the literature quality evaluation

The publication bias of cross-sectional studies was evaluated using the relevant criteria in the American Agency for Health Care Quality and Research (AHRQ), which included a total of 11 items. The answers were yes, no, or uncertain; a score of 0 denoted an answer of 'no' or 'uncertain', whereas a score of 1 indicated 'yes'. A score of 0–3 indicated a low-quality article, 4–7 signified a medium-quality article, and >8 denoted a high-quality article. The Newcastle-Ottawa Scale (NOS) was used to evaluate case-control and cohort studies, with a full score of 9 for 8 items; low-quality articles had a score of <5, while high quality

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articles had a score of ≥5.

Data extraction

After literature retrieval, Endnote X9 software was used for unified processing. Following exclusion of duplicate studies using the focus finder function, two evaluators independently screened the literatures back-to-back. After reading the titles and abstracts to exclude unqualified articles, the original texts and data were obtained, the full texts were read, and the literature inclusion and data extraction were performed according to the inclusion and exclusion criteria. The following data was extracted: (I) basic information of the study: title, author, publication date, contact address; (II) basic characteristics of the study: methods, total sample size, and number of groups; (III) basic characteristics of the participants: gender and age. In case of any dispute over the data extraction and quality evaluation, the two evaluators would negotiate or settle the difference of opinions with a third researcher.

Handling of data loss

If the data could not be obtained directly from an article, but there was an address link for the data, the required data was obtained through the link. If there was no data, the authors were contacted for access, and if it was still not available, the article was excluded.

Statistical analysis

Stata 15.1 software was used for combination and meta-analysis of the risk factors to generate forest plots. The I^2 statistic was used to evaluate the heterogeneity between the included studies, and fixed or random effects models were used to combine the relevant study results. Studies were excluded one by one for sensitivity analysis to judge the source of their heterogeneity. Egger's linear regression test was used to assess publication bias. The odds ratio (OR) was used as the analysis statistic, and each effect size was presented with a 95% confidence interval (CI). P<0.05 indicated that the difference was statistically significant.

Results

Literature search results and screening process

A total of 2,287 literatures were searched through the above databases and search expressions. In total, 1,824 documents were retrieved through Endnote X9; of these, 1,763 articles were excluded after primary screening of the titles and abstracts, and 61 studies were remained. After full-text reading and rescreening, 13 articles were included in this study. *Figure 1* shows the literature search results and screening process.

Basic characteristics of included literatures

According to the literature content and inclusion/exclusion criteria, 13 articles were finally included. The basic information of the studies is shown in *Table 1*.

Meta-analysis results

Among the 15 risk factor reports, eight had statistical significance (P<0.05) and seven did not (P>0.05), and the combined results were as follows:

Negative results

Six articles (9,10,14,17-19) mentioned the problem regarding age, four articles (10,14,18,19) mentioned the problem about gender, five articles (9,10,14,18,19) mentioned the problem regarding the course of diabetes, five articles (10,11,14,18,19) mentioned the problem about the course of ulcer, four articles (8,10,14,17) involved the retina, three articles (10,14,18) involved nephropathy, and four articles (14,17,18,20) involved neuropathy. The combined results of the above risk factors were P>0.05, indicating that there were no statistically significant differences in the analysis results, and the results are shown in *Table 2*.

Hospital records before admission

In total, five articles (8,12,13,16,17) mentioned the relationship between pre-admission records and MDRO infection, which involved 669 patients, including 307 patients with MDRO infection. The meta-analysis combined results showed that (OR =5.18, 95% CI: 1.45–18.51, P=0.011), and the difference was statistically significant (as shown in *Figure 2*).

Antibiotic use results before admission

A total of seven studies (10-13,16,17,20) on the use of antibiotics before admission involved the relationship between antibiotic use before admission and MDRO infection. A total of 947 subjects were included, including

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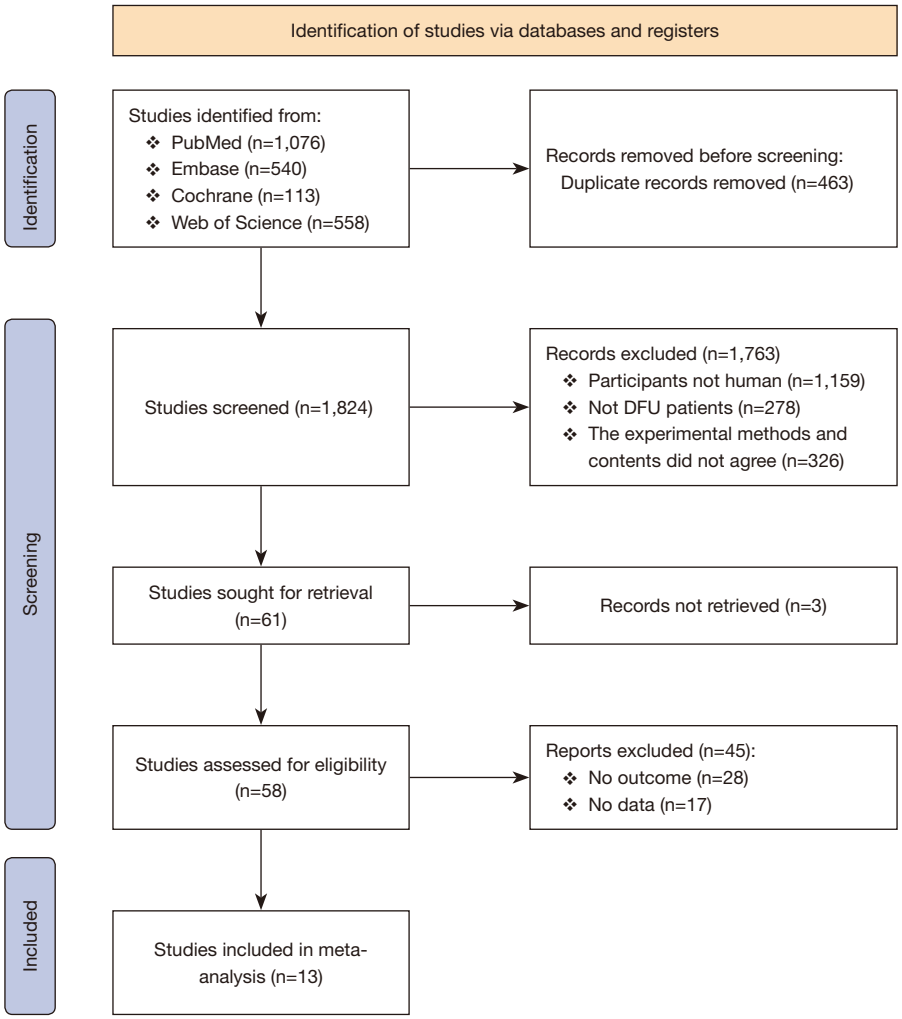

Figure 1 Literature screening flow chart.

429 patients with MDROs infection. The meta-analysis combined results showed that (OR =2.17, 95% CI: 1.24–3.79, P=0.006), and the difference was statistically significant (as shown in *Figure 3*).

Diabetes type

Four articles (10,14,18,19) mentioned the relationship between MDRO infection and diabetes type, with a total of 474 subjects, including 311 patients with MDRO infection. The meta-analysis combined results showed that (OR =2.44, 95% CI: 1.29–4.64, P=0.006), indicating that the difference was statistically significant (as shown in *Figure 4*).

Ulcer type

The relationship between ulcer type and MDROs infection was mentioned in five studies (12-14,16,17), with a total of 561 subjects, including 320 patients with MDRO infection. The meta-analysis combined results showed that (OR =2.17, 95% CI: 1.06–4.41, P=0.033), indicating that the results were statistically different (as shown in *Figure 5*).

Ulcer size

Eight articles (9,10,12,14,17-20) mentioned the relationship between MDRO infection and ulcer size, with a total of 1,027 subjects, including 539 patients with MDRO infection. The meta-analysis combined results showed that (OR =2.56, 95% CI: 1.53–4.28, P<0.001), and the difference was statistically significant (as shown in *Figure 6*).

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Table 1 Basic characteristics of included literatures

Author	Year	Country	Study type	Sample capacity (MDROs/non-MDROs)	The incidence of MDROs infection (%)	Study time	NOS quality score	Risk factors
Richard (8)	2008	France	Cohort study	45/143	24	2003.08–2004.07	8	(III) (XI)
Wang (9)	2010	China	Case-control study	21/97	18	2004.01–2006.12	6	(I) (VI) (IX) (X) (XV)
Zubair (10)	2011	India	Cohort study	46/56	45	2008.12–2010.02	8	(I) (II) (IV) (V) (VI) (VIII) (IX) (X) (XI) (XII) (XIII) (XV)
Feng (11)	2013	China	Case-control study	57/140	29	2009.06–2011.05	7	(IV) (VIII) (X)
Ji (12)	2014	China	Case-control study	64/54	54	2011.01–2012.01	7	(III) (IV) (VII) (IX) (X)
Zhang (13)	2014	China	Cohort study	43/74	37	2009.06–2013.06	8	(III) (IV) (VII) (X)
Gadepalli (14)	2006	India	Cohort study	58/22	73	–	6	(I) (II) (V) (VI) (VII) (VIII) (IX) (X) (XI) (XII) (XIII) (XIV) (XV)
Ertugrul (15)	2017	Japan	Cohort study	71/19	79	2012.01–2013.12	7	(XV)
Kang (16)	2017	India	Cohort study	56/40	58	2008.01–2013.06	6	(III) (IV) (VII) (X)
Kathirvel (17)	2018	India	Cohort study	99/51	66	2011.01–2012.07	7	(I) (III) (IV) (VII) (IX) (X) (XI) (XIII) (XIV) (XV)
Datta (18)	2019	India	Cohort study	56/44	56	2016.01–2016.06	7	(I) (II) (V) (VI) (VIII) (IX) (XII) (XIII) (XIV)
Zubair (19)	2019	India	Cohort study	151/41	79	2008.12–2015.06	7	(I) (II) (V) (VI) (VIII) (IX) (XV)
García Zafra (20)	2020	Spain	Cohort study	64/103	57	2003–2017	7	(IV) (IX) (X) (XIV)

(I) Age; (II) gender; (III) previous hospitalization; (IV) previous duration of antibiotic therapy; (V) type of diabetes; (VI) duration of diabetes; (VII) ulcer type; (VIII) duration of ulcer; (IX) ulcer size; (X) osteomyelitis; (XI) retinopathy; (XII) nephropathy; (XIII) neuropathy; (XIV) vascular lesion; (XV) surgery. MDROs, multidrug resistant organisms; NOS, Newcastle-Ottawa Scale.

Table 2 Summary of negative results

Risk factors	Number of studies	Heterogeneity test I^2 (%)	Effect Model	OR (95% CI)	P value
Age	6	0	F	0.98 (0.95–1.01)	0.27
Sex	4	0	F	0.79 (0.45–1.40)	0.42
Diabetes course	5	45	F	0.97 (0.91–1.03)	0.33
Canker course	5	0	F	0.91 (0.66–1.25)	0.55
Retinopathy	4	47	F	1.43 (0.80–2.53)	0.23
Nephrosis	3	13	F	1.92 (0.95–3.88)	0.07
Neuropathy	4	55	R	1.12 (0.47–2.70)	0.80

F, fixed effect model; R, random effect model; OR, odds ratio; CI, confidence interval.

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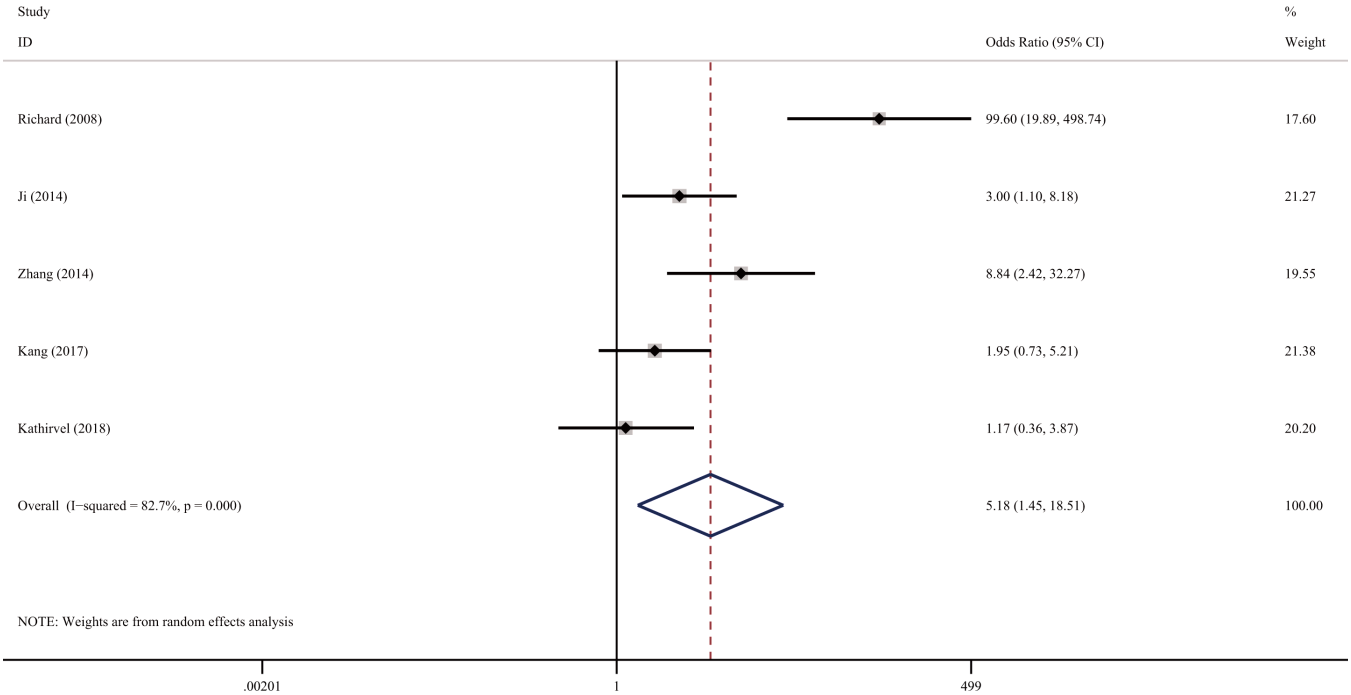

Figure 2 Forest plot of the results of hospitalization records before admission. CI, confidence interval.

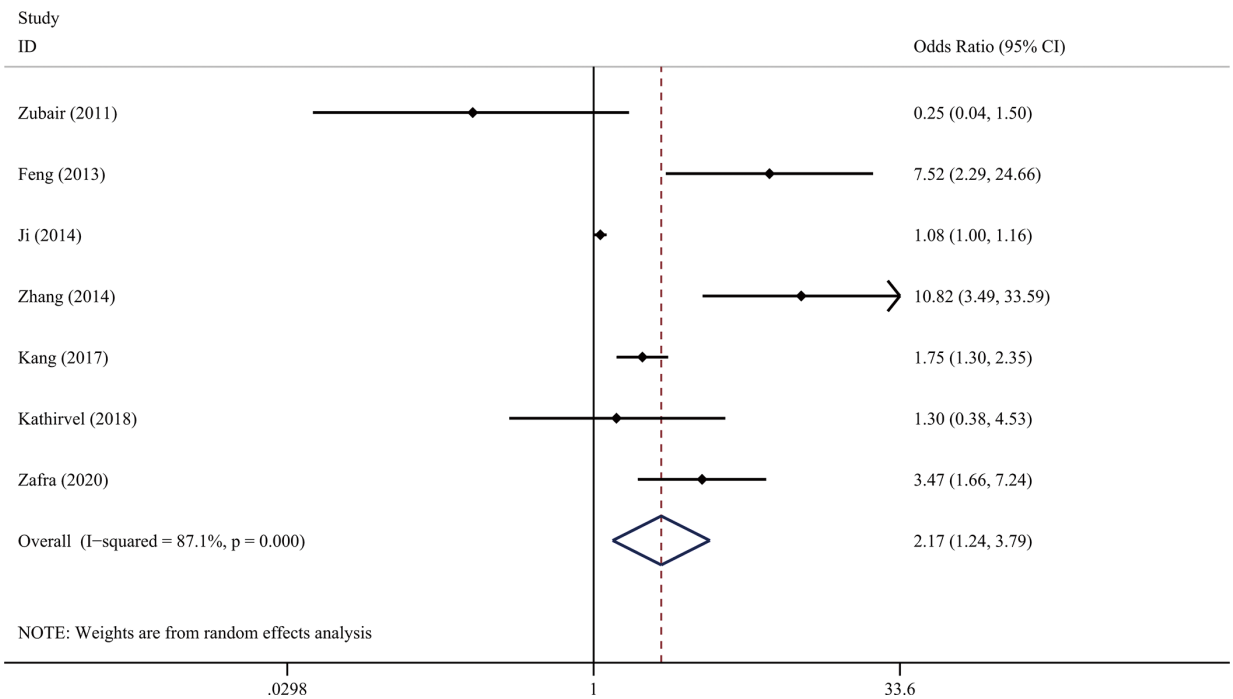

Figure 3 Pooled forest plot of antibiotic use results before admission. CI, confidence interval.

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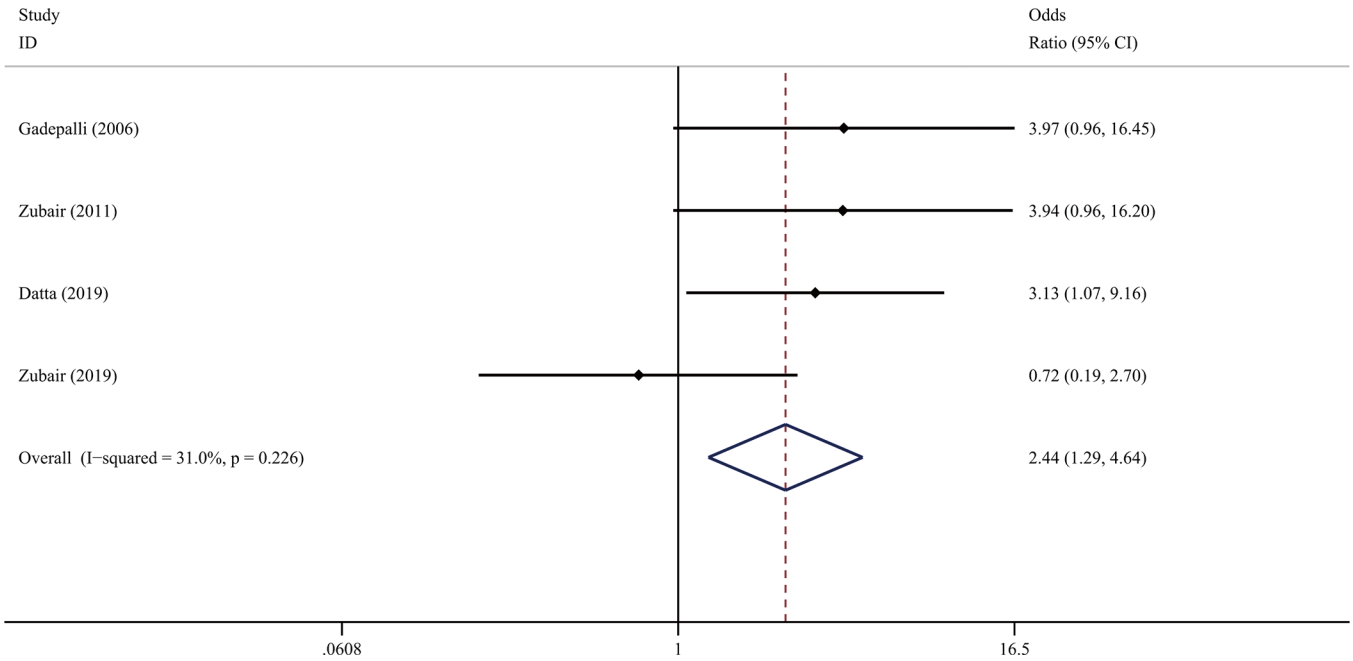

Figure 4 Forest plot of combined results of diabetes types. CI, confidence interval.

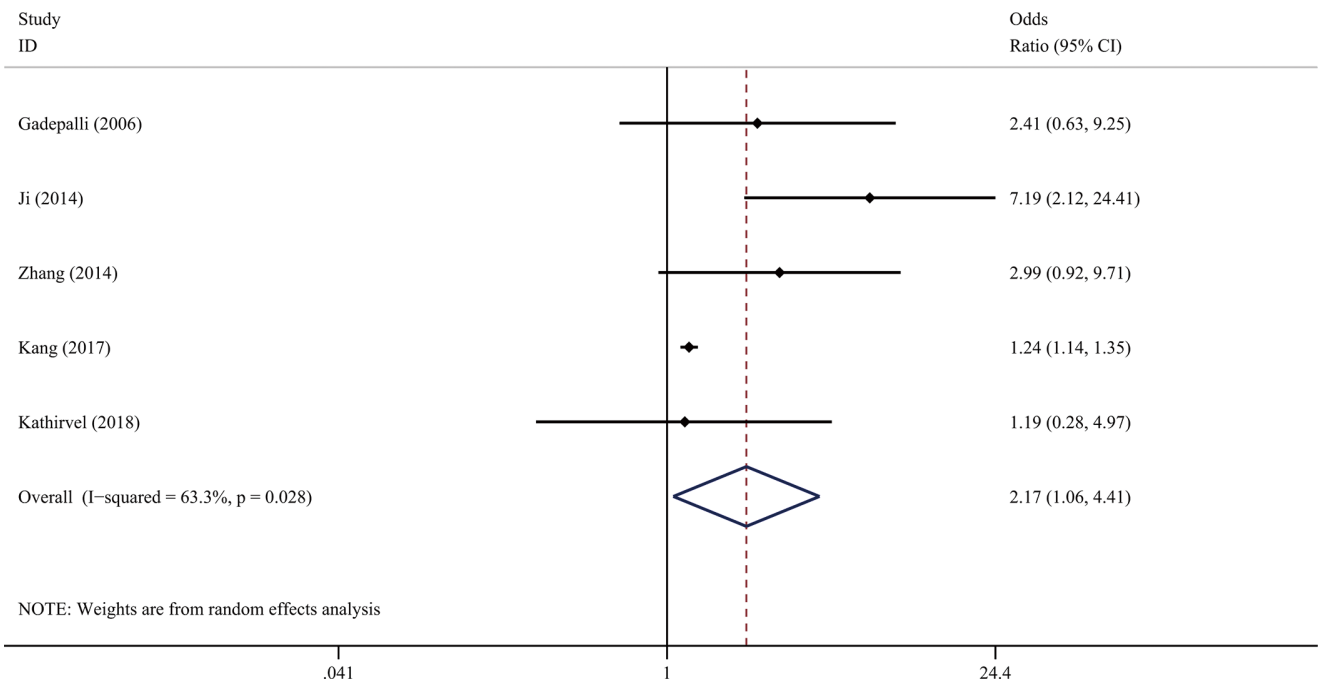

Figure 5 Pooled forest plot of ulcer type results. CI, confidence interval.

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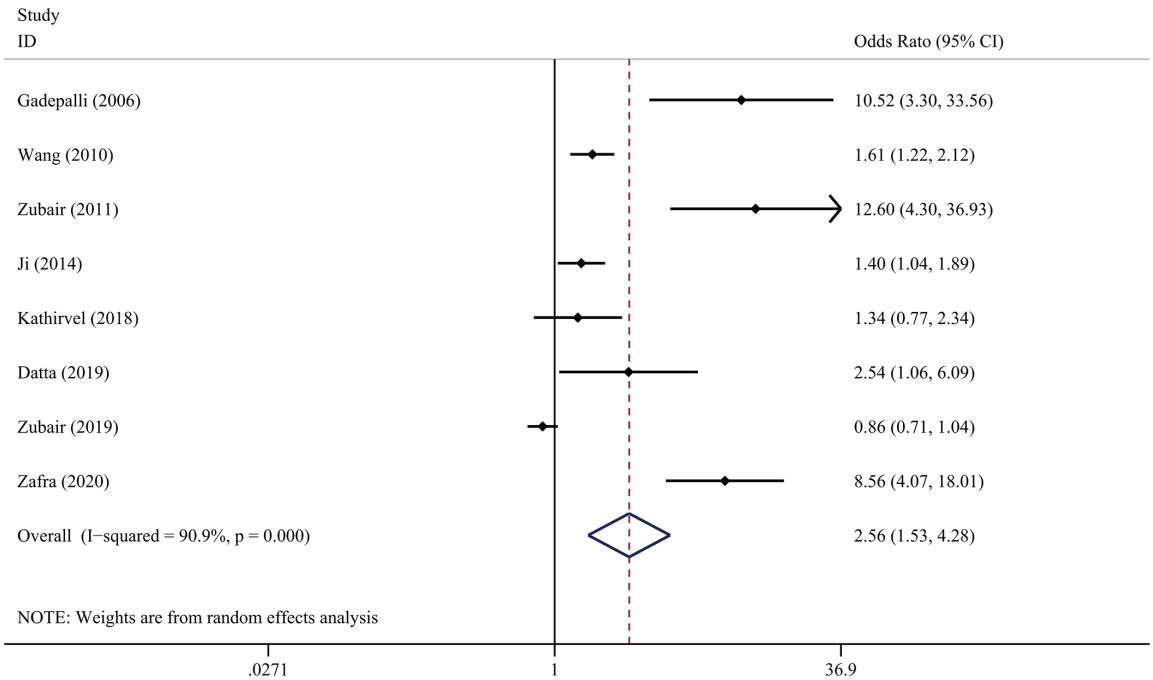

Figure 6 Pooled forest plot of ulcer size results. CI, confidence interval.

Osteomyelitis

Nine articles (9-14,16,17,20) mentioned the relationship between MDRO infection and osteomyelitis, with a total of 1,145 subjects, including 508 patients with MDRO infection. The meta-analysis combined results showed that (OR =3.50, 95% CI: 2.37–5.16, P<0.001), and the difference was statistically significant (as shown in *Figure 7*).

Vascular lesions

Four articles (14,17,18,20) mentioned the relationship between MDRO infection and vascular disease, with 497 subjects, including 277 patients with MDROs. The meta-analysis combined results showed that (OR =2.37, 95% CI: 1.41–3.99, P=0.001), indicating that the results were statistically different (as shown in *Figure 8*).

Surgical treatment

Six studies (9,10,14,15,17,19) mentioned the relationship between MDRO infection and surgical treatment, with 732 subjects, including 446 patients with MDROs. The meta-analysis combined results showed that (OR =4.80, 95% CI: 2.95–7.83, P<0.001), and the difference was statistically significant (as shown in *Figure 9*).

Risk of bias of infection risk factors of MDROs

The results of risk factor bias risk analysis are shown in *Table 3*.

Sensitivity analysis

Sensitivity analysis was performed for the records before admission. The heterogeneity results were (I^2=46%, OR =2.61, 95% CI: 1.51–4.51, P=0.001) after removing the article by Richard *et al.* (8), and the difference was statistically significant (as shown in *Figure 10*).

Subgroup analysis

Sensitivity analysis of the ulcer types revealed that heterogeneity might have been derived from the study by Kang *et al.* (16), which was excluded and analyzed according to neuroischemic ulcer (I^2=2.6%) and necrotic ulcer (I^2=0%). The combined results suggested no heterogeneity (as shown in *Figure 11*).

Discussion

According to the quality evaluation score, it can be seen that the overall quality of the included studies in this meta-

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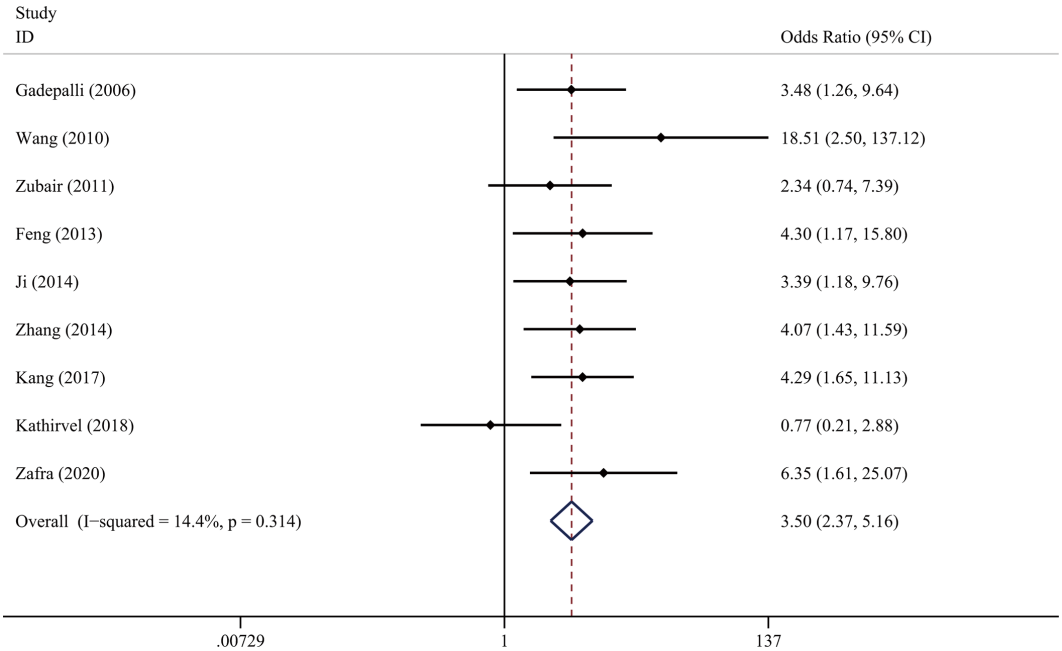

Figure 7 Combined forest plot of osteomyelitis results. CI, confidence interval.

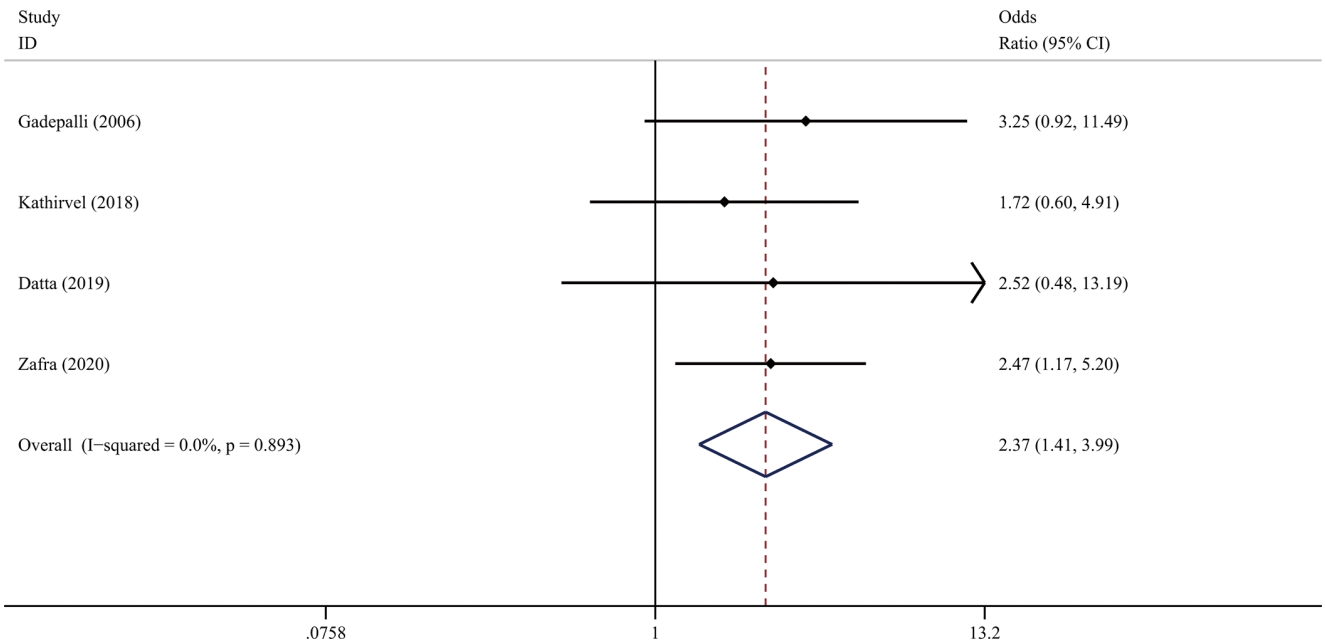

Figure 8 Forest plot of pooled vascular lesion results. CI, confidence interval.

analysis was high, and thus, the combined results have strong persuasiveness. We showed that eight indicators, including hospitalization records before admission, were risk factors for MDRO infection in DFU patients.

Hospital records before admission, use of antibiotics before admission, and surgical treatment are risk factors of MDRO infection. For patients with inpatient records prior to admission, most are due to unstable illness, should

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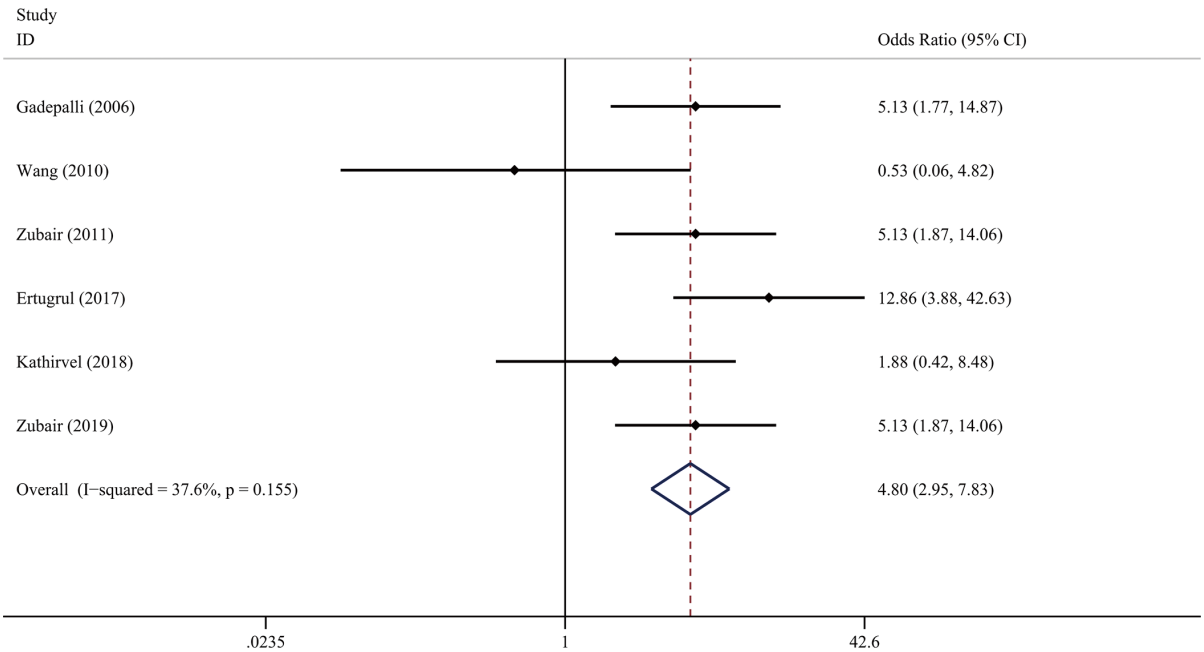

Figure 9 Forest plot of combined results of surgical treatment. CI, confidence interval.

Table 3 Publication bias of risk factors for MDRO infection

Hazards	Amount	Egger's test P value
Previous hospitalization	4	0.640
Previous duration of antibiotic therapy	7	0.096
Type of diabetes	4	0.966
Ulcer type	4	0.122
Ulcer size	8	0.004*
Osteomyelitis	9	0.470
Vascular lesion	4	0.857
Surgery	6	0.091

*, P<0.05. MDRO, multidrug resistant organism.

be alert to multiple drug-resistant bacteria infections when handling. MDRO infection has an important relationship with nosocomial infection (21), while nosocomial infection is largely due to the abuse of antibiotics (22,23). Antibiotic abuse can also lead to an increased rate of drug resistance, so clinicians will administer higher levels of antibiotics to treat infection, and over time creating a vicious cycle. Surgery is a common treatment for DFU at present; however, surgery also presents a risk of infection, and antibiotics are still needed for treatment after infection. Excessive or improper use of antibiotics may lead to MDRO infection (24). Therefore, when antibiotics are required during treatment, it is recommended to that they are used after performing susceptibility testing rather than treating empirically alone (25,26).

The category of diabetes, as well as the type and size of ulcers are also risk factors for MDRO infection. About half of all diabetic most ulcers belong to neuroischemic ulcers (27,28), which can destroy the microcirculation, hamper the nutrient absorption of local tissues, delay wound healing, and lead to the occurrence of MDRO infections. Also, when the ulcer area is ≥4 cm^2, the risk of MDRO infections is also increased. Therefore, healthcare workers should be more cautious in the face of neuroischemic ulcers and large areas of ulcers to avoid the occurrence of MDRO infection.

Moreover, the presence of vascular lesions and osteomyelitis can also increase the risk of MDRO infection. This study found that the risk of MDRO infection could be increased by about four times after suffering from osteomyelitis. According to the relevant research, pathogens can migrate to the bone tissue through the blood circulation, invade the lacunar reticular formation of bone cells, avoid the effect of mechanical debridement and antibiotics, form cysts in the skin, hinder the entry of immune cells, and induce the occurrence of MDRO infection (29,30). Therefore, when patients with DFU develop osteomyelitis, antibiotics should be used with

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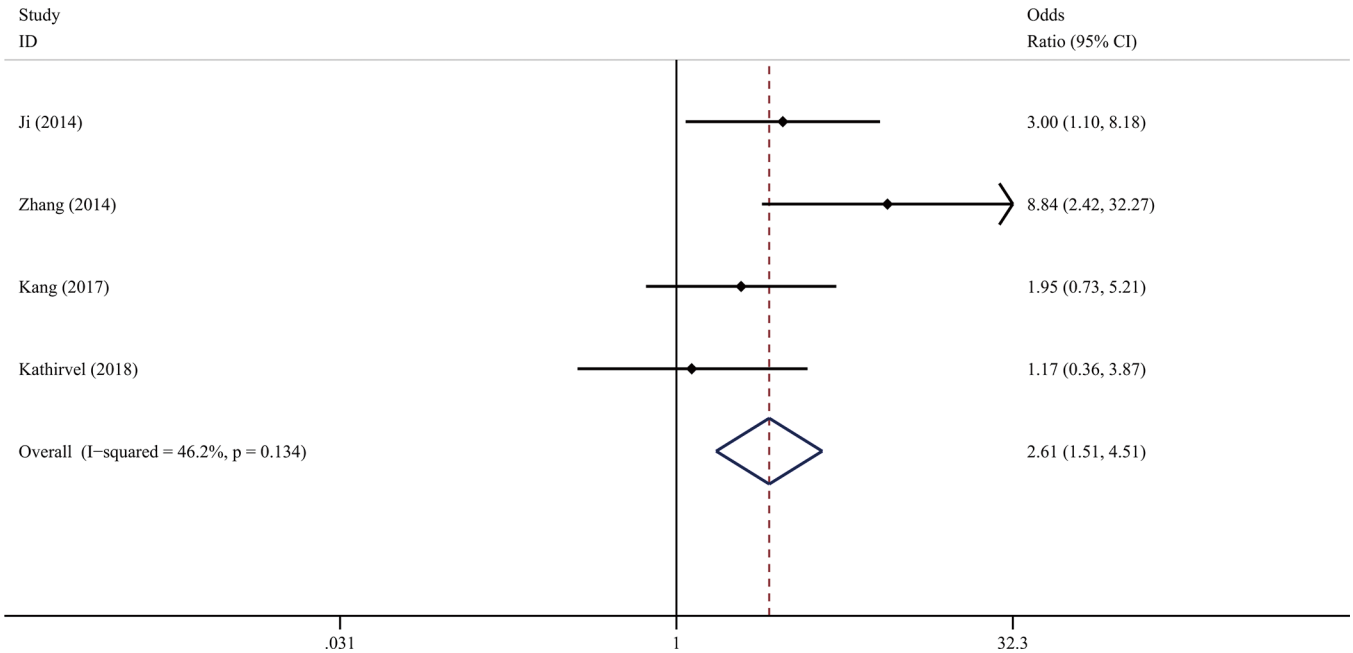

Figure 10 Forest plot of the combined results recorded before admission (sensitivity analysis). CI, confidence interval.

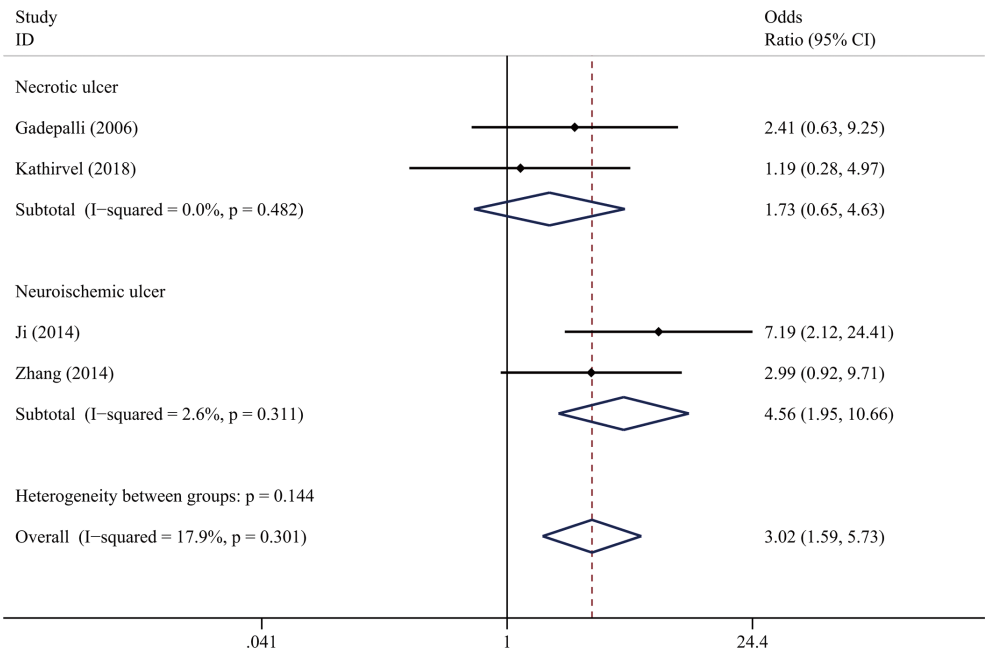

Figure 11 Forest plot of the pooled results of ulcer types (subgroup analysis). CI, confidence interval.

caution to prevent MDRO infection.

This study has the following limitations. Firstly, this study included case-control and cohort studies. Secondly, it was not possible to determine whether patients had been infected with MDROs before admission. Thirdly, the number of some risk factors was small. Future studies with higher quality and larger sample sizes need to be included for further confirmation of our findings.

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Conclusions

In summary, the risk factors for MDRO infection in DFU patients include hospital records before admission, antibiotic use before admission, type of diabetes, type of ulcer, size of ulcer, osteomyelitis, vascular lesions, and surgical treatment. When the above risk factors are prevalent in hospitalized patients with DFUs, medical staff should deal with them cautiously, and develop more effective and safer treatments and preventive measures to reduce the risk of MDRO infection in these patients.

Acknowledgments

Funding: This work was supported by the 2018 National Standardized Metabolic Disease Management Center (MMC) Special Research Fund.

Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3406

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3406). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: A. Kassem)

Cite this article as: Xia W, He W, Luo T, Tang N. Risk factors for multidrug-resistant bacterial infections in patients with diabetic foot ulcers: a systematic review and meta-analysis. Ann Palliat Med 2021;10(12):12618-12630. doi: 10.21037/apm-21-3406

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