Sex difference for the risk of amputation in diabetic patients: A systematic review and meta-analysis

Lei Fan¹,², Xue-Jian Wu¹*

¹ Department of Orthopedic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, ² Department of Orthopedic Surgery, People’s Hospital of Zhengzhou University, Zhengzhou, China

* wuxuejianedu@163.com

Abstract

The risk of amputation is a sequelae of diabetic foot ulceration, which are significantly increased in diabetic patients and caused huge morbidity and mortality. However, whether the risk amputation in diabetic patients are differing in male and female remains inconclusive. We therefore conducted a systematic review and meta-analysis to assess the sex difference for the risk of amputation in diabetic patients. We systematically searched PubMed, Embase, and the Cochrane library to identify eligible study from their inception up to November 2020. The diagnostic value of male patients on subsequent amputation risk were assessed by using sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUC). Twenty-two studies recruited a total of 33,686,171 diabetic patients were selected for quantitative analysis. The risk of amputation in male diabetic patients was greater than female diabetic patients (DOR: 1.38; 95%CI: 1.13–1.70; \( P < 0.001 \)). The sensitivity and specificity for male diabetic patients on the risk of amputation were 0.72 (95%CI: 0.72–0.73), and 0.51 (95%CI: 0.51–0.51), respectively. Moreover, the PLR and NLR of male diabetic patients for predicting amputation were 1.13 (95%CI: 1.05–1.22), and 0.82 (0.72–0.94), respectively. Furthermore, the AUC for male diabetic patients on amputation risk was 0.56 (95%CI: 0.48–0.63). This study found male diabetic patients was associated with an increased risk of amputation than female diabetic patients, and the predictive value of sex difference on amputation risk in diabetic patients was mild.

Introduction

Diabetic foot is a common complication in diabetic patients, which consisted the lesions in deep tissues in the lower limb and caused neurological disorders and peripheral vascular disease [1]. The prevalence of diabetic foot ulcers ranged from 19–34 percent in diabetic patients, and the annual incidence rates for diabetic foot ulcers in general diabetic patients nearly 6.3 percent [2, 3]. Study have already illustrated the complications could induce serious public health problem, and caused most common cause for hospital ingress, amputation, and mortality in diabetic patients [4]. Moreover, there was nearly USD 727 billion could spent for diabetic
patients aged 20–79 years based on data from the International Diabetes Federation [5]. Nearly two-thirds of diabetic foot ulcers could heal, and up to 28% of patients should treated with lower extremity amputation [6–8].

Major amputation often causes substantial functional disability, and associated with significant morbidity and mortality across world. Moreover, patients after major amputation always needs various type of prosthesis to walk by itself [9]. Several systematic reviews and meta-analyses have already conducted to identify potentially risk factors for amputation in patients resented diabetic foot ulcers [10–12]. However, whether the risk of major amputation in diabetic patients are differing in male and female remains inconclusive, which needed further clarifying to determine the diabetic population at high risk for further amputation. Therefore, the current systematic review and meta-analysis was conducted to assess the sex difference for the risk of amputation in diabetic patients.

**Materials and methods**

**Data sources, search strategy, and selection criteria**

This study was conducting and reporting following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [13]. Study reported the amputation occurred according to male and female diabetic patients was eligible in this study, and published language or status were not restricted. The electronic searches were performed in the databases of PubMed, EmBase, and the Cochrane library throughout November 2020, and the following terms were used as text word or Medical Subject Heading: “diabetic foot” and “amputation” (S1 File). Moreover, the reference lists of relevant review and original article were also reviewed by manually to identify any new study met the inclusion criteria.

Two reviewers independently performed literature search and study selection following a standardized process, and inconsistencies were settled by discussion after reviewing the original article. The details of inclusion criteria are listed as follows: (1) Patients: all of patients were diagnosed with diabetes, irrespective diabetes type; (2) Exposure: male and female; (3) Outcome: the incidence of major amputation; and (4) Study design: we did not restricted the study design, including prospective and retrospective studies.

**Data collection and quality assessment**

Two reviewers independently abstracted the following items: first authors’ name, publication year, country, study design, number of amputations, sample size, number of male and female, age, diabetes type, diabetes duration, HbA1c, setting, follow-up duration, and amputation cases in male and female groups. Then the methodological quality of individual study was independently assessed by 2 reviewers using the Newcastle-Ottawa Scale (NOS), which on the basis of selection (4 items), comparability (1 item), and outcome (3 items) [14]. Any disagreement between 2 reviewers for data collection and quality assessment was settled by an additional author referring to the full-text of included studies.

**Statistical analysis**

The diagnostic odds ratio (DOR) and 95% confidence intervals (CIs) was firstly applied to assess the sex difference for the risk of amputation in diabetic patients, and the pooled analysis was calculated using the random-effects model [15, 16]. After this, the pooled predictive values (sensitivity, specificity, positive likelihood ratio [PLR], negative likelihood ratio [NLR], and the area under the receiver operating characteristic curve [AUC]) were assessed on the basis of the prevalence of amputation in male and female diabetic patients [17]. After this, the heterogeneity
across studies were assessed by using $I^2$ and Q statistic, and the significant heterogeneity was defined as $I^2 > 50.0\%$ or $P < 0.10$ [18, 19]. Subgroup analyses for diagnostic parameters were also conducted based on study design, age, diabetes type, and HbA1c level. The funnel plot and Deeks’ asymmetry test was applied to assess any potentially publication bias [20]. The $P$ value for all pooled results are 2-sided, and the inspection level was 0.05. All of analyses in our study was conducted by using software STATA (version 10.0; Stata Corporation, TX, USA).

Results and discussion

Literature search

A total of 7,687 records were identified by initial electronic searches in PubMed, EmBase, and the Cochrane library. After this, the 4,813 articles were retained after duplicate titles were removed. Then 4,732 studies were excluded because of these studies reported irrelevant titles. The remaining 81 studies were retrieved for full-text evaluations, and 59 studies were excluded because of: Intervention studies ($n = 27$), no sufficient data ($n = 21$), and studies included general population ($n = 11$). Therefore, the remaining 22 studies were selected for final meta-analysis [21–42], and the details regarding study selection are presented in Fig 1.

Study characteristics

The characteristics of included studies and patients are presented in Table 1. Of included studies, 8 studies were designed as prospective cohort, while the remaining 14 studies were designed as retrospective design. The number of amputation events for included studies ranged from 10 to 14,627, and the sample size ranged from 37 to 27,562,858. Three studies were conducted in Eastern Asia, 9 studies were conducted in Central Asia, 4 studies were conducted in America, 4 studies were conducted in Europe or Australia, and the remaining 2 studies were conducted in Africa. The quality assessment for individual study was applied the NOS, 7 studies with 9 stars, 7 studies with 8 stars, and the remaining 8 studies with 7 stars (S1 Table).

DOR

After pooling all included studies, we noted male diabetic patients was associated with an increased risk of amputation as compared with female diabetic patients (DOR: 1.38; 95%CI: 1.13–1.70; $P < 0.001$; Fig 2), and significant heterogeneity was detected across included studies ($I^2 = 88.8\%; P < 0.001$). Subgroup analysis found the significant sex difference was detected when study designed as retrospective cohort, irrespective age of patients, irrespective diabetes type, and the level of HbA1c was not reported (Table 2).

Diagnostic parameters

After pooling all studies, we noted the pooled sensitivity and specificity for male patients on amputation risk were 0.72 (95%CI: 0.72–0.73; Fig 3), and 0.51 (95%CI: 0.51–0.51; Fig 4), respectively. The sensitivity was associated with statistically significant in all subgroups, while the specificity was associated with statistically significant if study designed as retrospective cohort, age of patients > 60.0 years, type 2 diabetes, and the level of HbA1c was not reported (Table 2). Moreover, we noted the pooled PLR and NLR for male patients on amputation risk were 1.13 (95%CI: 1.05–1.22; Fig 5), and 0.82 (0.72–0.94; Fig 6), respectively. Subgroup analyses found the pooled PLR were associated with statistically significant when pooled study designed as retrospective cohort, irrespective age of patients, or diabetes type, and the level of HbA1c was not reported (Table 2). Similarly, the pooled NLR with statistically significant when pooled study designed as retrospective cohort, age of patients > 60.0 years, type 2
diabetes, or the level of HbA1c was not reported (Table 2). Finally, the AUC for male patients on subsequent amputation was 0.56 (95%CI: 0.48–0.63; Fig 7), which was not associated with statistically significant. The results of subgroups indicated significant predictive value when pooled study designed as retrospective cohort, age of patients > 60.0 years, or the level of HbA1c was not reported (Table 2; Fig 8).

**Publication bias**

The publication bias could not rule out by review funnel plot, and significant publication bias was seen by Deeks’ test ($P<0.01$).

**Significance and impacts**

Numerous studies have already conducted to identify any potential risk factors for amputation risk in diabetic patients [10–12]. However, whether the sex difference was existed for
amputation risk in diabetic patients remains controversial. The current quantitative analysis involved 33,686,171 diabetic patients from 22 studies and found male diabetic patients was associated with an increased risk of amputation than female diabetic patients, while the predictive value of sex difference was mild. Moreover, subgroup analysis found the significant sex

Table 1. The baseline characteristics of included studies and patients.

| Study       | Country   | Study design | No. of amputations | Sample size | Male/ female | Age (years) | DM type | DM duration | HbA1c (%) | Setting                        | Follow-up |
|-------------|-----------|--------------|--------------------|-------------|--------------|-------------|---------|-------------|----------|--------------------------------|-----------|
| Armstrong 1997 [21] | USA       | Retrospective | 31                  | 77          | 51/26        | 52.5        | NA      | NA          | NA       | University Hospital             | NA        |
| Lin 2010 [22] | China     | Retrospective | 24                  | 90          | 47/43        | 69.7        | T2DM    | 15.2 years  | 9.32     | NA                             | NA        |
| Akinci 2011 [23] | Turkey    | Prospective  | 70                  | 165         | 109/56       | 60.2        | T2DM    | 15.0 years  | 9.50     | NA                             | 6.0 months|
| Aziz 2011 [24] | Singapore | Prospective  | 55                  | 100         | 51/49        | 59.8        | T2DM    | > 5.0 years | NA       | University Hospital             | 2.0 years |
| Tunccan 2012 [25] | Turkey    | Retrospective | 12                  | 71          | 46/25        | 60.6        | NA      | NA          | NA       | Infectious Diseases Clinic       | NA        |
| Ulcay 2014 [26] | Turkey    | Retrospective | 22                  | 37          | 27/10        | 65.0        | NA      | 17.2 years  | 8.40     | NA                             | 1.0 year  |
| Saltoglu 2015 [27] | Turkey    | Retrospective | 126                 | 455         | 310/145      | 61.3        | T2DM    | (99.3%)     | 15.4     | NA                             | 3.0–6.0 months |
| Pickwell 2015 [28] | Netherlands | Prospective  | 159                 | 575         | 359/216      | 65.6        | NA      | NA          | 9.50     | Multicentre                     | 1.0 year  |
| Tabur 2015 [29] | Turkey    | Retrospective | 10                  | 55          | 27/28        | 60.0        | T2DM    | 11.1 years  | 10.40    | Endocrinology Department         | NA        |
| Quilici 2016 [30] | Brazil    | Prospective  | 61                  | 100         | 68/32        | 62.0        | T2DM    | (99.0%)     | NA       | Vascular Surgery Clinic          | NA        |
| Uysal 2017 [31] | Turkey    | Prospective  | 126                 | 379         | 256/123      | 62.4        | T2DM    | (95.8%)     | 15.0     | Diabetic Foot Council            | NA        |
| Cervantes-Garcia 2017 [32] | Mexico  | Prospective  | 45                  | 100         | 60/40        | 51.2        | T2DM    | 10.0 years  | NA       | Emergency Department             | NA        |
| Ferreira 2018 [33] | Portugal  | Retrospective | 48                  | 479         | 294/185      | 68.0        | T2DM    | (90.8%)     | 15.0     | Diabetic Foot Clinic             | 1.0 year  |
| Musa 2018 [34] | Saudi Arabia | Prospective  | 33                  | 82          | 55/27        | 60.0        | NA      | 8.5 years   | 4.80     | King Abdul Aziz Armed Forces Hospital | NA        |
| Khalfallah 2018 [35] | Tunisia  | Retrospective | 95                  | 430         | 319/111      | 60.5        | NA      | NA          | NA       | Charles Nicolle hospital         | NA        |
| Peled 2019 [36] | Israel    | Retrospective | 229                 | 418         | 311/107      | 64.8        | T2DM    | (92.6%)     | NA       | Academic tertiary hospital        | NA        |
| Guo 2019 [37]   | China     | Retrospective | 59                  | 470         | 294/176      | 63.3        | NA      | 9.2 years   | 8.26     | Third Xiangya Hospital           | NA        |
| Jeyaraman 2019 [38] | Australia | Retrospective | 263                 | 513         | 322/191      | 56.1        | T2DM    | 7.0 years   | NA       | Multidisciplinary Foot Clinic    | 5.8 years |
| Ugwu 2019 [39]  | Nigeria   | Prospective  | 119                 | 336         | 185/151      | 55.9        | T2DM    | (96.1%)     | 8.5 years | Multicentre                     | 1.0 year  |
| Sayiner 2019 [40] | Turkey    | Retrospective | 143                 | 400         | 256/144      | > 18.0      | T2DM    | NA          | NA       | Endocrinology and Metabolism of the Faculty of Medicine of Gaziantep University | NA        |
| Aziz 2020 [41]  | Austria   | Retrospective | 2,165               | 27,562,858  | 13,358044/14,204,814 | 73.0 | T2DM | (83.3%) | NA | Austrian Health Insurance database | NA |
| Gandhi 2020 [42] | USA       | Retrospective | 14,627              | 6,117,981   | 3,180,967/2,937,014 | 56.5 | T2DM | NA | Truven Health MarketScan database | NA |

https://doi.org/10.1371/journal.pone.0243797.t001
difference mainly detected in the groups of study designed as retrospective cohort, irrespective of age of patients, or diabetes type, and the level of HbA1c was not reported.

Several systematic review and meta-analyses have already conducted to identify potentially risk factors for amputation in patients with diabetic foot ulcer. Shin et al contained 10 studies and found hypertension, ischemic heart disease, cerebrovascular disease, and peripheral vascular disease were associated with an increased risk of major amputation [10]. A meta-analysis conducted by Wang et al found ulcer reaching bone, gangrene, hindfoot position, decreased ankle-brachial index, infection, and peripheral arterial disease could induce excess risk of major amputation in diabetic foot patients [11]. Sen et al conducted a meta-analysis of 25 studies and given a comprehensive risk profiles for lower extremity amputation for patients with diabetic foot infections [12]. However, the stratified analyses according to study and patients’ characteristics were not illustrated. Moreover, the sex difference for the risk of amputation in

Fig 2. The summary DOR of male on subsequent amputation in diabetic patients.

https://doi.org/10.1371/journal.pone.0243797.g002
Table 2. Subgroup analyses.

| Parameters | Study design | Factors | Subgroup | Effect estimate and 95%CI | $I^2$ (%) | $P$ value for Q statistic |
|------------|--------------|---------|----------|---------------------------|----------|-------------------------|
| Sensitivity | Study design | Prospective | 0.66 (0.62–0.70) | 58.1 | 0.019 |
|             |             | Retrospective | 0.73 (0.72–0.73) | 90.0 | < 0.001 |
| Age (years) |             | ≥ 60.0 | 0.65 (0.64–0.67) | 59.2 | 0.002 |
|             |             | < 60.0 | 0.74 (0.73–0.74) | 84.2 | < 0.001 |
| DM type     |             | T2DM | 0.72 (0.72–0.73) | 90.9 | < 0.001 |
|             | Not reported | 0.71 (0.66–0.75) | 0.0 | 0.537 |
| HbA1c (%)   |             | ≥ 9.00 | 0.60 (0.53–0.67) | 21.2 | 0.283 |
|             | Not reported | 0.73 (0.72–0.73) | 91.0 | < 0.001 |
| Specificity | Study design | Prospective | 0.40 (0.37–0.43) | 61.8 | 0.011 |
|             |             | Retrospective | 0.51 (0.51–0.51) | 99.9 | < 0.001 |
| Age (years) |             | ≥ 60.0 | 0.52 (0.52–0.52) | 95.8 | < 0.001 |
|             |             | < 60.0 | 0.48 (0.48–0.48) | 64.5 | 0.010 |
| DM type     |             | T2DM | 0.51 (0.51–0.51) | 99.9 | < 0.001 |
|             | Not reported | 0.36 (0.33–0.38) | 71.3 | 0.002 |
| HbA1c (%)   |             | ≥ 9.00 | 0.43 (0.39–0.48) | 63.9 | 0.040 |
|             | Not reported | 0.51 (0.51–0.51) | 100.0 | < 0.001 |
| PLR         | Study design | Prospective | 1.09 (0.97–1.23) | 51.0 | 0.046 |
|             |             | Retrospective | 1.15 (1.06–1.25) | 91.2 | < 0.001 |
| Age (years) |             | ≥ 60.0 | 1.10 (1.01–1.20) | 77.1 | < 0.001 |
|             |             | < 60.0 | 1.19 (1.02–1.39) | 84.6 | < 0.001 |
| DM type     |             | T2DM | 1.15 (1.06–1.25) | 91.2 | < 0.001 |
|             | Not reported | 1.09 (1.00–1.19) | 13.8 | 0.324 |
| HbA1c (%)   |             | ≥ 9.00 | 1.10 (0.87–1.38) | 58.2 | 0.066 |
|             | Not reported | 1.18 (1.09–1.28) | 91.2 | < 0.001 |
| NLR         | Study design | Prospective | 0.88 (0.72–1.07) | 50.7 | 0.048 |
|             |             | Retrospective | 0.79 (0.67–0.93) | 91.0 | < 0.001 |
| Age (years) |             | ≥ 60.0 | 0.85 (0.75–0.96) | 41.9 | 0.044 |
|             |             | < 60.0 | 0.76 (0.57–1.01) | 89.2 | < 0.001 |
| DM type     |             | T2DM | 0.81 (0.69–0.95) | 92.1 | < 0.001 |
|             | Not reported | 0.85 (0.72–1.00) | 0.0 | 0.540 |
| HbA1c (%)   |             | ≥ 9.00 | 1.10 (0.87–1.38) | 58.2 | 0.066 |
|             | Not reported | 0.99 (0.82–1.20) | 0.0 | 0.699 |
| DOR         | Study design | Prospective | 1.26 (0.91–1.73) | 52.1 | 0.041 |
|             |             | Retrospective | 1.47 (1.16–1.86) | 90.2 | < 0.001 |
| Age (years) |             | ≥ 60.0 | 1.29 (1.04–1.60) | 56.8 | 0.004 |
|             |             | < 60.0 | 1.57 (1.02–2.41) | 86.9 | < 0.001 |
| DM type     |             | T2DM | 1.43 (1.14–1.81) | 91.2 | < 0.001 |
|             | Not reported | 1.30 (1.01–1.66) | 0.0 | 0.491 |
| HbA1c (%)   |             | ≥ 9.00 | 0.97 (0.79–1.20) | 3.9 | 0.374 |
|             | Not reported | 1.59 (1.27–2.00) | 90.4 | < 0.001 |

(Continued)
| Parameters | Factors       | Subgroup       | Effect estimate and 95%CI | I² (%) | P value for Q statistic |
|------------|---------------|----------------|---------------------------|--------|------------------------|
| AUC        | Study design  | Prospective    | 0.49 (0.36–0.61)          | -      | -                      |
|            |               | Retrospective  | 0.61 (0.52–0.69)          | -      | -                      |
|            | Age (years)   | ≥ 60.0         | 0.62 (0.60–0.64)          | -      | -                      |
|            |               | < 60.0         | 0.46 (0.37–0.54)          | -      | -                      |
|            | DM type       | T2DM           | 0.55 (0.46–0.64)          | -      | -                      |
|            |               | Not reported   | 0.55 (0.41–0.70)          | -      | -                      |
|            | HbA1c (%)     | ≥ 9.00         | 0.50 (0.39–0.62)          | -      | -                      |
|            |               | < 9.00         | 0.56 (0.33–0.78)          | -      | -                      |
|            |               | Not reported   | 0.59 (0.51–0.68)          | -      | -                      |

Fig 3. The summary sensitivity for male on subsequent amputation in diabetic patients.

https://doi.org/10.1371/journal.pone.0243797.g003

Sensitivity (95% CI)

- Armstrong 1997: 0.68 (0.49 - 0.83)
- Lin 2010: 0.54 (0.33 - 0.74)
- Akinci 2011: 0.66 (0.53 - 0.77)
- Aziz 2011: 0.43 (0.24 - 0.63)
- Tuncan 2012: 0.83 (0.52 - 0.98)
- Ulcay 2014: 0.68 (0.45 - 0.86)
- Saltoglu 2015: 0.76 (0.68 - 0.83)
- Pickwell 2015: 0.70 (0.63 - 0.77)
- Tabur 2015: 0.80 (0.44 - 0.97)
- Quilici 2016: 0.70 (0.57 - 0.81)
- Uysal 2017: 0.66 (0.57 - 0.74)
- Cervantes-Garcia 2017: 0.78 (0.63 - 0.89)
- Ferreira 2018: 0.67 (0.52 - 0.80)
- Musa 2018: 0.73 (0.54 - 0.87)
- Khalfallah 2018: 0.76 (0.66 - 0.84)
- Peled 2019: 0.74 (0.68 - 0.80)
- Guo 2019: 0.61 (0.47 - 0.73)
- Jeyaraman 2019: 0.67 (0.60 - 0.72)
- Ugwu 2019: 0.56 (0.47 - 0.65)
- Sayiner 2019: 0.71 (0.62 - 0.78)
- Aziz 2020: 0.63 (0.61 - 0.65)
- Gandhi 2020: 0.74 (0.73 - 0.75)

Pooled Sensitivity = 0.72 (0.72 to 0.73)
Chi-square = 160.15; df = 21 (p = 0.0000)
Inconsistency (I-square) = 86.9 %
diabetic patients remains inconclusive. We therefore conducted a systematic review and meta-analysis to assess potential sex difference for the risk of amputation in diabetic patients.

The summary result of this study found male versus female diabetic patients was associated with an increased risk of amputation. However, mostly included studies did not found significant difference between male and female for the risk of amputation, while several studies reported similar results. A study conducted by Saltoglu et al found 76% of patients with amputation were male, while only 65% of patients without amputation were male [27]. Pickwell et al found male patients was associated with an increased risk of amputation excluding lesser toes as compared with female [28]. Tabur et al found the prevalence of male patients in lower extremity amputation group was 80%, while this prevalence in non-lower extremity amputation group was 42.2% [29]. Cervantes-García conducted a prospective study of 100 patients with infected diabetic foot ulcers and found 35 of 45 patients in amputation group was male, 

Fig 4. The summary specificity for male on subsequent amputation in diabetic patients.

https://doi.org/10.1371/journal.pone.0243797.g004
while just 25 of 55 patients in non-amputation group was male [32]. Sayiner et al conducted a retrospective study and found male patients was associated with an increased risk of amputation as compared with female patients [40]. Austrian Health Insurance database found male sex was associated with an increased risk of lower extremity amputation using adjusted negative binomial regression [41]. The Truven Health MarketScan database suggested male and older diabetic patients with high risk of lower limb amputations [42]. The potential reason for this could be the predisposing factor for the risk of amputation was not fully illustrated [43]. Moreover, the behavior in male and female are differences, which could explain the sex difference for the risk of amputation. Furthermore, male patients always under more physical and social pressure than female, which could be as a reason to force male feel healthy and strong than female. In addition, the hormonal protective role of estrogen could lead to differences in immune system function between male and female [44, 45]. Finally, the biological factors of
diabetic foot ulcer, peripheral vascular disease, coronary artery disease, and peripheral neuropathy might accounts for the significant sex difference for the amputation rates [46, 47].

The predictive vale of male on subsequent amputation in diabetic patients were mild, and stratified analyses indicated the high predictive value were observed in the groups of studies designed as retrospective cohort, irrespective age of patients, or diabetes type, and the level of HbA1c was not reported. Several potential reasons could explained the above results: (1) the results from retrospective studies might induce overestimate effect estimates owing the uncontrolled selection and recall biases; (2) elderly patients always presented more serious disease, and event rates of amputation were higher than younger patients, caused the result with statistically significant was easily obtained. However, the pooled results for younger patients was associated with statistically significant was attributed to the result from Truven Health Market-Scan database; (3) although mostly studies did not reported diabetes type, while the type 2
Several shortcomings of this study should be mentioned. Firstly, mostly included studies designed as retrospective cohort, and the selection and recall biases were inevitable. Secondly, the characteristics of patients were not adjusted, which could affect the further amputation risk in diabetic patients. Thirdly, stratified analyses according to patients' characteristics were restricted owing to the analysis based on pooled data. Fourthly, the analysis based on published articles, while unpublished data were not available, and the publication bias was inevitable.

**Conclusions**

In conclusion, this study found male diabetic patients was associated with an increased risk of amputation than female diabetic patients, while the predictive value for male on amputation
risk in diabetic patients were mild. Moreover, the findings of this study needed further verified in further large-scale prospective cohort studies.

**Supporting information**

S1 File. Search strategy.
(ODCX)

S1 Table. The Newcastle-Ottawa scale of individual study.
(ODCX)

**Author Contributions**

Conceptualization: Lei Fan, Xue-Jian Wu.

Data curation: Lei Fan.

Formal analysis: Lei Fan.

Writing – original draft: Lei Fan.

Writing – review & editing: Xue-Jian Wu.

**References**

1. Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine. 2012; 41(3): 384–397. https://doi.org/10.1007/s12020-012-9619-x PMID: 22367583

2. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017; 376(24): 2367–2375. https://doi.org/10.1056/NEJMra1615439 PMID: 28614678
3. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis (†). Ann Med. 2017; 49(2): 106–116. https://doi.org/10.1080/07853890.2016.1231932 PMID: 27585063

4. Buowari OY. Diabetes Mellitus in Developing Countries and Case Series. In: Oguntibeju OO, editor. Diabetes Mellitus—Insights and Perspectives. London, UK: IntechOpen; 2013; p. 19. PMID: 24283104

5. International Diabetes Federation. IDF Diabetes atlas2017[150 p.]. Available from: https://www.idf.org/component/attachments/attachments.html?id=1093&task=download.

6. Jeffrey WW, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care. 2006; 29(8): 1784–1787. https://doi.org/10.2337/diacare.29.8.1784 PMID: 16873780

7. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008; 51(5): 747–755. https://doi.org/10.1007/s00125-008-0940-0 PMID: 18297261

8. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998; 21(5): 855–859. https://doi.org/10.2337/diacare.21.5.855 PMID: 9589255

9. Chitraragi G, Mahler DB, Sumpio BJ, Blume PA, Sumpio BE. Prosthetic options available for the diabetic lower limb amputee. Clin Podiatr Med Surg. 2014; 31(1): 173–185. https://doi.org/10.1016/j.cpm.2013.09.008 PMID: 24296024

10. Shin JY, Roh SG, Sharaf B, Lee NH. Risk of major limb amputation in diabetic foot ulcer and accompanying disease: A meta-analysis. J Plast Reconstr Aesthet Surg. 2017; 70(12): 1681–1688. https://doi.org/10.1016/j.bjps.2017.07.015 PMID: 28865989

11. Wang N, Yang BH, Wang G, Gao Y, Cao X, Zhang XF, et al. A meta-analysis of the relationship between foot local characteristics and major lower extremity amputation in diabetic foot patients. J Cell Biochem. 2019; 120(6): 9091–9096. https://doi.org/10.1002/jcb.28183 PMID: 30784095

12. Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. Diabetes Metab Res Rev. 2019; 35(7): e3165. https://doi.org/10.1002/dmrr.3165 PMID: 30953392

13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

14. Wells GS, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: Ottawa (ON): Ottawa Hospital Research Institute; 2009. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3): 177–188. https://doi.org/10.1016/0197-2456(86)90046-2 PMID: 3802833

16. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making. 2005; 25(6): 646–654. https://doi.org/10.1177/0272989X05282643 PMID: 16282215

17. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med. 2002; 21(9): 1237–1256. https://doi.org/10.1002/sim.1099 PMID: 12111876

18. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. Cochrane handbook for systematic reviews of interventions: Cochrane book series. 2008: 243–296.

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003; 327(7414): 557–560. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

20. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005; 58(9): 882–889. https://doi.org/10.1016/j.jclinepi.2005.01.016 PMID: 16085191

21. Armstrong DG, Lavery LA, Quebedeaux TL, Walker SC. Surgical morbidity and the risk of amputation due to infected puncture wounds in diabetic versus nondiabetic adults. South Med J. 1997; 90(4): 384–389. https://doi.org/10.1097/00007611-199704000-00004 PMID: 9114827

22. Lin CW, Hsu LA, Chen CC, Yeh JT, Sun JH, Lin CH, et al. C-reactive protein as an outcome predictor for percutaneous transluminal angioplasty in diabetic patients with peripheral arterial disease and infected foot ulcers. Diabetes Res Clin Pract. 2010; 90(2): 167–172. https://doi.org/10.1016/j.diabres.2010.08.002 PMID: 20822820

23. Akinci B, Yener S, Yesil S, Yapar N, Kucukyavas Y, Bayraktar F. Acute phase reactants predict the risk of amputation in diabetic foot infection. J Am Podiatr Med Assoc. 2011; 101(1): 1–6. https://doi.org/10.7547/10100001 PMID: 21242464
24. Aziz Z, Lin WK, Nather A, Huak CY. Predictive factors for lower extremity amputations in diabetic foot infections. Diabet Foot Ankle. 2011; 2. https://doi.org/10.3402/dfa.v2i0.7463 PMID: 22396824

25. GUZEl TurÇan O, DilÇbey M, Hizel K, KarakuÇ R, Kanat DO, Ata N. Diabetic Foot Infections and the Role of Doppler USG in Prognosis. Turkiye Klinikleri Journal of Medical Sciences. 2012; 32(1): 32–38. https://doi.org/10.5336/medsci.2010-21385

26. Ulcay A, Karakas A, Mutluoglu M, Uzun G, Turhan V, Ay H. Antibiotherapy with and without bone debridement in diabetic foot osteomyelitis: A retrospective cohort study. Pak J Med Sci. 2014; 30(1): 28–31. https://doi.org/10.12669/pjms.301.4266 PMID: 24639825

27. Saltoglu N, Yemisen M, Ergonul O, Kadanali A, Karagoz G, Batirel A, et al. Predictors for limb loss among patient with diabetic foot infections: an observational retrospective multicentric study in Turkey. Clin Microbiol Infect. 2015; 21(7): 659–664. https://doi.org/10.1016/j.cmi.2015.03.018 PMID: 25861844

28. Pickwell K, Siersma V, Kars M, Apelqvist J, Bakkers K, Edmonds M, et al. Predictors of lower-extremity amputation in patients with an infected diabetic foot ulcer. Diabetes Care. 2015; 38(5): 852–857. https://doi.org/10.2337/dc14-1598 PMID: 25665817

29. Tabur S, Eren MA, Çelik Y, Dağ OF, Sabuncu T, Sayiner ZA, et al. The major predictors of amputation and length of stay in diabetic patients with acute foot ulceration. Wien Klin Wochenschr. 2015; 127(1–2): 45–50. https://doi.org/10.1007/s00508-014-0630-5 PMID: 25398288

30. Quilici MT, Del Fiol Fde S, Vieira AE, Toledo MI. Risk Factors for Foot Amputation in Patients Hospitalized for Diabetic Foot Infection. J Diabetes Res. 2016; 2016: 8931508. https://doi.org/10.1155/2016/8931508 PMID: 26998493

31. Uysal S, Arda B, Taşbakancı M, Çetinkalp Ş, Şimşir İY, Öztürk AM, et al. Risk factors for amputation in patients with diabetic foot infection: a prospective study. Int Wound J. 2017; 14(6): 1219–1224. https://doi.org/10.1111/iwj.12788 PMID: 28722354

32. Cervantes-García E, Salazar-Schettino PM. Clinical and surgical characteristics of infected diabetic foot ulcers in a tertiary hospital of Mexico. Diabet Foot Ankle. 2017; 8(1): 1367210. https://doi.org/10.1080/2000625X.2017.1367210 PMID: 28904744

33. Ferreira L, Carvalho A, Carvalho R. Short-term predictors of amputation in patients with diabetic foot ulcers. Diabetes Metab Syndr. 2018; 12(6): 875–879. https://doi.org/10.1016/j.dsx.2018.05.007 PMID: 29820273

34. Musa IR, Ahmed MON, Sabir EI, Alsheneber IF, Ibrahim EME, Mohamed GB, et al. Factors associated with amputation among patients with diabetic foot ulcers in a Saudi population. BMC Res Notes. 2018; 11(1): 260. https://doi.org/10.1186/s13104-018-3372-z PMID: 29703224

35. Khalafallah M, Gouta EL, Dougaz W, Jerraya H, Samaali I, Nouira R, et al. Predictive factors for major amputation of lower limb in diabetic foot: about 430 patients. Tunis Med. 2018; 96(5): 298–301. PMID: 30430504

36. Peled S, Pollack R, Elishooov O, Haze A, Cahn A. Association of Inpatient Glucose Measurements With Amputations in Patients Hospitalized With Acute Diabetic Foot. J Clin Endocrinol Metab. 2019; 104(11): 5445–5452. https://doi.org/10.1210/jc.2019-00774 PMID: 31246256

37. Guo Z, Yue C, Qian O, He H, Mo Z. Factors associated with lower-extremity amputation in patients with diabetic foot ulcers in a Chinese tertiary care hospital. Int Wound J. 2019; 16(6): 1304–1313. https://doi.org/10.1111/iwj.13190 PMID: 31448507

38. Jeyaraman K, Berhane T, Hamilton M, Chandra AP, Falhammar H. Amputations in patients with diabetic foot ulcer: a retrospective study from a single centre in the Northern Territory of Australia. ANZ J Surg. 2019; 89(7–8): 874–879. https://doi.org/10.1111/ans.15351 PMID: 31293074

39. Ugwu E, Adeleye O, Gezawa I, Okpe I, Enamino M, Ezeani I. Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study. J Foot Ankle Res. 2019; 12: 34. https://doi.org/10.1186/s13047-019-0345-y PMID: 31223342

40. Sayiner ZA, Can FI, Akarsu E. Patients’ clinical characteristics and predictors for diabetic foot amputation. Prim Care Diabetes. 2019; 13(3): 247–251. https://doi.org/10.1111/pcd.2018.12.002 PMID: 30600172

41. Aziz F, Reichardt B, Sourj c D, Dimal HP, Reichard D, Köhler G, et al. Epidemiology of major lower extremity amputations in individuals with diabetes in Austria, 2014–2017: A retrospective analysis of health insurance database. Diabetes Res Clin Pract. 2020; 170: 108477. https://doi.org/10.1016/j.diabres.2020.108477 PMID: 33002552

42. Gandhi SK, Waschbusch M, Michael M, Zhang M, Li X, Juhaeri J, et al. Age- and sex-specific incidence of non-traumatic lower limb amputation in patients with type 2 diabetes mellitus in a U.S. claims database. Diabetes Res Clin Pract. 2020; 169: 108452. https://doi.org/10.1016/j.diabres.2020.108452 PMID: 32949656
43. Başkal N, Gülü S, İlgin ŞD, Erdoğan MF, Kamel N, Erdoğan G. Evaluation of the Patients with Diabetic Foot Ulcerations. Turkish Journal of Endocrinology and Metabolism. 1998; 1: 31–35.

44. Tivesten A, Mellström D, Jutberger H, Fagerberg B, Lernfelt B, Orwoll E, et al. Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden. J Am Coll Cardiol. 2007; 50(11): 1070–1076. https://doi.org/10.1016/j.jacc.2007.04.088 PMID: 17825717

45. Nather A, Bee CS, Huak CY, Chew JL, Lin CB, Neo S, et al. Epidemiology of diabetic foot problems and predictive factors for limb loss. J Diabetes Complications. 2008; 22(2): 77–82. https://doi.org/10.1016/j.jdiacomp.2007.04.004 PMID: 18280436

46. Peek ME. Gender differences in diabetes-related lower extremity amputations. Clin Orthop Relat Res. 2011; 469(7): 1951–1955. https://doi.org/10.1007/s11999-010-1735-4 PMID: 21161738

47. Ferranti KM, Osler TM, Duffy RP, Stanley AC, Bertges DJ. Association between gender and outcomes of lower extremity peripheral vascular interventions. J Vasc Surg. 2015; 62(4): 990–997. https://doi.org/10.1016/j.jvs.2015.03.066 PMID: 26209578