UPDATES ON RISK FACTORS AND PREDICTORS FOR AMPUTATION IN PATIENTS WITH DIABETIC FOOT AND TYPE 2 DIABETES: SYSTEMATIC REVIEW

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Abstract

Objectives: The frequency of diabetic foot (DF) problems is expected to rise in tandem with the global increase in type 2 diabetes (T2D) patients. To better identify individuals who are at high risk, a systematic analysis of available data regarding risk factors and predictors for amputation in patients with DF was conducted. **Methods:** We conducted a thorough search of PubMed, SCOPUS, Web of Science, Google Scholar, and Science Direct to find pertinent literature. Rayyan QRCI was utilized during the entire process. **Results:** We included thirteen studies with a total of 4106 patients and 2484 (60.5%) were males. Among patients with DF, a history of previous amputation ranged from 6.5% to 29.5%. Patients who recorded a Wagner classification (≥ Grade 3, n) ranged from 23.5% to 80.2%. Male sex, old age, greater ulcer size, greater Wagner classification grades, a higher incidence of peripheral artery disease (PAD), osteomyelitis, raised fibrinogen level, anaemia, HbA1C >7, smoking histories, smoking histories, cardiovascular disease (CAD), infection, osteomyelitis, lower body mass index (BMI), and leucocytosis were found to be independent predictors of lower limb amputation in patients with DF.

Conclusion: With DF infections, amputation is frequently necessary and inevitable, although the outcome of the procedure is not always clear-cut. This systematic study made clear how crucial it is to identify and assess data from laboratories, sociodemographics, previous medical history, and associated comorbidities. Subsequent analyses will delve deeper, examining the correlation between ulceration and amputation as well as between amputation and death.

Keywords: Diabetic foot; Type 2 diabetes; Amputation; Systematic review.

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Introduction

Ischemia, neuropathy (deficits in sensation, motor, and autonomic function), or combined can result in DF [1]. It is a dangerous side effect of diabetes that frequently leads to amputation [2, 3]. Patients with DF ulcers (DFUs) are said to have a prevalence of 4% to 10% and a lifetime incidence of up to 25% [4]. The International Diabetes Federation's 2015 prevalence statistics indicate that between 9.1 million and 26.1 million diabetics worldwide get foot ulcers each year [5]. Patients with DF experience mobility limitations, pain, and discomfort, all of which negatively impact their overall health-related quality of life [6].

In addition to lowering life expectancy, DFUs significantly affect the quality of life [7, 8]. Furthermore, the cost of treating diabetes patients with ulcers is 1.5–2.4 times higher than that of treating patients without ulcers [9]. Peripheral artery disease can cause costs to rise to almost four times the amount of simply neuropathic wounds [10].

Even after the foot ulcer heals, DFUs recurrence is a frequent issue [5]. The rate at which DFUs return is unknown, though. The incidence of DF recurrence in the available literature varied somewhat. From 28% at 12 months to 100% at 40 months, the overall recurrence rates varied [11].

DF problems rank among the most significant and avoidable late consequences of diabetes, particularly when associated with severe complications and amputation requirements. In addition to the work being done on risk classification systems and routine foot exams, better prevention and early detection techniques are needed [12]. Finding risk factor profiles that enable the identification of patients at high risk for foot illness is another essential component of prophylaxis.

The frequency of DF problems associated with T2D is expected to rise in tandem with the global increase in T2D patients. In order to better identify individuals who are at high risk, a systematic analysis of available data regarding risk factors and predictors for amputation in patients with DF was conducted.

Methodology

Study Design and Duration

This systematic review was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13]. The initial phase of this systematic review was in March 2024.

Search strategy

To find relevant material, four key databases were exhaustively searched: PubMed, SCOPUS, Web of Science, Google Scholar, and Science Direct. We searched only English databases, keeping in mind the unique requirements of each. The following keywords were converted to PubMed Mesh terms so that we could find the relevant studies; "Diabetes mellitus," "Type 2 diabetes," "T2D," and "Atrial Fibrillation." "OR," "AND," and "NOT," three Boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Studies that summarized the available data regarding risk factors and predictors for amputation in patients with DF.
- Studies conducted between 2019-2024.
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

Two verifications of the search method's output were conducted using Rayyan (QCRI) [14]. By applying inclusion/exclusion criteria to the aggregated search results, the researchers evaluated the relevance of the titles and abstracts. Every paper that met the inclusion requirements was thoroughly scrutinized by the reviewers. The authors talked about methods for resolving disputes. A pre-made data extraction form was used to upload the approved study. The authors extracted data about the study titles, authors, study year, country, participants, gender, AF prevalence, smoking status, diabetes duration, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

By assembling summary tables with information from relevant studies, a qualitative assessment of the research's findings and components was given. After gathering the data for the systematic review, the most efficient way to use the information from the included study articles was chosen.

Risk of bias assessment

Using the ROBINS-I risk of bias assessment technique for non-randomized trials of treatments, the quality of the included studies was evaluated [15]. The seven examined themes included confounding, study participant selection, intervention classification, deviation from planned interventions, incomplete data, outcome evaluation, and choice of reported result.

Results

Search results

The systematic search produced 1060 study articles in total, of which 455 duplicates were eliminated. After 605 studies had their titles and abstracts screened, 551 were not included. After 54 reports were requested to be retrieved, 2 articles were found. After screening 52 studies for full-text assessment, 15 were rejected due to incorrect study results, 22 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review included thirteen eligible study articles. A synopsis of the procedure for choosing studies is provided in **Figure 1.**

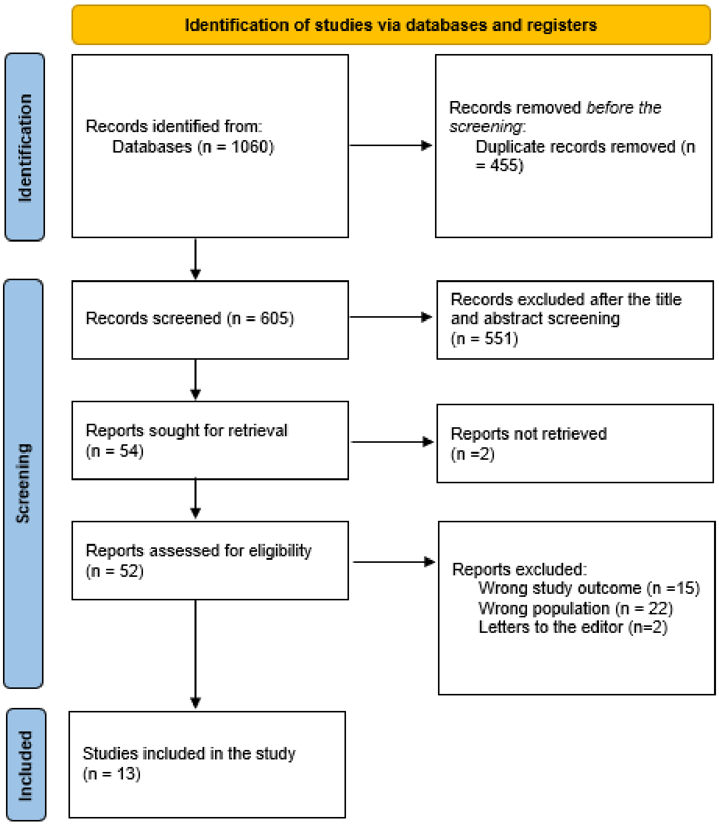

Figure (1): Study selection is summed up in a PRISMA flowchart.

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included thirteen studies with a total of 4106 T2D patients and 2484 (60.5%) were males. Eight studies were retrospective in nature [19-22, 24-26, 28], four were cross-sectional studies [16-18, 23], and one was prospective in nature [27]. Four studies were conducted in China [16, 20, 25, 26], two in Pakistan [23, 27], two in Indonesia [24, 28], one in Tanzania [17], one in Turkey [18], one in Saudi Arabia [19], one in Italy [21], and one in Nigeria [22],

Table (2) presents the clinical characteristics. Among patients with DF, a history of previous amputation ranged from 16 (6.5%) [25] to 107 (29.5%) [26]. Patients who recorded a Wagner classification (≥ Grade 3, n) ranged from 94 (23.5%) [18] to 291 (80.2%) [26]. Male sex, old age, greater ulcer size, greater Wagner classification grades, a higher incidence of PAD, osteomyelitis, raised fibrinogen level, anaemia, HbA1C >7, smoking histories, smoking histories, CAD, infection, osteomyelitis, lower BMI, and leucocytosis, were found to be independent predictors of lower limb amputation in patients with DF [16-28].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age	Gender (Males)
Wang et al., 2022 [16]	Cross-sectional	China	487	63.8 ± 11.5	302 (62%)
Shabhay et al., 2021 [17]	Cross-sectional	Tanzania	60	60.1 ± 11.3	35 (58.3%)
Sayiner et al., 2019 [18]	Cross-sectional	Turkey	400	NM	260 (65%)
Almohammadi et al., 2022 [19]	Retrospective cohort	Saudi Arabia	358	63.9 ± 13.9	238 (66.5%)
Che et al., 2024 [20]	Retrospective cohort	China	526	63.3 ± 12.1	347 (66%)
Gazzaruso et al., 2021 [21]	Retrospective cohort	Italy	583	71.1 ± 8.8	326 (55.9%)
Ugwu et al., 2019 [22]	Retrospective cohort	Nigeria	336	55.9 ± 12.5	185 (55.1%)
Ammar et al., 2021 [23]	Cross-sectional	Pakistan	135	13-70	82 (60.7 %)
Kurniawati et al., 2019 [24]	Retrospective cohort	Indonesia	73	47	10 (13.7%)
Zhu et al., 2023 [25]	Retrospective cohort	China	247	67.3 ± 0.7	189 (76.5)
Lu et al., 2021 [26]	Retrospective cohort	China	363	NM	256 (70.5%)
Nanwani et al., 2019 [27]	Prospective cohort	Pakistan	51	58.6 ± 11.1	37 (72.5%)
Yunir et al., 2022 [28]	Retrospective cohort	Indonesia	487	61	217 (44.6%)

*NM=Not-mentioned

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Diabetes duration (years)	History of previous amputation (%)	Smoking status (%)	Wagner classification (≥Grade 3, n) (%)	Main outcomes	ROBIN-I
Wang et al., 2022 [16]	18.4 ± 9.5	85 (17.5%)	251 (51.5%)	388 (79.7%)	Male sex (p=0.003), greater ulcer size (p=0.001), greater Wagner classification grades (p=0.002), a higher incidence of peripheral arterial disease (p=0.02) osteomyelitis (p=0.0001), and raised fibrinogen level (p=0.004) were found to be independent predictors of lower limb amputation in patients with DF, according to a stepwise multiple logistic regression analysis.	High
Shabhay et al., 2021 [17]	1 to >5	NM	NM	42 (70%)	There was a significant correlation found between the first grade of the Meggit-Wagner ulcer classification and the chance of amputation. Anaemia and elevated blood glucose appear to be significant risk factors as well, yet the connection did not show statistical significance.	Moderate
Sayiner et al., 2019 [18]	NM	56 (14%)	138 (34.5%)	94 (23.5%)	Compared to non-amputees, amputees experienced a considerably higher frequency of	High

					proteinuria (p < 0.05). Additionally, smoking histories were much longer in amputees (p < 0,001), and reamputation rates were significantly greater in individuals with prior amputation histories (p = 0.038).	
Almohammadi et al., 2022 [19]	17.1 ± 8.1	NM	NM	NM	Infection was the most frequent reason for amputation (50.3%). The 7-year mortality rate was 20% with 75 deaths. Significant correlations were found between high mean creatinine levels and low mean hemoglobin levels and death (p < 0.05).	Moderate
Che et al., 2024 [20]	10	97 (18.4%)	108 (20.5%)	402 (76.4%)	Amputation development in DFU patients is independently influenced by Wagner 3–5, PAD, and bacteria culture-positive.	Low
Gazzaruso et al., 2021 [21]	14.4 ± 8.8	51 (8.7%)	190 (32.6%)	NM	Renal impairment, PAD indicators, osteomyelitis, lower body mass index, and prior CAD were linked to DFU persistence, amputation, and death.	Moderate
Ugwu et al., 2019 [22]	8.5 ± 5.7	NM	NM	266 (79.2%)	The following factors were shown to be uncorrelated with leucocytosis (P 0.001), osteomyelitis (P 0.001), ulcer duration longer than one month previous to hospitalization (P 0.001), Wagner grade ≥ 4 (P 0.001), wound infection (P 0.041), and proteinuria (P 0.021).	Moderate
Ammar et al., 2021 [23]	NM	NM	NM	75 (55.6%)	Of all the amputations, 56 (41.5%) were performed on patients with stage 4 wounds, and 91 (67.4%) were performed on patients with poor glycemic control at presentation. Significantly higher total leukocyte counts, osteomyelitis-like bone, and local wound infections were linked to a higher probability of lower limb amputations (p<0.05).	Moderate
Kurniawati et al., 2019 [24]	NM	NM	NM	NM	Significant risk variables were neuropathy (adjusted OR = 5.6; p = 0.005), poor ankle-brachial index (ABI) (< 0.8; adjusted odds ratio [OR] = 17.9; p = 0.003), and HbA1C > 8.0% (adjusted OR = 4.7; p = 0.016).	Moderate
Zhu et al., 2023 [25]	17	16 (6.5%)	96 (38.9%)	NM	The findings demonstrated that ulcer severity (p < 0.01), ulcer location in the plantar forefoot (p < 0.01), PAD (p < 0.01), neutrophil-to-lymphocyte ratio (p < 0.01), and Managing Nutritional Status score (p < 0.05) were unique risk factors for	Moderate

					amputation in patients with DFUs and had predictive values for the progression of DFUs to amputation.	
Lu et al., 2021 [26]	15.2 ± 6.6	107 (29.5%)	215 (59.2%)	291 (80.2%)	Previous history of amputation (p = 0.02), smoking status (p = 0.01), CAD (p = 0.03), ABI <0.4 (p < 0.01), Wagner 5 (p < 0.01), activated partial thromboplastin time (APTT) (p = 0.01), Hb (p = 0.01), HbA1c (p = 0.03), Hb (p = 0.01), plasma albumin (p < 0.01), and leucocytosis (p < 0.01).	Moderate
Nanwani et al., 2019 [27]	15.2 ± 8.5	NM	31 (60.8%)	NM	The amputation group had a higher male population (p<0.00001) and a longer duration of diabetes (p=0.03). Amputation was substantially correlated with all three of the atherosclerosis risk factors: smoking, hyperlipidemia, and hypertension (p≤0.05).	Moderate
Yunir et al., 2022 [28]	9	NM	NM	NM	Individuals who were 60 years of age or older (P =.012), had a high risk of developing foot ulcers (P =.003), and had an HbA1C of 7% or higher (P =.031) were all independently linked to death or amputation.	Low

*NM=Not-mentioned

Discussion

DFUs are a feared consequence because they indicate severe social and medical limitations. The effectiveness of several risk factors in foretelling amputations in DF patients with T2D is examined in this systematic review.

The majority of the reviews' research showed no evidence of a meaningful correlation between amputation and any of the demographic variables. This conclusion was refuted by the findings of a few other studies that were not reviewed, since it was shown that variables like age and male gender were predictive of amputation. They are both linked to an increased incidence of PAD [29], which may explain this finding.

In the context of laboratory results, six risk factors were significant in predicting amputations. Leucocytosis, HbA1C >7, raised fibrinogen level, low hemoglobin level, ESR, and CRP as markers of infection and inflammation are strong indicators of amputation; high levels appeared to be associated with treatment failure in DFU in this review. These results were similar to a systematic review conducted by **Mansoor and Modaweb** [30].

It has been shown by previously published narrative reviews of observational research that there is still no obvious relationship between glycemic control and wound outcomes among DFUs [31, 32]. As far as we are aware, this subject has only been addressed in two meta-analyses of observational studies [33, 34]. greater A1C and fasting glucose were linked to a greater amputation risk, according to a meta-analysis by **Kim et al.** [33] that examined a wide range of laboratory results related to LEA in DFU patients. Nevertheless, that meta-analysis only included three trials. A meta-analysis by **Margolis et al.** included only five studies with DFUs of purely neuropathic etiology and showed no correlation between wound healing and glycemic control [34]. The link between perioperative glycemic control and surgical and systemic challenges, mortality rate, and duration of hospital stay has been the subject of recent orthopaedic literature. Poor glycemic control had a detrimental impact on all parameters assessed [35, 36].

Wagner classification is a grading tool for treating DF [37]; studies included in our review stated that Wagner classification ≥ grade 3 (Deep abscess formation or osteomyelitis). This was in line with **Mansoor and Modaweb**'s findings [30]. Wagner grade predicts the course of the ulcer by providing information about the degree of tissue damage. Numerous more papers that were evaluated during the preparation of this evaluation but were not included in the systemic review further corroborated this [22].

In the future, we plan to investigate the incidence and timing of amputation following newly developed ulcerations, as well as the interval between amputation and death in both ulcerated and non-ultimate patients. This will provide an idea of how directly amputation affects mortality. By working together, we intend to have a better understanding of how lower extremity amputation contributes to the death of diabetic patients. Furthermore, we anticipate that the data gathered will offer fresh angles for investigation to better elucidate these problems.

Conclusion

With DF infections, amputation is frequently necessary and inevitable, although the outcome of the procedure is not always clear-cut. This systematic study made clear how crucial it is to identify and assess data from laboratories, sociodemographics, previous medical history, and associated comorbidities. Subsequent analyses will delve deeper, examining the correlation between ulceration and amputation as well as between amputation and death.

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