

Risk factors of amputation in patients with diabetic foot: a comprehensive review

Zeinab Mohseni Afshar¹, Arefeh Babazadeh^{*1}, Soheil Ebrahimpour¹, Rahmat Jokar², Mohammad Barary³

1. Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

2. Department of Orthopedic and Trauma Surgery, Shahid Beheshti Hospital, Babol University of Medical Sciences, Iran

3. Student Research Committee, Virtual School of Medical Education and Management, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Background: Amputation remains a major complication of diabetic foot disease, associated with substantial morbidity and mortality. To synthesise the available evidence on demographic, metabolic, vascular, infectious, and ulcer-related factors associated with amputation in adults with diabetic foot ulcers, using a transparent narrative framework augmented by systematic-narrative elements

Materials and Methods: This narrative review was conducted within a transparent narrative framework, without undertaking meta-analysis. Four electronic databases—PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library—were searched for studies published between 2000 and 2024 that examined adults with diabetic foot ulcers and reported associations with amputation. Conference abstracts and non-indexed sources were excluded. Study selection, data extraction, and quality appraisal were undertaken independently by reviewers according to predefined criteria. The extracted data were organised into modifiable and non-modifiable factors, where available

Results: The included studies identified several modifiable factors—such as glycaemic control, infection, osteomyelitis, peripheral arterial disease severity, and adequacy of wound care—and non-modifiable factors, including age, duration of diabetes, and comorbidity burden, that were significantly associated with the risk of amputation.

Conclusion: Targeted multidisciplinary strategies focusing on modifiable factors may reduce the risk of amputation among individuals with diabetic foot ulcers. High-quality prospective studies are warranted to quantify these associations and to inform clinical guidelines

Keywords: peripheral arterial disease, diabetic foot ulcer, complication

Received:

May 10,2025

Revised:

September 12,2025

Accepted:

September 22,2025

Published on:

December 10,2025

Corresponding author:

Arefeh Babazadeh

Address: Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

E-mail:

drbabazadeh.a@yahoo.com

Introduction

Diabetes mellitus (DM) is a leading cause of morbidity and mortality worldwide. As both the prevalence and duration of DM increase, the burden of DM-related complications also rises, including atherosclerosis, diabetic nephropathy, neuropathy, retinopathy, and peripheral arterial disease (PAD) (1). Among these, diabetic foot ulcers (DFUs) are among the most visible and impactful complications, resulting from a complex interplay of microvascular and macrovascular pathology, peripheral neuropathy, peripheral vascular disease, repetitive trauma, and secondary infection (2). Ulcers located below the ankle in individuals with diabetes are typically classified as DFUs, whereas diabetic foot gangrene (DFG) represents a more severe manifestation that may arise from arterial obstruction or advanced infection (3, 4).

Healing rates for DFUs vary according to patient and ulcer characteristics and the type of care setting, reaching up to 90% in specialised centres (5).

Nonetheless, DFUs often prove difficult to heal and constitute one of the leading causes of non-traumatic lower-limb amputation. Individuals with DM have a markedly increased risk—estimated at 15- to 20-fold-of lower-extremity amputation (LEA) compared with those without diabetes, and untreated DFUs frequently progress to amputation within a few years (6–8). Consequently, identifying and mitigating the risk factors for amputation is essential for improving long-term prognosis (9–11). This study therefore aims to comprehensively review the risk factors associated with amputation in individuals with diabetes.

Materials and methods

Study design and rationale:

This study is a narrative review incorporating explicit methodological elements; no meta-analysis was performed.

Search strategy and sources:

Four electronic databases—PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library—were searched for studies published between 2000 and 2024. Search terms included combinations of diabetic foot, diabetic foot ulcer, amputation, risk factors, peripheral

arterial disease, osteomyelitis, infection, glycaemic control, and related synonyms. The search was limited to publications written in English.

Inclusion Criteria

- Adults with diabetic foot ulcers (DFUs) or other diabetic foot conditions.
- Studies reporting associations with lower-extremity amputation (major or minor).
- Publications appearing in indexed, peer-reviewed journals.
- Full text available in English.

Exclusion Criteria

- Conference abstracts, editorials, or letters lacking original data.
- Publications from non-indexed journals.
- Studies without clearly reported amputation outcomes.
- Studies involving paediatric populations.

The incidence of amputation in diabetic patients:

Amputation of the lower extremities is both common and devastating, representing one of the most feared complications among patients with diabetes. It is often an inevitable consequence of diabetic foot ulcer (DFU) or diabetic foot infection (DFI) that has not been adequately controlled or managed. The majority of diabetes-related amputations are precipitated by DFUs that progress to osteomyelitis or gangrene (12).

The incidence of diabetes-associated amputation varies between countries; however, estimates suggest an annual incidence exceeding 5%, rising to as high as 50% among patients hospitalised with DFUs. This occurs despite advances in ulcer management and revascularisation techniques, particularly in diabetic individuals with peripheral arterial disease (PAD).

Approximately 40% of DFUs ultimately lead to amputation, and the risk of amputation in those with diabetes is 10–15 times higher than in non-diabetic individuals. The risk is even greater among patients with diabetic foot gangrene, who often require major amputation—below-knee or above-knee—typically associated with poor functional outcomes. Moreover, nearly half of diabetic patients who undergo a first lower-extremity amputation (LEA) require a repeat amputation within 3–5 years. Therefore, targeted efforts should be directed towards reducing amputation

rates through the control and modification of risk factors (13–15).

Amputations are generally classified as major or minor. Major amputations are those performed above the ankle, whereas minor amputations occur below the ankle. Major amputations are of greater clinical significance, as they substantially limit functional capacity and impair quality of life. Furthermore, pain and social functioning are typically more adversely affected following major than minor amputations. Patients who undergo major amputation also require a different type of prosthesis to achieve independent ambulation (16–18).

Risk factors of amputation in diabetic patients

Risk factors associated with diabetes-related amputation are multifactorial, encompassing patient-specific, ulcer-related, and systemic aspects. Some of these factors—such as demographic characteristics, comorbidities, and smoking status—are non-modifiable, whereas others, including lipid profile and glycaemic control, are modifiable.

Patient's demographic factors

Age

It has been demonstrated that advanced age is a principal risk factor and predictor of amputation, particularly major amputation. The mean age of diabetic patients undergoing amputation exceeds 50 years, which may be attributed to the higher prevalence of vascular conditions—including peripheral arterial disease (PAD) and coronary artery disease (CAD)—among older individuals (19).

Gender

Several studies have demonstrated that diabetic men are at a higher risk of amputation compared with diabetic women. This disparity may be explained by behavioural and physiological differences between the sexes. Men tend to pay less attention to personal hygiene and appearance, leading to less frequent self-inspection of the feet. Furthermore, they are generally less inclined to seek medical advice, whereas women attend medical consultations more regularly. These factors may contribute to delays in the detection of foot ulcers or other foot problems in men, thereby increasing the likelihood of disease progression and the subsequent need for amputation.

In addition, women generally have greater pain sensitivity than men, which encourages them to attend to even minor painful lesions on their feet—lesions that might otherwise be overlooked by men. Consequently, diabetic women are more likely to detect foot ulcers at earlier and less severe stages, resulting in a more favourable prognosis and a reduced likelihood of future amputation (20, 21).

Ethnicity

Different studies have reported conflicting findings regarding the influence of ethnicity on the rate of amputation associated with diabetic foot ulcers (DFUs). It has been demonstrated that African American, Native American, and Hispanic populations have a higher prevalence of DFUs and tend to develop more severe ulcerations compared with their Caucasian counterparts. Consequently, DFU-related adverse outcomes, including amputation, are more likely to occur within these populations than among other ethnic groups. This disparity may be partly attributed to genetic predisposition or to socioeconomic factors that contribute to delayed presentation and access to medical care (22, 23).

BMI

Although obesity is a well-established risk factor for the development of diabetes mellitus (DM) and its associated complications—such as cardiovascular disease (CVD), diabetic foot ulcer (DFU), and diabetic foot infection (DFI)—it has been observed that DFU-related amputations are more common among diabetic patients with a lower body-mass index (BMI) than among those with a higher BMI.

This paradox may be explained by the comparatively better nutritional status of patients with higher BMI, who may possess greater physiological reserves to withstand severe conditions such as DFU and osteomyelitis. In addition, obese patients typically have greater muscle mass than those with lower BMI, which may reduce ulcer fragility and slow the rate of progression to deeper structures such as bone. Conversely, a lower BMI may predispose to poorer ulcer healing, faster disease progression, and consequently a higher risk of amputation.

This phenomenon—commonly referred to as the *obesity paradox*—reflects the observation of more

favourable health outcomes and improved survival in patients with higher BMI (24, 25).

Socioeconomic state

It can be readily predicted that patients with diabetic foot ulcers (DFUs) and low socioeconomic status are significantly more likely to require an amputation compared with those of high socioeconomic status. This disparity can be attributed to delayed presentation for clinical care and suboptimal levels of self-management among these patients. Such factors contribute to delays in the diagnosis and management of DFUs and, consequently, to adverse outcomes, including gangrene and amputation (26).

Atherosclerosis risk factors and comorbidities

Smoking

Smoking has been shown to be an independent risk factor for amputation. This can be explained by the fact that smoking is a significant risk factor for both peripheral arterial disease (PAD) and cardiovascular disease (CVD), both of which are critical precipitating factors for DFUs and non-healing ulcers. Accordingly, smoking cessation is strongly recommended as a preventative measure against amputation in diabetic patients presenting with lower-extremity ulcers (27–9).

Cardiovascular disorders

It has been demonstrated that cardiac comorbidity is a major precipitating factor for adverse events associated with diabetic foot infection (DFI) in diabetic patients. Coronary artery disease (CAD) has been shown to increase the risk of amputation through several mechanisms. Firstly, CAD can elevate the risk of peripheral arterial disease (PAD) and severe limb ischaemia, both of which are significant risk factors for lower-extremity amputation in diabetic patients. Conversely, patients with CAD are also at an increased risk for other microvascular complications, such as neuropathy and nephropathy, which predispose them to non-healing lower-limb ulcers and eventual amputation. Accordingly, patients who have undergone coronary artery bypass graft (CABG) surgery are at a heightened risk of diabetes mellitus (DM)-associated lower-extremity amputation and may require revascularisation and major amputation due to the combined effects of microvascular and macrovascular disease (30, 31).

PAD

Peripheral arterial disease (PAD) is a vascular system disorder that primarily results in poor circulation and perfusion of the lower extremities. The condition is associated with underlying factors such as atherosclerosis, hypertension, trauma, and smoking, which contribute to the obstruction of peripheral arteries. Severe PAD frequently progresses to critical limb ischaemia due to tissue hypoxia (32).

It is well established that diabetic patients are at an increased risk of PAD and lower-extremity ischaemia owing to the high prevalence of atherothrombosis. Consequently, peripheral vascular disease can impair blood flow, leading to lower-limb ischaemia, necrosis, gangrene, poor ulcer healing, and ultimately, amputation. The concomitant presence of neuropathy and PAD further exacerbates the risk of amputation in diabetic patients with foot ulcers. Moreover, PAD can induce an immunocompromised state in diabetic patients, contributing to a higher risk of infection, delayed healing, and adverse outcomes such as amputation. Therefore, PAD should be routinely screened for and confirmed in diabetic patients with foot ulcers to accurately predict amputation risk. The ankle-brachial index (ABI) is the first-line screening indicator of PAD. A low ABI (less than 0.4) has been demonstrated to be a significant risk factor for major amputation as it reflects severe lower-limb ischaemia. Such a finding can alert clinicians that the patient may require early referral to a vascular surgeon and revascularisation or aggressive vascular intervention to mitigate the risk of amputation (33–35).

Hypertension and hyperlipidemia

As previously established, atherosclerosis can accelerate peripheral arterial disease (PAD) progression and heighten the risk of non-healing foot ulcers, thus leading to the subsequent need for amputation. Consequently, any factor that promotes atherosclerosis can increase the risk of amputation in diabetic foot ulcers (DFUs). Hypertension and hyperlipidaemia, which are more prevalent in diabetic patients than in non-diabetic individuals, are the main risk factors for atherosclerosis and peripheral ischaemia; they obstruct blood flow, leading to delayed or non-healing DFUs and the resultant need for

amputation. This suggests that both hypertension and hyperlipidaemia can worsen the prognosis of diabetic patients with foot ulcers. Hence, diabetic patients should manage their blood pressure and lipid profile to mitigate other DM-associated adverse events (36, 37).

Nephropathy

It has been demonstrated that the risk of DFU-associated amputation is several times higher in diabetic patients with nephropathy compared with those without. Nephropathy, a microvascular complication of DM, serves as a useful marker for the patient's overall vascular status. Therefore, a diabetic patient with nephropathy is at an increased risk of arterial occlusive disease and is prone to developing PAD, which is the principal cause of amputation. Diabetic nephropathy is typically indicated by albuminuria; the incidence of DFU-associated adverse events, including amputation, has been shown to increase in patients with albuminuria. Thus, screening for albuminuria in DM patients for the early detection of nephropathy may prevent future adverse outcomes such as amputation (38).

Neuropathy

Neuropathy is another microvascular complication of DM reported to be a significant risk factor for lower-extremity amputation. Most diabetic foot ulcers represent a combination of neuropathic and vascular ulcers, collectively known as neuroischaemic ulcers. Neuropathy renders diabetic patients susceptible to recurrent ulceration, which can be explained by the increased risk of trauma and subsequent ulceration due to sensory loss and decreased sweating. Furthermore, neuropathic changes, such as foot deformity, can be an additional cause of ulceration. Concurrently, neuropathy can delay ulcer healing, which may be followed by an increased risk of adverse events, including amputation (39).

Retinopathy

Diabetic retinopathy is a major global cause of visual impairment and has been reported to be significantly associated with cardiovascular diseases. Furthermore, diabetic retinopathy has been shown to predict other DM-associated adverse outcomes, such as lower-extremity arterial disease (LEAD), diabetic foot ulcer (DFU) development, and amputation. A diabetic

patient who develops retinopathy as a microvascular complication typically has long-standing DM and is consequently at risk for other microvascular complications, including neuropathy, nephropathy, and peripheral arterial disease (PAD). This increases susceptibility to non-healing DFUs, diabetic foot infection (DFI), and amputation. Additionally, diabetic retinopathy and LEAD share several pathophysiological processes-including inflammation, oxidative stress, and endothelial dysfunction-all of which contribute to vascular microthrombosis and the consequent impaired oxygen exchange in foot tissues. This impairment delays ulcer healing, compromises infection control, and elevates the risk of amputation (40, 41).

Cerebrovascular diseases

As a matter of fact, a great majority of DM-associated lower-limb amputations are attributable to arterial obstructive disease. Since patients with cerebrovascular diseases, including stroke and transient ischaemic attacks (TIA), are more likely to have arterial obstruction and insufficiency, these patients are more prone to DM-associated adverse events such as amputation (36).

Chronic Renal Insufficiency

Severe chronic kidney disease (CKD) and reliance on dialysis have been reported as risk factors for amputation in diabetic patients with lower-extremity ulcers. Diabetic patients with low estimated glomerular filtration rates (eGFRs) are at an increased risk of severe foot ulceration. Furthermore, diminished GFR accompanied by concomitant proteinuria further heightens the risk of amputation (42, 43).

Charcot Neuroarthropathy

Charcot neuroarthropathy is a destructive process of the foot that most commonly occurs in the setting of DM. This deformity is typically accompanied by bone destruction, subluxation, dislocation, or instability, rendering the diabetic patient susceptible to repetitive trauma, recurrent ulcerations, and amputation (44).

Dementia

Critical limb threatening ischaemia (CLTI) is a disease predominantly observed in the elderly; this population frequently suffers from comorbidities such as dementia. Accordingly, the risk of CLTI-associated

amputation is high in vascular patients with dementia. Although there is no established causal relationship between dementia and CLTI-associated amputation, it is hypothesised that diabetic patients with cognitive impairment, such as dementia, are highly susceptible to falls and traumatic injuries, demonstrate suboptimal adherence to blood glucose and lipid control, and fail to maintain proper foot hygiene. All these factors are recognised as precipitating elements for DFU, diabetic foot infection (DFI), and associated adverse events such as amputation (45, 46).

Depression

Diabetic patients are at an increased risk of depression, and when these two conditions coexist, adherence to diabetes management (e.g., exercise, blood glucose monitoring, and regular medical visits) significantly decreases. This consequently leads to DM-associated complications, such as non-healing DFUs and the eventual necessity for amputation. Conversely, any psychological distress, including depression and anxiety, can compromise the host immune system, leading to impaired ulcer healing and an elevated risk of amputation (47, 48).

Diabetes associated factors

Type of DM

Both Type 1 DM and Type 2 DM can cause foot ulcers; thus, both can influence the incidence of amputation. However, as individuals with Type 2 DM are typically older than those with Type 1 DM, the prevalence of comorbidities is higher in these patients, which may lead to a worse DFU outcome in Type 2 compared with Type 1 (49).

Diabetes Duration

The duration of DM may also play a critical role in the risk of DM-associated adverse events, including amputation. This is partly due to the deterioration of metabolic control in diabetic patients over time following diagnosis, and the associated adverse effects of sustained hyperglycaemia on foot ulcer healing and infection control (50).

Hypoglycaemic Agents

Antidiabetic therapies can also influence the risk of lower-extremity amputation, meaning that different diabetic treatment regimens have an impact on diabetic foot ulcer healing. Insulin therapy has been

demonstrated to significantly increase the ulcer healing rate. Conversely, newer hypoglycaemic agents, such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors, have been shown to decrease DM-associated adverse events, including amputation and mortality, when compared with older antidiabetic agents (51, 52).

Uncontrolled Blood Glucose

Severe hyperglycaemia has been found to be associated with an increased risk for DFU. Poor glycaemic control inherently leads to poor ulcer healing in diabetic patients. Furthermore, the risk of progression and the future need for amputation is increased in non-healing foot ulcers. Accordingly, intensive glycaemic control is a significant prognostic healing factor that can decrease DM-associated amputations and mortality rates. Glycated haemoglobin (HbA1c) reflects average blood glucose levels over the preceding three months. Thus, the regular measurement of HbA1c and maintaining good glycaemic control are necessary for the prevention of DFU progression to osteomyelitis and the resultant need for amputation (53, 54).

Foot Anatomy

Foot anatomy also affects the risk of amputation in diabetic patients. Deformities of the toes and metatarsophalangeal joints (MTPJs) are associated with foot ulcers and the consequent amputation risk. Anatomic abnormalities and deformities, such as acromegalic toes, hammer toe, claw foot deformity, *pes cavus*, and *hallux valgus*, contribute to amputation risk by precipitating foot ulceration. Additionally, diabetes itself causes muscle atrophy and imbalance as a result of motor neuropathy, which induces certain foot deformities such as Charcot neuroarthropathy. These deformities, which occur in diabetic patients of more than 10 years' duration and in the presence of peripheral neuropathy, elevate plantar pressure and influence the biomechanics of gait, leading to repetitive foot trauma and ulceration, which precede the majority of amputations (55, 56).

Ulcer characteristics

Diabetic foot ulcer (DFU) characteristics also influence the risk of amputation; diabetic patients with multiple foot ulcers are at a higher risk of amputation compared with those with a single DFU. Moreover,

there is a strong association between ulcer healing and ulcer duration; in fact, longer-duration DFUs are less likely to heal and are more likely to progress to adverse events such as amputation (57).

Because of reduced perfusion in the forefoot region, forefoot ulcers are more likely to be associated with amputation risk than ulcers located in the midfoot or hindfoot (58). Ulcer severity, most commonly assessed by the Wagner classification system, is another significant risk factor for amputation. Ulcers with greater width and depth, or those that progress to fascia, muscle, tendon, or bone, are at an increased risk of amputation (59).

Conversely, the concomitant presence of cellulitis, necrosis, gangrene, and osteomyelitis also affects prognosis. DFUs with accompanying cellulitis wider than 3 cm carry an increased risk of amputation. Furthermore, the presence of necrosis or gangrene has a significant impact on both future amputation needs and mortality, as these conditions reflect underlying peripheral arterial disease in diabetic patients (60).

Osteomyelitis may be the leading cause and the most critical indicator for amputation in diabetic foot ulcers. Deep ulcers invading the bone significantly increase the risk of major amputation despite aggressive surgical debridement to control infection. DFUs with osteomyelitis typically present in late stages, leading to treatment failure and a higher likelihood of lower-extremity amputation (61, 62).

History of DFU or Diabetic Foot Infection (DFI)

It is well established that a history of foot ulcers increases the risk of subsequent ulceration in diabetic patients. These recurrent ulcers are more challenging to heal compared with first-time presentations; thus, the risk of amputation is increased in repeated foot ulcers (63, 64).

Previous Amputation History

Studies have shown that patients who have undergone minor amputations are at an increased risk of future need for major amputation; this reflects the fact that amputation history is a risk factor for re-amputation. This outcome may result from reliance on the contralateral extremity for ambulation in individuals who can no longer fully use the amputated limb. Moreover, the contralateral extremity becomes

more susceptible to trauma, which is a predisposing factor for foot ulceration and the resultant consequences, such as amputation, in diabetic patients. Therefore, preventive measures are essential in individuals with a history of amputation to decrease the risk of re-amputation (65, 66).

Infection with Drug-Resistant Pathogens

Diabetic foot infections can be caused by Gram-positive, Gram-negative, and anaerobic bacteria. However, the isolation of Gram-negative pathogens and fungi has been associated with treatment failure and an increased risk of amputation in DFI. In recent years, multidrug-resistant (MDR) pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, have been identified as the causative agents of infection in diabetic foot ulcers. Accordingly, lower-limb amputation is more prevalent in infections involving MDR organisms (67, 68).

Longer Hospitalisation

It is plausible that longer hospitalisation is associated with amputation in DFU, as both non-healing ulcers and those with bone involvement—which predict amputation—are more likely to require a prolonged hospital stay and extended treatment duration. However, there is no direct evidence that prolonged hospitalisation *causes* amputation. Instead, an extended hospital stay may result in colonisation with antibiotic-resistant pathogens, which are a leading cause of medical therapy failure and the subsequent need for amputation (69).

Laboratory abnormalities

Some laboratory abnormalities are associated with a poor prognosis in patients with diabetic foot ulcers (DFUs).

1. White Blood Cell (WBC) Count

The white blood cell (WBC) count is a common inflammatory marker; therefore, it may be elevated in patients with DFUs, particularly those with acute osteomyelitis. Moreover, the WBC level can reflect the severity of diabetic foot infection. This elevation represents an acute-phase response that may contribute to the progression of DFUs to amputation (70-72).

2. Neutrophil and Platelet Ratios

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are readily

available and economically affordable indices that can predict osteomyelitis, septic complications, and the future need for amputation in patients with DFU (73, 74).

3. Coagulation Markers

Activated partial thromboplastin time (APTT) has been found to predict amputation risk in diabetic patients. This coagulation test reflects the activity of the endogenous coagulation system and can be used to assess thrombosis risk. Indeed, an increased APTT is associated with a pro-thrombotic state and severe systemic inflammation, both of which are risk factors for amputation. Accordingly, increased D-dimer and fibrinogen levels are also associated with an increased amputation risk (75).

4. Nutritional Markers

Serum albumin and haemoglobin levels are indicators of nutritional status and the capacity for ulcer healing. Thus, these two markers are negatively correlated with amputation risk in patients with DFUs (76, 77).

5. nflammatory Markers

Other inflammatory markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin, may also be beneficial in predicting poor outcomes, such as amputation, in diabetic patients. Increased levels of these biomarkers are associated with infection, inflammation, and tissue

injury-predisposing factors for non-healing ulcers in diabetics and predicting the need for amputation (78-80).

6. Renal Function

Moreover, diabetic patients with increased creatinine and decreased estimated glomerular filtration rate (eGFR) (e.g., <60 mL/min/1.73 m²) are at an increased risk of poor ulcer healing and amputation (81).

Conclusion

This comprehensive narrative review identifies a range of modifiable factors (e.g., glycaemic control, infection management, peripheral arterial disease severity, wound care adequacy) and non-modifiable factors (e.g., age, diabetes duration, comorbidity burden) associated with amputation risk in adults with diabetic foot ulcers. The findings underscore the importance of early, aggressive, multidisciplinary management to mitigate modifiable risk factors and potentially reduce amputation rates.

Given the heterogeneity and limitations of retrospective data, high-quality prospective studies are needed to quantify the strength of associations, refine risk stratification, and inform clinical guidelines for preventing lower- extremity amputations in this population. **(Table).**

Table 1

risk factor	Example	Notes
Demographics	Age, Gender, Ethnicity, BMI, Socioeconomic status	Basic patient characteristics
Diabetes-related factors	Type of DM, Diabetes duration, Hypoglycemic agents, Uncontrolled HbA1c	Disease management context
Ulcer characteristics	Ulcer number, Ulcer duration, Forefoot vs others, Wagner grade/size/depth, Presence of cellulitis/necrosis/gangrene, Osteomyelitis	Ulcer-specific factors
Infection / Inflammation	DFIs etiology (MDR risk), WBC/NLR/PLR, ESR/CRP/Procalcitonin	Inflammatory/infectious status
Vascular factors	PAD/ABI, CAD and microvascular disease, Hypertension, Hyperlipidemia	Blood flow and cardiovascular risk
Common comorbidities	Nephropathy/CKD, Retinopathy, Neuropathy/Charcot, Dementia, Depression	Coexisting conditions
History	History of DFU/DFI, Previous amputation	Prior events and risk history
Treatment-related	Revascularization status, Debridement adequacy, Antibiotic therapy, Length of hospitalization	Interventions and care processes
Outcome	Increased risk of amputation (major or minor)	Final observed risk / endpoint

Conflict of Interest:

The authors declare no conflicts of interest

References

1. Deshmukh CD, Jain A, Nahata B. Diabetes mellitus: a review. *Int J Pure Appl Biosci.* 2015; 3 (3): 224-30.
2. Balaji R, Duraisamy R, Kumar M. Complications of diabetes mellitus: A review. *Drug Invention Today.* 2019; 12(1). 98-103
3. Brownrigg JR, Griffin M, Hughes CO, et al. Influence of foot ulceration on cause-specific mortality in patients with diabetes mellitus. *Journal of Vascular Surgery.* 2014; 60(4): 982-6. e3.
4. Park J-Y, Jung H-G. Diabetic foot: ulcer, infection, ischemic gangrene. *Foot and Ankle Disorders: An Illustrated Reference.* 2016: 555-84.
5. Zhang P, Lu J, Jing Y, et al. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Annals of medicine.* 2017; 49 (2): 106-16.
6. Songer TJ. The role of cost-effectiveness analysis and health insurance in diabetes care. *Diabetes research and clinical practice.* 2001; 54: 7-11.
7. Thewjitcharoen Y, Krittiyawong S, Porramatikul S, et al. Outcomes of hospitalized diabetic foot patients in a multi-disciplinary team setting: Thailand's experience. *Journal of clinical & translational endocrinology.* 2014; 1(4): 187-91.
8. Beyaz S, Güler ÜÖ, Bağır GŞ. Factors affecting lifespan following below-knee amputation in diabetic patients. *Acta orthopaedica et traumatologica turcica.* 2017; 51(5): 393-7.
9. Williams MD, Nadler JL. Inflammatory mechanisms of diabetic complications. *Current diabetes reports.* 2007;7(3):242-8.
10. Papatheodorou K, Papanas N, Banach M, Papazoglou D, Edmonds M. Complications of diabetes 2016. *Journal of diabetes research.* 2016;2016.
11. Turns M. The diabetic foot: an overview for community nurses. *British journal of community nursing.* 2012;17(9):422-33.
12. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arteriosclerosis, thrombosis, and vascular biology.* 2020;40(8):1808-17.
13. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? *Diabetes/metabolism research and reviews.* 2000;16(S1):S75-S83.
14. Jiang Y, Wang X, Xia L, et al. A cohort study of diabetic patients and diabetic foot ulceration patients in China. *Wound Repair and Regeneration.* 2015;23(2):222-30.
15. Edo AE, Edo GO, Ezeani IU. Risk factors, ulcer grade and management outcome of diabetic foot ulcers in a Tropical Tertiary Care Hospital. *Nigerian Medical Journal.* 2013; 54(1): 59-63.
16. Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: A meta-analysis. *PloS one.* 2020;15(9):e0239236.
17. Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. *Diabetes/metabolism research and reviews.* 2019; 35(7): e3165.
18. Abbas ZG. Reducing diabetic limb amputations in developing countries. *Expert review of endocrinology & metabolism.* 2015;10(4):425-34.
19. Rommers G, Vos L, Groothoff J, Schuiling C, Eisma W. Epidemiology of lower limb amputees in the north of The Netherlands: aetiology, discharge destination and prosthetic use. *Prosthetics and Orthotics International.* 1997;21(2):92-9.
20. Hämäläinen H, Rönnemaa T, Halonen JP, Toikka T. Factors predicting lower extremity amputations in patients with type 1 or type 2 diabetes mellitus: a population-based 7-year follow-up study. *Journal of internal medicine.* 1999;246(1):97-103.
21. Keogh E. Men, masculinity, and pain. *Pain.* 2015; 156(12): 2408-12.
22. Young BA, Maynard C, Reiber G, Boyko EJ. Effects of ethnicity and nephropathy on lower-extremity amputation risk among diabetic veterans. *Diabetes care.* 2003;26(2):495-501.
23. Robinson T, Kenealy T, Garrett M, et al. Ethnicity and risk of lower limb amputation in people with type 2 diabetes: a prospective cohort study. *Diabetic Medicine.* 2016; 33(1): 55-61.
24. Lin C-W, Hsu BR-S, Tsai J-S, Yang H-M, Lin J-R, Lin C-H, et al. Effect of limb preservation status and body mass index on the survival of patients with limb-threatening diabetic foot ulcers. *Journal of diabetes and its complications.* 2017; 31(1): 180-5.
25. Sohn MW, Budiman-Mak E, Lee TA, Oh E, Stuck RM. Significant J-shaped association between body mass index

(BMI) and diabetic foot ulcers. *Diabetes/metabolism research and reviews*. 2011;27(4):402-9.

26. Girijala RL, Bush RL. Review of socioeconomic disparities in lower extremity amputations: a continuing healthcare problem in the United States. *Cureus*. 2018; 10(10). e3418

27. Pan A, Wang Y, Talaei M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. *Circulation*. 2015; 132(19): 1795-804.

28. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *Jama*. 2007; 298(22): 2654-64.

29. Chaturvedi N, Stevens L, Fuller JH, Group WHOMS. Which features of smoking determine mortality risk in former cigarette smokers with diabetes? The World Health Organization Multinational Study Group. *Diabetes care*. 1997; 20(8): 1266-72.

30. Biancari F, Kangasniemi O-P, Mahar M, Ylönen K. Need for late lower limb revascularization and major amputation after coronary artery bypass surgery. *European Journal of Vascular and Endovascular Surgery*. 2008; 35(5): 596-602.

31. Nallegowda M, Lee E, Brandstater M, et al. Amputation and cardiac comorbidity: analysis of severity of cardiac risk. *PM&R*. 2012; 4(9): 657-66.

32. Cimminiello C. PAD: Epidemiology and pathophysiology. *Thrombosis research*. 2002; 106(6): V295-V301.

33. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *Journal of the American College of Cardiology*. 2006;47(5):921-9.

34. Arruda-Olson AM, Moussa Pacha H, Afzal N, et al. Burden of hospitalization in clinically diagnosed peripheral artery disease: a community-based study. *Vascular Medicine*. 2018; 23(1): 23-31.

35. Paisey R, Abbott A, Paisey C, et al. Diabetic foot ulcer incidence and survival with improved diabetic foot services: an 18-year study. *Diabetic Medicine*. 2019; 36(11): 1424-30.

36. Shin JY, Roh S-G, Sharaf B, Lee N-H. Risk of major limb amputation in diabetic foot ulcer and accompanying disease: a meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2017; 70(12): 1681-8.

37. Pemayun TGD, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case-

control study. *Diabetic foot & ankle*. 2015; 6(1): 29629. 7:6:29629.

38. Akha O, Kashi Z, Makhloogh A. Correlation between amputation of diabetic foot and nephropathy. 2010; 4(1): 27-31

39. Sadriwala QS, Gedam BS, Akhtar MA. Risk factors of amputation in diabetic foot infections. *International Surgery Journal*. 2018;5(4):1399-402.

40. Borderie G, Foussard N, Larroumet A, et al. Diabetic retinopathy relates to the incidence of foot ulcers and amputations in type 2 diabetes. *Diabetes/Metabolism Research and Reviews*. 2023; 39(3): e3605.

41. Foussard N, Saulnier P-J, Potier L, et al. Relationship between diabetic retinopathy stages and risk of major lower-extremity arterial disease in patients with type 2 diabetes. *Diabetes Care*. 2020; 43(11): 2751-9.

42. Rodrigues BT, Vangaveti VN, Urkude R, Biros E, Malabu UH. Prevalence and risk factors of lower limb amputations in patients with diabetic foot ulcers: a systematic review and meta-analysis. *Diabetes & Metabolic Syndrome: clinical research & reviews*. 2022; 16(2): 102397.

43. Lavery LA, Hunt NA, Ndip A, et al. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. *Diabetes care*. 2010; 33(11): 2365-9.

44. Yammine K, Boulous K, Assi C, Hayek F. Amputation and mortality frequencies associated with diabetic Charcot foot arthropathy: a meta-analysis. *Foot and Ankle Surgery*. 2022; 28(8): 1170-6.

45. Steunenbergh SL, Te Slaa A, Ho GH, Veen EJ, de Groot HG, van der Laan L. Dementia in patients suffering from critical limb ischemia. *Annals of Vascular Surgery*. 2017; 38: 268-73.

46. Coffey L, O'Keeffe F, Gallagher P, Desmond D, Lombard-Vance R. Cognitive functioning in persons with lower limb amputations: a review. *Disability and rehabilitation*. 2012; 34(23): 1950-64.

47. O'Neill SM, Kabir Z, McNamara G, Buckley CM. Comorbid depression and risk of lower extremity amputation in people with diabetes: systematic review and meta-analysis. *BMJ Open Diabetes Research and Care*. 2017; 5(1): e000366.

48. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes care*. 2001; 24(6): 1069-78.

49. Ezzatvar Y, García-Hermoso A. Global estimates of diabetes-related amputations incidence in 2010-2020: a

- systematic review and meta-analysis. *Diabetes Research and Clinical Practice*. 2023; 195: 110194.
50. Santos VPd, Silveira DRd, Caffaro RA. Risk factors for primary major amputation in diabetic patients. *Sao Paulo Medical Journal*. 2006;124:66-70.
51. Vatankhah N, Jahangiri Y, Landry GJ, Moneta GL, Azarbal AF. Effect of systemic insulin treatment on diabetic wound healing. *Wound Repair and Regeneration*. 2017; 25(2): 288-91.
52. Chang H-Y, Chou Y-Y, Tang W, et al. Association of antidiabetic therapies with lower extremity amputation, mortality and healthcare cost from a nationwide retrospective cohort study in Taiwan. *Scientific reports*. 2021; 11(1): 7000.
53. Suckow BD, Newhall KA, Bekelis K, et al. Hemoglobin A1c testing and amputation rates in black, Hispanic, and white Medicare patients. *Annals of vascular surgery*. 2016; 36: 208-17.
54. Goldman MP, Clark CJ, Craven TE, Davis RP, Williams TK, Velazquez-Ramirez G, et al. Effect of intensive glycemic control on risk of lower extremity amputation. *Journal of the American College of Surgeons*. 2018; 227(6): 596-604.
55. Allan J, Munro W, Figgins E. Foot deformities within the diabetic foot and their influence on biomechanics: A review of the literature. *Prosthetics and orthotics international*. 2016; 40(2): 182-92.
56. Tang UH, Zügner R, Lisovskaja V, et al. Foot deformities, function in the lower extremities, and plantar pressure in patients with diabetes at high risk to develop foot ulcers. *Diabetic foot & ankle*. 2015; 6(1): 27593.
57. Oyibo S, Jude E, Tarawneh I, Nguyen H, Armstrong D, Harkless L, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabetic Medicine*. 2001; 18(2): 133-8.
58. Moon K-C, Kim S-B, Han S-K, Jeong S-H, Dhong E-S. Risk factors for major amputation in hospitalized diabetic patients with forefoot ulcers. *Diabetes Research and Clinical Practice*. 2019; 158: 107905.
59. Lee JH, Yoon JS, Lee HW, et al. Risk factors affecting amputation in diabetic foot. *Yeungnam University Journal of Medicine*. 2020; 37(4): 314-20.
60. Lipsky BA, Polis AB, Lantz KC, Norquist JM, Abramson MA. The value of a wound score for diabetic foot infections in predicting treatment outcome: a prospective analysis from the SIDESTEP trial. *Wound Repair and Regeneration*. 2009; 17(5): 671-7.
61. Miller W, Berg C, Wilson ML, et al. Risk factors for below-the-knee amputation in diabetic foot osteomyelitis after minor amputation. *Journal of the American Podiatric Medical Association*. 2019; 109(2): 91-7.
62. Wukich DK, Hobizal KB, Sambenedetto TL, Kirby K, Rosario BL. Outcomes of osteomyelitis in patients hospitalized with diabetic foot infections. *Foot & ankle international*. 2016; 37(12): 1285-91.
63. Wu S, Armstrong DG. Risk assessment of the diabetic foot and wound. *International wound journal*. 2005; 2(1): 17-24.
64. Ertugrul B, Oncul O, Tulek N, et al. A prospective, multi-center study: factors related to the management of diabetic foot infections. *European journal of clinical microbiology & infectious diseases*. 2012; 31: 2345-52.
65. Liu R, Petersen BJ, Rothenberg GM, Armstrong DG. Lower extremity reamputation in people with diabetes: a systematic review and meta-analysis. *BMJ Open Diabetes Research and Care*. 2021; 9(1): e002325.
66. Acar E, Kacira BK. Predictors of lower extremity amputation and reamputation associated with the diabetic foot. *The journal of foot and ankle surgery*. 2017; 56(6): 1218-22.
67. Matta-Gutierrez G, Garcia-Morales E, Garcia-Alvarez Y, et al. The influence of multidrug-resistant bacteria on clinical outcomes of diabetic foot ulcers: a systematic review. *Journal of Clinical Medicine*. 2021; 10(9): 1948.
68. Kandregula S, Behura A, Behera CR, et al. A clinical significance of fungal infections in diabetic foot ulcers. *Cureus*. 2022; 14(7): e26872.
69. Tabur S, Eren MA, Celik Y, 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.
70. Lin C-W, Hsu L-A, Chen C-C, 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 research and clinical practice*. 2010; 90(2): 167-72.
71. Perng C-K, Chou H-Y, Chiu Y-J. Identifying major predictors of lower-extremity amputation in patients with diabetic foot ulcers. *Journal of the Chinese Medical Association*. 2021; 84(3): 285-9.
72. Demirkol D, Aktaş Ş, Özcan T, Tannier X, Erol ÇS. Analysis of risk factors for amputation in patients with

diabetic foot ulcers: a cohort study from a tertiary center. *Acta Orthopaedica et Traumatologica Turcica*. 2022; 56(5): 333.

73. Demirdal T, Sen P. The significance of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and lymphocyte-monocyte ratio in predicting peripheral arterial disease, peripheral neuropathy, osteomyelitis and amputation in diabetic foot infection. *Diabetes research and clinical practice*. 2018; 144: 118-25.

74. Pierre-Louis WS, Bath J, Mikkilineni S, et al. Neutrophil to lymphocyte ratio as a predictor of outcomes after amputation. *Annals of Vascular Surgery*. 2019; 54: 84-91.

75. Huang Y, Zhong Z, Liu F. The Association of Coagulation Indicators and Coagulant Agents with 30-day mortality of critical diabetics. *Clinical and Applied Thrombosis/Hemostasis*. 021;27:10760296211026385.

76. Gülcü A, Etili M, Karahan O, Aslan A. Analysis of routine blood markers for predicting amputation/re-amputation risk in diabetic foot. *International wound journal*. 2020; 17(6): 1996-2004.

77. Coşkun B, Ayhan M, Ulusoy S. Relationship between prognostic nutritional index and amputation in patients with diabetic foot ulcer. *Diagnostics*. 2024; 14(7): 738.

78. Walinjkar RS, Khadse S, Kumar S, Bawankule S, Acharya S. Platelet indices as a predictor of microvascular complications in type 2 diabetes. *Indian journal of endocrinology and metabolism*. 2019; 23(2): 206-10.

79. Wang L, Li Q, Chen X, Wang Z. Clinical characteristics and risk factors of lower extremity amputation in patients with diabetic foot. *Pakistan Journal of Medical Sciences*. 2022; 38(8): 2253.

80. Li X, Guan L, Lin H, et al. Fibrinogen: a marker in predicting diabetic foot ulcer severity. *Journal of diabetes research*. 2016; 2016(1): 2358321.

81. Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower-extremity amputation in patients with diabetes. *Diabetes care*. 2008; 31(7): 1331-6.