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Risk Factors for Amputation in Diabetic Foot Ulcers: A Retrospective Analysis

ABSTRACT

Objectives: This study aims to identify the risk factors contributing to minor and major amputations in patients undergoing amputation due to diabetic foot, analyze the differences between these two groups, and develop strategies to prevent amputation progression.

Methods: This retrospective observational study included 337 patients who underwent amputation due to diabetic foot at the Chronic Wound Unit of Ankara Bilkent City Hospital between April 15, 2022, and December 31, 2024. Demographic data, comorbidities, clinical characteristics, and laboratory findings of the patients were evaluated. Statistical analyses were performed using the Mann-Whitney U test, Chi-square test, and Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Results: Among the study population, 221 patients underwent minor amputation, while 116 patients underwent major amputation. The mean age was significantly higher in the major amputation group (p=0.043). The length of hospital stay was also significantly longer in this group (p=0.019). Peripheral artery disease (p<0.001), chronic kidney disease (p=0.001), and congestive heart disease (p=0.001) were significantly more prevalent in the major amputation group. Osteomyelitis (p=0.002) and gangrene (p<0.001) were strongly associated with major amputation. Although HbA1c levels were higher in the minor amputation group (p=0.022), hemoglobin and glomerular filtration rate were significantly lower (p<0.001, p=0.0019). White blood cell, urea, and creatinine levels were significantly higher in the major amputation group (p=0.031, p=0.013, p=0.005).

Conclusion: Advanced age, peripheral artery disease, congestive heart disease, presence of infection, and elevated inflammatory markers are significant predictors of major amputation. Early diagnosis, vascular assessment, and infection control play a crucial role in reducing amputation rates in diabetic foot patients. Close monitoring of patients with PAD and CKD, along with the implementation of early intervention strategies, is essential in minimizing the risk of major amputation.

Keywords: Diabetic foot ulcer, major amputation, minor amputation, lower extremity amputation, risk factor

Diabetes mellitus (DM) is recognized as a major public health issue due to its rapidly increasing prevalence and associated complications worldwide (1). The sharp rise in diabetes incidence has led to an increasing burden of disease-related complications and healthcare system demands (2). DM is a chronic condition characterized by numerous complications that contribute to increased morbidity and mortality. Among these, diabetic foot ulcers (DFUs), which primarily affect the lower extremities, pose a significant clinical challenge (3). It is estimated that 19–34% of individuals with diabetes will develop a DFU at some point in their lives, and approximately 20% of these patients will undergo either minor or major lower extremity amputation (LEA) (4,5).

LEAs performed due to DFUs have profound negative consequences on patient health and quality of life. The primary goal in the management of diabetic foot is to prevent all amputations; however, in certain cases, minor amputations become unavoidable to control infection and preserve tissue integrity. Compared to major amputations, minor amputations result in less functional loss and dependency, allowing patients to retain a relatively better level of mobility. However, if not adequately managed, recurrent ulcerations and progressive tissue damage may lead to the progression from minor to major amputation (6,7). Moreover, it has been reported that approximately 50% of patients undergo a second amputation within 3–5 years after the initial LEA (8).

Major amputations, on the other hand, severely restrict patient independence, necessitate the use of wheelchairs or prosthetic devices, and require long-term rehabilitation. Additionally,

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the five-year mortality rate for patients undergoing major amputation is reported to be between 50% and 70%, comparable to the mortality rates of certain malignancies (9). Given the substantial impact of DFUs and amputations on patients' quality of life, their families, and healthcare systems, identifying and evaluating the risk factors associated with DFU-related LEA is a critical necessity (10).

This study aims to identify risk factors in patients undergoing amputation due to diabetic foot, analyze the differences between minor and major amputations, and propose preventive strategies to mitigate the progression of amputation. In particular, the study focuses on identifying the key determinants of major amputations, developing limb-salvaging strategies and establishing preventive approaches to guide clinical practice.

METHODS

Study Design and Ethical Approval

This retrospective observational study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (Decision number: TABED 2-25-962, Date: 19/02/2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

A total of 337 patients who underwent amputation due to diabetic foot at the Chronic Wound Unit of Ankara Bilkent City Hospital between April 15, 2022, and December 31, 2024 were included in the study. Data were retrospectively retrieved from patient medical records. Patients under 18 years of age, those who had undergone amputation for reasons other than diabetic foot, patients with diabetic foot ulcers managed without amputation, and those with any form of cancer or immune deficiency were excluded from the study.

Amputation Definitions

Minor Amputation: Includes all amputations performed distal to the ankle joint.

Major Amputation: Includes all amputations performed proximal to the ankle joint.

Evaluated Variables

The study analyzed patients' demographic data (age, sex, amputation level), comorbidities [duration of diabetes mellitus, hypertension (HT), congestive heart disease (CHD), chronic kidney disease (CKD), hyperlipidemia, peripheral arterial disease (PAD)], clinical parameters (history of prior amputation, presence of osteomyelitis, presence of gangrene, smoking status), and laboratory findings [glycated hemoglobin (HbA1c), white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), serum albumin, urea, creatinine, glomerular filtration rate (GFR), and C-reactive protein (CRP) levels].

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was employed to compare non-normally distributed continuous variables between groups, while the Chi-square test was used for categorical data analysis. In cases of small sample sizes, Fisher's exact test was applied to ensure statistical accuracy. The relationships between continuous variables were assessed using Spearman's rank correlation coefficient, whereas the associations between categorical variables were evaluated using Cramer's V and Phi coefficients. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

A total of 337 patients who underwent major or minor amputation at our hospital were included in the study. Among them, 221 patients underwent minor amputation, while 116 patients underwent major amputation (Table 1).

The mean age of patients who underwent minor amputation was 64.48±11.28 years, whereas the mean age of those who underwent major amputation was 67.21±11.01 years. Patients in the major amputation group were significantly older compared to those in the minor amputation group (p=0.043). Regarding hospital stay duration, major amputations were associated with a significantly longer hospitalization period than minor amputations (p=0.019). However, no statistically significant differences were observed between the minor and major amputation groups concerning diabetes mellitus duration, gender distribution, and smoking status (Table 2).

Table 1. Demographic data of included patients

	Minor Amputation	Major Amputation	p
Age	64.48±11.28	67.21±11.01	**0.043**
Duration of Diabetes (years)	15.45±6.12	16.98±6.83	0.099
Hospital Stay (days)	23.27±16.88	28.33±20.45	**0.019**
Gender			
Male	175 (79.2)	90 (77.8)	0.758
Female	46 (20.8)	26 (22.2)	
Smoking			
Yes	119 (53.8)	53 (46.0)	0.161
No	102 (46.2)	63 (54.0)	

p: value.

Table 2. Distribution of comorbidities by amputation level

	Minor Amputation n (%)*	Major Amputation n (%)*	p
Hypertension			
Yes	121 (54.8)	73 (62.6)	0.150
No	100 (45.2)	43 (37.3)	
Congestive Heart Disease			
Yes	117 (52.9)	83 (71.4)	**0.001**
No	104 (47.1)	33 (28.6)	
Chronic Kidney Disease			
Yes	45 (20.4)	42 (36.5)	**0.001**
No	176 (79.6)	74 (63.5)	
Hyperlipidemia			
Yes	43 (19.5)	20 (17.5)	0.647
No	178 (80.5)	96 (82.5)	
Peripheral Arterial Disease			
Yes	80 (36.2)	69 (59.5)	**0.000**
No	141 (63.8)	47 (40.5)	

*n: Number of patients; p: value.

According to the data, the prevalence of congestive heart disease (p=0.001), chronic kidney disease (p=0.001), and peripheral arterial disease (p<0.001) was significantly lower in the minor amputation group compared to the major amputation group. However, the presence of hypertension and hyperlipidemia did not show a statistically significant difference between the minor and major amputation groups (p>0.05) (Table 3).

There was no statistically significant difference in fasting glucose levels between the two groups. However, HbA1c levels were significantly higher in the minor amputation group compared to the major amputation group (p=0.022).

Additionally, Hb and GFR values were significantly higher in the minor amputation group compared to the major amputation group (p<0.001 and p=0.001, respectively). WBC, urea, and creatinine levels were significantly lower in the minor amputation group (p=0.031, p=0.013, p=0.005, respectively).

There were no statistically significant differences between the two groups regarding CRP, PLT and serum albumin levels (p>0.05) (Table 4).

Table 3. Laboratory results

	Minor Amputation (Mean±SD)	Major Amputation (Mean±SD)	p
HbA1c	8.66±2.14	8.23±2.27	**0.022**
Fasting Glucose	203.33±234.35	189.49±109.1	0.712
Hemoglobin	12.01±2.05	11.09±1.83	**0.000**
WBC	10.64±5.26	11.79±5.184	**0.031**
Platelet Count	355.06±123.68	368.28±145.53	0.599
Serum Albumin	38.01±3.70	37.32±4.26	0,183
Urea	52.05±31.57	59.63±32.57	**0.013**
Creatinine	1.47±1.54	1.66±1.40	**0.005**
GFR	69.74±29.56	59.39±28.77	**0.001**
CRP	76.91±66.32	85.69±72.86	0.259

p: value; HbA1c: Glycated hemoglobin (%)/Fasting Glucose (mg/dL)/ Hemoglobin (mg/dL)/White Blood Cell Count (WBC) ($x10^9$/L)/Platelet Count ($x10^3$/µL)/Serum Albumin (g/dL)/Urea (mg/dL)/Creatinine (mg/dL)/Glomerular Filtration Rate (GFR) (mL/min 1.73m^2)/C-Reactive Protein (CRP) (mg/L).

Table 4. Characteristics of diabetic foot ulcers

	Major Amputation	Minor Amputation	p
Previous Amputation			
Yes	51 (23.1)	55 (47.6)	**0.000**
No	170 (76.9)	61 (52.4)	
Osteomyelitis			
Yes	100 (45.2)	30 (28.6)	**0.002**
No	121 (54.8)	86 (71.4)	
Gangrene			
Yes	155 (70.1)	102 (88.1)	**0.000**
No	66 (29.9)	14 (11.9)	

p: value.

According to Table 4, the rate of previous amputation history was significantly lower in minor amputation cases compared to major amputation cases (p<0.001). Additionally, the presence of osteomyelitis and gangrene was significantly higher in major amputation cases compared to minor amputation cases (p=0.002 and p<0.001, respectively).

DISCUSSION

This study aims to comprehensively evaluate the risk factors leading to minor and major amputations in patients undergoing lower extremity amputation (LEA) due to diabetic foot complications. The findings indicate that the development of amputation in diabetic foot patients is influenced by a complex interplay of demographic, clinical and biochemical variables. In particular, PAD, CKD, osteomyelitis, and gangrene have been identified as strong predictors of major amputation. Early identification and multidisciplinary management of vascular and metabolic disorders, such as PAD and CKD, may contribute to a reduction in major amputation rates. Moreover, timely diagnosis and aggressive treatment of osteomyelitis and gangrene are critical interventions for limb preservation. While gender and smoking status were not found to be statistically significant factors in determining amputation severity, it should be noted that smoking negatively affects vascular circulation and may play an indirect role in the progression of diabetic foot disease.

The findings of this study highlight the multifactorial nature of the amputation process in diabetic foot patients and underscore the influence of various clinical parameters in shaping this outcome. Therefore, a proactive, individualized and comprehensive management strategy is essential to minimize the risk of amputation in diabetic foot patients. This strategy should incorporate a multidisciplinary approach that addresses vascular, infectious and metabolic factors while implementing preventive interventions aimed at reducing the likelihood of amputation progression.

The incidence of amputation in diabetic foot patients is known to increase with age. In our study, the mean age of patients undergoing major amputation was significantly higher than that of those undergoing minor amputation (p=0.043). This finding aligns with previous research indicating that advanced age is a significant risk factor for amputation (8,11). As age progresses, comorbid conditions such as PAD, CHD and CKD become more prevalent, further increasing the risk of amputation (12). Additionally, the slower wound healing processes observed in older patients further contribute to the necessity for amputation.

The role of gender in amputation risk remains a debated topic. Some studies report a higher incidence of amputation in male patients, attributing this to delayed healthcare-seeking behavior and a higher prevalence of smoking among men. However, our study found no statistically significant difference between the minor and major amputation groups in terms of gender distribution. This suggests that gender alone may not be a decisive factor in determining amputation risk and should be considered alongside other clinical risk factors.

Cardiovascular diseases and kidney failure play a critical role in the amputation process among diabetic foot patients. In our study, patients who underwent major amputation had significantly higher rates of PAD (p<0.001), CKD (p=0.001), and CHD (p=0.001). Literature also supports that PAD is a strong predictor of amputation, as

critical limb ischemia significantly increases the need for amputation (13,14). The study by Thorud et al. (15) further reinforces this finding, reporting that patients with both diabetes and PAD experience significantly higher post-major amputation mortality rates (15).

PAD contributes to amputation risk by causing limb ischemia, while CKD exacerbates systemic inflammation and delays wound healing. Therefore, early diagnosis and timely interventions, particularly revascularization procedures, are crucial in reducing overall amputation rates, particularly major amputations. In this context, clinical assessments, ankle-brachial index (ABI) measurements, color doppler ultrasonography (DUSG), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) should be utilized for comprehensive vascular evaluation (16).

Additionally, renal dysfunction is a significant risk factor for amputation. CKD increases amputation risk by both amplifying inflammatory responses and triggering vascular complications. In our study, creatinine (p=0.005) and urea (p=0.013) levels were significantly higher in the major amputation group, findings that are consistent with previous studies by Kim et al. (14) and Kaminski et al. (17), which highlight the impact of CKD on amputation risk.

For patients with CKD and elevated urea/creatinine levels, traditional contrast-based imaging techniques pose a risk of nephrotoxicity, necessitating the use of alternative diagnostic approaches. Carbon dioxide angiography (CO_2) has been suggested as a safer vascular imaging modality compared to nephrotoxic contrast agents. Since CO_2 is not excreted through the kidneys, it does not contribute to contrast-induced nephropathy, making it particularly advantageous for patients with advanced renal failure requiring PAD assessment. However, CO_2 angiography may have limitations in image quality for certain patients, and its application should be performed in experienced centers to ensure optimal diagnostic accuracy (18).

In addition to conditions that exacerbate vascular complications, such as kidney failure, smoking is a significant risk factor in the amputation process for diabetic foot patients. Smoking has been shown to adversely affect amputation outcomes by inducing vascular endothelial damage, accelerating the progression of PAD, reducing blood flow to the extremities, and worsening tissue ischemia. In this study, no statistically significant difference was observed between the major and minor amputation groups regarding smoking status (p=0.161). However, this finding may be influenced by patient characteristics, duration and amount of smoking, presence of comorbidities, or individual variations in vascular structure. Existing literature has demonstrated that smoking significantly increases amputation rates in patients with PAD and elevates the risk of lower extremity amputation in individuals with diabetic foot ulcers (19). Furthermore, smoking has been shown to enhance systemic inflammatory responses, impair tissue healing, and reduce the success rates of revascularization procedures. These mechanisms collectively lead to delayed wound healing, increased infection risk, and a higher likelihood of postoperative complications. These findings emphasize that smoking is a crucial modifiable risk factor in the amputation process for diabetic foot patients. Therefore, it is imperative to actively promote smoking cessation programs for diabetic foot patients and to conduct further research into the long-term effects of smoking on amputation risk.

Infections are one of the most critical determinants of amputation risk in diabetic foot patients. In particular, the presence of osteomyelitis and gangrene significantly increases the likelihood of major amputation (20,21). In our study, the prevalence of osteomyelitis (p=0.002) and gangrene (p<0.001) was significantly higher in the major amputation group. Similarly, previous studies have reported that diabetic foot ulcers create a favorable environment for infection development, and amputation rates are markedly higher in cases associated with osteomyelitis (22).

As the infection spreads and progresses into deep tissues, conservative treatment options become inadequate, ultimately making amputation inevitable. In addition to infections, inflammatory markers play a crucial role in assessing the amputation process. Our study found that WBC levels were significantly higher in the major amputation group (p=0.031). Several systematic reviews and meta-analyses have demonstrated that elevated inflammatory markers (WBC, CRP) increase the risk of major amputation (14,23). However, CRP levels did not show a statistically significant difference between the minor and major amputation groups (p>0.05). This finding suggests that WBC may serve as a more dynamic marker of acute infection, making it a more reliable predictor of amputation risk. In contrast, CRP reflects systemic inflammation but may be influenced by various clinical and metabolic factors, leading to variability in its prognostic value during the amputation process. Chronic hyperglycemia in diabetic foot patients impairs immune system function, facilitating infection development and intensifying the inflammatory process, which accelerates tissue damage. Therefore, regular monitoring of WBC levels and managing inflammation in the early stages with appropriate treatment strategies are critical in preventing limb loss in clinical practice.

Metabolic factors also play a role in the amputation process. While HbA1c levels are known to be associated with diabetic foot ulcer formation, it is believed that HbA1c alone cannot determine the level of amputation. A meta-analysis conducted by Crawford et al. (24) demonstrated that high HbA1c levels are linked to an increased risk of diabetic foot ulcer development. However, in our study, HbA1c levels were found to be significantly higher in the minor amputation group (p=0.022). This finding suggests that additional factors such as PAD, infection, and kidney failure may be more influential in the progression to major amputation.

In our study, hemoglobin levels were significantly lower in the major amputation group (p<0.001). This finding suggests that anemia may reduce tissue oxygenation and delay wound healing, increasing the risk of amputation. A study conducted in a vascular surgery unit in Brazil reported that anemia, particularly in the presence of PAD, significantly increases the risk of both amputation and mortality in diabetic foot patients (25). Regular monitoring of hemoglobin levels in diabetic foot patients, early detection and management of anemia, and integration of anemia treatment with revascularization strategies and oxygen therapies may play a crucial role in reducing limb loss risk, particularly in patients with PAD or CKD.

Early intervention and multidisciplinary patient management play a crucial role in reducing amputation rates. Endovascular revascularization is one of the most effective strategies for lowering the risk of amputation in diabetic foot patients. In a study by Kang et al. (20), early revascularization was shown to reduce the likelihood of

major amputation. In our study, data on whether revascularization was performed on the patients were not available. However, the significantly higher prevalence of PAD in patients who underwent major amputation (p<0.001) suggests that early vascular assessment and interventions could play a critical role in this patient population.

The amputation process is not limited to surgical intervention alone. Post-amputation physical rehabilitation and prosthetic use are essential in improving patients› quality of life and functional independence. Studies have demonstrated that multidisciplinary approaches improve post-amputation functional outcomes and reduce mortality rates (26). Therefore, early inclusion of amputee patients in rehabilitation programs is of great importance for long-term clinical outcomes.

This study has several limitations: Due to its retrospective design, some clinical data may be incomplete, making it difficult to establish causality. As a single-center study, the findings may have limited generalizability to different patient populations. Factors such as socioeconomic status and patient education, which may influence the amputation process, were not evaluated. Variables such as smoking history and diabetes duration were based on patient-reported information, which may be subject to recall bias. To overcome these limitations, future prospective, multicenter studies are needed to provide more comprehensive analyses of the factors influencing amputation in diabetic foot patients.

CONCLUSION

This study presents a comprehensive analysis of the risk factors contributing to major and minor amputations in patients with diabetic foot. The findings indicate that advanced age, PAD, CKD, presence of infection, and elevated inflammatory markers serve as significant predictors of major amputation. These results underscore the imperative role of early diagnosis, evidence-based therapeutic interventions, and a multidisciplinary approach in mitigating amputation rates and optimizing patient outcomes.

To further enhance risk stratification and improve clinical management, future investigations should incorporate long-term patient follow-up data and advanced predictive modeling techniques**.** The integration of artificial intelligence-driven risk assessment tools and large-scale prospective studies has the potential to refine individualized risk prediction, facilitate early intervention strategies, and ultimately contribute to the advancement of limb preservation efforts in diabetic foot care**.**

Ethics Committee Approval: This retrospective observational study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki (No: TABED 2-25-962, Date: 19/02/2025).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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