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Risk Factors Associated with Amputation for Patients with Diabetic Foot Ulcers: A Retrospective Study

Bo Yang[1,*], Xuwen Zha[2,*], Yunling Ding[1]

[1]Department of Burn & Plastic Surgery, The First People's Hospital of Hefei, Binhu Hospital of Hefei, The Third Affiliated Hospital of Anhui Medical University, Hefei, 230000, People's Republic of China; [2]Department of Rheumatology and Immunology, The First People's Hospital of Hefei, Binhu Hospital of Hefei, The Third Affiliated Hospital of Anhui Medical University, Hefei, 230000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yunling Ding, Department of Burn & Plastic Surgery, The First People's Hospital of Hefei, Binhu Hospital of Hefei, The Third Affiliated Hospital of Anhui Medical University, Hefei, 230000, People's Republic of China, Email yunlinding@163.com

Objective: Diabetic foot ulcer (DFU) and related amputation significantly contribute to morbidity rates. The objective of this study was to assess the risk factors correlated with amputation in Chinese patients with DFU.

Methods: A prospective study was implemented on DFU patients at Third Affiliated Hospital of Anhui Medical University from February 2016 to May 2024. Patients were categorized into two groups based on whether they underwent amputation: the amputation group (n = 33) and the non-amputation group (n = 29). A comparative analysis was conducted between two groups, focusing on demographic data, disease characteristics, and laboratory indicators. Binary and multivariate logistic regressions were employed to evaluate the risk factors associated with amputation. Receiver Operating Characteristic curve analysis was used to assess the risk factors in predicting amputation in patients with DFU.

Results: The incidence of history of amputation, duration of diabetes in the amputation group were significantly increased compared to the non-amputation group ($P < 0.05$). On the contrary, the red blood cell count, hemoglobin level, and hematocrit in the amputation group were significantly lower compared to the non-amputation group ($P < 0.05$). Moreover, in the bi-variable logistic regression analysis, the duration of diabetes, duration of DFU, history of amputation, and hemoglobin levels were significantly associated with amputation ($P < 0.05$). After controlling potential confounding factors in multiple logistic regression analysis, duration of DFU was identified as a determining factor for amputation ($P < 0.05$). Additionally, the values for the area under curve (AUC) in relation to the duration of diabetes, duration of DFU, history of amputation, and a combined panel in predicting the occurrence of amputation in patients with DFU were 0.890, 0.868, 0.730, and 0.916, respectively.

Conclusion: Our findings indicate that duration of DFU is an independent risk factor for amputation in patients with DFU.

Keywords: amputation, diabetic foot ulcer, risk factors, diabetes mellitus

Introduction

Diabetes mellitus, along with its associated complications, represents a group of metabolic diseases characterized by high morbidity, leading to a significant deterioration in health and quality of life. According to the World Health Organization's report, the global population affected by diabetes mellitus is estimated to be around 425 million in 2017.[1] Future projections anticipate an increase to 578 million by 2030, escalating further to an alarming 700 million by 2045.[2] An epidemiological survey revealed that the prevalence of diabetes mellitus in China was 12.8% in 2017, underscoring the fact that diabetes mellitus has evolved into a critical public health issue globally, especially in China.[3]

Diabetic foot ulcer (DFU), a prevalent and severe complication of diabetes mellitus, impacts approximately 15% of patients with diabetic mellitus throughout their lifespan.[4,5] These ulcers, a type of wound, can escalate into infection and ulcer exacerbation if not promptly and appropriately treated, potentially resulting in amputation. DFU-associated

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amputations significantly contribute to morbidity and mortality rates among diabetic patients.[6,7] Globally, the recurrence rates of DFU are 40% within the first year, 60% within three years, and 65% within five years.[8] The five-year mortality rate for patients suffering from DFU is estimated to be approximately 30%, a figure that rises to over 70% for those who have undergone a major amputation.[7] Consequently, identification of risk factors leading to amputation is of paramount importance for predicting the prognosis of patients with DFU. However, the specific risk factors contributing to amputation in patients with DFU, as well as the degree to which these various factors amplify the risk of amputation, remain unclear.

The rates of amputation varied significantly across different countries. It has been reported that the annual incidence of DFU and limb amputation among Japanese patients with type 2 diabetes was 0.3% and 0.05%, respectively.[9] In Sweden, the annual incidence rate of lower limb amputation was recorded at 0.044%, equating to 44.2 cases per 100,000 individuals with diabetes.[10] A more recent retrospective study has highlighted a substantial risk of DFU-related amputation (44%) among adult patients, predominantly from Black and/or Hispanic backgrounds.[11] In China, the annual incidence of amputation and the 7-year average incidence among patients with DFU were significantly high, recorded at 5.1% and 9.9%, respectively.[12] Moreover, a meta-analysis indicates an amputation incidence of 22.4% in Chinese patients with DFU.[13] It is important to acknowledge that the risk factors for amputation in patients with DFU are diverse and multifaceted, leading to potential variations in conclusions across different studies.[5,14] This phenomenon may be attributed to variations in geographic location, ethnicity, socioeconomic conditions, and individual cognitive factors among patients with DFU. Given the disparities in amputation rates and associated risk factors across diverse populations and regions, this study aims to analyse the risk factors for amputation of DFU patients in China, and provide a reference for further exploring the reduction of amputation rate of DFU patients.

This research undertook a retrospective analysis of data from Chinese patients with DFU, with the aim to identify potential risk factors linked to DFU amputation, so as to contribute to the development of early intervention to reduce the prevalence of amputation and enhance the treatment outcomes for patients with DFU.

Patients and Methods

Subjects

Clinical data was gathered from the electronic medical records of 62 patients with DFU admitted to Third Affiliated Hospital of Anhui Medical University between February 2016 and May 2024. The inclusion criteria for the participants were as follows: (1) Age above 18 years; (2) Inpatients; (3) Fulfillment of the International Diabetic Foot Working Group's diagnostic criteria for DFU; (4) Complete clinical cases and follow-up data. The exclusion criteria were as follows: (1) Patients diagnosed with lower extremity thrombosis or acute arterial embolism; (2) Patients with a Wagner grading of level 0 for diabetic foot; (3) Patients with concurrent diseases causing lower limb pain including nerve pain, arthritis, venous disease, or bony or ligamentous trauma. Patients were categorized into two groups based on whether they underwent amputation: the amputation group (n = 33) and the non-amputation group (n = 29). The research protocol received approval from the Ethics Committee of Binhu Hospital of Hefei (approval number: 2024-162-01). It was a retrospective study, without direct intervention. All patient data are anonymous. Subjects' information and privacy are fully protected. Therefore, the institutional review board waived the need for written informed consent provided by participants. This study complied with the Declaration of Helsinki.

Demographic and Clinical Data Collection

A demographics questionnaire was employed to gather comprehensive participant information: (1) Demographic data: age, sex, BMI, drinking history, smoking history, and hypertension; (2) Disease characteristics: duration of diabetes, duration of DFU, history of amputation, Wagner grading, ulcer area, hemoglobin A1c (HbA1c), C-reactive protein (CRP), fasting blood glucose, and fasting C-peptide; (3) Hematological variables; (4) Biochemical parameters; (5) Thyroid function parameters; and (6) Coagulation parameters.

Statistical Analysis

The analysis of the data was executed employing SPSS (Version 17.0; SPSS, Inc, Chicago, IL, USA). The Kolmogorov–Smirnov one-sample test was utilized as a tool to identify normal distributions. The study incorporated descriptive analyses, wherein quantitative variables with a normal distribution were represented as means ± standard deviation (SD), and those with skewed distribution were represented as median and interquartile range (IQR; 25–75%). For the comparison of variables with a normal distribution between the two groups, the independent samples *t*-test was employed. Conversely, the Mann–Whitney *U*-test was utilized for variables that deviated from a normal distribution. For categorical variables, the Chi-square test was applied. The study utilized univariate analyses to explore the risk factors linked to amputation by comparing demographic and clinical variables between the two groups. Subsequent binary logistic regression was conducted on variables that exhibited a significance level of P-value < 0.05 in univariate analyses. To determine the association between the different predictor variables with the dependent variable, first bi-variable analysis between each independent variable and outcome variable was investigated using a binary logistic regression model and then all variables having P-value < 0.25 in the bi-variable analysis were suggested as a criterion for variable selection for inclusion into a multivariable logistic regression analysis to see the relative effect of confounding variables and interaction of variables. Adjusted odd ratio (AOR) with 95% CI was performed to determine the strength of association of variables with a P-value < 0.05 was declared as statistically significant. Receiver Operating Characteristic (ROC) curve analysis was used to assess the risk factors in predicting the occurrence of amputation in patients with DFU. The threshold for statistical significance was set at a P-value of less than 0.05 (two-tailed).

To determine the sample size for this study, a prior statistical power analysis for a logistic regression analysis was performed using G*Power 3.1.9.4. (Heinrich Heine University Düsseldorf, Düsseldorf, Germany) according to recommendations by Faul et al.[15] This analysis indicated that a total of 60–70 participants would be needed, depending on a statistical power of 80% at an α level of 0.05 (assumptive incidence rate = 20–30%, OR ratio = 2.5). Therefore, the sample size in this study meets the minimal requirements for statistical analysis.

Results

Comparison of Demographic Data and Disease Characteristics Between Amputation Group and Non-Amputation Group

As shown in Table 1, the incidence of history of amputation was significantly higher in the amputation group compared to the non-amputation group (χ^2 = 13.175, P < 0.001). Moreover, the duration of diabetes (t = −3.381, P = 0.001) and duration of DFU (t = −3.476, P = 0.001) in the amputation group were significantly increased compared to the non-amputation group. No significant differences were observed in other variables between the two groups (all P > 0.05; Table 1).

Comparison of Hematological, Biochemical, Thyroid Function, and Coagulation Parameters Between Amputation Group and Non-Amputation Group

Table 2 shows the differential hematologic parameters in the amputation group and the non-amputation group. The red blood cell (RBC) count (t = 2.983, P = 0.004), hemoglobin level (t = 3.387, P = 0.001), and hematocrit (HCT) (t = 3.241, P = 0.002) in the amputation group were significantly lower compared to the non-amputation group. No significant differences were observed in other hematological variables, biochemical parameters, thyroid function parameters, or coagulation parameters between the two groups (all P > 0.05; Supplementary Tables S1 and S2).

Risk Factors for Amputation in Patients with DFU

In the univariate analyses, variables exhibiting P values less than 0.05 were incorporated into a binary logistic regression model (Table 3). The variables selected for risk estimation of amputation encompassed duration of diabetes, duration of DFU, history of amputation, RBC count, hemoglobin levels, and HCT.

In the bi-variable logistic regression analysis, the duration of diabetes (COR = 11.812, 95% CI: 3.550–39.311), duration of DFU (COR = 17.333, 95% CI: 4.286–70.091), history of amputation (COR = 7.667, 95% CI: 2.419–24.303),

Table 1 Comparison of Demographic Data and Disease Characteristics Between Amputation Group and Non-Amputation Group

Indicators	Non-Amputation Group (n = 29)	Amputation Group (n = 33)	$t/Z/\chi^2$	*P*
Sex			2.304	0.129
Male	22	19		
Female	7	14		
Age (years)	63.86 ± 12.98	67.39 ± 13.55	−1.044	0.301
BMI (kg/m^2)	25.42 ± 3.73	24.22 ± 3.27	0.835	0.413
Smoking history			3.566	0.059
Yes	5	1		
No	24	32		
Drinking history			0.501	0.479
Yes	2	1		
No	27	32		
Hypertension			2.285	0.131
Yes	12	20		
No	17	13		
Duration of diabetes (years)	8.48 ± 2.79	11.76 ± 4.70	−3.381	0.001
Duration of DFU (months)	27.76 ± 11.83	42.64 ± 21.10	−3.476	0.001
History of amputation			13.175	<0.001
Yes	6	22		
No	23	11		
Wagner grading			2.541	0.111
Grade 0–3	23	20		
Grade 4–5	6	13		
Ulcer area (cm^2)	4 (3, 16.5)	3.5 (2, 6.75)	−1.712	0.087
HbA1c (%)	9.00 ± 2.65	9.93 ± 1.59	−1.277	0.210
CRP (mg/L)	101.36 ± 74.35	106.26 ± 97.11	−022.135	0.894
Fasting blood glucose (mmol/L)	10.14 ± 5.53	9.22 ± 5.03	0.649	0.519
Fasting C-peptide (nmol/L)	0.71 ± 0.58	0.75 ± 0.48	−0.190	0.851

Table 2 Comparison of Differential Hematologic Parameters Between Amputation Group and Non-Amputation Group

Indicators	Non-Amputation Group (n = 29)	Amputation group (n = 33)	*t*	*P*
RBC count (10^{12}/L)	4.42 ± 0.55	3.96 ± 0.59	2.983	0.004
Hemoglobin (g/L)	131.34 ± 18.34	114.41 ± 18.73	3.387	0.001
HCT (%)	39.99 ± 5.41	35.33 ± 5.25	3.241	0.002

Abbreviations: RBC, red blood cell; HCT, haematocrit value.

and hemoglobin levels (COR = 0.316, 95% CI: 0.104–0.963) were significantly associated with amputation in patients with DFU (Table 3).

Multivariable logistic regression analysis was done for variables having $P < 0.2$ in binary logistic regression analysis (duration of diabetes, duration of DFU, history of amputation, RBC count, hemoglobin levels).

After controlling potential confounding factors in multiple logistic regression analysis, duration of DFU (AOR = 12.263, 95% CI: 2.074–72.508) was identified as a determining factor for amputation in patients with DFU (Table 3).

ROC Curve Analysis to Assess the Risk Factors in Predicting the Occurrence of Amputation in Patients with DFU

The ROC curve was employed to assess the predictive capacity of the duration of diabetes, duration of DFU, and history of amputation. The Area Under the Curve (AUC) for the duration of diabetes in forecasting the incidence of amputation

Table 3 Binary and Multivariate Logistic Regressions of Factors Associated with Amputation

Variables	Amputation		COR (95% CI)	*P*	AOR (95% CI)	*P*
	Yes, n (%)	No, n (%)				
Duration of diabetes						
≤10	6 (22.2)	21 (77.8)	1	<0.001	1	0.121
>10	27 (77.1)	8 (22.9)	11.812 (3.550–39.311)		3.614 (0.711–18.353)	
Duration of DFU						
≤30	11 (29.7)	26 (70.3)	1	<0.001	1	0.006
>30	22 (88.0)	3 (12.0)	17.333 (4.286–70.091)		12.263 (2.074–72.508)	
History of amputation						
No	11 (32.4)	23 (67.6)	1	0.001	1	0.113
Yes	22 (78.6)	6 (21.4)	7.667 (2.419–24.303)		4.278 (0.709–25.829)	
RBC count						
≤4.2	16 (61.5)	10 (38.5)	1	0.138	1	0.977
>4.2	12 (41.4)	17 (58.6)	0.441 (0.150–1.301)		0.934 (0.009–92.589)	
Hemoglobin						
≤120	16 (66.7)	8 (33.3)	1	0.043	1	0.393
>120	12 (38.7)	19 (61.3)	0.316 (0.104–0.963)		0.132 (0.001–13.784)	
HCT						
≤38	16 (59.3)	11 (40.7)	1	0.226		
>38	12 (42.9)	16 (57.1)	0.516 (0.176–1.506)			

Abbreviations: AOR, adjusted OR; COR, crude OR.

in patients with DFU was determined to be 0.890 (95% CI = 0.810–0.971, $P < 0.001$), with an optimal cutoff of 11.5 and corresponding sensitivity and specificity values of 78.8% and 82.8%, respectively (Figure 1A). The AUC for the duration of DFU was calculated to be 0.868 (95% CI = 0.779–0.958, $P < 0.001$), with a determined cutoff value of 27.5. The sensitivity and specificity of this cutoff were observed to be 72.7% and 86.2%, respectively (Figure 1B). The AUC for the history of amputation was ascertained to be 0.730 (95% CI = 0.602–0.858, $P = 0.002$; Figure 1C).

Additionally, a ROC curve analysis was performed to assess the discriminatory ability of the combined variables (duration of diabetes, duration of DFU, and history of amputation) in predicting the occurrence of amputation in patients with DFU. The AUC for this combination was calculated to be 0.916 (95% CI = 0.844–0.989, $P < 0.001$; Figure 1D). The sensitivity and specificity were found to be 87.9% and 86.2%, respectively.

Discussion

The present study conducted a comparative analysis of demographic data, disease characteristics, hematological variables, biochemical parameters, thyroid function parameters, and coagulation parameters between patients in the amputation group and the non-amputation group, with the objective of identifying risk factors associated with amputation in patients with DFU. Four principal findings were identified in this study. Firstly, individuals in the amputation group exhibited a higher prevalence of history of amputation and a longer duration of diabetes and duration of DFU, along with a lower RBC count, hemoglobin level, and HCT compared to those in the non-amputation group. Secondly, the duration of diabetes, duration of DFU, history of amputation, and hemoglobin levels were significantly associated with amputation in the bi-variable logistic regression analysis. Thirdly, duration of DFU was identified as a determining factor for amputation after controlling potential confounding factors in multiple logistic regression analysis. Fourthly, a combined assessment panel incorporating the duration of diabetes, duration of DFU, and history of amputation demonstrated high predictive accuracy for the occurrence of amputation in patients with DFU.

The present study demonstrate that individuals in the amputation group exhibited lower RBC count, hemoglobin levels, and HCT compared to those in the non-amputation group. In the bi-variable logistic regression analysis, hemoglobin levels demonstrated a significant association with amputation. This observation is consistent with previous study indicating that low hemoglobin levels constitute a risk factor for major amputation and mortality in patients with

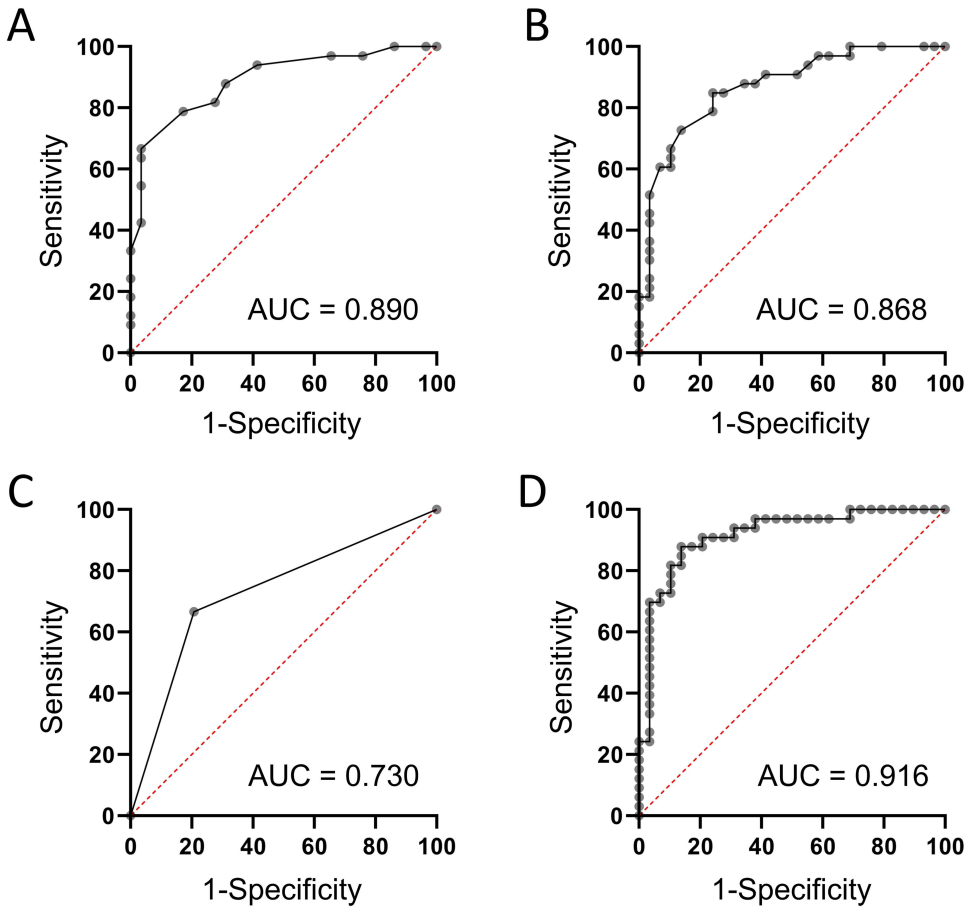

Figure 1 ROC analysis of duration of diabetes, duration of DFU, and history of amputation in predicting the occurrence of amputation in patients with DFU. (**A**) ROC curve of duration of diabetes; (**B**) ROC curve of duration of DFU; (**C**) ROC curve of history of amputation; (**D**) ROC curve of a combined panel of duration of diabetes, duration of DFU, and history of amputation.

DFU.[16] Conversely, elevated hemoglobin levels have been reported as protective against DFU-related amputations.[17] Anemia is highly prevalent among patients with diabetes and is commonly associated with adverse outcomes in patients with DFU.[18,19] A meta-analysis has further elucidated a significant association between low hemoglobin levels and increased rates of non-healing ulcers, amputation, and mortality in patients with DFU.[20] Another study identified a 1.44-fold increased risk of amputation and mortality in patients with anemia.[21] Numerous studies have indicated that reduced hemoglobin levels may hinder tissue perfusion in patients with compromised peripheral vascular status.[22] In healthy individuals, low hemoglobin levels are counterbalanced by a decrease in blood viscosity, enhanced peripheral circulation, vascular smooth muscle responsiveness, and elevated erythropoietin levels, all of which serve as triggers for neovascularization. Although the clinical impact is minimal in healthy individuals, each of these compensatory mechanisms is impaired in patients with microvascular diabetic disease. Reduced hemoglobin levels are believed to exacerbate lower limb ischemia due to diminished blood oxygenation.[23,24] Moreover, anemia may contribute to thrombus formation by inducing a hyperkinetic circulatory state.[25] Furthermore, research indicates that DFU significantly reduces erythrocyte deformability compared to diabetic patients without foot complications, potentially hindering capillary flow and delaying ulcer healing.[26] Additionally, diabetes-induced chronic kidney disease results in earlier and more severe anemia than non-diabetic chronic nephropathy.[27] Anemia may also be associated with malnutrition, characterized by insufficient dietary protein intake among patients with DFU.[28] Determining whether anemia serves as a marker or an independent risk factor for serious complications in patients with DFU necessitates randomized intervention trials to assess whether treatments designed to elevate hemoglobin concentrations can significantly mitigate adverse outcomes.

Prolonged disease duration is necessary for the onset of neuropathic and angiopathic complications, which subsequently contribute to the development of diabetic foot syndrome. Consequently, the risk of major amputations escalates with the duration of diabetes.[29] A growing body of evidence has substantiated that the length of time a patient has had diabetes is positively correlated with an increased risk of amputation.[30–32] It has been reported that the proportion of patients with a diabetes duration exceeding 10 years is significantly higher among those with DFU who undergo amputations compared to those with DFU who do not undergo amputations.[33] Another study has demonstrated that a duration of type 2 diabetes of 10 years or more is a significant predictive factor for major lower limb amputation among patients with type 2 diabetes.[34] Similarly, in the present study, subjects in the amputation group exhibited a significantly longer duration of diabetes compared to those in the non-amputation group. Moreover, logistic regression analysis identified the duration of diabetes as an independent risk factor for amputation in patients with DFU. Therefore, heightened attention should be directed towards DFU patients with a prolonged duration of diabetes to mitigate the risk of amputation.

DFU that fail to heal is a significant cause of lower limb amputations.[35] The development of DFU arises from a confluence of multiple factors, with peripheral neuropathy being the most critical.[36] Peripheral neuropathy can affect motor, sensory, and autonomic nerves. Damage to motor innervation leads to an imbalance between lower limb flexion and extension, causing deformities and alterations in pressure points, which subsequently result in skin damage and the formation of ulcers. The involvement of sensory nerves results in diminished responsiveness to noxious stimuli, whereas autonomic neuropathy contributes to the development of dry, fissured skin on the foot, thereby increasing its vulnerability to injury. Consequently, 85% of these ulcerations progress to severe gangrene or infection.[37] It is noteworthy that the incidence of infected DFU is significantly higher among patients who undergo amputations compared to those who do not.[33] Moreover, substantial evidence indicates that history of prior foot ulceration is a significant risk factor for amputation.[38–40] Additionally, prolonged duration of DFU has been identified as a risk factor for major amputation in patients with DFU.[41] In the present study, we also observed that subjects in the amputation group exhibited a significantly longer duration of DFU compared to those in the non-amputation group. After controlling potential confounding factors in multiple logistic regression analysis, duration of DFU was identified as a determining factor for amputation in patients with DFU. Our findings contribute additional evidence supporting the association between prolonged duration of DFU and an elevated risk of subsequent amputation in affected patients.

The present study identified history of prior amputation as a significant risk factor for future amputations in individuals with DFU. It is well-established that patients who have undergone debridement or amputation for DFU are at a heightened risk for requiring further amputations.[42] The occurrence of an earlier amputation suggests that the patient has already experienced severe complications related to diabetic foot conditions. Prior surgical interventions and subsequent amputations may be associated with heightened susceptibility to complications in the residual limb, as well as the progression of underlying disease.[43,44]

To evaluate these risk factors in predicting the occurrence of amputation in patients with DFU, ROC analysis was employed. According to established criteria, an AUC value greater than 0.7 is considered clinically valuable for screening purposes.[45] The three risk factors including duration of diabetes, duration of DFU, and history of amputation all satisfied this criterion. Notably, the duration of diabetes demonstrated exceptional discriminatory ability, with an AUC value of 0.890. Previous studies have demonstrated that the simultaneous detection of multiple serum proteins as a composite panel can enhance the sensitivity or specificity relative to individual biomarkers.[46] Consequently, we incorporated a combination of diabetes duration, duration of DFU, and history of amputation to predict the likelihood of amputation in patients with DFU. Our findings revealed that the AUC value for this panel increased to 0.916, signifying a high level of accuracy in predicting amputation occurrence in this patient population. While ROC curve analysis demonstrates that the selected variables possess a degree of predictive capability, their efficacy in practical clinical applications requires further validation. This necessity arises from limitations in sample size and the over-simplification inherent in the data analysis.

Two limitations of this study warrant further discussion. Firstly, the study populations were derived from hospital-based cohorts, indicating the necessity for validation of the model in unselected patients across diverse clinical settings.

Secondly, the current study includes only 62 patients with DFU; thus, additional prospective studies with larger sample sizes are required to accurately determine the predictive value of these risk factors for amputation in patients with DFU.

Conclusion

In conclusion, duration of DFU was considered to be an independent risk factor for amputation in patients with DFU. Our results also suggest that duration of diabetes, duration of DFU, and history of amputation might be helpful in predicting amputation in patients with DFU. To further validate and support the predictive value of these risk factors in the wound healing process and the likelihood of amputation, multicenter, large-scale, long-term observational studies are warranted.

Disclosure

The authors report no conflicts of interest in this work.

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