Clinical Research

# Diabetic foot score: a predictive model for leg amputation in patients with diabetic foot disease

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**ABSTRACT**

**BACKGROUND** Patients with diabetes mellitus are at a higher risk for peripheral artery disease (PAD) and diabetic foot disease (DFD), which can ultimately result in leg amputation. This study aimed to develop a novel scoring system to predict the risk of leg amputation using widely available modalities, including demographic characteristics and various laboratory data.

**METHODS** This study was conducted at Dr. Soetomo General Hospital and analyzed risk factors for leg amputation in 99 patients with DFD who underwent leg amputation compared with 80 control patients. This study presented a predictive model for leg amputation in patients with DFD, using odds ratio (OR) analysis and logistic regression approach with confidence intervals (CIs) set at 95%. The data analysis was conducted using SPSS software version 25.0.

**RESULTS** PAD (OR 6.52, 95% CI = 2.19–19.37, $p$ = 0.001), high low-density lipoprotein cholesterol (OR 5.97, 95% CI = 2.31–15.43, $p$<0.001), type of DFD (OR 4.58, 95% CI = 2.14–9.79, $p$<0.001), poor glycemic control (OR 4.48, 95% CI = 1.78–11.28, $p$ = 0.001), and neutrophil-to-lymphocyte ratio level (OR 1.04, 95% CI = 1.00–1.07, $p$ = 0.025) were the independent predictors for leg amputation. The predictive model, developed using multivariate analysis with an area under the curve of 89%, optimum threshold of 0.5 (score 6), sensitivity of 84.8%, and specificity of 78.8%, indicating a promising approach for predicting leg amputation outcomes.

**CONCLUSIONS** The newly developed diabetic foot score may assist in making decisions regarding therapeutic options for patients with DFD.

**KEYWORDS** amputation, diabetic foot, leg, risk factors

Diabetes is a prevalent and rapidly growing pandemic in the 21st century, presenting a major global public health challenge.[1] In 2015, statistical data revealed that approximately 415 million people worldwide were diagnosed with diabetes. Predictions indicate a continuous rise, with an estimated 642 million individuals expected to have diabetes by 2040, marking a 55% increase over the next 20 years.[2] This rising prevalence has also led to a significant surge in diabetes-related complications, especially in low-income countries, substantially impacting mortality rates.[3] Individuals with diabetes mellitus (DM) face a significantly higher risk of leg amputation compared to those without the condition, and most amputations in diabetes cases are preceded by poorly healing ulcers, with up to 85% of cases linked to this underlying condition.[4] Consequently, given the global increase in the diabetic population and the high incidence of diabetic foot disease (DFD), diabetes-related leg amputations are estimated to remain a major cause of both morbidity and mortality in the future.[5]

DFD significantly contributes to nontraumatic leg amputation and is associated with higher mortality rates.[5,6] The prognosis following a leg amputation, especially when linked to DFD, is extremely poor, with a 35% to 50% mortality rate within 3 years.[7] Furthermore, the 5-year mortality rate is even more alarming, ranging from 53% to 100% for those who undergo any form of amputation.[8] Thus, given that the severe complications of DFD, such as amputation, have devastating consequences for patients, including prolonged hospital stays, substantial financial burdens, complex treatment regimens, a significantly reduced quality of life, and a high mortality risk, it is crucial to develop effective strategies for the prevention and treatment of DFD.[9]

Research has shown that various factors, including diabetes, history of amputation, poor blood sugar control, hypertension, abnormal lipid levels, peripheral artery disease (PAD), peripheral neuropathy, osteomyelitis, and wound severity, can serve as predictors of the possibility of leg amputation, with some contributing factors such as older age, smoking history, anemia, elevated white blood cell count, low albumin levels, and other microvascular and macrovascular comorbidities.[10–13] Despite this, there is limited published evidence on the risk factors for diabetes-related leg amputations in Indonesia. Therefore, this study aimed to present a scoring system to predict the occurrence of leg amputations in patients with DFD to effectively reduce and manage leg amputation rates within healthcare facilities by leveraging available local resources.

## METHODS

### Study population and study design

This observational case-control study involved 179 adult patients treated at a hospital in Indonesia. The study received approval from the Ethical Committee of Dr. Soetomo Hospital under reference number 2078/101/4/III/2023. The minimum sample size was determined using the Lehman formula for case-control studies.[14] Based on previous research with an odds ratio (OR) of 2.85,[15] the minimum sample size was 80 for each group.

The inclusion criteria included patients with diabetes-related foot ulcers hospitalized at our institution between March 1, 2021, and February 28, 2022, who had either minor or major amputations. The patients were divided into two groups: those who underwent leg amputation (n = 99) and those who did not (control, n = 80). Patient data, including details of leg amputations, were collected from medical records. We evaluated all patients with DFD and leg amputations to determine if demographic characteristics (age and history of leg amputation), clinical features (presence and evaluation of hypertension, coronary artery disease [CAD], PAD, and diabetic foot type), and various laboratory data (including low-density lipoprotein [LDL] levels, hemoglobin A1c [HbA1c] levels, albumin levels, C-reactive protein [CRP] levels, hemoglobin [Hb] levels, and neutrophil-to-lymphocyte ratio [NLR] levels) could predict the probability of amputation. As reported in previous studies, these potential risk factors were selected based on their prevalence as risk factors for leg amputation.[16–19] Exclusion criteria included cases of ulcers, gangrene, amputations caused by factors other than DM (e.g., trauma), and acute peripheral arterial thrombosis cases. The decision to proceed with amputation was made during a conference involving internist-endocrinologists and surgeons, with surgery subsequently performed by either vascular or orthopedic staff. Patients without medical records information on any of the categorized factors were also excluded from the analysis.

### Data collection

We examined initial outcomes, including age, history of leg amputation, presence and assessment of hypertension, CAD, PAD, and type of diabetic foot. We also considered poor glycemic control (HbA1c >9%) and laboratory data, such as anemia (Hb level <10 g/dl), high LDL cholesterol (LDL level >100 mg/dl), hypoalbuminemia (albumin level <3 g/dl), NLR, and elevated CRP levels (CRP >10 mg/dl). Hypertension was defined as either using antihypertensive medication or a blood pressure reading of systolic ≥140 mmHg and/or diastolic ≥90 mmHg. PAD was confirmed based on a history of intermittent claudication, non-palpable pedal pulses, and ankle-brachial index <0.9. CAD was diagnosed based on abnormalities detection through electrocardiography, echocardiography, or coronary angiography. DFD was classified into four grades: grade 1 (cellulitis), grade 2 (deep ulcer penetrating the tendon), grade 3 (deep ulcer with abscess or osteomyelitis), and grade 4 (DFD with gangrene or necrosis).

### Statistical analysis

Statistical analyses were conducted using SPSS software version 25.0 (IBM Corp., USA). Data distribution normality was assessed using the Kolmogorov–Smirnov test. Continuous variables were presented as medians (interquartile ranges). The Mann–Whitney *U* test was utilized for continuous data, while the chi-square test was employed for categorical data. The correlation between variables and their impact on leg amputation was evaluated using univariate and multivariate analyses. Statistical significance was determined as $p<0.05$. Components of the multiparametric model were determined based on regression outcomes. A receiver operating characteristic (ROC) curve analysis was performed to identify the optimal threshold value for the practical application of the model. Point allocation for each predictor was based on the OR calculated in the multivariate analysis.

## RESULTS

A total of 179 patients were screened according to the specified inclusion and exclusion criteria. Subject's characteristics were shown in Table 1. Figure 1 illustrates the workflow used to select the participants. Patient outcomes and leg amputation occurrence were considered dependent variables. The correlations between these variables and their impact on leg amputation are presented in Table 2. Our findings revealed that patients who underwent leg amputation were more likely to have a history of leg amputation, severe DFD, and comorbidities such as PAD. They also exhibited poor glycemic control, higher LDL levels, lower Hb levels, decreased albumin levels, elevated NLR, and higher CRP levels than the control group. However, we found no statistically significant impact of hypertension and a history of CAD on leg amputation.

### Diabetic foot score

PAD, high LDL cholesterol, type of DFD, poor glycemic control, and NLR level emerged as independent factors for leg amputation. Subsequently, these parameters were used as predictors in the scoring system, with their ORs serving as references to determine the scores. The scoring system is shown below (Equation 1):

$$g(x) = -6.0 + 1.8\,(PAD) + 1.5\,(type\ of\ DFD)^{a} + 1.5\,(high\ LDL\ cholesterol) + 1.4\,(poor\ glycemic\ control) + 0.043\,(NLR\ levels) \quad (1)$$

[a]coding for type of DFD
1=cellulitis
2=ulcers
3=osteomyelitis
4=necrotizing fasciitis
DFD=diabetic foot disease; LDL=low-density lipoprotein; NLR=neutrophil-to-lymphocyte ratio; PAD=peripheral artery disease

**Table 1.** Patient characteristics

| Characteristics | N = 179 |
|---|---|
| Male sex, n (%) | 92 (51.4) |
| Age (years), median (range) | 54 (30–80) |
| Leg amputation, n (%) | 99 (55.3) |
| Discharge status, n (%) | |
| Recovered | 141 (78.8) |
| Deceased | 38 (21.2) |
| Presence of PAD, n (%) | 75 (42.0) |
| Previous leg amputation, n (%) | 29 (16.2) |
| Type of diabetic foot, n (%) | |
| Cellulitis | 6 (3.4) |
| Ucer | 118 (65.9) |
| Osteomyelitis | 24 (13.4) |
| Necrotizing fasciitis | 31 (17.3) |
| Hypertension, n (%) | 87 (48.6) |
| Presence or history of CAD, n (%) | 16 (9.0) |
| Hb (gr/dl), mean (SD) | 9.8 (8.1) |
| ≥10 | 66 (36.9) |
| <10 | 113 (63.1) |
| NLR ratio, mean (SD) | 16.9 (13.1) |
| ≥4.2 | 165 (92.2) |
| <4.2 | 14 (7.8) |
| CRP level (mg/l), mean (SD) | 16.7 (8.3) |
| ≥10 | 133 (74.3) |
| <10 | 46 (25.7) |
| Albumin level (gr/dl), mean (SD) | 2.5 (0.5) |
| ≥3 | 38 (21.2) |
| <3 | 141 (78.8) |
| HbA1C (%), n (%) | 10.2 (6.2) |
| ≥9 | 95 (53.1) |
| <9 | 84 (46.9) |
| LDL (mg/dl), mean (SD) | 91.8 (39.2) |
| ≥100 | 68 (38.0) |
| <100 | 111 (62.0) |

CAD=coronary artery disease; CRP=C-reactive protein; Hb=hemoglobin; HbA1C=hemoglobin A1c; LDL=low-density lipoprotein; NLR=neutrophil-to-lymphocyte ratio; PAD=peripheral artery disease; SD=standard deviation

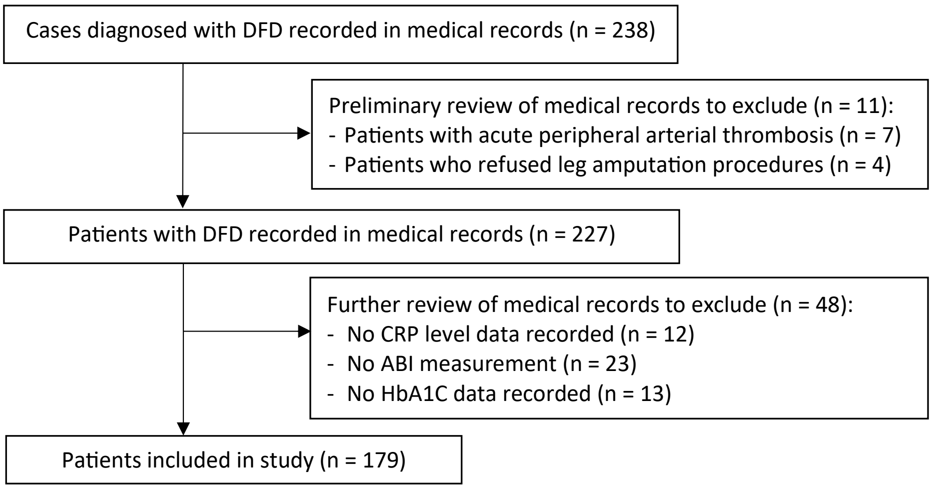


**Figure 1.** Flowchart of participant selection. ABI=ankle-brachial index; CRP=C-reactive protein; DFD=diabetic foot disease; HbA1C=hemoglobin A1c

A cut-off value of 6 for the scoring system was selected based on ROC analysis due to its optimal sensitivity (84.8%) and specificity (78.8%) (Figure 2). This cut-off point was chosen to prioritize a high-sensitivity model over specificity. Consequently, the DFD scoring system was established, categorizing scores from 0 to 5 as low risk and those ≥ 6 as high risk for leg amputation.

## DISCUSSION

This study identified a significant association between PAD and leg amputations. The PAD prevalence in the study population was approximately 42.0%, where the leg amputation group prevalence was higher than the control group. This association is likely due to impaired wound healing caused by insufficient circulation. When revascularization is not feasible, the risk of leg amputation increases significantly by 4.5-fold. Prompers et al[20] reported lower ulcer cure in patients with PAD compared to those without it. Similarly, Reiber et al[21] found PAD to be a strong predictor of amputation in patients with diabetes, with an OR of 4.3 for mild to moderate PAD and 55.8 for severe PAD. Additionally, Calle-Pascual et al[22] found that all major amputations were linked to PAD, whereas a smaller proportion (62%) of minor amputations were associated with PAD.

Poor control of blood sugar levels significantly impacts the occurrence of leg amputations. Studies conducted in Japan[19] and Pakistan[23] observed an association between chronic hyperglycemia, indicated by elevated HbA1c levels, and leg amputations. In the current study, approximately 53.1% of the population had HbA1c levels >9%, suggesting poor diabetes control and a significant risk of leg amputation. Among them, those who underwent leg amputation had a higher proportion of patients with poor glycemic control compared to the control group. Research has shown that for every 1% decrease in HbA1c levels, there is a 43% reduced risk of death from amputation.[24] For instance, the Steno-2 study demonstrated that implementing a comprehensive and intensive intervention, including strict glucose control, can effectively decrease the risk of complications by 50% and markedly reduce the risk of amputations in patients with DM compared to the usual treatment.[25] A meta-analysis also supports this growing evidence that hyperglycemia is an independent and significant risk factor for leg amputation.[26]

Patients with diabetes are known to have a higher prevalence of specific lipoprotein abnormalities compared to those without diabetes.[24,25,27] However, there is limited research on the impact of lipid and lipoprotein abnormalities on the risk of amputation in patients with DFD. High LDL cholesterol levels have been linked to an increased risk of amputation.[28] According to these findings, this study revealed a strong association between elevated LDL levels and the risk of leg amputation.

Diabetic foot problems often result from angiopathy and may manifest as infections.[1] Furthermore, research has associated elevated NLR levels with the severity of infection in patients with DM.[29] Compared to other studies, our results showed a higher prevalence of infection in diabetic foot lesions, possibly due to factors such as poor glycemic control, PAD, and significant variations in foot care practices across different cultures.

**Table 2.** Variables associated with leg amputation

| Variables | Univariate analysis | | | Logistic regression | |
|---|---|---|---|---|---|
| | Leg amputation | | *p* | OR (95% CI) | *p* |
| | Yes (N = 99) | No (N = 80) | | | |
| Age (years), n (%) | | | 0.328 | 1.71 (0.81–3.63) | 0.162 |
| <40 | 9 (9) | 5 (6) | | | |
| 40–60 | 60 (61) | 57 (71) | | | |
| >60 | 30 (30) | 18 (22) | | | |
| Presence of PAD, n (%) | | | **<0.001** | 6.52 (2.19–19.37) | **0.001** |
| Yes | 58 (59) | 17 (21) | | | |
| No | 41 (41) | 63 (79) | | | |
| Previous leg amputation, n (%) | | | **0.004** | 1.92 (0.44–8.35) | 0.386 |
| Yes | 23 (23) | 6 (8) | | | |
| No | 76 (77) | 74 (93) | | | |
| Presence or history of CAD, n (%) | | | 0.607 | 0.24 (0.05–1.21) | 0.85 |
| Yes | 10 (10) | 6 (8) | | | |
| No | 89 (90) | 74 (93) | | | |
| Type of diabetic foot, n (%) | | | **<0.001** | 4.58 (2.14–9.79) | **<0.001** |
| Cellulitis | 0 (0) | 6 (8) | | | |
| Ulcer | 52 (52) | 66 (83) | | | |
| Osteomyelitis | 19 (19) | 5 (6) | | | |
| Necrotizing fasciitis | 28 (28) | 3 (4) | | | |
| Hypertension status, n (%) | | | 0.135 | 1.77 (0.69–4.51) | 0.229 |
| Yes | 43 (43) | 44 (55) | | | |
| No | 56 (57) | 36 (45) | | | |
| LDL level (mg/dl), n (%) | | | **<0.001** | 5.97 (2.31–15.43) | **<0.001** |
| ≥100 | 56 (57) | 12 (15) | | | |
| <100 | 43 (43) | 68 (85) | | | |
| Poor glycemic control (HbA1C [%]) n (%) | | | **<0.001** | 4.48 (1.78–11.28) | **0.001** |
| ≥9 | 67 (68) | 28 (35) | | | |
| <9 | 32 (32) | 52 (65) | | | |
| Hypoalbuminemia (gr/dl), n (%) | | | **0.016** | 1.36 (0.45–4.12) | 0.584 |
| <3 | 85 (86) | 56 (70) | | | |
| ≥3 | 14 (14) | 24 (30) | | | |
| CRP (mg/l), n (%) | | | **0.038** | 2.45 (0.85–6.99) | 0.09 |
| ≥10 | 80 (81) | 53 (66) | | | |
| <10 | 19 (19) | 27 (34) | | | |
| Hb, median (IQR) | 9.0 (7.3–10.1) | 9.4 (8.2–11.4) | **0.013** | 1.02 (0.97–1.07) | 0.442 |
| NLR, median (IQR) | 14.5 (9.4–24.7) | 11.1 (6.7–20.1) | **0.012** | 1.04 (1.00–1.07) | **0.025** |

CAD=coronary artery disease; CI=confidence interval; CRP=C-reactive protein; Hb=hemoglobin; HbA1C=hemoglobin A1c; IQR=interquartile range; LDL=low-density lipoprotein; NLR=neutrophil-to-lymphocyte ratio; OR=odds ratio; PAD=peripheral artery disease

Furthermore, we found a correlation between higher NLR levels and an increased risk of leg amputation; the higher the NLR, the greater the likelihood of leg amputation. Elevated CRP levels were also linked to leg amputation, although this association did not reach statistical significance. This lack of significance may be attributed to the effects of hyperglycemia and poor glycemic control.

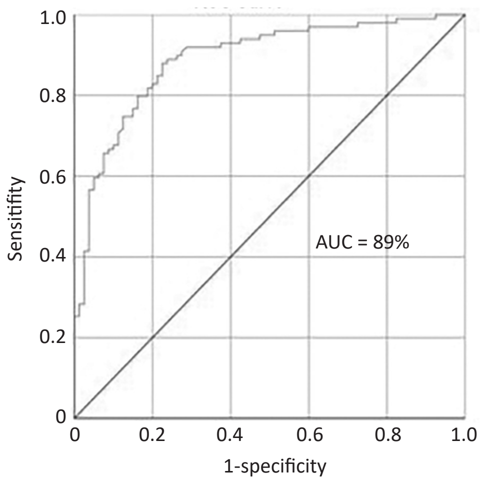


**Figure 2.** ROC curve of the predictor model for leg amputation. AUC=area under the curve; ROC=receiver operating characteristic

The role of hypertension as a risk factor for leg amputation remains unclear despite its known association with atherosclerosis and diabetic complications. While systolic blood pressure has been identified as a significant predictor of leg amputation in certain populations, such as American Indians,[18] previous studies have shown conflicting results regarding the relationship between hypertension and leg amputation.[17,18,30] In the present study, hypertension did not emerge as an independent risk factor for leg amputation. We speculate that variations in defining hypertension, demographic differences, and sample group characteristics may be attributed to the difficulty encountered in directly comparing the impact of hypertension on predicting lower limb amputation across studies.

In patients with CAD, reduced cardiac contractility heightens the inadequate oxygen supply and decreases blood flow to the lower limbs, thereby increasing the risk of amputation and even mortality.[27] However, this study revealed no relation between CAD and leg amputation, which counters Lu et al[30] and Nishijima et al[31] who found a higher prevalence of CAD in patients who underwent major amputations compared to minor amputations. This discrepancy may be attributed to a lack of distinction between major and minor leg amputations in these studies.

Reduced Hb levels indicate inadequate nutrition, which may impede wound healing and increase the risk of amputation in patients with DFD.[32] In this study, while univariate analysis revealed a strong correlation between anemia and leg amputation in patients with DFD, multivariate analysis did not show anemia as an independent risk factor. This finding contradicts previous studies that found a substantial correlation between anemia and leg amputation in patients with DFD.[32,33] Specifically, Pemayun et al[15] identified an Hb concentration threshold of <10 g/dl as a risk factor. According to the World Health Organization classification, these discrepancies may be due to the lack of categorization of variables based on the severity of anemia. Additionally, reduced Hb levels in patients with DFD can result from various factors such as bleeding, medication use, dietary imbalances, and opportunistic infections, which were not explicitly assessed in this study. Furthermore, our results showed a significant correlation between hypoalbuminemia and leg amputation in patients with DFD, as shown by the univariate analysis. However, multivariate analysis did not identify hypoalbuminemia as a predictor of amputation in the DFD group, which aligns with previous studies[15,34] but contrasts with the findings of Mansoor and Modaweb[33] and Lu et al[30].

Notably, PAD, elevated LDL levels, specific types of DFD, poor glycemic control, and heightened NLR were identified as independent risk factors for leg amputation. The diabetic foot score includes these five elements representing metabolic, vascular, and infectious aspects that must be strictly managed when treating DFD. Multiple studies have established PAD as a distinct and specific risk factor for leg amputation, a consensus recognized in numerous studies.[11,12,16,21,35] Yesil et al[36] found that Wagner grades 4 and 5 significantly predicted leg amputation in Turkey. Similarly, a study in Pakistan found a correlation between the severity of ulcers, particularly those classified as Wagner grade >3, and an increased risk of amputation. Both studies underscored the importance of understanding the Wagner grade in assessing amputation risk.[23,36] LDL cholesterol is a major risk factor for leg amputation.[3] Elevated LDL levels cause abnormal cholesterol accumulation in the walls of the heart and blood vessels, forming atherosclerotic plaques that obstruct the corresponding blood arteries. This can lead to peripheral artery obstructive disease and, ultimately, amputation. The strong association between HbA1c levels and leg amputation suggests that chronic hyperglycemia plays a significant role in the development of leg amputation. This could be due to various processes, including neuropathy, autonomic dysfunction, PAD, and increased susceptibility to infection.[26,37] Foot infection is a known contributing factor to diabetic amputation.[9] Elevated CRP levels are also commonly associated with infection, inflammation, tissue death, autoimmune conditions, and severe infectious diseases.

This study has some limitations that must be acknowledged. Firstly, the retrospective cohort design might have introduced potential bias due to relying on existing data. This study was also conducted at a single-center high-referral hospital in the eastern Indonesian region, limiting the generalizability of our findings. The time variation between symptom onset and hospital admission is a potential confounder that may have influenced the study outcomes. Moreover, the high percentage of severe illness in the study population could impact the applicability of our results. Factors like low Hb levels (<10 g/dl) might also affect the accuracy of HbA1c measurements, potentially impacting the interpretation of our results. Lastly, the lack of information on treatment received during hospitalization further increases potential bias, as treatment strategies could influence patient outcomes.

In conclusion, this study successfully employed a scoring system based on existing hospitalization data for the initial risk stratification of patients with DFD. Our results revealed that high-risk patients should be closely monitored to prevent leg amputations. However, despite the impressive performance of the scoring system, further validation using more recent data is necessary to obtain more conclusive results.

**Conflict of Interest**

The authors affirm no conflict of interest in this study.

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