

Article

Identifying Risk Factors Associated with the Severity of Foot Ulcers in Type 2 Diabetic Patients: Evidence from a Hospital-Based Study in Rajshahi, Bangladesh

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Abstract

Background: Diabetic foot ulcer (DFU) is a major complication of type 2 diabetes (T2D), frequently resulting in disability, lower-limb amputation, and substantial healthcare burden. Early identification of patients at high risk of progressing to severe DFU is essential for timely intervention, yet evidence on associated risk factors remains limited in Bangladesh. This study aims to identify demographic, clinical, and behavioral predictors of severe DFU to support early management strategies. **Methods:** A cross-sectional study was conducted among 159 DFU patients attending the Rajshahi Diabetic Association General Hospital, Bangladesh. Data on demographic characteristics, clinical variables, and behavioral factors were obtained through structured questionnaires and standardized examinations. Severe DFU was defined as Wagner grades 3–5, while grades 0–2 were considered non-severe. Firth's penalized logistic regression was used to identify determinants of severe DFU. Model performance was assessed using ROC analysis, calibration belt analysis, and decision curve analysis (DCA). **Results:** Among the 159 participants, 101 (63.5%) presented with severe DFU. Patients with severe DFU had significantly higher BMI (26.1 vs. 23.7 kg/m²), treatment costs (50,000 vs. 20,000 BDT), and were older (57 vs. 54 years). Severe DFU was also associated with higher prevalence of peripheral arterial disease (PAD) (29.7% vs. 3.4%), prior amputation (31.7% vs. 3.4%), peripheral neuropathy (PN) (86.1% vs. 58.6%), and poor glycemic control (71.3% vs. 30.7%) (all $p < 0.05$). Firth's regression identified older age (aOR 1.08), poor glycemic control (aOR 3.90), PN (aOR 3.41), PAD (aOR 7.54), and previous amputation (aOR 13.67) as independent predictors of severe DFU. **Conclusions:** Older age, uncontrolled glycemia, PN, PAD, and prior amputation were significantly associated with severe stages of DFU. Early detection and targeted management of these factors are critical to reducing complications and lowering the healthcare burden.

Keywords: diabetic foot ulcer; type 2 diabetes mellitus; risk factors; ulcer progression; early intervention



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1. Introduction

Diabetes mellitus (DM) is a common metabolic disorder, affecting 10.5% of adults worldwide, projected to rise to 12.2% by 2045 [1]. Diabetic foot complications involve ulceration of lower limb tissues, often accompanied by neuropathy and PAD [2]. Approximately 35% of individuals with diabetes develop foot ulcers during their lifetime [3], and 60–70% of all lower extremity amputations (LEA) are attributable to diabetes [4]. Following amputation for DFU, 85% of patients remain at risk of developing chronic infection and different forms of gangrene, which affects the quality of life [5]. DFUs account for nearly 20% of diabetes-related hospitalizations and incur management costs that are 33% higher than those of non-DFU patients, increasing up to 8-fold with severe ulcers [6,7]. The amputation rates may reach 90% in severe or osteomyelitis cases and are associated with increased mortality [8,9]. These severe outcomes underscore the urgent need for research to develop effective prevention and treatment strategies for DFU.

Bangladesh has one of the highest and most rapidly increasing rates of DM, rising from approximately 5% in 2001 to 13% in 2017 [10]. By 2045, an estimated 15 million people are expected to be affected [11]. About 44.5% of adult diabetic patients are at risk of developing DFUs [6]. DFUs are a major diabetes-related complication, causing high morbidity, amputation, and mortality, particularly in low- and middle-income countries (LMICs) like Bangladesh [12]. Given that the working-age population comprises individuals aged 15–64 years, DM and its complications, especially DFUs, significantly affect the national economy by reducing work efficiency and productivity [13,14]. Although the burden of DFU in Bangladesh is substantial, the average annual cost of treatment per patient in Bangladesh is approximately \$865 [15]. These costs place a heavy strain on low- and middle-income households, while government support remains limited. Early detection and management are crucial to prevent progression and reduce the economic and health burden of DFUs.

Studies from South Asia have substantially advanced the understanding of diabetic foot pathology, high-risk foot status, and ulcer outcomes [16–18]. Collectively, this body of work has informed diabetic foot care in tertiary-care settings across the region. However, despite these important contributions, limited evidence exists on how these established factors specifically influence progression to severe ulcer stages among patients with already established diabetic foot ulcers. Most prior studies have focused on ulcer occurrence, early biomechanical risk markers, or composite high-risk classifications that include both ulcerated and non-ulcerated individuals, rather than explicitly modeling severity progression within an ulcer-only population. Moreover, findings from tertiary-care settings in neighboring countries may not be directly applicable to Bangladesh due to differences in healthcare resources and socioeconomic conditions.

To address these issues, this study focused on patients with established diabetic foot ulcers (DFUs) at different stages. First, unlike previous research in Bangladesh that often combined ulcerated and non-ulcer populations, our study concentrated only on ulcerated patients to generate DFU-specific evidence associated with severity progression. Second, this design allowed us to explore in greater depth the clinical, behavioral, and socioeconomic determinants that contribute to ulcer severity, rather than simply examining the factors linked to the first appearance of ulcers. Third, by conducting the study in a remote area of Bangladesh, we aimed to capture context-specific insights using advanced statistical techniques from a population that has been largely underrepresented in earlier studies, despite bearing a high burden of disease. Collectively, this approach provides methodological advancement and Bangladesh-specific external validation of South Asian DFU evidence, offering actionable insights for targeted interventions, risk stratification, and resource-limited health policy planning.

2. Methods

2.1. Study Design and Participants

This cross-sectional study was conducted at the Rajshahi Diabetic Association General Hospital, the only tertiary-level foot care center in Rajshahi Division, the northern part of Bangladesh. The data collection period spanned from December 2024 to July 2025 at the foot care department of the hospital. During the study period, patients with T2D and visual ulceration below the knees who came to the hospital for clinical treatment and were willing to participate in the study were included. The data were collected from adults (≥ 18 years). Individuals who were mentally stable and willing to provide informed consent were selected for interviews. We excluded patients with type 1 diabetes, patients with T2D without DFUs, patients with comorbid communicable diseases or severe cognitive impairments that hindered reliable participation, and patients with T2D who had ulcers in body parts other than below the knees.

A consecutive sampling method was applied, yielding 172 participants. After data cleaning, 159 patients were retained for analysis. The overall study workflow is illustrated in Figure 1.

2.2. Sample Size Determination

The required sample size was calculated prior to the study. We used the Cochran's formula (1963) for sample size calculation [19,20].

$$n = \frac{z^2}{d^2} pq$$

where n is the desired sample size, $z_{1-\alpha/2}$ is the critical value, and the standard value for the corresponding level of confidence (at 95% CI, $z = 1.96$), p indicates the expected active prevalence rate of DFU ($p = 11.6\%$) [21], and d is the margin of errors or precision ($d = 5\%$). By inserting all values, we calculated the required sample size as $n = 158$. Therefore, we collected additional samples to account for potential exclusions during the data-cleaning stage.

2.3. Study Definitions and Measurements

In this study, a DFU was defined as any full-thickness skin lesion located distal to the ankle in patients with type 2 diabetes, excluding minor abrasions, blisters, or fissures. Data were collected through a structured and pretested questionnaire-based interview and clinical examinations performed by a trained diabetic foot surgeon. The questionnaires incorporated clinical factors associated with DFU [22,23], as well as demographic and socioeconomic variables. Duration of diabetes, information about physical exercise, smoking habits, duration of DFU, cost of treatment, and sociodemographic data were self-reported and collected through face-to-face interviews. Monthly family income was categorized as low ($<19,400$) and standard income ($19,400 <$) [6]. BMI of patients was calculated using kg/m^2 and categorized as underweight ($18.5 < \text{BMI}$), normal ($18.5 \leq \text{BMI} < 24.9$), overweight ($25 \leq \text{BMI} < 29.9$), or obese ($30 \leq \text{BMI}$) [24].

HbA1c levels of 7.0% or higher were considered uncontrolled glycemic levels [25]. DM duration (years) was categorized as short ($\text{DM} < 5$ years), medium ($5 \leq \text{DM} < 10$ years), and long ($\text{DM} \geq 10$ years) term. DFU severity was evaluated by a foot surgeon using Wagner classification, such as grade 0 (skin is intact, but the foot is at risk due to bony deformities or neuropathy), grade 1 (superficial ulcer that affects only the outer layers of the skin), grade 2 (deep ulcer that extends to underlying structures), grade 3 (deep ulcer with abscess formation or osteomyelitis), grade 4 (localized gangrene affecting part of the foot), grade 5 (extensive gangrene of the foot) [26]. No patients with Wagner grade 0 DFU

were included. Wagner grades 1–2 were considered non-severe DFU, and grades 3–5 were considered severe DFU [27,28].

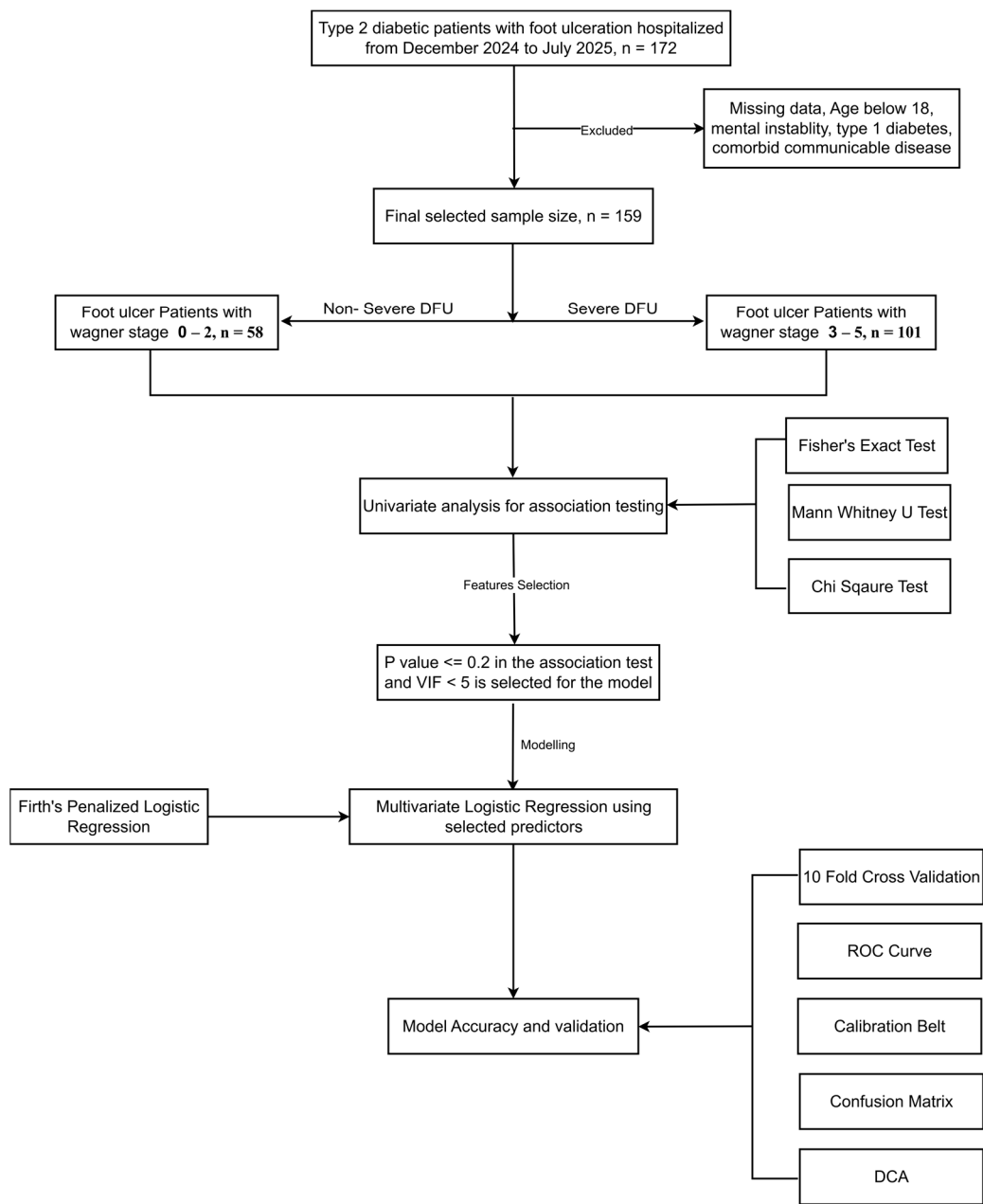


Figure 1. Overall study pipeline: Flow diagram depicting the complete analytical workflow for developing and validating the Firth logistic regression model predicting severe (Wagner Grade 3–5) versus non-severe (Grade 1–2) diabetic foot ulcer. Starting from 172 patients screened at the Rajshahi Diabetic Association General Hospital (December 2024–July 2025), 18 cases with missing data were excluded, yielding a final analytical cohort of 159 patients (101 severe, 58 non-severe).

History of infection was defined as any previous episode of clinically diagnosed infection (minor or major, in the lower limb) that had fully resolved before the onset of the index diabetic foot ulcer episode, as ascertained from patient report and available medical records. This variable, therefore, reflects a patient’s prior infection burden and susceptibility, rather than current ulcer status. Wound infection was defined as the presence of an active infection in the lower-limb ulcer at the time of study enrollment, based on contemporaneous clinical assessment. This variable specifically characterizes the infectious

status of the index ulcer at baseline and is conceptually distinct from a remote history of infection.

Peripheral neuropathy was assessed using the vibration perception threshold (VPT) test at the great toe with a calibrated biothesiometer. VPT values within 0–15 volts were considered normal (peripheral neuropathy absent), whereas values > 15 volts were classified as peripheral neuropathy present for the purposes of analysis. PAD was evaluated by clinical examination of distal lower-limb pulses. The dorsalis pedis artery was palpated in each affected limb; absence of a palpable dorsalis pedis pulse was considered indicative of PAD in that limb and coded as PAD present, while a clearly palpable pulse was coded as PAD absent. Patients with foot ulcers caused by structural deformities were not identified in this cohort.

2.4. Statistical Analysis

Descriptive statistics were used to summarize sociodemographic and clinical variables. We used the median, first quartile (Q1), and third quartile (Q3) for continuous variables; moreover, frequencies and percentages were used for categorical variables. Associations between DFU and categorical characteristics were tested with chi-square or Fisher's exact test. For continuous variables, comparisons were performed using Mann–Whitney U tests.

Before regression modeling, we assessed multicollinearity (see Supplementary Table S1) among the predictor variables using the variance inflation factor ($VIF < 5$) [29], and no predictors exceeded the threshold. We employed Firth's penalized logistic regression to mitigate the bias and overfitting risk due to small sample size or rare events [30] and to identify the independent risk factors associated with DFU severity. Because the sample size was modest, the prevalence of key clinical events was low, conventional maximum-likelihood logistic regression could yield biased or unstable estimates due to small-sample bias and potential data separation [31–33]. Features were selected for inclusion in the multivariable regression model based on a univariate association threshold of $p < 0.20$ [34,35]. This screening criterion was adopted to avoid premature exclusion of potentially important predictors and to reduce the risk of residual confounding. In addition, variables with established clinical relevance to DFU were retained in the multivariable model regardless of their univariate statistical significance. Results of the regression model were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI) and p -values.

To assess potential overfitting and evaluate the internal validity of the prediction model, a 10-fold cross-validation procedure was performed. The full dataset was randomly partitioned into 10 approximately equal folds. In each iteration, the Firth logistic regression model with the pre-specified predictors was fitted on 9 folds and used to generate predicted probabilities for the remaining fold. Discrimination was quantified in each held-out fold using the area under the receiver operating characteristic curve (AUC), and the distribution of the 10 fold-specific AUCs was visualized. The predictive performance of the model was assessed using a confusion matrix (CM), and overall accuracy, sensitivity, specificity, and predictive values were reported. Moreover, we performed the Hosmer and Lemeshow test to assess the goodness of fit of the model. We used the receiver operating characteristic (ROC) curve to evaluate the model discrimination. Moreover, calibration belt analysis was performed to assess the calibration. The clinical utility was examined using decision curve analysis (DCA). All the data were analyzed using R (v4.4.3) and SPSS (v26).

3. Results

3.1. Sociodemographic and Behavioral Characteristics of the Study Population

A total of 159 T2D patients with foot ulcers were included in the study, of whom 101 (63.5%) had severe DFU and 58 (36.5%) had non-severe DFU. The median

age of participants was 56 years (IQR: 50–61), with patients in the severe DFU group being significantly older (median 57 years, IQR: 51–63) compared to the non-severe group (median 54 years, IQR: 45–60, $p < 0.05$). No significant difference was observed in sex distribution between the groups ($p > 0.05$), although 52 of 84 male patients (61.9%) developed severe DFU. Educational attainment did not differ significantly between the groups ($p > 0.05$). Overall, 33.9% of patients were illiterate, 33.9% had completed primary education, 23.9% had secondary education, and 8.2% had higher education. Similarly, occupational distribution was comparable across the severity groups ($p > 0.05$). Among all patients, 16.4% were involved in business, 15.7% were day laborers, 13.8% were in service jobs, 44.0% were housewives, and 10.1% were retired.

The median BMI was significantly higher in patients with severe DFU (26.1 kg/m², IQR: 22.1–27.9) than in those with non-severe DFU (23.7 kg/m², IQR: 21.5–26.6, $p < 0.05$). A greater proportion of severe DFU patients were overweight (45.5%) compared to the non-severe group (25.9%), although BMI category differences did not reach statistical significance ($p = 0.069$). Regarding socioeconomic status, the majority of patients (83.7%) belonged to families with standard monthly income, with no significant difference between severe and non-severe groups ($p > 0.05$). In terms of residential location, 62.3% of patients were from rural areas, with 66.3% of these developing severe DFU; however, this difference was not statistically significant ($p > 0.05$). Most participants were non-smokers (83.6%, $p > 0.05$), and a majority engaged in regular physical exercise (72.3%, $p > 0.05$). For diabetes management, 61.6% of patients relied on insulin therapy, and no significant differences were observed between the severe and non-severe groups ($p > 0.05$).

Overall, these findings suggest that age and BMI were higher among patients with severe DFUs, while other sociodemographic and behavioral characteristics, including sex, education, occupation, income, residence, smoking, exercise habits, and type of diabetes treatment, were broadly comparable between the two groups (see Table 1).

Table 1. Baseline characteristics of patients with severe versus non-severe diabetic foot ulcers ($n = 159$). Parameters are expressed using n (%), median (IQR). The Mann–Whitney U test, Pearson’s chi-squared test, and Fisher’s exact test were used to test the association. Data represents the socio-economic and behavioral characteristics of 159 patients with active diabetic foot ulcers from a tertiary referral center in northern Bangladesh, stratified by ulcer severity according to Wagner classification (non-severe: Grade 1–2, $n = 58$; severe: Grade 3–5, $n = 101$). Continuous variables presented as * median (IQR); categorical variables as frequency, n (%). (a) p -values from the Mann–Whitney U test for continuous variables and the chi-square test; (b) p -values for categorical variables comparing severe vs. non-severe DFU groups using Pearson’s chi-squared test or Fisher’s exact test.

Characteristics	Overall (N = 159) (%)	Non-Severe (n = 58) (%)	Severe (n = 101) (%)	<i>p</i> -Value
Age (Years)	56 (50–61) *	54 (45–60) *	57 (51–63) *	0.004 ^a
Sex				0.7 ^b
Female	75 (47.16%)	26 (44.82%)	49 (48.51%)	
Male	84 (52.83%)	32 (55.17%)	52 (51.49%)	
Education Level				0.2 ^a
Illiterate	54 (33.9%)	17 (29.31%)	37 (36.63%)	
Primary	54 (33.9%)	19 (32.75%)	35 (34.65%)	
Secondary	38 (23.89%)	19 (32.75%)	19 (18.81%)	
Higher Education	13 (8.17%)	3 (5.17%)	10 (9.90%)	
Occupation				0.067 ^b
Business	26 (16.35%)	15 (25.86%)	11 (10.89%)	
Housewife	70 (44.02%)	23 (39.65%)	47 (46.53%)	
Retired	16 (10.06%)	4 (6.9%)	12 (11.88%)	

Table 1. Cont.

Characteristics	Overall (N = 159) (%)	Non-Severe (n = 58) (%)	Severe (n = 101) (%)	p-Value
Service Worker	22 (13.83%)	5 (8.6%)	17 (16.83%)	
Family Income (Monthly, BDT)	25 (15.72%)	11 (18.96%)	14 (13.86%)	
Income Category	30,000 (20,000–50,000) *	30,000 (20,000–50,000) *	30,000 (20,000–40,000) *	0.9 ^a
Low Income	26 (16.35%)	10 (17.24%)	16 (15.84%)	0.8 ^b
Standard Income	133 (83.65%)	48 (82.75%)	85 (84.15%)	
Residential Area				0.2 ^b
Rural	99 (62.26%)	32 (55.17%)	67 (66.33%)	
Urban	60 (37.73%)	26 (44.82%)	34 (33.67%)	
Body Mass Index (kg/m ²)	25.1 (22.0, 27.6) *	23.7 (21.5, 26.6) *	26.1 (22.1, 27.9) *	0.04 ^a
BMI Category				0.069 ^b
Underweight	5 (3.1%)	2 (3.4%)	3 (2.97%)	
Normal	74 (46.54%)	34 (58.62%)	40 (39.60%)	
Overweight	61 (38.36%)	15 (25.86%)	46 (45.54%)	
Obese	19 (11.94%)	7 (12.06%)	12 (11.88%)	
Physical Exercise				0.14 ^b
Irregularly	44 (27.67%)	12 (20.69%)	32 (31.68%)	
Regularly	115 (72.32%)	46 (79.31%)	69 (68.31%)	
Smoking Habit				0.8 ^b
Non-smoker	133 (83.64%)	48 (82.75%)	85 (84.15%)	
Addicted	26 (16.35%)	10 (17.24%)	16 (15.84%)	

3.2. Clinical Characteristics

The median duration of diabetes was 12 years (IQR: 7–16, $p > 0.05$), with a majority of patients (66.66%) having a long-term duration (≥ 10 years) of diabetes, and 64.35% of severe grouped patients had long-term T2D. Glycemic control was significantly poorer in the severe group. A significantly higher proportion of patients with severe DFU (71.3%) had uncontrolled diabetes, compared to only 30.7% in the non-severe group ($p < 0.001$), highlighting the strong association between poor glycemic control and ulcer progression. The prevalence of PN was also higher among severe DFU cases (86.1%) compared to the non-severe group (58.6%), with a statistically significant ($p < 0.05$) difference. The proportion of patients with infection history was significantly higher ($p < 0.05$) among severe DFU patients compared to the non-severe group. Moreover, median ulcer duration was 31 days (IQR: 15–150, $p < 0.05$). More than half of the patients (52.21%) experienced foot complications due to wound infection, with a significant difference ($p < 0.05$) observed between the groups. Patients with a history of amputation (21.38%) tended to progress to the severe DFU (31.68%) compared to non-severe stages (3.44%), and this factor was significantly associated ($p < 0.05$) with DFU severity. Among all the patients, $n = 32$ had developed PAD and significantly differed ($p < 0.05$) between the severe ($n = 30$; 29.70%) and non-severe ($n = 2$; 3.44%) DFU groups. The cost of treatment for foot ulcers also differed significantly between the groups. The median cost for all patients was 30,000 BDT (IQR: 10,000–70,000), with severe DFU patients incurring higher median costs (50,000 BDT, IQR: 15,000–100,000) compared to non-severe patients (20,000 BDT, IQR: 5000–50,000, $p < 0.05$).

These findings demonstrate that poor glycemic control, PN, history of foot infection, prior amputation, and PAD are strongly associated with the severity of DFU. Additionally, longer ulcer duration and higher treatment costs were observed in patients with severe DFUs, highlighting both the clinical and economic burden associated with advanced foot complications in T2D patients (see Table 2).

Table 2. Comparison of clinical characteristics between those who had developed severe stages of DFU and non-severe DFU. Parameters are expressed using *n* (%), median (IQR). The Mann–Whitney U test, Pearson’s chi-squared test, and Fisher’s exact test were used to test the association. Abbreviations used: DM = diabetes mellitus, PN = peripheral neuropathy, DFU = diabetic foot ulcer, PAD = peripheral arterial disease.

Characteristics	Overall (N = 159) (%)	Non-Severe (n = 58) (%)	Severe (n = 101) (%)	p-Value
Duration of DM (Years)	12 (7–16) *	12 (8–15) *	10 (7–16) *	0.6 ^a
Diabetes Duration Categories				0.5 ^b
Short	17 (10.69%)	7 (12.06%)	10 (9.9%)	
Mid	36 (22.64%)	10 (17.24%)	26 (25.74%)	
Long	106 (66.66%)	41 (70.68%)	65 (64.35%)	
Diabetes Controller				0.9 ^b
Medicine	30 (18.86%)	10 (17.24%)	20 (19.80%)	
Insulin	98 (61.63%)	37 (63.79%)	61 (60.39%)	
Both	31 (19.49%)	11 (18.96%)	20 (19.80%)	
Glycemic Level				0.001 ^b
Controlled	69 (43.39%)	40 (68.96%)	29 (28.71%)	
Uncontrolled	90 (56.60%)	18 (31.03%)	72 (71.28%)	
PN				0.001 ^b
Negative	38 (23.89%)	24 (41.37%)	14 (13.86%)	
Positive	121 (76.1%)	34 (58.62%)	87 (86.13%)	
Nephropathy				0.3 ^b
Negative	127 (89.87%)	49 (84.48%)	78 (77.22%)	
Positive	32 (20.12%)	9 (15.51%)	23 (22.77%)	
Retinopathy				0.2 ^b
Negative	59 (37.1%)	18 (31.03%)	41 (41.59%)	
Positive	100 (62.9%)	40 (68.96%)	60 (59.41%)	
History of Infection				0.034 ^b
No	98 (61.63%)	42 (72.41%)	56 (55.44%)	
Yes	61 (38.36%)	16 (27.58%)	45 (44.55%)	
Self-Treatment Attempted				0.8 ^b
No	86 (54.08%)	32 (55.17%)	54 (53.46%)	
Yes	73 (45.91%)	26 (44.82%)	47 (46.53%)	
Physician Consultation				0.059 ^b
Irregularly	29 (18.23%)	15 (25.86%)	14 (13.86%)	
Regularly	130 (81.76%)	43 (74.13%)	87 (86.13%)	
Duration of DFU (Days)	31 (15, 150) *	30 (10, 60) *	45 (18, 180) *	0.01 ^a
Wound Infection				0.001 ^b
Negative	76 (47.79%)	8 (13.79%)	68 (67.33%)	
Positive	83 (52.21%)	50 (86.21%)	33 (32.67%)	
Amputation History				0.001 ^b
Negative	125 (78.61%)	56 (96.55%)	69 (68.31%)	
Positive	34 (21.38%)	2 (3.44%)	32 (31.68%)	
PAD				0.001 ^b
Negative	127 (89.87%)	56 (96.55%)	71 (70.29%)	
Positive	32 (20.12%)	2 (3.44%)	30 (29.70%)	
Cost of Treatment (BDT)	30,000 (10,000–70,000) *	20,000 (5000–50,000) *	50,000 (15,000–100,000) *	0.003 ^a

^a Mann–Whitney U test; ^b Pearson’s chi-squared test or Fisher’s exact test. * Median (IQR).

3.3. Distribution of Foot Ulcer Classification Based on Wagner Grades (WGs)

The distribution of foot ulceration was assessed by a foot surgeon using the Wagner grading system. The majority of the patients were classified as Grade 2, which was the most common stage, affecting 26.42% of patients ($n = 42$). The next most frequent stages were Grade 5 ($n = 38$, 23.9%), Grade 3 ($n = 33$, 20.8%), and Grade 4 ($n = 30$, 18.9%). The least common stage was Grade 1, found in 10.1% of cases ($n = 16$). Consistent with the study’s inclusion criteria, no patients were classified as having Grade 0 ulcers. The distribution of WG among the study population is illustrated in Table 3 and Supplementary Figure S1.

Table 3. Frequency distribution of different stages of diabetic foot ulcer and severity classification based on the Wagner scale. Distribution of diabetic foot ulcer severity stages among 159 patients from a tertiary referral center in northern Bangladesh, classified according to the Wagner scale. Non-severe DFU defined as Wagner Grade 1 ($n = 16$, 10%) or Grade 2 ($n = 42$, 26%), totaling 58 patients (36%). Severe DFU defined as Wagner Grade 3 ($n = 33$, 21%), Grade 4 ($n = 30$, 19%), or Grade 5 ($n = 38$, 24%), totaling 101 patients (64%).

	Diabetic Foot Stage	Frequency (n)	Percentage ($n\%$)
Non-severe	Grade 1	16	10
	Grade 2	42	26
	Grade 3	33	21
Severe	Grade 4	30	19
	Grade 5	38	24
Total	-	159	100

3.4. Risk Factors Analysis

Firth’s penalized logistic regression was used to identify independent risk factors associated with the progression of diabetic foot ulcers (DFU) to severe stages. The results are summarized in Supplementary Table S2 and Figure 2. Patient age was significantly associated with DFU severity, with each additional year increasing the odds of severe DFU by 1.08 times (aOR = 1.08, 95% CI: 1.02–1.16, $p = 0.010$). Uncontrolled glycemic levels were strongly predictive of severe DFU, with affected patients being 3.90 times more likely to have severe ulcers compared to those with controlled glycemia (aOR = 3.90, 95% CI: 1.43–11.64, $p = 0.008$). The presence of PN was a significant independent predictor. Patients with PN were over 3.4 times more likely to develop a severe DFU compared to those without the condition (aOR = 3.41, 95% CI: 1.13–11.27, $p = 0.029$). The history of amputation was another major predictor, increasing the likelihood of severe DFU by 13.67 times (95% CI: 2.01–122.18, $p = 0.007$). Similarly, patients with PAD were 7.54 times more likely to have severe DFU (95% CI: 1.09–64.10, $p = 0.040$).

Other covariates, including BMI, residential area, physical activity, nephropathy, retinopathy, infection history, and wound infection, were not significantly associated with DFU severity in the multivariate model.

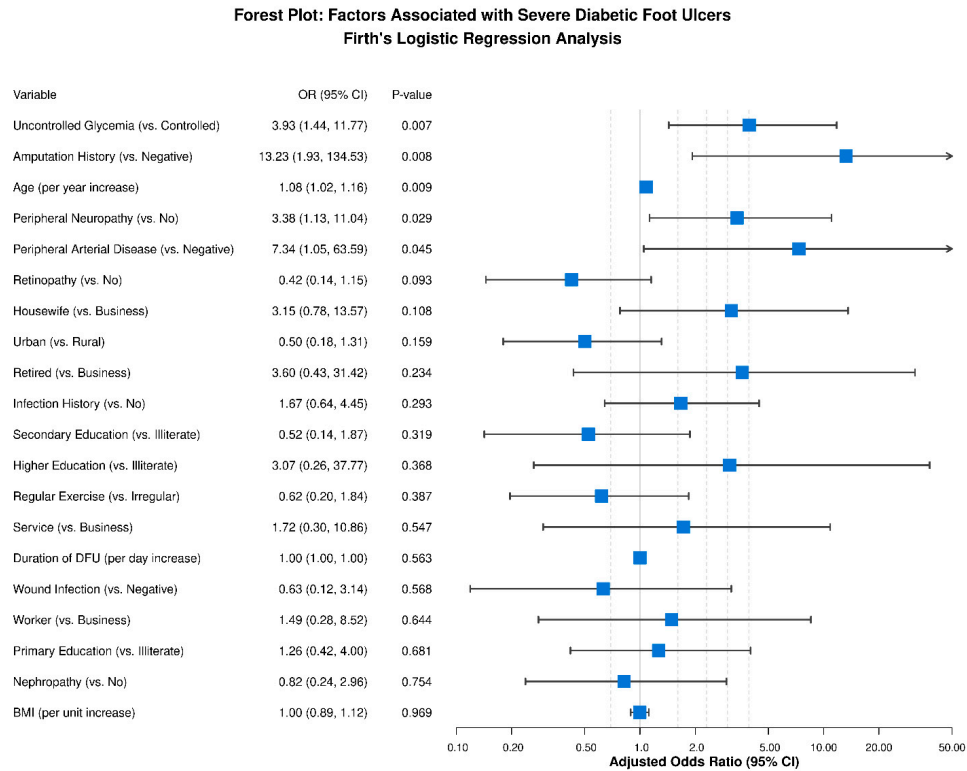


Figure 2. Forest plot of adjusted odds ratios for predictors associated with severe diabetic foot ulcer from Firth’s penalized logistic regression analysis. Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals from the Firth logistic regression model predicting severe (Wagner Grade 3–5) versus non-severe (Grade 1–2) diabetic foot ulcer in 159 patients (101 severe cases). Predictors were selected through purposeful univariable screening ($p < 0.20$) with forced inclusion of clinically important variables. Significant predictors ($p < 0.05$) include poor glycemic control (OR 3.94, 95% CI 1.07–14.51), peripheral neuropathy (OR 3.41, 95% CI 1.02–11.42), peripheral arterial disease (OR 7.54, 95% CI 1.87–30.40), and prior amputation (OR 13.00, 95% CI 1.91–88.44). The vertical dashed line at OR = 1.00 indicates the null hypothesis of no association.

3.5. Model Performance and Validation

The performance of the Firth logistic regression model in predicting severe versus non-severe diabetic foot ulcers (DFU) was evaluated using multiple statistical metrics. Using the confusion matrix (see Supplementary Table S3), the model achieved an overall accuracy of 85.5% (95% CI: 79.1–90.6). The sensitivity for correctly identifying severe DFU cases was 89.1%, while the specificity for non-severe cases was 79.3%. The positive predictive value (PPV) was 88.2%, and the negative predictive value (NPV) was 80.7%, indicating strong predictive ability for both outcome categories. Agreement between predicted and observed outcomes was substantial, with a Kappa statistic (κ) of 0.69. The Hosmer–Lemeshow goodness-of-fit test indicated that the model adequately fit the data ($p = 0.5942$), showing no evidence of lack of fit.

The model’s discrimination ability was assessed using the receiver operating characteristic (ROC) curve. As illustrated in Figure 3a, the area under the ROC curve (AUC) was 0.924. Ten-fold cross-validation yielded a mean AUC of 0.874 ± 0.084 (95% CI 0.822–0.926), with noticeable variability across folds, as illustrated by the violin plot of fold-specific AUCs (see Supplementary Figure S3). This finding indicates that the apparent AUC was somewhat optimistic. However, the cross-validated AUC still demonstrates good discriminative ability of the model for distinguishing severe from non-severe DFU in this sample. Calibration of the model was further evaluated using a calibration belt generated with a second-degree polynomial to detect potential miscalibration. Figure 3b also shows that

there was no significant deviation from the ideal bisector line ($p = 0.10$), indicating good agreement between predicted probabilities and observed outcomes.

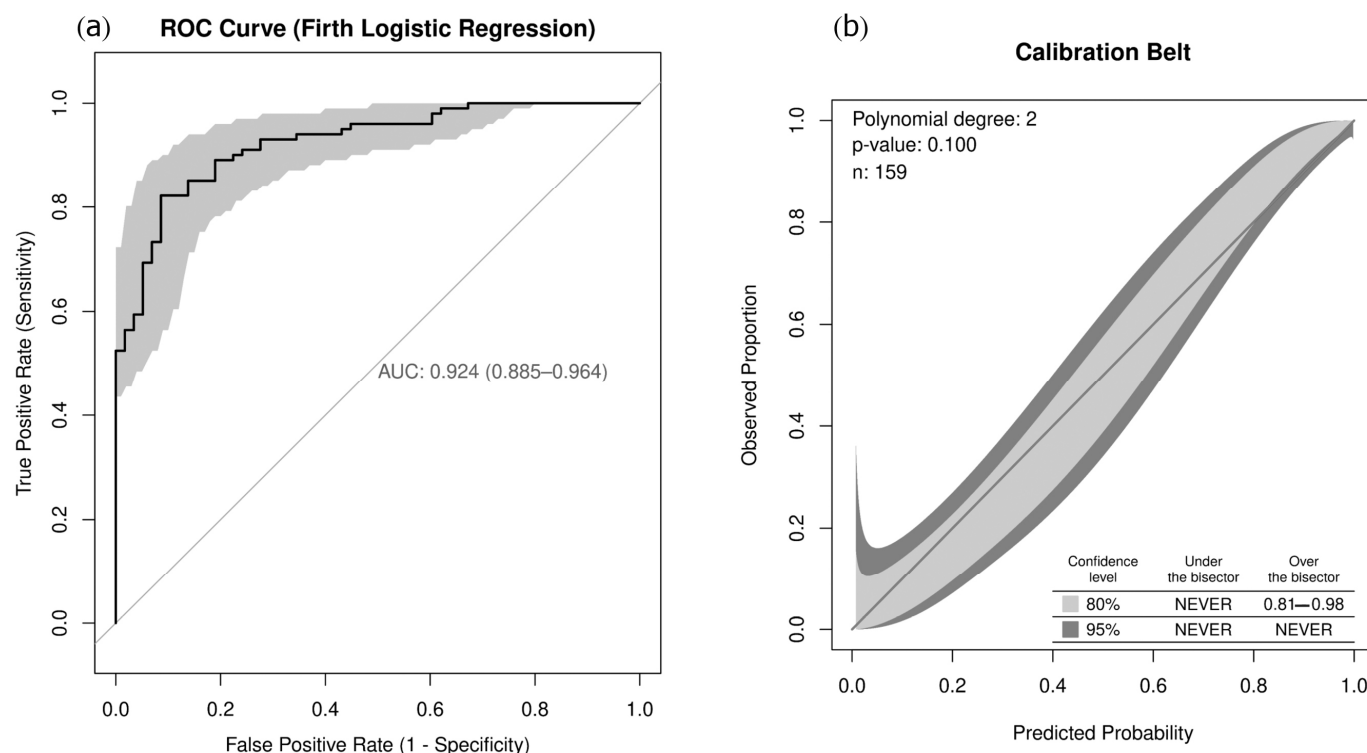


Figure 3. (a) Model performance for predicting severe DFU using Firth’s penalized logistic regression: (a) receiver operating characteristic (ROC) curve demonstrating strong discrimination (AUC = 0.924; 95% CI: 0.885–0.964) and (b) calibration belt indicating good agreement between predicted and observed probabilities ($n = 159$; $p = 0.100$).

Finally, clinical utility was assessed using Decision Curve Analysis (DCA). As presented in the Supplementary Figure S2, the model provided a positive net benefit compared to both “treat-all” and “treat-none” strategies across a broad range of clinically relevant threshold probabilities, supporting its potential applicability in clinical decision-making.

Overall, these performance assessments demonstrate that the model is robust, accurate, and clinically relevant for identifying severe DFU cases among patients with type 2 diabetes, supporting its potential application in routine clinical decision-making and resource allocation.

4. Discussion

Diabetic foot ulcers (DFUs) represent debilitating complications of diabetes, associated with increased morbidity, amputation, and mortality worldwide. Their burden is particularly critical in LMICs, where limited access to early diagnosis and specialized care is linked to delayed presentation and poor outcomes. Almost 9.1 million to 26.1 million people with diabetes develop DFU every year [36]. Poor prognosis, insufficient awareness, and socio-economic burden are commonly reported in relation to this complication. Within a year of the onset of the DFU, up to 17% patients undergo minor amputation, and 5% patients undergo major amputation, and the risk of amputation is significantly higher among patients with lower limb ischemia [37]. According to previous studies, approximately 20% of DFU patients require hospitalization [38], which is associated with increased healthcare utilization and costs, placing a burden on both the healthcare system and the broader economy [39].

In this cross-sectional study of T2D patients with active DFUs, age, poor glycemic control, peripheral neuropathy, PAD, and prior amputation history were independently associated with severe DFU presentation. These findings suggest that metabolic dysregulation alongside neuropathic and vascular complications may play important roles in DFU severity in northern Bangladesh. Older age showed a strong association with severe DFU. Older adult patients with T2D often experience impaired immune responses, prolonged wound repair, and macro- and microvascular complications [40], which may partly explain this association. A study by Yuanying Yao et al. [41] in South Asia and other LMICs reported that age is one of the key determinants of DFU severity. We observed higher BMI among severe cases, although the categorical BMI was not statistically significant. These patterns may indicate potential roles for metabolic and weight management strategies in mitigating DFU progression risk. Furthermore, we found no significant association between sociodemographic factors (sex, education, occupation, and socioeconomic status) and severe DFU in our cohort, in contrast to prior studies [20,42–44]. This discrepancy may reflect overlapping clinical risk factors across groups in our population.

Our study clearly indicates that poor glycemic control, PN, PAD, and prior amputation exhibited the strongest associations with severe DFU [see Figure 2 and Table S2]. Hyperglycemia has been linked to vascular damage and impaired endothelial function [45,46], reduced leukocyte activity, and prolonged collagen synthesis [47,48], which are mechanisms plausibly related to impaired wound healing and leading to severe DFU. PN damages sensory nerves and impairs protective sensation [49,50], which may increase susceptibility to unrecognized lesion detection and secondary infection [51], thereby facilitating progression to more severe ulcer stages. Early gait alterations, such as lateral shift in the center of pressure toward the medial heel and restricted subtalar/first metatarsophalangeal joint motion, further exacerbate uneven plantar pressure distribution even before overt foot deformity develops, as demonstrated in Chennai cohorts without morphological changes [17]. PAD is associated with critical limb ischemia (CLI) [52], poor oxygenation, and inadequate nutrient delivery [53], which is linked to impaired healing capacity. PAD has also been associated with higher risks of major lower-limb amputation among DFU patients [54], which demands routine PAD screening in diabetic patients with foot lesions. Studies from India similarly report high amputation rates despite relatively lower prevalence of clinically overt PAD, highlighting how infection, neuropathy, delayed presentation, and vascular disease co-occur to influence limb loss [16].

Prior amputation underscores the chronic and recurrent condition of DFU. A history of tissue loss is associated with increased vulnerability to subsequent complications [55]. Patients who undergo major or minor amputation cannot ignore the risk of recurrent DFU complications. A meta-analysis results in the finding that patients with prior amputation have an 11.96-fold increased risk of DFU recurrence [56]. This recurrence has been attributed to factors such as inadequate post-amputation care, limited patient and caregiver awareness, and restricted access to specialized services [57], which are commonly associated with early re-ulceration and more severe disease courses.

The predominance of Wagner Grade 4–5 ulcers in our cohort likely reflects delayed presentation typical of LMICs [58,59], compounded by high infection rates and substantially elevated treatment costs in severe cases. Recent national-level Indian data likewise show a high burden of high-risk feet and advanced lesions at first contact with care, particularly in resource-constrained settings [18]. These patterns underscore the dual clinical and economic burden of advanced DFU in resource-limited settings. A study in Nigeria found that in LMICs, the financial burden of treating DFUs becomes significantly heavier in severe conditions. Treatment costs increase with severe DFU, costing over \$1100 for stage 3 and

\$1800 for stage 4 [60]. Hospital admission for infected DFUs can incur costs exceeding \$3000 per case [61].

This study employed Firth's penalized logistic regression to account for rare but clinically important predictors such as PAD and prior amputation. This approach improves the stability of effect estimates in small-sample clinical datasets and supports more reliable severity risk stratification. Our model demonstrated strong discriminatory ability and clinical utility for severity stratification among DFU patients. Compared to meta-analyzed DFU prediction models (AUC 0.78–0.84) [62] and systematic reviews establishing C-statistics > 0.75 as clinically valuable [63], our approach achieved superior performance while addressing methodological limitations of prior regional work.

Beyond performance metrics, decision curve analysis (DCA) was performed to assess the model's clinical utility. The DCA suggests a net benefit in supporting individualized clinical decision-making among DFU patients. DCA accounts for the relative harms of false positives and false negatives, providing a more realistic assessment of whether implementation of the model may support improved decision-making patient outcomes in real-world practice [64]. These findings highlight the potential value of severity-based screening pathways, particularly in resource-limited healthcare systems where early identification of high-risk patients is critical.

Our findings align with global recommendations for DFU prevention and management. The International Working Group on the Diabetic Foot (IWGDF) emphasizes systematic screening for PN and PAD, strict metabolic control, and structured patient care to prevent worldwide DFU [65]. The predictors identified in this study align with established high-risk features of IWGDF guidelines. This coherence underscores that although our study was conducted in northern Bangladesh, the insights generated are globally relevant and may inform both local and international strategies for DFU care. The methodological transition from conventional descriptive analysis to Firth's penalized regression and DCA enhances the clinical reliability of these findings. The model has important implications for resource-limited settings such as Bangladesh. In secondary and tertiary care facilities, where advanced DFU cases are commonly managed, the proposed model may support early risk stratification, clinical decision-making, and prioritization of high-risk patients. When integrated into existing referral pathways, it could complement primary-care screening by identifying patients who would benefit most from early referral to specialized DFU services. By addressing small-sample biases through penalized likelihood, this study provides a more stable evidence base for clinical decision-making than has been previously available in South Asian DFU research.

5. Strengths of the Study

The major strength of this study is the use of clinically validated diagnostic criteria for PN, PAD, glycemic levels, and other DFU-related complications, which were assessed by a trained diabetic foot surgeon. Additionally, we used statistically suitable and rigorous analytical methods to predict the associated factors with the model accuracy measures that reflect minimum bias and statistically sound analysis. Although this was a single-center study, the study site is the only diabetes-specialized hospital in the Rajshahi division, which may reasonably reflect the clinical scenario of the entire area.

6. Limitations of the Study

The cross-sectional design precludes causal inference, and longitudinal studies are needed to establish temporal relationships between risk factors and ulcer progression. Some behavioral and lifestyle factors, such as dietary patterns and footwear habits, were not included in the study, which may contribute to the severity of ulceration. Ulcer duration and

treatment-related costs were self-reported by participants and are therefore subject to recall bias and potential misclassification. Patients may have underestimated or overestimated the duration of ulcer symptoms or incurred costs, particularly in the context of prolonged disease courses and multiple care episodes. However, such misclassification is likely to be non-differential with respect to ulcer severity and would tend to bias associations toward the null rather than inflate observed effects. The study was conducted in a single tertiary diabetic foot referral center with limited resources, resulting in a relatively small sample size and a high proportion of severe DFU cases; these features may limit generalizability to primary care or community-based populations. Consequently, the proposed risk model is most applicable to secondary and tertiary DFU clinics managing moderate to severe cases, and future multi-center prospective studies with larger cohorts are warranted to more comprehensively characterize clinical and socio-demographic determinants of DFU severity across different levels of care.

7. Conclusions

This study identifies key factors associated with severe diabetic foot ulcer (DFU) among type 2 diabetic patients in Rajshahi, Bangladesh. Older age, poor glycemic control, peripheral neuropathy, peripheral arterial disease, and prior amputation were independent predictors of severe DFU (Wagner grades 3–5). Severe ulcers were also associated with longer ulcer duration and higher treatment costs, reflecting a substantial clinical and socio-economic burden and suggesting delayed presentation in this tertiary-care setting. These findings reinforce evidence from prior South Asian studies and provide context-specific validation in a Bangladeshi population. Overall, the results highlight the importance of early risk stratification and systematic screening, particularly for neuropathy and PAD, to enable timely intervention and appropriate referral. Strengthening glycemic control, improving access to vascular assessment and management, and implementing structured post-amputation follow-up and preventive foot care may help reduce progression to severe DFU, prevent avoidable amputations, and improve patient outcomes in resource-limited settings.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/diabetology7040076/s1>. Figure S1. The chart demonstrates the proportion of patients in different stages of foot ulceration according to the Wagner classification scale. Figure S2. Decision Curve Analysis (DCA) for the assessment of the clinical utility of the prediction model of severe diabetic foot ulcer. Figure S3. Distribution of fold-specific cross-validated AUCs from 10-fold cross-validation of the Firth logistic regression model for severe diabetic foot ulcer prediction. Table S1. Variance Inflation Factor (VIF) for Predictors in the Logistic Regression Model. Table S2. Multivariate analysis of factors associated with severe diabetic foot ulcer (DFU) using Firth's penalized logistic regression model. Table S3. Confusion Matrix and Performance Metrics of the Prediction Model.

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Institutional Review Board Statement: This study was conducted in accordance with the ethical principles outlined in the World Medical Association's Declaration of Helsinki for medical research involving human participants. Ethical approval was obtained from the Institutional Animal, Biosafety, and Biosecurity Committee (IAMEBBC) of the Institute of Biological Sciences (IBSc), University of

Rajshahi (Approval No. 195(69)/320/IAMEBBC/IBSc; Approval date: 21 November 2024). Written consent was taken from all the participants/guardians. All procedures were carried out in accordance with relevant guidelines and regulations.

Data Availability Statement: The raw data from this study are not openly shared because of confidentiality reasons but can be requested from the corresponding author. All other data used or analyzed are included in this paper and its additional files.

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Abbreviations

T2D	Type II Diabetes
DFU	Diabetic Foot Ulcer
ROC	Receiver Operating Characteristic
AUC	Area Under Curve
DCA	Decision Curve Analysis
BMI	Body Mass Index
aOR	Adjusted Odds Ratio
PAD	Peripheral Arterial Disease
PN	Peripheral Neuropathy
DM	Diabetes Mellitus
LEA	Lower Extremity Amputations
LMICs	Low and Middle-Income Countries
CI	Confidence Interval
VIF	Variance Inflation Factor
CM	Confusion Matrix
IQR	Interquartile Range
WGs	Wagner Grades
PPV	Positive Predictive Value
NPV	Negative Predictive Value
CLI	Critical Limb Ischemia
DPN	Diabetic Peripheral Neuropathy
IWGDF	International Working Group on the Diabetic Foot

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