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ORIGINAL ARTICLE

Retrospective Study

Predictive model and risk analysis for outcomes in diabetic foot ulcer using eXtreme Gradient Boosting algorithm and SHapley Additive exPlanation

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Abstract

BACKGROUND

Diabetic foot ulcer (DFU) is a serious and destructive complication of diabetes, which has a high amputation rate and carries a huge social burden. Early detection of risk factors and intervention are essential to reduce amputation rates. With the development of artificial intelligence technology, efficient interpretable predictive models can be generated in clinical practice to improve DFU care.

AIM

To develop and validate an interpretable model for predicting amputation risk in DFU patients.

METHODS

This retrospective study collected basic data from 599 patients with DFU in Beijing Shijitan Hospital between January 2015 and June 2024. The data set was randomly divided into a training set and test set with fivefold cross-validation. Three binary variable models were built with the eXtreme Gradient Boosting (XGBoost) algorithm to input risk factors that predict amputation probability. The model performance was optimized by adjusting the super parameters. The predictive performance of the three models was expressed by sensitivity, specificity, positive predictive value, negative predictive value and area under the curve (AUC). Visualization of the prediction results was realized through SHapley Additive exPlanation (SHAP).

RESULTS
A total of 157 (26.2%) patients underwent minor amputation during hospitalization and 50 (8.3%) had major amputation. All three XGBoost models demonstrated good discriminative ability, with AUC values > 0.7. The model for predicting major amputation achieved the highest performance [AUC = 0.977, 95% confidence interval (CI): 0.956-0.998], followed by the minor amputation model (AUC = 0.800, 95%CI: 0.762-0.838) and the non-amputation model (AUC = 0.772, 95%CI: 0.730-0.814). Feature importance ranking of the three models revealed the risk factors for minor and major amputation. Wagner grade 4/5, osteomyelitis, and high C-reactive protein were all considered important predictive variables.

CONCLUSION
XGBoost effectively predicts diabetic foot amputation risk and provides interpretable insights to support personalized treatment decisions.

Key Words: Diabetic foot ulcer; Amputation risk stratification; Clinical risk prediction; eXtreme Gradient Boosting; SHapley Additive exPlanation; Machine learning

Core Tip: This study developed and validated an eXtreme Gradient Boosting-based predictive model for stratifying amputation risk in patients with diabetic foot ulcers. By integrating 29 clinical variables and applying SHapley Additive exPlanation for interpretability, the model achieved high predictive accuracy, especially for major amputations (area under the curve = 0.977). Key predictors included Wagner grade, albumin, infection markers, and vascular intervention. The model allows for the early identification of high-risk patients and supports individualized treatment decisions, offering a clinically interpretable tool for improving diabetic foot management.

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INTRODUCTION

Diabetic foot ulcer (DFU) is one of the most serious complications of diabetes, and it is primarily caused by diabetic peripheral neuropathy and peripheral arterial disease. It is also the leading cause of nontraumatic lower extremity amputation (LEA)[1,2]. Amputation has a significant impact on the prognosis of DFU patients, reducing their quality of life and increasing their mortality rate[3-5]. Amputation increases treatment costs fivefold, thereby increasing the burden on the national healthcare system[6]. DFU amputations can be divided into minor amputations below the ankle joint and major amputations above the ankle joint. A meta□analysis from China showed that the overall LEA rate in DFU patients was 31%[7]. Major amputation leads to more severe physical disability and poor socio-economic function than minor amputation. Over one million diabetes patients lose part of their legs every year due to improper management of DFU[8]. Therefore, early detection of amputation risk in DFU can potentially benefit many patients[9,10].

An effective classification system that provides early indicators of disease severity could assist clinical decision-making [10-12]. Oyibo *et al*[13] showed that the Wagner and Texas systems are effective for predicting DFU outcomes, with higher grades of DFU in these classifications correlating with an increased amputation risk. However, these classification methods are limited in describing wounds as they do not account for factors such as infection severity, wound size, and vascular pathology. Hicks *et al*[14] suggested that the WIFI (W: wound; I: Ischemia; FI: Foot infection) system might be relevant for limb preservation and wound healing, as it can predict 1-year healing outcomes in DFU patients. In contrast, the prediction model based on statistical methods integrates more factors to estimate the probability of amputation risk early and offer more direct guidance for clinicians.

In recent decades, machine learning has evolved from a primitive technology to the cornerstone of medical data analysis[15]. Previous predictive modeling methods, such as artificial neural networks (ANNs) and support vector machines (SVMs), are commonly used for single linear relationship analysis and feature extraction[16,17]. eXtreme Gradient Boosting (XGBoost) is an integrated tree lift algorithm that can flexibly process missing data and combine weak predictive models to screen significant features of accurate models[18]. However, most people consider this algorithm to be indescribable. The trust of patients and clinicians in model predictions has been limited[19]. SHapley Additive exPlanations (SHAP) can be used to analyze feature importance, where all features are treated as contributors. The influence of each predictor on the target variable can be directly expressed, whether positive or negative[20,21]. SHAP can be utilized to interpret and analyze model output results and to improve the model's efficiency. Liu *et al*[22] developed an XGBoost-based mortality prediction model for intensive care unit patients with acute kidney injury, demonstrating its potential for early risk stratification and timely intervention in critically ill individuals. Hou *et al*[23] and Hu *et al*[24] both applied

XGBoost to mortality prediction in sepsis patients. Hou *et al* achieved an area under the curve (AUC) of 0.857 for 30-day mortality, outperforming logistic regression, while Hu *et al* reported an AUC of 0.884 for in-hospital mortality, further enhancing model interpretability with SHAP values.

Here, we attempt to study a hierarchical predictive model that fully incorporated risk factors for diabetic foot amputation and analyzed the relationship between these factors. We hope that early intervention of patients with high risk factors can reduce amputation rate and improve the long-term prognosis.

MATERIALS AND METHODS

Study design and participants

This study was performed in accordance with the International Conference on Harmonization of Good Clinical Practice Guidelines and the Declaration of Helsinki and approved by the Ethical Review Committee of Beijing Shijitan Hospital, Capital Medical University [Ethical approval number (IIT2025-049-001)]. This study was a retrospective analysis of anonymized clinical data. Ethical approval was obtained from the Institutional Review Board, and the requirement for informed consent was waived.

Patients with DFU who were admitted to the Beijing Shijitan Hospital Affiliated to Capital Medical University between January 2015 and June 2024 were randomly selected and assembled into groups, as outlined in Figure 1. Patients who died during hospitalization, underwent amputation prior to transfer to Beijing Shijitan Hospital, those who sought treatment at other medical institutions during hospitalization, and those with incomplete information where missing values were identified in the dataset, were excluded. Participants' clinical information was extracted from electronic health records (EHRs).

Based on clinical practice, international guidelines from the International Working Group on the Diabetic Foot, and a comprehensive literature review[25-27], candidate variables were screened for inclusion. Further selection was conducted according to the availability and completeness of data within the EHRs, ensuring data integrity and no missing values to support robust statistical analysis and model performance. This process yielded a final set of 29 variables encompassing patient demographics, medical history, clinical and laboratory indicators, Wagner ulcer classification, nutritional status, wound characteristics, ischemia-related factors, and clinical outcomes (*e.g.*, amputation status).

Subjects were divided into three groups based on treatment outcomes: (1) Non-amputation group (n = 392); (2) Minor amputation group (n = 157); and (3) Major amputation group (n = 50).

Statistical analysis

Descriptive statistical analysis of the data was performed for each of the three groups. The Shapiro-Wilk test was used to assess the normality of continuous variables. The characteristics of the normal distribution are represented as mean ± SD, whereas those with non-normal distribution are denoted by median with interquartile range. To evaluate statistical significance between two groups, the t test was applied for normally distributed features, and the Mann-Whitney U test for abnormally distributed features. Categorical variables are expressed as counts (n) and percentages (%). The intergroup difference variables were tested by Pearson's χ^2 test. $P < 0.05$ was considered statistically significant. All of the above calculations were performed using SPSS Version 27.0.

Model construction

Variable selection for model training: No dimensionality reduction or manual prescreening was applied before model training. Instead, a data-driven approach was adopted by inputting all 29 clinically relevant variables, selected based on guidelines and literature, directly into the model. The XGBoost algorithm automatically assessed the contribution of each variable during training through its built-in feature selection mechanism based on split gain and frequency.

Class weighting for the imbalanced dataset: To address the potential class imbalance between different amputation groups (non-amputation, minor amputation, and major amputation), the scale_pos_weight parameter was applied in the XGBoost algorithm, referencing the methodological approach of Méndez Barrera *et al*[28], who applied machine learning techniques to address data imbalance in predictive modeling. This parameter adjusts the weight of the positive class to counterbalance the disparity in sample sizes across the classes.

Specifically, for each binary classification model, we calculated the scale_pos_weight as the ratio of number of negative samples to the number of positive samples, as follows: scale_pos_weight = Number of negative samples/number of positive samples.

This adjustment ensured that the model gave more emphasis to the minority class (major amputation), thereby improving the predictive accuracy for rare outcomes. integration of the scale_pos_weight parameter into the XGBoost model helped to mitigate the effect of class imbalance and enhance the model's ability to predict the minority class with greater accuracy.

Data preprocessing: The dataset was confirmed to not contain any missing values during data preprocessing; therefore, no imputation or data cleaning for incomplete entries was necessary.

Data preprocessing included continuous variable discretization and dummy variable processing. The quantile method for discretizing continuous variables was chosen over equal-width binning or k-means clustering primarily because it effectively handles skewed data distributions. Unlike equal-width binning, which divides the data range into equal-sized intervals, the quantile method ensures that each bin contains an equal number of samples, preventing bins from having

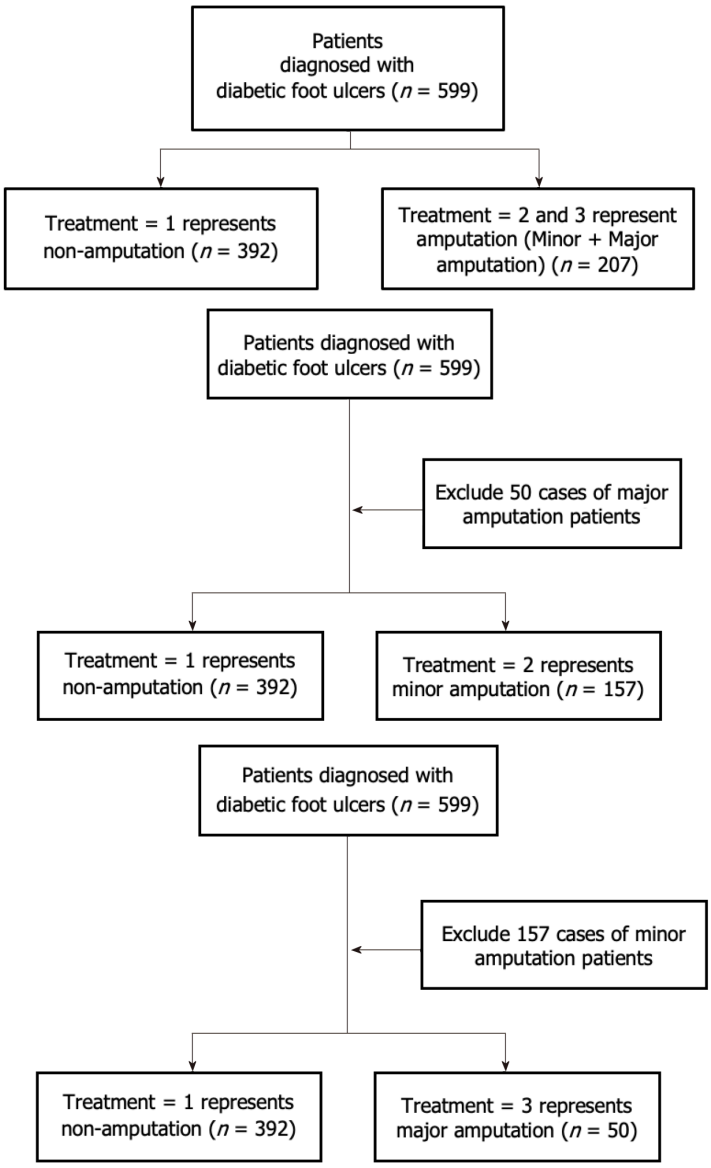


Figure 1 Multi-classification grouping flow chart of amputation prediction for diabetic foot ulcer patients.

too few data points, especially when outliers are present. Compared to k-means clustering, the quantile method is simpler, more stable, and does not require complex initialization or iterative optimization. Additionally, it better preserves the distributional characteristics of the data, improving the predictive accuracy and robustness of the model. The discretization process replaced continuous variables with ordered classification variables using the quantile method, while dummy variable processing was applied to convert categorical variables into a format suitable for model handling [29].

Dataset partitioning: After the above steps, the training set and test set were converted to matrix format. The dataset was randomly divided into training (80%) and calibration datasets (20%). The training set was constructed using fivefold cross-validation to ensure that the model learned enough features and patterns. The validation set evaluated the generalization ability of the model after model training.

Add validation set and early stopping strategy: To avoid overfitting, an early stop strategy was built into the training process. When performance was no longer improved on the verification set, the training was stopped.

Model parameter setting: Parameters of the model were defined in the study and model performance was optimized through hyperparameter optimization. A grid search strategy combined with fivefold cross-validation was applied to optimize the XGBoost model hyperparameters. By systematically evaluating predefined combinations of parameter values, the optimal configuration for model performance was identified. Key parameters tuned during this process included the maximum tree depth (max_depth), learning rate (eta), subsample ratio (subsample), column sampling ratio (colsample_bytree), and min_child_weight. Model performance was assessed using logarithmic loss (logloss) and the AUC, and the best-performing parameter set was selected for final model training[20].

Parameters: Booster: Specifies the type of tree model used; gbtree was selected, which is the gradient boosting tree. Objective: Defines the optimization objective of the model; binary was used here. Logistic, which is for binary classification and suitable for classification problems. ETA: Learning rate, which controls the complexity of the tree in each iteration. A smaller value can increase model stability. Max_depth: Maximum depth of the tree, which controls model complexity and prevents overfitting. Eval_metric: The metric used to evaluate model performance; logloss (logarithmic loss) was used here. Min_child_weight: A hyperparameter in XGBoost that controls the minimum sum of instance weights (Hessian) required in a child node. Subsample: A hyperparameter in XGBoost that controls the fraction of training data randomly sampled for each boosting iteration. It acts as a form of regularization by introducing randomness into the model training process, which can help reduce overfitting and improve generalization. Colsample_bytree: A hyperparameter in XGBoost that specifies the fraction of features (columns) randomly sampled when constructing each decision tree. It introduces feature-level randomness during training, which serves as a regularization technique to reduce overfitting and improve model generalization-particularly useful in datasets with many correlated variables.

Model prediction: The characteristic variables passed through multiple decision trees in turn. Each tree classified the sample to a leaf node and output the predicted value of that sample. The predicted values of all trees were added to form the overall prediction of the model. The output result was the probability of amputation, which transformed accumulation to the second classification result of an amputation through logical regression.

Model evaluation

Five model evaluation indicators were used: AUC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). These indicators helped to evaluate the model when predicting different amputation types. Overall performance was represented by weighted average performance across categories. Category weights represent the proportion of each category.

The standard formulas for calculating sensitivity, specificity, PPV and NPV are below. These metrics were derived from the confusion matrix using the following definitions[30]: Sensitivity (Recall) = TP/(TP + FN); Specificity = TN/(TN + FP); PPV = TP/(TP + FP); NPV = TN/(TN + FN); where, TP = true positives; TN = true negatives; FP = false positives; FN = false negatives.

The default threshold of 0.5 was used for binary classification, where predicted probabilities ≥ 0.5 were classified as positive. This threshold was used consistently across models to allow for standard comparison of classification performance[31].

Calibration assessment

To evaluate the calibration performance of the three amputation risk prediction models (non-amputation, minor amputation, and major amputation), a comprehensive calibration analysis was conducted that included: (1) Calibration curve plotting; (2) Hosmer-Lemeshow goodness-of-fit test; and (3) Brier score calculation[32].

For each model, calibration curves were constructed using bootstrapping (B = 1000 iterations) to visualize the agreement between predicted probabilities and observed event rates. The mean absolute error and mean squared error were calculated from the calibration curves to quantify deviation.

The Hosmer-Lemeshow test was used to assess fit between observed and expected probabilities. A nonsignificant *P* value (> 0.05) indicated good calibration.

The Brier score, representing the mean squared difference between predicted probabilities and actual binary outcomes, was calculated for each model. Lower Brier scores indicated better calibration.

Feature importance ranking

As an efficient multithreaded model processing method, XGBoost has built-in feature importance analysis function to optimize model efficiency by removing irrelevant features that contribute little to the model[33]. Each observation within the dataset could be elucidated by a distinct set of SHAP values. Model construction, evaluation and feature importance ranking were performed using standard Python packages (Python 3.8.1).

RESULTS

Univariable analysis results

Between January 2015 and June 2024, there were 599 patients with DFUs, comprising 420 (70.1%) males and 179 (29.9%) females, aged 46-96 years. The demographic characteristics, disease profiles, and treatment modalities of all patients categorized by amputation status are presented in Table 1. Among these individuals, 157 (26.2%) underwent minor amputation during hospitalization, while 50 (8.3%) underwent major amputation.

Markers of inflammation [including white blood cells, C-reactive protein (CRP), and procalcitonin] and renal function indicators [creatinine and blood urea nitrogen (BUN)] dramatically increased. More severe foot ulcerations, as assessed by the Wagner scale and wound extent, as well as history of coronary heart disease and renal dysfunction were notably prevalent among amputees. Additionally, most patients received antibiotic treatment prior to admission, with an increase in the proportion of osteomyelitis cases. In contrast with patients who underwent minor amputation, those with major amputation had elevated markers of myocardial injury (myoglobin), reduced albumin and triglyceride levels, significantly higher frequencies of Wagner grades 4/5, and diminished rates of interventional therapy.

Table 1 Descriptive statistics and test analysis of variables, mean (SD)

Variables	Non-amputation (*n* = 392)	Minor amputation (*n* = 157)	Major amputation (*n* = 50)	*P* value
Demographic data				
Gender				
Female	129 (32.9)	36 (22.9)	14 (28.0)	0.067
Male	263 (67.1)	121 (77.1)	36 (72.0)	
Age: year	68.28 (9.99)	67.06 (9.20)	68.88 (9.25)	0.336
Diabetes duration (years)				
Diabetes duration	17.13 (9.43)	18.66 (9.00)	18.89 (8.99)	0.138
Medical history				
Hypertension				
No	152 (38.8)	71 (45.2)	15 (30.0)	0.128
Yes	240 (61.2)	86 (54.8)	35 (70.0)	
Hyperlipidemia				
No	279 (71.2)	118 (75.2)	36 (72.0)	0.640
Yes	113 (28.8)	39 (24.8)	14 (28.0)	
Coronary heart disease				
No	145 (37.0)	41 (26.1)	23 (46.0)	0.012
Yes	247 (63.0)	116 (73.9)	27 (54.0)	
Heart attack				
No	354 (90.3)	145 (92.4)	44 (88.0)	0.604
Yes	38 (9.7)	12 (7.6)	6 (12.0)	
Atrial fibrillation				
No	370 (94.4)	149 (94.9)	48 (96.0)	0.881
Yes	22 (5.6)	8 (5.1)	2 (4.0)	
Cerebrovascular disease				
No	280 (71.4)	107 (68.2)	31 (62.0)	0.343
Yes	112 (28.6)	50 (31.8)	19 (38.0)	
Chronic lung disease				
No	355 (90.6)	139 (88.5)	44 (88.0)	0.705
Yes	37 (9.4)	18 (11.5)	6 (12.0)	
Renal insufficiency				
No	38 (9.7)	35 (22.3)	12 (24.5)	< 0.001
Yes	354 (90.3)	122 (77.7)	37 (75.5)	
Clinical and laboratory data				
WBC (10^9/L)	8.38 (4.53)	9.88 (5.00)	11.45 (6.34)	< 0.001
CRP (mg/L)	41.51 (51.90)	73.31 (77.84)	99.43 (88.93)	< 0.001
PCT (ng/mL)	0.25 (0.63)	0.44 (1.01)	0.67 (1.19)	< 0.001
HbA1c (%)	8.07 (2.50)	8.43 (2.02)	8.38 (1.86)	0.218
Mb (ng/mL)	51.27 (68.78)	52.15 (77.34)	96.16 (123.04)	< 0.001
Tn (ng/mL)	8.64 (68.71)	4.70 (13.29)	10.44 (34.59)	0.720
CK-MB (μg/mL)	1.89 (1.97)	1.63 (1.17)	2.08 (1.48)	0.180
Cr (μmol/L)	107.44 (138.29)	144.60 (191.22)	167.62 (202.93)	0.006

BUN (mmol/L)	7.77 (4.50)	8.92 (5.40)	9.47 (7.07)	0.010
Albumin (g/L)	37.04 (5.74)	34.75 (5.48)	31.79 (5.21)	< 0.001
TC (mmol/L)	4.07 (1.21)	3.84 (1.15)	3.72 (1.93)	0.055
TG (mmol/L)	1.48 (0.89)	1.32 (0.68)	1.25 (0.73)	0.038
LDL-C (mmol/L)	2.37 (0.91)	2.38 (0.90)	2.12 (0.77)	0.166
Medication history				
Antibiotic use before hospitalization				
No	194 (49.5)	56 (35.7)	16 (32.0)	0.002
Yes	198 (50.5)	101 (64.3)	34 (68.0)	
Wound characteristics				
Wagner classification				
0-3	298 (76.0)	53 (33.8)	14 (28.0)	< 0.001
4/5	94 (24.0)	104 (66.2)	36 (72.0)	
Range				
≤ 5 cm	307 (78.3)	122 (77.7)	23 (46.0)	< 0.001
≥ 5 cm	85 (21.7)	35 (22.3)	27 (54.0)	
Osteomyelitis				
No	196 (50.0)	21 (13.4)	3 (6.0)	< 0.001
Yes	196 (50.0)	136 (86.6)	47 (94.0)	
Vascular intervention surgery				
No	310 (79.1)	87 (55.4)	33 (66.0)	< 0.001
Yes	82 (20.9)	70 (44.6)	17 (34.0)	

P values represent the results of intergroup trend analyses among the three groups, with $P < 0.05$ deemed significant. All continuous variables have been standardized, and binary variables with 0 representing no and 1 representing yes. WBC: White blood cell; CRP: C-reactive protein; PCT: Procalcitonin; HbA1c: Glycated hemoglobin; Mb: Myoglobin; Tn: Troponin; CK-MB: Creatine kinase isoenzyme; Cr: Creatinine; BUN: Blood urea nitrogen; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol.

Model manifestation

Parameter selection is crucial to the learning depth of the decision tree[34]. Therefore, we adjusted the parameters through fivefold cross-validation and grid search to identify the appropriate combination of parameters. The optimal parameters of the XGBoost model are shown in Table 2. To correct for class imbalance in each binary classification task, we applied the scale_pos_weight parameter in XGBoost, calculated as the ratio of negative to positive samples. The values were set as follows: 0.53 for the non-amputation model, 2.82 for the minor amputation model, and 10.98 for the major amputation model.

Patients were categorized into three distinct groups: Non-amputation, minor amputation, and major amputation. We conducted a binary classification analysis comparing the non-amputation group to the amputation groups, yielding a receiver operating characteristic (ROC) curve value of 0.772 for the model. Similarly, when we performed a binary classification analysis contrasting the non-amputation group with the minor amputation group, the ROC curve value for predicting minor amputations was 0.800. In our binary classification study comparing the non-amputation group with the major amputation group, we achieved an ROC curve value of 0.977 for predicting major amputations (Figure 2). Other assessment indexes of the model, such as sensitivity, specificity, NPV and PPV, are shown in Table 3.

Table 3 indicated that the multi-classification predictive model based on XGBoost had strong predictive ability: Minor amputation group AUC (0.800), sensitivity (78.1%), specificity (69.4%), NPV (61.0%) and PPV (83.8%); major amputation group AUC (0.977), sensitivity (98.7%), specificity (88.9%), NPV (88.9%) and PPV (98.7%). The confusion matrix identifies category blurring in machine learning and evaluated the accuracy of model predictions[29]. Figure 3 shows that the proportion of cases presenting false positives and false negatives was < 30%. Among them, the minor amputation model had the highest predictive accuracy, with only four prediction errors and an accuracy rate > 95%.

Model calibration metrics

Calibration curves: These calibration results suggest that all three models performed well. The major amputation model had the best performance, with the lowest error and excellent calibration, indicating strong predictive accuracy

Table 2 Parameter optimization results of eXtreme Gradient Boosting model

Parameter	Default	Value
Booster	Gbtree	Gbtree
Objective	Reg: Linear	Binary: Logistic
Eta	0.3	0.1
Max_depth	6	6
Eval_metric	Logloss	Logloss
Colsample_bytree	1.0	0.5
Subsample	1.0	0.5
Min_child_weight	1.0	1.0

Table 3 Various evaluation indicators of different models in the test set

Evaluation_metrics	Non amputation (%)	Minor amputation (%)	Major amputation (%)
Sensitivity	75.7	78.1	98.7
Specificity	77.8	69.4	88.9
NPV	66.0	61.0	88.9
PPV	84.8	83.8	98.7

NPV: Negative predictive value; PPV: Positive predictive value.

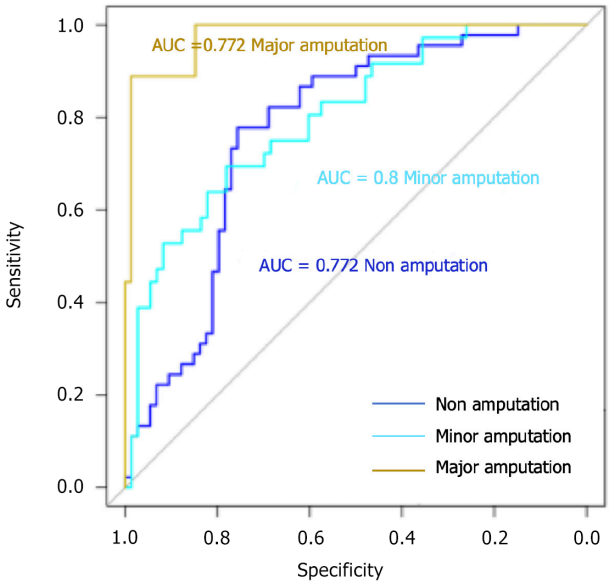


Figure 2 Receiver operating characteristic curves of the multi-category classification model. AUC: Area under the curve.

(Figure 4A). The minor amputation and non-amputation models were also well-calibrated, but with more errors, which suggests opportunities for refinement, particularly in the minor amputation model (Figure 4B and C).

Hosmer-Lemeshow Goodness-of-Fit Test: Non-amputation model: χ^2 = 5.9833, df = 8, P = 0.6491; minor amputation model: χ^2 = 7.6315, df = 8, P = 0.4703; major amputation model: χ^2 = 4.5485, df = 8, P = 0.8046. All models yielded P values > 0.05, indicating no significant deviation between predicted and observed outcomes and suggesting good overall model fitness.

Brier scores: Non-amputation model: 0.1643; minor amputation model: 0.1544; major amputation model: 0.0846. The lower Brier score for the major amputation model supports its superior predictive accuracy and calibration performance.

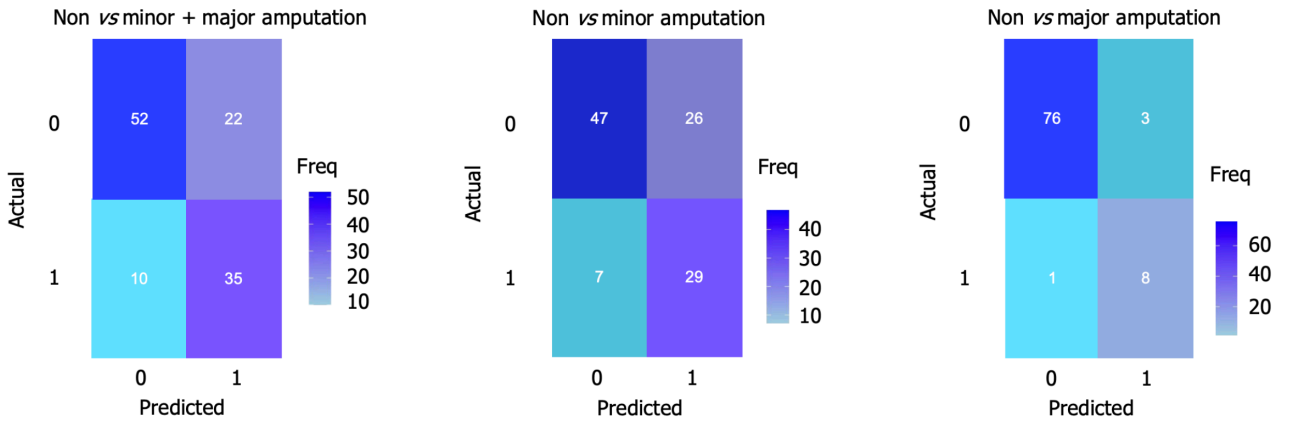


Figure 3 Confusion matrix of three classification models based on eXtreme Gradient Boosting. Different colors represent different frequencies, with the horizontal axis representing predicted values and the vertical axis representing actual values.

Interpretable explanatory model

We ranked the feature importance of the three models separately and obtained the following results (Figure 5). Wagner grading, CRP and procalcitonin (PCT) were important features among the three models. Osteomyelitis and higher BUN were also noteworthy risk factors in the minor and major amputation models. SHAP calculated the marginal contribution of features to the model output, helping to understand the impact of features on the predictive results of the model. We inputted the variables selected by ranking the importance of features into the SHAP library and constructed a Beeswarm graph (Figure 4A). For example, when explaining the minor amputation model, Wagner (grades 4/5), osteomyelitis, and vascular intervention therapy were ranked in the top three, all of which were positively correlated with outcomes. Similar explanations can also be used to analyze features that have a significant impact on decision-making in models of minor amputation and major amputation.

DISCUSSION

This study presents an analysis of the clinical characteristics and amputation outcomes of DFU patients admitted to our hospital over the past decade. We used an XGBoost model to develop a multi-category classification framework encompassing 29 variables. Although our model was initially developed using 29 clinically relevant variables informed by international guidelines, existing literature, and EHR availability, we recognize that incorporating such a broad set may pose practical limitations in routine clinical environments. All 29 variables were retained during model training to avoid premature exclusion of potential predictors, ensuring that clinically meaningful yet less obvious features were not overlooked. To enhance real-world applicability, we utilized the embedded feature selection of XGBoost in conjunction with SHAP to quantify the predictive contribution of each variable. This analysis revealed that model performance was predominantly driven by a subset of 10-12 key variables, such as Wagner classification, serum albumin, PCT, vascular intervention status, and major comorbidities; all of which are commonly accessible in inpatient settings. These findings support the feasibility of developing a more streamlined model that retains predictive power and reduces clinical implementation burden.

The AUC of the XGBoost model for predicting non-amputation, minor amputation, and major amputation was 0.772, 0.800, and 0.977, respectively. These findings align with those of Wang *et al*[30], who evaluated various amputation prediction models and reported the accuracy for XGBoost (AUC: 0.726). However, their model was based solely on patients with Texas grade 3 DFUs, limiting its generalization to broader patient populations. In contrast, our study included a wider clinical spectrum, encompassing non-amputation, minor amputation, and major amputation groups, allowing for more nuanced stratification of amputation risk.

Traditional approaches to feature selection typically rely on expert judgment, univariate statistical methods, or logistic regression, often overlooking the potential for nonlinear interactions among variables. In contrast, our study integrated the embedded feature selection of XGBoost, which utilizes tree-based splitting gains, followed by SHAP values to rank and interpret the contribution of each feature. Rather than selecting features based solely on statistical significance, we used SHAP to identify those that consistently played a pivotal role in model predictions across different patient subgroups. This dual-step approach, combining the feature importance of XGBoost with SHAP validation, unearthed clinically relevant but previously underexplored predictors such as albumin, myoglobin, and vascular intervention, which were not highlighted in prior models. Traditional machine learning models[35], including logistic regression, SVMs and ANNs, often suffer from a lack of transparency and interpretability, which limits their applicability in clinical settings. In our study, we addressed this issue by constructing hierarchical binary classification models (*e.g.*, non-amputation *vs* minor amputation; non-amputation *vs* major amputation), rather than a flat multiclass model, enabling more granular risk stratification aligned with clinical decision-making processes. The integration of XGBoost and SHAP enhanced both predictive accuracy (with AUC reaching 0.977 for major amputation) and model interpretability,

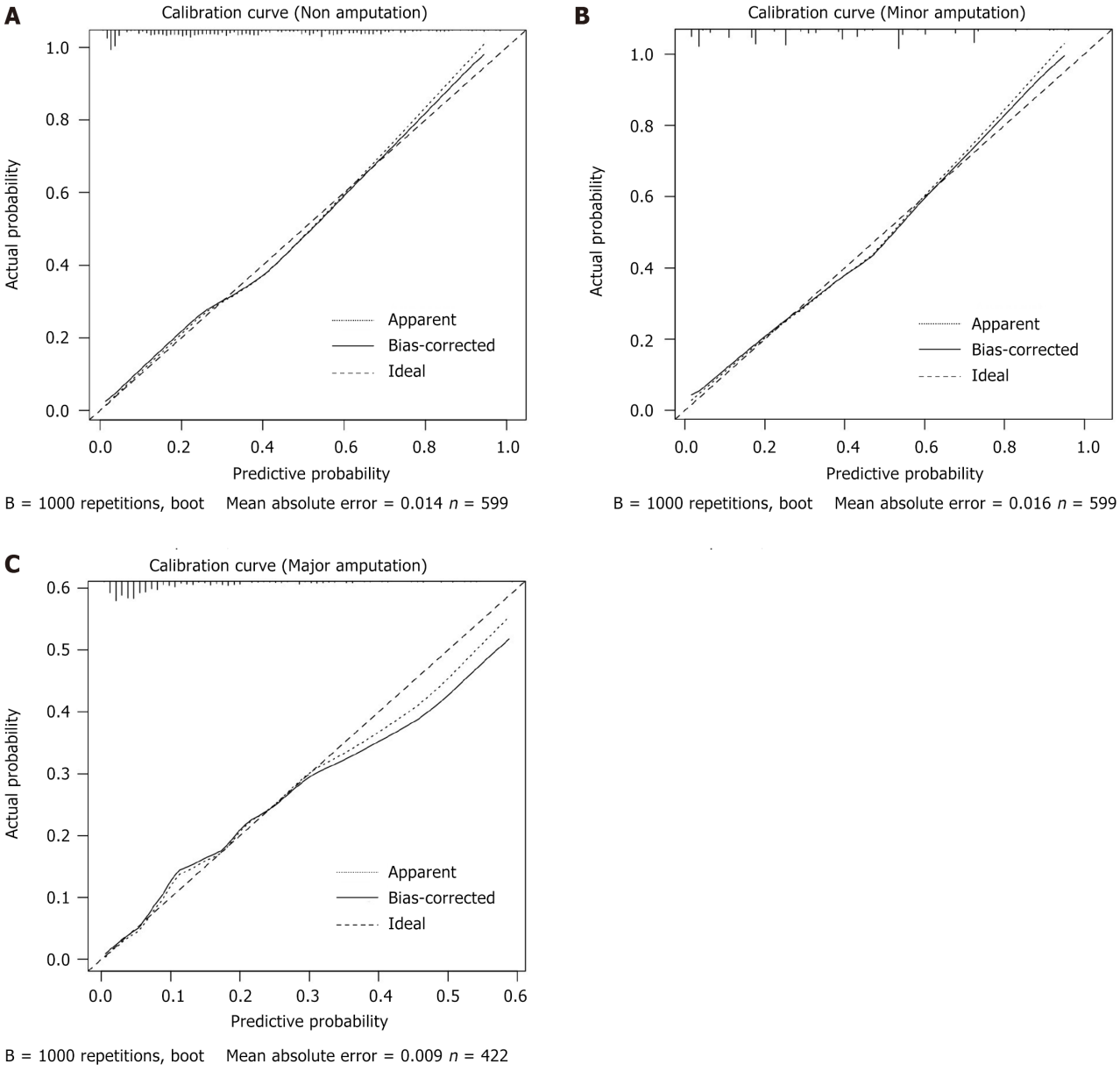
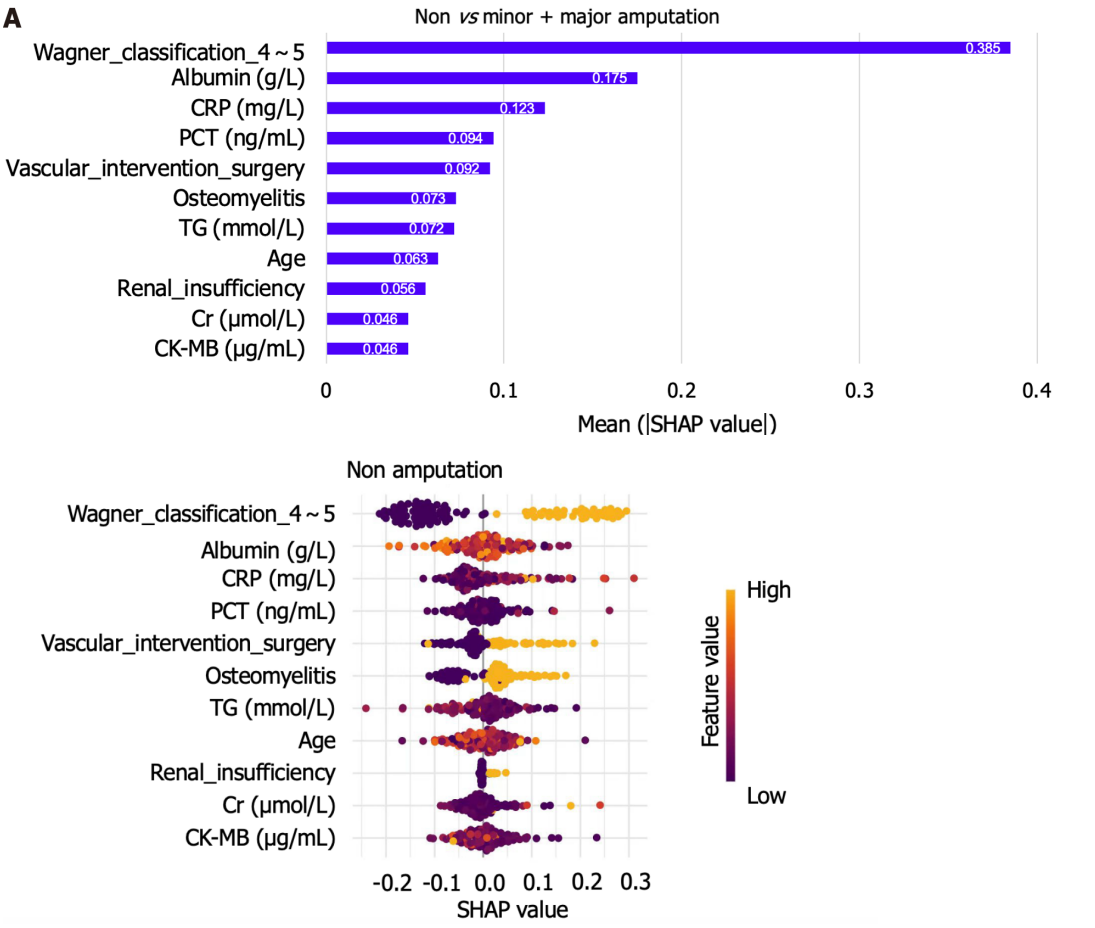
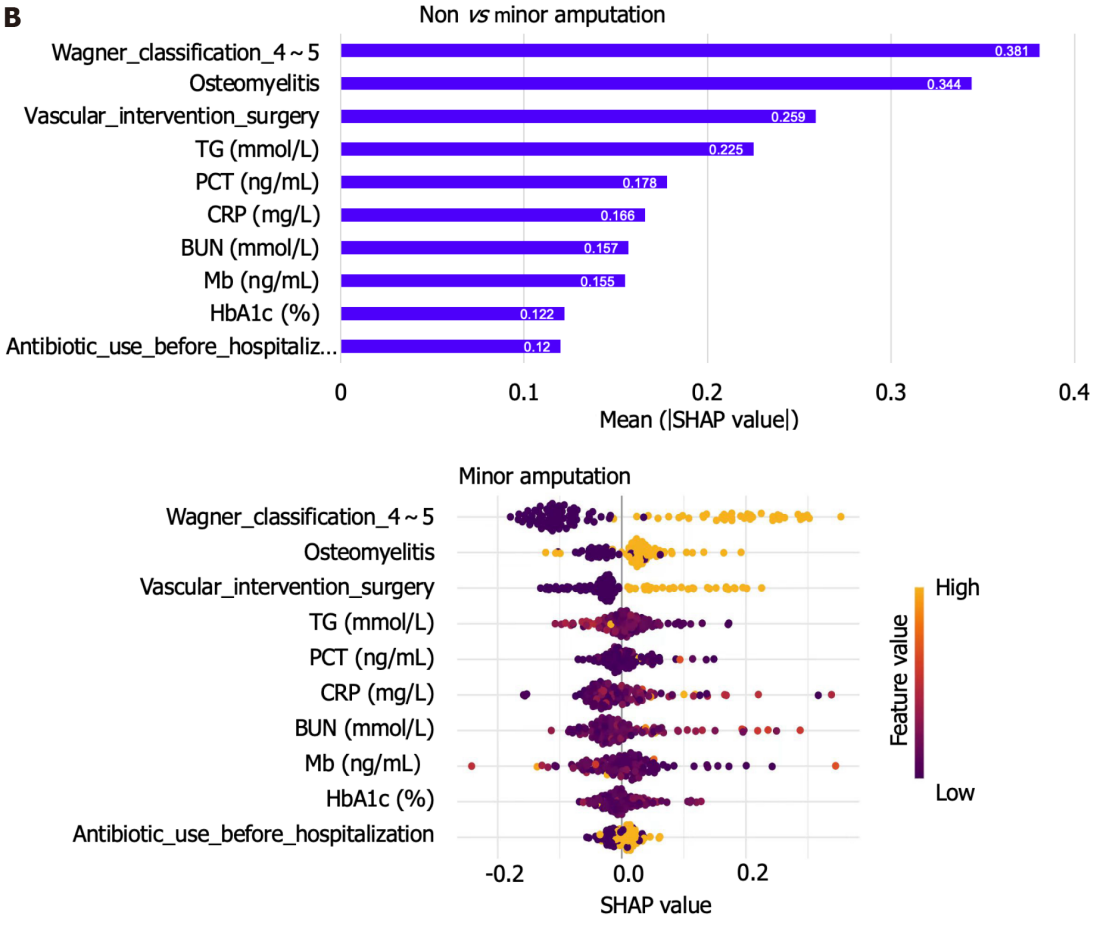


Figure 4 Calibration curves for three classification models. A: Calibration curves for non-amputation model; B: Calibration curves for minor amputation model; C: Calibration curves for major amputation model. Apparent calibration (dotted line): This curve represents the raw, uncorrected calibration of the predicted probabilities of the model against the actual probabilities. The predictions of the model are plotted directly, and the apparent curve often deviates from the ideal (diagonal) line, indicating some level of bias in the model's prediction. Bias-corrected calibration (solid line): This curve corrects for the bias observed in the apparent calibration curve. It adjusts the predictions to improve alignment with the observed outcomes, reducing the systematic under- or overestimation of probabilities. Ideal calibration (dashed line): This represents perfect calibration, where the predicted probabilities perfectly match the actual probabilities. In an ideally calibrated model, the curve would coincide with the dashed line, indicating perfect agreement between predicted and observed probabilities. Mean absolute error (0.009): The calculated error value indicates the average discrepancy between the predicted probabilities and the actual outcomes. A lower value (such as 0.009 in this case) suggests good calibration, with minor deviations between predicted and actual probabilities. B = 1000 repetitions, boot: This suggests that bootstrapping was used to calculate confidence intervals and improve the stability of the calibration curve, based on 1000 resampling iterations.

overcoming the "black-box" limitation commonly associated with traditional machine learning algorithms. To optimize performance, we implemented early stopping, hyperparameter tuning, and class weighting (*via* the scale_pos_weight parameter) to improve model generalization under imbalanced conditions. The use of XGBoost facilitated high predictive performance through its advanced techniques, such as hyperparameter optimization and imbalance handling, while SHAP provided transparency, enabling clinicians to interpret individual model predictions and understand the underlying risk factors for amputation. The novelty of our approach lies in the seamless combination of the predictive power of XGBoost with the interpretability of SHAP, leading to more precise predictions and improved clinical insights.

Diabetic foot is a multifactorial syndrome requiring comprehensive evaluation from multiple perspectives[36]. In this context, we categorize the key influencing factors into four primary dimensions: wound characteristics, nutritional status, infection severity, and lower limb perfusion. The Wagner classification system is used to assess ulcer depth and the presence of osteomyelitis, with scores ranging from 0 to 5.


A
Non *vs* minor + major amputation
Wagner_classification_4 ~ 5
Albumin (g/L)
CRP (mg/L)
PCT (ng/mL)
Vascular_intervention_surgery
Osteomyelitis
TG (mmol/L)
Age
Renal_insufficiency
Cr (μmol/L)
CK-MB (μg/mL)
0.385
0.175
0.123
0.094
0.092
0.073
0.072
0.063
0.056
0.046
0.046
0
0.1
0.2
0.3
0.4
Mean (|SHAP value|)
Non amputation
Wagner_classification_4 ~ 5
Albumin (g/L)
CRP (mg/L)
PCT (ng/mL)
Vascular_intervention_surgery
Osteomyelitis
TG (mmol/L)
Age
Renal_insufficiency
Cr (μmol/L)
CK-MB (μg/mL)
-0.2 -0.1 0.0 0.1 0.2 0.3
SHAP value
Feature value
High
Low


B
Non *vs* minor amputation
Wagner_classification_4 ~ 5
Osteomyelitis
Vascular_intervention_surgery
TG (mmol/L)
PCT (ng/mL)
CRP (mg/L)
BUN (mmol/L)
Mb (ng/mL)
HbA1c (%)
Antibiotic_use_before_hospitaliz...
0.381
0.344
0.259
0.225
0.178
0.166
0.157
0.155
0.122
0.12
0
0.1
0.2
0.3
0.4
Mean (|SHAP value|)
Minor amputation
Wagner_classification_4 ~ 5
Osteomyelitis
Vascular_intervention_surgery
TG (mmol/L)
PCT (ng/mL)
CRP (mg/L)
BUN (mmol/L)
Mb (ng/mL)
HbA1c (%)
Antibiotic_use_before_hospitalization
-0.2
0.0
0.2
SHAP value
Feature value
High
Low

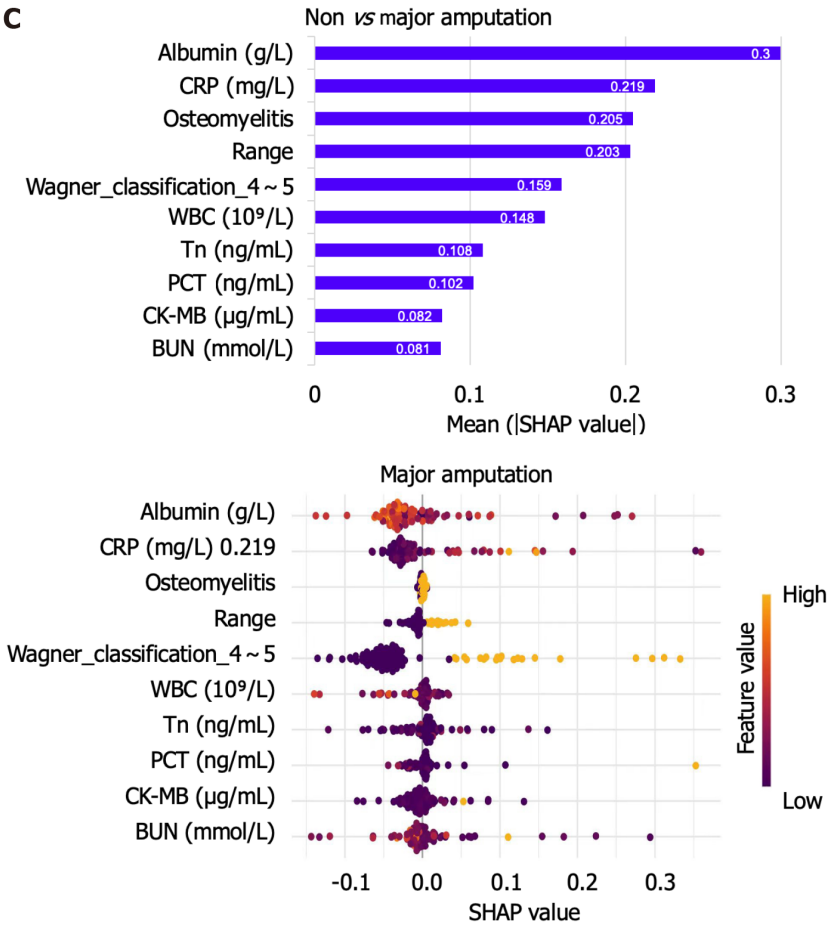


Figure 5 The weights of variable importance and the Beeswarm diagram drawn by SHapley Additive exPlanation to explain the three classification models. A: The weights of variable importance and the Beeswarm diagram drawn by SHapley Additive explanation (SHAP) to explain the non-amputation model; B: The weights of variable importance and the Beeswarm diagram drawn by SHAP to explain the Minor amputation model; C: The weights of variables importance and the Beeswarm diagram drawn by SHAP to explain the Major amputation model. The values in the bar chart represent the contribution value of each feature, the colors in SHAP value represent the level of correlation, and the left side of 0 represents negative correlation, while the right side represents positive correlation. SHAP: SHapley Additive exPlanation.

Feature selection was conducted using XGBoost, and the selected features were incorporated into SHAP analysis to determine their association with target outcomes. In the overall amputation model, the five most influential predictors identified were Wagner classification, albumin, CRP, PCT, and vascular interventional therapy. Notably, Wagner classification, CRP, and vascular interventional therapy were positively associated with the risk of amputation, while albumin was negatively associated. The model was refined to differentiate between minor and major amputation outcomes. In the minor amputation model, the top three predictors were Wagner classification, osteomyelitis, and vascular interventional therapy, all of which demonstrated significant correlations with the outcome. In the major amputation model, Wagner classification, wound size, and osteomyelitis were the strongest predictors, exhibiting significant positive correlations with amputation risk. In summary, our findings preliminarily suggest that a Wagner classification of 4/5 and the presence of osteomyelitis significantly increase the likelihood of amputation in DFU patients.

Numerous studies on the risk of DFU-associated amputation have consistently highlighted the reliability of the Wagner classification in predicting the likelihood of amputation[37,38]. For patients with diabetic foot presenting with gangrene at Wagner grade 4 or higher, amputation is often the most effective, life-saving intervention[27]. We observed a positive correlation between wound area and the risk of major amputation, which aligns with previous research demonstrating that larger wounds generally require more extensive surgical interventions, including major amputations [39,40]. Malnutrition is prevalent among patients with DFUs and significantly impacts prognosis[38]. The wound healing process requires an adequate supply of nutrients to the tissues, which may be compromised by impaired circulation and protein loss[41,42]. Low albumin levels reflect protein-energy malnutrition, which compromises collagen synthesis, angiogenesis, and fibroblast proliferation, thereby delaying tissue regeneration. Albumin also has anti-inflammatory and antioxidant properties. Reduced levels may reflect a heightened proinflammatory state, which contributes to persistent wound infection and impairs the resolution phase of wound healing. Our findings are consistent with prior clinical studies demonstrating that serum albumin is a strong prognostic marker for poor healing outcomes and major amputation in DFU cohorts[43]. This supports its role as not only a predictor in our model but also a potential target for nutritional intervention and monitoring in diabetic foot care. Prior studies have established that infection severity is a key predictor of amputation risk[44]. Our findings further support this, as elevated CRP levels were associated with an

increased likelihood of major amputation. This association may be attributed to impaired immune response or compromised peripheral circulation[45]. Arterial stenosis or occlusion in the lower extremities can result in inadequate blood supply to local tissues, leading to foot gangrene. Thus, the severity of lower limb arterial stenosis serves as a critical determinant in assessing the necessity for amputation. It should also be emphasized that osteomyelitis is a strong predictor of amputation, but not the sole indication-particularly in cases of major amputation. Other clinical factors, such as severe ischemia, extensive soft tissue infection, or a poor overall prognosis, may also play a critical role in the decision to proceed with amputation.

To evaluate the clinical utility of the proposed model, we compared its decision-making capability with the Wagner classification system, a widely used clinical tool for assessing DFU severity and guiding treatment decisions. While Wagner grade is a strong and well-validated predictor of amputation risk, it is a 1D scale that does not account for key factors such as infection severity, ischemia, comorbidities, or nutritional status[46]. In contrast, our XGBoost-based model incorporated 29 multidimensional clinical features and provided individualized risk predictions supported by SHAP, allowing clinicians to interpret the contribution of each variable to a patient's predicted risk. For example, two patients with the same Wagner grade may receive different risk scores from our model due to differences in laboratory parameters (*e.g.*, CRP or albumin), vascular status, or history of revascularization. This highlights the added value of the model in refining risk stratification beyond what is possible with Wagner grading alone. Therefore, our model has the potential to complement existing clinical tools by providing more nuanced, data-driven risk assessments that support personalized clinical decision-making.

In our study, we observed a minimal correlation between pre-admission antibiotic usage and the incidence of amputation. This lack of correlation may be attributed to the limited efficacy of antimicrobial therapy alone in the presence of osteomyelitis[47-49]. For acute diabetic foot infections, surgical incision and abscess drainage are essential components of treatment and should be performed in conjunction with systemic antibiotic therapy[50,51]. Cultures from wound biopsy or curetted necrotic tissue remain the preferred methods for identifying the causative pathogens[52]. Osteomyelitis plays a critical role in the management of diabetic foot infections, with surveys indicating that approximately 50% of patients with osteomyelitis-related DFUs undergo amputation[53]. Consequently, early debridement in patients with diabetic foot infections suspected of osteomyelitis may expedite wound healing.

Our findings indicated that vascular intervention was positively associated with minor amputation risk but showed no significant correlation in the major amputation model. This discrepancy may reflect fundamental differences in pathophysiological mechanisms and patient characteristics between the two groups. Patients undergoing major amputation often present with advanced peripheral arterial disease and critical limb ischemia, where tissue necrosis is already extensive. In such cases, vascular interventions, if performed, typically represent salvage attempts rather than proactive measures, and may not be sufficient to prevent limb loss. Consequently, the presence of vascular intervention in this group may serve as a surrogate marker for disease severity rather than therapeutic success, thereby diminishing its predictive utility. In contrast, in the minor amputation group, vascular interventions are more likely to be applied earlier in the disease trajectory, when ischemia is less severe and tissues are still viable. Under these conditions, revascularization may serve as an effective modifying factor, helping to preserve limb integrity and prevent progression to major amputation. This may explain its positive association with minor amputation outcomes. Additionally, differences in timing, patient selection criteria, and clinical decision-making processes may further account for the observed variability in the relevance of vascular intervention between the two models[54,55].

Early identification and management of risk factors associated with diabetic foot can significantly influence surgical decision-making[56-58]. In clinical diagnosis, it is crucial to enhance regular foot examinations, promptly identify high-risk patients, and initiate vascular interventional therapy at the earliest opportunity for those experiencing lower limb ischemia. In clinical treatment, continuous wound evaluation is imperative to monitor changes in wound characteristics, assess infection status, and determine the efficacy of therapeutic interventions. Additionally, it is essential to closely monitor blood glucose fluctuations and address hypoproteinemia. Compared to patients with mild DFUs (Wagner grades 1/2), those with moderate to severe ulcers (Wagner grades 3-5) typically present with deeper lesions, a greater demand for nutrients (such as protein) for wound healing, and exhibit a more compromised nutritional status[59]. Our XGBoost-SHAP predictive model combines high accuracy with clinical interpretability, making it suitable for real-world use. It can support early identification of high-risk patients and guide individualized care strategies. Importantly, it can be integrated into clinical decision support systems within EHRs to provide patient-specific risk estimates and SHAP-based explanations, facilitating informed and timely clinical decision-making.

Our study had several limitations. Firstly, although we used the efficient XGBoost algorithm to predict the probability of amputation in diabetic foot, we did not compare its predictive accuracy with that of traditional machine learning methods, which limits the robustness of our findings. Moreover, the retrospective nature of the study and the clinical data derived primarily from EHRs, described and organized by clinicians, introduce the potential for subjective variability in ulcer description and grading. Secondly, the decision to amputate is influenced by multiple factors. Patients with Wagner grade 4/5 ulcers who had gangrene but did not undergo amputation may reflect differences in clinical judgment, patient preferences, or comorbidities, with decisions influenced by factors such as conservative treatment, surgical risk, or refusal of surgery. Nonmedical factors, such as limited financial resources, lack of social support, or patient refusal of limb-salvage interventions, can influence the decision to perform major amputations, and may introduce confounding data when evaluating medically driven risk factors. Prospective studies should incorporate standardized assessments of nonclinical factors. Doing so would help distinguish between medically indicated amputations and those driven by extrinsic constraints, thereby improving the precision and generalizability of amputation risk models. Thirdly, the primary outcome focused on amputation events. However, we acknowledge that some patients in the non-amputation group may have had unhealed wounds due to factors such as poor overall health status, severe ischemia, or limited treatment tolerance, despite not undergoing surgery. Due to the retrospective nature of our dataset and limitations in

long-term follow-up documentation, we were unable to consistently capture wound healing status across the entire cohort. Future prospective studies should incorporate systematic tracking of wound healing outcomes, as wound closure represents a critical clinical endpoint. This would enable a more nuanced evaluation of treatment efficacy and patient trajectories beyond the binary outcome of amputation. Fourthly, the retrospective, single-center design may have introduced selection bias and limit the generalization of the model, as clinical practices, patient characteristics, and data availability can vary across settings. To improve external validity, future work should include multicenter validation across diverse populations, prospective data collection to reduce bias, external validation with recalibration, and the development of adaptable or region-specific models. These steps will enhance the robustness, clinical relevance, and real-world applicability of the model.

CONCLUSION

We developed a multi-class classification model using the XGBoost algorithm to predict the risk of amputation among patients with DFUs during hospitalization. We ensured the interpretability of the model outcomes through feature selection and elucidation of significant variables. The results demonstrated that this machine learning model exhibited superior predictive performance, providing clinicians with comprehensive insights into each patient's risk factors and their respective contributions, thereby supporting timely interventions to reduce the incidence of major amputations.

FOOTNOTES

Author contributions: Gao L conducted experiments and guided the writing of the manuscript; Liu ZX collected and analyzed the data; Wang JN is the corresponding author of this manuscript; Wang JN designed the experimental program and chaired the seminar. This manuscript has been read and approved by all the co-authors. Gao L and Liu ZX contributed equally to this work and they are co-first authors.

Institutional review board statement: This study was performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki and approved by the Ethical Review Committee of Beijing Shijitan Hospital, Capital Medical University, No. IIT2025-049-001.

Informed consent statement: This study was a retrospective analysis of anonymized clinical data. Ethical approval was obtained from the Institutional Review Board, and the requirement for informed consent was waived.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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