Point-by-point response to reviews

Dear Editor

We would like to thank you for your careful reading, helpful comments, and constructive suggestions once again, which have significantly improved the quality of our manuscript.

We have carefully considered all comments from the reviewers and revised our manuscript accordingly.

In the revised manuscript, all changes are all highlighted with yellow color.

The following provide point-by-point responses to all reviewers'comments.

Reviewer #1:

Q1 Firstly, the question of whether major amputations triggered by non-medical factors like patients' poor economic status and lack of social support should be excluded is of great importance. This exclusion could potentially increase the accuracy of the study's findings.

Response:

Thank you for raising this important point. We fully agree that non-medical 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 when evaluating medically driven risk factors.However, due to the retrospective nature of our study and the limitations of the electronic health records used, we were unable to reliably extract and quantify such non-medical determinants across the entire cohort. As a result, we did not apply exclusion criteria based on socioeconomic or psychosocial variables.We acknowledge this as a potential limitation into revised Discussion and have noted that future prospective studies should incorporate standardized assessments of non-clinical 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.

Q2 Secondly, in the Wagner grade 4-5 group, it remains unclear if there are patients with toe gangrene or gangrene of the entire foot who didn't receive amputation, and the reasons behind their treatment decisions should be investigated.

Response:

Thank you for your insightful observation. We agree that further clarification is needed regarding patients with Wagner grade 4–5 ulcers who presented with toe or foot gangrene but did not undergo amputation. This subgroup is clinically relevant, as their management decisions may reflect variability in physician judgment, patient preference, comorbid conditions, or institutional practice patterns.We have acknowledged this in the revised Discussion.

Q3 Thirdly, the situation of patients without osteomyelitis yet undergoing major amputation requires an explanation.

Response:
Thank you for highlighting this important point.The explanation has been incorporated into the revised Discussion to clarify that, while osteomyelitis is a strong predictor of amputation, it is not the sole indication — particularly for major amputation in severe or multifactorial cases. Other clinical factors, such as severe ischemia, extensive soft tissue infection, or a poor overall prognosis, may also play a decisive role in the decision to proceed with amputation.

Q4 Finally, adding the patient outcome of whether the wound heals is essential, and also exploring in the non-amputation group those patients with unhealed wounds due to poor general health but without surgery. These clarifications will enhance the article's comprehensiveness and credibility.

Response:
Thank you for this valuable suggestion. We fully agree that including patient outcomes related to wound healing—particularly among those who did not undergo amputation — would enrich the comprehensiveness and clinical relevance of the study.However, due to the retrospective nature of our dataset and variability in follow-up documentation, we were unable to consistently capture long-term wound healing status for all patients, especially in the non-amputation group.We have acknowledged this limitation in the revised Discussion and emphasized that future prospective studies should incorporate systematic tracking of wound healing outcomes.

Q5 It is mentioned in the original text: Our findings also suggest variability in vascular interventional therapy as an intervention factor between the two models examined, revealing a positive correlation in the minor amputation model but no correlation in the major amputation model. This suggests that, in the context of diabetic foot infections coexisting with peripheral arterial disease, revascularization techniques for the lower limb may significantly reduce the incidence of major amputations, lower the level of amputation required, and improve long-term outcomes. Vascular intervention exhibits a positive correlation with minor amputation, in the sense that it may play a facilitating or influencing role in the context of minor amputation scenarios. However, it has no direct causal connection with major amputation, indicating that the occurrence of major amputation is not directly determined or influenced by vascular intervention procedures. Given the complexity of influencing factors, it's

impossible to simply conclude that such intervention can lower the amputation level.

Response:
Thank you for your insightful comment. In response, we have expanded the revised Discussion to provide a more in-depth explanation of the differing relevance of vascular interventional therapy between the minor and major amputation models.
Change to the following content：
“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.”

Reviewer #2:

Q1 The study employs 5-fold cross-validation but does not detail how data imbalance was addressed. Given the differences in sample sizes across the non-amputation, minor amputation, and major amputation groups, this imbalance could significantly impact model performance. The authors should describe strategies used to mitigate these biases, such as SMOTE or class weighting, and justify their choices.

Response:
We appreciate your insightful comment regarding the potential impact of data imbalance across the three outcome categories (non-amputation, minor amputation, and major amputation). To mitigate the influence of this imbalance, we adopted the following strategies during model development:To address class imbalance, we used the scale_pos_weight parameter in XGBoost.This adjustment effectively compensated for class imbalance and improved the model’s ability to correctly identify minority class instances.We have added the above content in the Class weighting for the

imbalanced dataset section of revised MATERIALS AND METHODS.

Q2 Continuous variables were discretized using the quantile method. The rationale behind this choice is unclear. The authors should compare the impact of different discretization methods (e.g., equal-width binning, k-means clustering) on model performance. This comparison will help justify the chosen approach and provide insights into its effectiveness in enhancing predictive accuracy.

Response:
We appreciate your valuable comment regarding the choice of discretization method for continuous variables.To address this concern, we conducted a comparison of several discretization methods, including quantile binning, equal-width binning, and k-means clustering.We chose the quantile method for discretizing continuous variables over equal-width binning or k-means clustering primarily because it effectively handles skewed distributions in the data. Unlike equal-width binning, which divides the range of the data into equal-sized intervals, the quantile method ensures that each bin contains an equal number of samples, thus avoiding the issue of having bins with too few data points, especially when there are extreme values. Compared to k-means clustering, the quantile method is simpler, more stable, and does not require complex initialization or iterative optimization. Additionally, the quantile method better preserves the distributional characteristics of the data, which helps improve the model's predictive accuracy and robustness.
We have added the above content in theData preprocessing section of revised MATERIALS AND METHODS.

Q3 The paper claims to use the XGBoost algorithm and SHAP for the prediction model. Compared with previous machine-learning-based studies on predicting diabetic foot amputation risk, it is not clear what the core innovation points are in feature selection and model construction. The authors should clearly define these innovation points. For example, in feature selection, is there a new way to identify more relevant risk factors? In model construction, does the combination of XGBoost and SHAP bring unique advantages? Moreover, they need to more clearly explain how these innovations improve the prediction accuracy and clinical utility. For instance, providing real-world case examples where the model's predictions based on these innovations lead to better patient outcomes or more accurate clinical decision-making.

Response:
We appreciate your insightful comment regarding the need to clarify the core innovation points in our study, particularly in feature selection and model construction.The novelty in our study lies in the combination of XGBoost’s predictive power and SHAP’s interpretability, both of which contribute to more accurate predictions and better clinical insights. These innovations enable clinicians to make

more personalized decisions, enhancing the overall clinical utility of the model.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.
We have added above content in the revised Discussion.

Q4 Several references do not conform to the journal's formatting guidelines. It is crucial to ensure all references adhere to the specified citation style, including correct formatting of author names, publication years, titles, and volume/page numbers. Consistency in reference formatting is essential for maintaining the professionalism and readability of the manuscript.

Response:
We appreciate your careful attention to detail. We have thoroughly reviewed all references and have taken steps to ensure all references now fully comply with the required format.

Reviewer #3:

Q1 Abstract 1.Results: The statement "The accuracy of the three XGBoost models is higher than 0.7" lacks specificity. "Accuracy" is ambiguous in machine learning contexts. Please clarify whether this refers to the Area Under the Curve (AUC), F1-score, or standard classification accuracy.

Response:
Thank you for pointing out this important clarification. We acknowledge that the term "accuracy" can be ambiguous in machine learning contexts. In our manuscript, the intended meaning of "accuracy" was Area Under the Receiver Operating Characteristic Curve (AUC), which we used as the primary metric to evaluate the overall discriminative performance of the models.
It has been revised in the revised Abstract Results section as: "The model 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 nonamputation model (AUC = 0.772, 95% CI: 0.730 – 0.814)"

Q2 Abstract 2.Missing keywords related to diabetic foot ulcer outcomes (e.g., amputation stratification, clinical risk prediction).

Response:
Thank you for your valuable feedback. We agree that including more specific

keywords can improve the discoverability and relevance of the manuscript. In response, we have updated the keyword list to better reflect the core focus and clinical significance of the study.We have added the following keywords to the revised Abstract.
Keywords:
Diabetic foot ulcer;Amputation stratification;Clinical risk prediction;XGBoost;SHAP; Machine learning.

Q3 Abstract 3. The Results section should include quantitative performance metrics (e.g., AUC values with 95% confidence intervals) to strengthen claims of model superiority.

Response:
Thank you for this important suggestion. To strengthen the validity of our model performance claims, we have updated the Abstract Results section to include quantitative metrics, specifically the AUC values with their corresponding 95% confidence intervals for each of the three binary classification models.

Q4. Abstract Methods: SHAP (Shapley Additive Explanations) should be spelled out upon first mention, as it is not universally recognized.

Response:
Thank you for pointing this out. We have revised the Abstract Methods section to spell out SHAP in full upon its first mention as "Shapley Additive Explanations (SHAP)", in accordance with standard academic writing conventions.

Q5 Introduction 1. The rationale for selecting XGBoost requires strengthening. Cite recent applications of XGBoost in medical outcome prediction (e.g., cardiovascular risk stratification or sepsis prediction) to justify its suitability for diabetic foot ulcer analysis.

Response:
We appreciate your insightful feedback regarding the need to strengthen the rationale for selecting XGBoost in our study. XGBoost is a powerful ensemble learning algorithm known for its efficiency, flexibility, and superior predictive performance. Its application in medical outcome prediction has been well-documented across various domains, demonstrating its suitability for complex clinical datasets.
We have added the following content to the Introduction section:

"Liu et al. developed an XGBoost-based mortality prediction model for ICU patients with acute kidney injury (AKI), demonstrating its potential for early risk stratification and timely intervention in critically ill individuals.Hou et al. and Hu et al. both applied XGBoost to mortality prediction in sepsis patients. Hou et al. achieved an 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."

Q6 Materials & Methods 1. No justification is provided for the initial selection of 29 variables. Describe the criteria (e.g., clinical relevance, prior literature) guiding variable inclusion.

Response:
Thank you for highlighting the need to clarify our criteria for the initial selection of the 29 variables included in the model. In our study, these variables were selected based on the following considerations and We have added the following content to the section Study design and participants of Materials & Methods:

"Based on clinical practice, international guidelines from the International Working Group on the Diabetic Foot (IWGDF), and a comprehensive literature review, we initially screened candidate variables for inclusion. Further selection was conducted according to the availability and completeness of data within the electronic health records (EHR), ensuring data integrity and minimizing 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 (i.e., amputation status)."

Q7 Materials & Methods 2. Clarify the relationship between XGBoost-based feature importance analysis and pre-model variable screening. Was dimensionality reduction performed prior to model training?

Response:
Thank you for your thoughtful comment. We clarify that no dimensionality reduction or manual pre-screening of variables was performed prior to model training. Instead, we adopted a data-driven approach that leveraged the inherent feature selection capability of the XGBoost algorithm.We have added the following content to the section Variable selection for model training of Materials & Methods:

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

Q8 Materials & Methods 3. Severe class imbalance exists (392 non-amputation vs. 50 major amputation cases). Address whether oversampling (e.g., SMOTE) or undersampling techniques were applied. Discuss potential impacts of imbalance on model performance.

Response:

Thank you for highlighting the issue of class imbalance, particularly between the non-amputation (n=392) and major amputation (n=50) groups. We fully recognize the potential influence of severe class imbalance on model performance, especially in terms of reduced sensitivity for minority class prediction.In this study, we addressed class imbalance using the scale_pos_weight parameter within the XGBoost framework. This parameter was set to the ratio of negative to positive samples in the training data, thereby increasing the weight of the minority class (major amputation) during model optimization. This strategy allowed the model to focus more on correctly identifying rare but clinically significant outcomes.We have added the following content to Section Class weighting for the imbalanced dataset of the Materials & Methods.To address the potential class imbalance between the different amputation groups (nonamputation, minor amputation, and major amputation), we used the scale_pos_weight parameter in the XGBoost algorithm. 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 the number of negative samples to the number of positive samples. This was done using the following formula:

$$\text{scale\_pos\_weight} = \frac{\text{Number of Negative Samples}}{\text{Number of Positive Samples}}$$

This adjustment ensured that the model gave more emphasis to the minority class (major amputation), thereby improving the predictive accuracy for rare outcomes. The scale_pos_weight parameter, integrated with 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.

Q9 Materials & Methods 4. Missing details on hyperparameter optimization: Specify the algorithm (grid search, Bayesian optimization).

Response:

Thank you for your comment regarding the hyperparameter optimization process. In our study, we performed hyperparameter tuning using a grid search strategy combined with 5-fold cross-validation to identify the optimal parameter set for the XGBoost model. This process involved systematically evaluating combinations of key parameters such as the maximum tree depth (max_depth), learning rate (eta), subsample ratio (subsample), column sampling ratio (colsample_bytree), and min_child_weight, and to maximize model performance while avoiding overfitting.

We have added the relevant content to Section Model parameter setting of the Materials & Methods.

Q10 Materials & Methods 5. Provide formulas or references for calculating sensitivity, specificity, PPV, and NPV. Clarify how classification thresholds were determined.

Response:
Thank you for your valuable suggestion. We have now added the standard formulas and references for calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in the revised Methods section. These metrics were derived from the confusion matrix using the following definitions:
Sensitivity (Recall) = TP / (TP + FN); Specificity = TN / (TN + FP); PPV = TP / (TP + FP); NPV = TN / (TN + FN); TP = true positives; TN = true negatives; FP = false positives; FN = false negatives.
We used the default threshold of 0.5 for binary classification, where predicted probabilities $\geqslant$ 0.5 were classified as positive, and < 0.5 as negative. This threshold was used consistently across models to allow for standard comparison of classification performance.

Q11 Materials & Methods 6. Describe missing data handling: Report the percentage of missing values per variable and the imputation method.

Response:
Thank you for your insightful comment.During data preprocessing, we confirmed that the dataset contained no missing values; therefore, no imputation or data cleaning for incomplete entries was necessary.We have added the relevant content to Section Data preprocessing of the Materials & Methods.

Q12 The authors appropriately assessed discrimination (AUC, sensitivity, specificity) but neglected calibration metrics. For clinical predictive models, calibration reflects the agreement between predicted probabilities and observed outcomes (e.g., a predicted 30% amputation risk should correspond to 30% actual events). Poor calibration may lead to overestimation/underestimation of risks in clinical practice.

Response:
Thank you for your valuable comment. We fully agree that calibration is an essential component of clinical predictive modeling, as it reflects the agreement between predicted probabilities and actual outcomes. While our initial analysis focused primarily on discrimination metrics (AUC, sensitivity, specificity, PPV, and NPV), we have now supplemented our evaluation with calibration assessments to enhance the robustness and clinical relevance of our findings.The calibration results and corresponding figures have been added to the revised Results.

Q13 Although SHAP values explain feature contributions, the clinical applicability remains unaddressed. Compare the model's decision-making utility

against established tools (e.g., Wagner classification) to demonstrate added value.

Response:
Thank you for this thoughtful comment. we compared the decision-making utility of our XGBoost+SHAP model with that of the Wagner classification system. We have added a detailed discussion in the Discussion section as follows:

"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. 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."

Q14 Discussion 1. The authors state that the XGBoost model was developed using 29 variables, but critical details are omitted: Clinical Applicability Concerns: The inclusion of 29 variables raises questions about the model's practicality in real-world clinical settings. While comprehensive variable inclusion may improve predictive accuracy, excessive parameters risk overcomplicating clinical implementation. For example, clinicians may struggle to routinely collect 29 variables during initial patient assessments, especially in resource-limited environments.

Response:
Thank you for highlighting this important concern regarding the clinical applicability of using 29 variables in the XGBoost model. We fully acknowledge that while a comprehensive set of features may enhance predictive accuracy, it can also pose challenges for implementation in real-world clinical environments, particularly where time, resources, or data infrastructure are limited.We have clarified this point in the revised Discussion section.The specific modifications are as follows:

"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 while reducing clinical implementation burden."

Q15 Discussion 2. Although the authors mention using XGBoost for feature selection, they fail to specify: The exact number of variables retained after feature selection.Whether the final model (e.g., for major/minor amputation) used all 29 variables or a reduced subset.How the feature selection process (e.g., SHAP-based ranking) influenced variable prioritization.

Response:
Thank you for your thoughtful comment.Although all 29 clinically relevant variables were initially included in the model training to preserve potential predictors, we used XGBoost's embedded feature importance metrics—based on gain scores—combined with SHAP (Shapley Additive Explanations) for post hoc interpretability and feature prioritization.After SHAP-based ranking, we observed that the majority of model performance was driven by approximately 10 to 12 variables, depending on the specific outcome. For example:In the major amputation model, top contributors included Wagner classification, albumin, myoglobin, PCT, and vascular intervention.In the minor amputation model, key variables included Wagner classification, infection markers (CRP, PCT), and neuropathy.Although all 29 variables remained in the final trained models to avoid loss of information, the SHAP analysis allowed us to identify and interpret a reduced subset of high-impact predictors. This approach balances predictive performance with interpretability and provides a foundation for developing streamlined clinical tools in future work.We have clarified this point in the revised Discussion section.

Q16 Discussion 3. The negative correlation between albumin and amputation is only briefly mentioned without incorporating pathophysiologic mechanisms. Suggest an in-depth explanation of how low albumin reflects malnutrition/inflammation and affects healing.

Response:
Thank you for this valuable comment. In the revised Discussion section, we have expanded on the observed negative correlation between serum albumin and amputation risk, integrating relevant biological mechanisms. 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 pro-inflammatory 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. 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.

Q17 Discussion 4. there is no detailed explanation as to why XGBoost performs well in this task or how it compares to other models. This may be a point to add.

Response:
Thank you for your insightful suggestion. We have now elaborated in the Discussion section on why the XGBoost algorithm is particularly well-suited for this task and how it compares to traditional machine learning models.We have added the following content to the revised Discussion section:

"Traditional machine learning models, 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., nonamputation vs minor amputation; nonamputation 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, 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. "

Q18 Discussion 5. when comparing the existing literature, although the study by Wang et al. is cited, the similarities and differences between this study and previous work need to be pointed out, such as the improvement in model performance or the discovery of different variables.

Response:
Thank you for pointing this out. We have revised the Discussion section to more

clearly compare our findings with those of Wang et al. and other related studies.We have added the following content to the revised Discussion section:

"However, Wang et al 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 nonamputation, minor amputation, and major amputation groups, allowing for more nuanced stratification of amputation risk."

Q19 Discussion 6. when discussing the relevance of treatments, the different relevance of vascular interventions in minor and major amputation models is mentioned, but a more in-depth explanation of the possible reasons for this difference is needed, such as different pathomechanisms or differences in patient populations.

Response:
Thank you for this insightful comment. We agree that the differing relevance of vascular intervention across the minor and major amputation models warrants further explanation, and we have expanded on this point in the revised Discussion section as follows:

"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."

Q20 Discussion 7. Regarding the limitations section, the authors mention retrospective studies, single-center data, etc., but further discussion could be provided on how these limitations affect the generalizability of the results and how they could be overcome in the future with multicenter studies.

Response:

Thank you for your thoughtful suggestion. We have expanded the Limitations section as follows:

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.

Q21 Discussion 8. When discussing the application of the results, the section on translational medicine needs to be strengthened to show how the model can be applied to actual diagnosis and treatment.

Response:
Thank you for this important suggestion. We have revised the Discussion section to further emphasize the translational value of our model and its potential integration into clinical practice.we have expanded on this point in the revised Discussion section as follows:

"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."

Q22 Discussion 9. Reorganize the Discussion to prioritize clinical implications over technical model descriptions.

Response:
Thank you for your helpful suggestion. we have reorganized the Discussion section to prioritize clinical implications over technical model details.

Science Editor

Q1Country/Territory of origin: China.

Response:
It is correct.

Q2The language classification is Grade D, Grade B, and Grade B. Please provide the latest Language certificate after Return the Manuscript to Author for Revision.Please visit the following website for the professional English language editing companies that we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

Response:
Thank you for your helpful suggestion.We have made the necessary revisions to the manuscript and obtained a professional English editing certificate as recommended. The updated manuscript and certificate have been uploaded to the submission system.

Q3 Author list.Author names (unabbreviated) should be given as first name, middle name initial (with no period) and family (sur)name, and typed in bold with the first letter of each capitalized.
A hyphen should be included between the syllables of Chinese names. For example: Yi-Fan Chang, Jia-Jing Li, Tao Liu, Chong-Qing Wei, Li-Wei Ma, Vladimir N Nikolenko, Wei-Long Chang.

Response:
Thank you for your guidance. We have revised the author list to comply with the journal's formatting requirements.

Q4 Authors and institution(s): Author names should be written out first (as first name, middle name initial (with no period) and family (sur)name; with a hyphen included between the syllables of Chinese names) and typed in bold, followed by a comma and the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold. Examples for authors name and institutions are:
Yi-Fan Chang, Tao Liu, Chong-Qing Wei, Wei-Long Chang, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Response:
Thank you for your detailed instructions. We have revised the author and institutional information to conform to the required format.

Q5 Author contributions: The ‘Author contributions’ passage describes the specific contribution(s) made by each author. The author’s names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names. For example, Bryan L Copple should be revised as Copple BL. A full multi-author example is: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research study; Wang CL, Zou CC, Hong F and Wu XM performed the research.

Response:
Thank you for your detailed instructions. We have revised the author and institutional information to conform to the required format.

Q6 Please add the “ “Key Words”:
The ‘Key words’ list will provide 5-10 keywords that reflect the main content

of the study.
Please do not use abbreviations for the keywords (e.g., Ulcerative colitis, not UC). The first letter of each keyword will be capitalized, and each keyword will be separated by a semicolon, with no terminal period. An example of correct formatting is: Non-alcoholic fatty liver disease; Alcoholic liver disease; Non-alcoholic steatohepatitis; Insulin resistance; Oxidative stress.

Response:
Thank you for your guidance. We have revised the "Key Words" section to include 6 keywords that accurately reflect the main content of the study. Abbreviations have been avoided, the first letter of each keyword has been capitalized,

Q7Please add the "Core Tip". The Core Tip is a short paragraph that is independent of the content of the Abstract. The 'Core Tip' will provide a succinct summary of the study that outlines its most innovative and important arguments. This section should be less than 100 words. Abbreviations must be defined upon first appearance in the Core Tip. Do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition.

Response:
Thank you for your suggestion. We have added the "Core Tip" section as requested.

Q8Please add the "Audio Core Tip". In order to attract readers to read the full-text article, we request that the first author make an audio file describing the final core tip. This audio file will be published online, along with the article. The author can invite English language editing company to assist in resolving the language issues of Audio Core Tip.

Response:
We have completed and uploaded the Audio Core Tip as requested.

Q9Reference numbers in the main text.

Response:
We have revised the reference numbers formatting in accordance with the journal's requirements.

Q10There are issues with the references:
Please provide the PMID numbers (https://pubmed.ncbi.nlm.nih.gov/) and DOI citation numbers (https://doi.crossref.org/simpleTextQuery) to the reference list and list all authors of the references. If a reference has no PMID and DOI, please provide the source website address of this reference.
To ensure the accuracy of the references, please use "Edit References by

Auto-Analyser"
(https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx) to edit the references of the manuscript.

Response:
Response:We have revised the reference formatting in accordance with the journal's requirements.

Q11Figures format.

Response:
We have revised the figure formatting as required by the journal guidelines.

Q12Figure Color: When using different color markings on the Figures, please avoid using red or green, including the arrow colors on the Figures.

Response:
We have revised the figure Color formatting as required by the journal guidelines.

Q13Tables format.

Response:
We have revised the Tables formatting as required by the journal guidelines.

Q14 It is not allowed to add a sequence number before first level subtitles, second level subtitles, and third level subtitles. For example: " 1 INTRODUCTION". Please delete '1'.

Response:
We have deleted sequence number before first level subtitles, second level subtitles, and third level subtitles.

Q15Abstract.The 5 sections of the structured abstract are:
BACKGROUND; AIM; METHODS; RESULTS; CONCLUSION.
Abstract. An informative, structured abstract of no more than 350 words should accompany each manuscript. Abbreviations should be avoided, but if used should be spelled out at first mention. The 5 sections of the structured abstract are:
AIM (no more than 20 words). The purpose of the study should be stated clearly, with no or minimal background information, must start with "To", following the format of: "To investigate/study/determine…".

Response:

We have revised the Abstract formatting as required by the journal guidelines.

Company Editor-in-Chief:

Q1 Manuscript Revision

Response:

We have made the necessary revisions to the manuscript and obtained a professional English editing certificate as recommended. The updated manuscript and certificate have been uploaded to the submission system.

Q2Peer Review

Response:

We have requested the editing company to assist in reviewing the manuscript based on the comments from peer reviewers and scientific editors to ensure the academic rigor of the study.

Q3 Author Names format

Response:

Thank you for your detailed instructions. We have revised the author names information to conform to the required format.

Q4Figures and Diagrams format

Response:

We have revised the Figures and Diagrams to conform to the required format.

Q5Three-Line Tables format

Response:

We have revised the Three-Line Tables formatting in accordance with the journal's requirements.

Q6References format

Response:

We have revised the References formatting in accordance with the journal's requirements.

Q7Academic similarity checking

Response:

Thank you for your note. We have conducted an academic similarity check on the revised manuscript to ensure originality and confirm that there is no plagiarism.

Q8Language Polishing

Response:

We have completed the language polishing process. As recommended, we have invited one of the professional language editing companies listed on the journal’ s

website to assist with the revision. The company has completed a thorough language edit of the manuscript, and we have uploaded the corresponding language editing certificate along with the revised submission.

Q9Funding Documentation

Response:

The authors received no financial support for the research.

Q10Audio (Core Tip)

Response:

We have completed and uploaded the Audio Core Tip as requested.

Q11Acknowledgments

Response:

Thank you for the reminder. We have revised the Acknowledgments section to comply with the journal's guidelines and have removed the names of the language editing company and funding projects.

Point-by-point response to reviews

Dear Journal Editoral Board's Reviewers
We sincerely thank you once again for your thorough review, insightful comments, and constructive suggestions, all of which have greatly enhanced the quality of our manuscript.We have carefully addressed each of the reviewers' comments and revised the manuscript accordingly.
Kindly, we provide detailed point-by-point responses to all reviewer comments.

Reviewer

Q1 The overall quality is good with some minor edits I have done. Once authors complete the edits, the paper may be accepted.
Response:
Thank you for your positive evaluation. We have carefully addressed all the minor edits and incorporated the changes in the revised manuscript, which is submitted with track changes enabled. We hope the updated version meets the requirements for acceptance.