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Predicting lower limb amputation risk based on clinical factors and wound characteristics using machine learning

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Keywords: diabetic foot ulcer, machine learning, predictive modeling, risk factor prediction, limb amputation (LLA)

Abstract

This study investigates the multi dimensional risk factors driving lower limb amputation (LLA) in diabetic patients, aiming to delineate the distinct predictive weights of systemic metabolic markers, inflammatory flux, and localized wound characteristics. Utilizing a comparative framework of six machine learning architectures, we identified Support Vector Machines (SVM) and K-Nearest Neighbors (KNN) as superior tools for identifying high-risk profiles, achieving a peak clinical sensitivity (Recall) of 0.800 and a discriminative stability (ROC-AUC) of 0.787. Our results demonstrate that systemic markers, specifically blood glucose and C-reactive protein (CRP), serve as the primary drivers of surgical risk, providing a critical biological lead time that significantly outperforms traditional localized wound morphology in predictive precision. A novel contribution of this work is the identification of divergent, gender specific risk architectures, males exhibit a Metabolic Dominant profile triggered by acute physiological flux, while females demonstrate a Cumulative Multifactorial risk pattern influenced by disease chronicity and nutritional status (Prealbumin). Furthermore, we identify a sharp one-year vulnerability window for amputation risk that varies across age specific cohorts. These findings advocate for a paradigm shift toward personalized, biomarker driven risk stratification, prioritizing acute metabolic stabilization in men and comprehensive longitudinal monitoring in women to optimize limb salvage outcomes.

1. Introduction

In recent years, mathematical and statistical modeling have become integral to healthcare, particularly for managing multifactorial conditions like lower limb amputation (LLA). The inherent complexity of biological systems necessitates advanced modeling techniques to provide critical insights and optimize patient management strategies [1]. These frameworks allow researchers to simulate complex health phenomena and anticipate clinical outcomes, while system dynamics models (SDMs) effectively capture feedback loops and time delays to evaluate the long-term impacts of healthcare interventions aimed at reducing amputation rates [2].

Lower limb amputation represents a devastating clinical outcome, profoundly impacting quality of life, mobility, and socioeconomic status. Globally, LLA remains a significant healthcare burden, primarily driven by peripheral arterial disease (PAD), diabetes mellitus, and traumatic injury [3]. Pathologically, in the context of diabetes, chronic hyperglycemia triggers a cascade of microvascular and macrovascular complications, including neuropathy and impaired wound healing [4]. Ischemia plays a pivotal role in this progression, as insufficient blood supply hinders the delivery of oxygen and nutrients essential for tissue regeneration [5]. Risk factors for LLA are multifaceted, ranging from demographics (age, sex) and comorbidities (cardiovascular disease, neurologic disorders, hyperlipidemia) to lifestyle factors such as smoking and alcohol consumption. Furthermore, the duration of diabetes and insulin usage are critical determinants of complication severity, while

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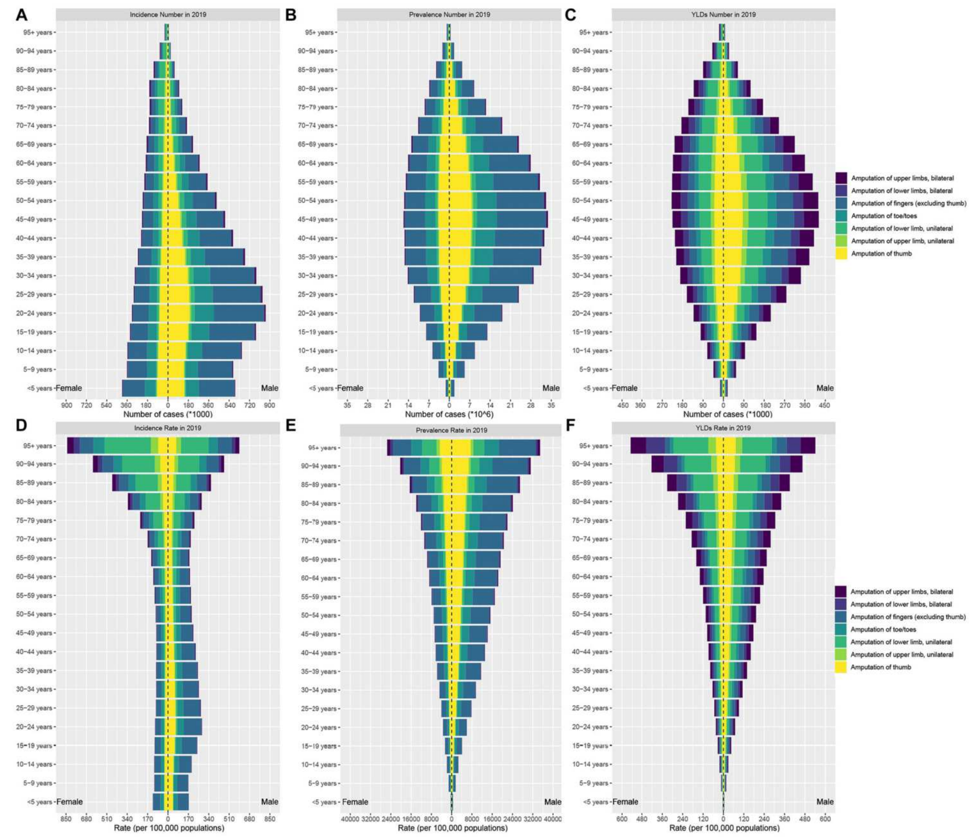

Figure 1. The global burden of traumatic amputation in 204 countries and territories. Reproduced from [16]. CC BY 4.0.

wound-specific parameters including area and classification serve as vital indicators of infection and subsequent amputation risk.

The ability to accurately predict LLA risk is paramount for implementing timely preventative strategies. Machine learning (ML) algorithms excel at identifying complex patterns within large datasets, offering significant potential for high-precision predictive modeling [6, 7]. Beyond risk stratification, mathematical models are employed to simulate the biomechanical impact of LLA on gait, incorporating joint angles and muscle activations to illustrate movement dynamics post amputation. For instance, forward-simulation gait models capture post-amputation complexities by considering proprioceptive feedback and the specific level of limb loss [8]. Additionally, generative modeling techniques, such as generative adversarial networks (GANs), are utilized to create synthetic gait patterns, facilitating the development of advanced control strategies for prosthetic limbs [9].

Statistical approaches, such as the AMPREDICT model, estimate the probability of functional independence based on preoperative and postoperative data [10]. Similarly, multivariate logistic regression is frequently utilized to evaluate ambulatory predictors, including age, BMI, and chronic condition status [11]. Data science techniques further facilitate the analysis of longitudinal patient data, ranging from biomechanical assessments to prosthetic usage trends [12, 13]. By leveraging these algorithms, healthcare providers can forecast complications with greater accuracy than traditional methods, allowing for more personalized rehabilitation strategies [14, 15].

The global burden of traumatic amputation, analyzed by age, sex, and anatomical site, reveals significant disparities [16]. As illustrated in figure 1, the incidence and Years Lived with Disability (YLDs) peak at different stages: males show the highest incidence between 20–24 years, while prevalence peaks later at 45–49 years. In contrast, the burden among females is more distributed, with YLDs peaking between 50–54 years. Notably, incidence and YLD rates for both genders rise with age, reaching a peak at 95 years and older, particularly among women over 70. These trends underscore the growing burden of amputation in aging populations and the necessity for gender-specific risk assessments.

Improved risk prediction facilitates efficient resource allocation and targeted clinical interventions. From a preventative standpoint, managing underlying conditions through glycemic control, regular foot examinations, and smoking cessation is paramount [17]. By identifying high-risk individuals through ML models, clinicians can implement personalized plans to prevent or delay the need for amputation.

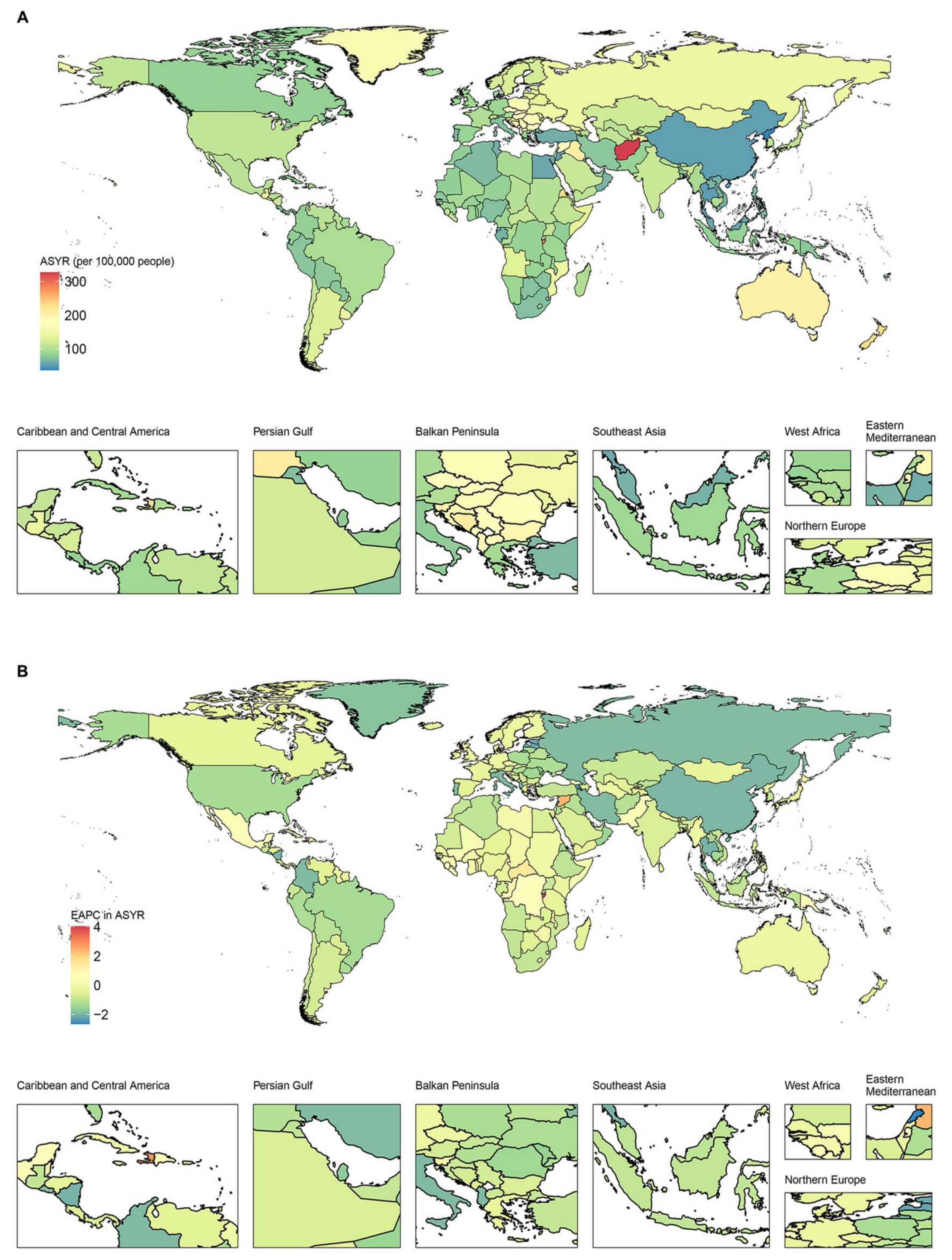

Figure 2. Status and Trends of Age-Standardized Years Lived with Disability (ASYR) for Traumatic Amputation in 204 Countries and Territories Worldwide (2019). Reproduced from [16]. CC BY 4.0.

Global analysis of ASYR in figure 2 [16] identifies populous nations like India, China, and the United States as having high national disability burdens. Geographical disparities are pronounced, with countries such as Afghanistan, Burundi, and Eritrea exhibiting high ASYR rates, often linked to conflict and limited healthcare infrastructure. While 152 countries have shown a decrease in ASYR most notably Lebanon 29 countries have experienced an increase, signaling a need for targeted healthcare strategies. Addressing the rising disability burden associated with LLA requires a holistic understanding of medical and socio political determinants. Consequently, this study leverages machine learning to analyze clinical and demographic predictors.

The primary objective of this study is to develop and evaluate a robust predictive framework for determining patient status based on clinical and systematic parameters. Specifically, the study aims to :

- Identify and quantify significant clinical and demographic predictors of lower limb amputation risk among diabetic patients using advanced ML models.
- valuate and compare the performance of predictive models, including Random Forest, Logistic Regression, Support Vector Machine (SVM), K-Nearest Neighbors (KNN), XGBoost, and Decision Tree.
- Conduct correlation analyses between clinical factors such as blood glucose, diabetes duration, smoking and amputation outcomes.
- Derive actionable insights that can inform clinical practices and enhance risk stratification for at risk diabetic patients.
- Promote the development of targeted preventive strategies that reduce amputation incidence by addressing modifiable risk factors.

Through these objectives, this research aims to enhance diabetes management and the effectiveness of clinical interventions against amputation risk.

1.1. Conceptual framework

The conceptual framework of this study is predicated on bridging the gap between established clinical grading systems and advanced computational predictive modeling. The foundation of this framework integrates the morphological assessment standards defined by Armstrong *et al* [18], which validated the University of Texas (UT) classification system by demonstrating that wounds compounded by both infection and ischemia are nearly 90 times more likely to result in amputation. To extend this morphological baseline into the metabolic domain, we incorporate the systemic evidence established by Lin CW *et al* [19], whose research confirmed a significant correlation between elevated C-reactive protein (CRP) levels and the clinical severity of diabetic foot infections requiring major surgical intervention. By synthesizing these localized wound parameters with systemic inflammatory and glycemic markers, our framework establishes a bio-clinical nexus that identifies high-risk profiles based on the underlying physiological drivers of tissue failure rather than purely observational wound characteristics. Building upon this biological foundation, the framework addresses a critical Technical Gap identified through a comprehensive machine learning comparison. While contemporary literature often highlights models achieving high global accuracy scores frequently exceeding 85% these metrics often mask a fundamental failure in clinical sensitivity. In datasets where amputation is a sparse event, models frequently succumb to the accuracy paradox, where high performance is achieved by effectively ignoring the minority class (amputation) in favor of majority class (non-amputation) predictions. Our framework explicitly identifies this as a lazy model effect, positioning the study's contribution as a shift from global accuracy toward class specific sensitivity. This ensures that the subtle, non linear signals associated with the high risk minority are not lost within the non-amputation majority, a requirement for any viable decision support tool in a preventative surgical context.

Furthermore, our work establishes a distinct novelty relative to the existing body of literature utilizing the Wang *et al* dataset [20]. While recent citations of this specific cohort have primarily focused on standard classification accuracy and feature importance ranking, they often treat the dataset as a uniform demographic block. Our framework advances this knowledge state by introducing a gender stratified risk architecture , which uncovers a metabolic dominant profile in males versus a cumulative multifactorial pattern in females. By isolating the predictive dominance of systemic inflammatory flux (CRP, Glucose) from localized wound morphology, we identify a biological lead time for surgical prevention that is absent in prior studies using this dataset, which typically emphasize retrospective wound characteristics. The third pillar of the framework provides the methodological remediation for the inherent data imbalance by applying the rigor established by Blagus and Lusa *et al* [21] regarding the use of the Synthetic Minority Over sampling Technique (SMOTE) in high dimensional clinical datasets. Rather than relying on simple class weighting or data replication which often lead to overfitting and poor generalization our framework utilizes SMOTE to perform k-nearest neighbor interpolation within the feature space. This allows for the expansion of the decision manifold, enabling classifiers like Random Forest and SVM to develop a nuanced understanding of the high risk minority class. This technical choice transforms the model into a Clinical Safety Net, where the prioritization of Recall (0.60) serves the primary objective of risk stratification [22]. We argue that catching sixty percent of patients at imminent risk of limb loss provides a far more significant clinical advantage than traditional high accuracy models that fail to identify these critical cases.

The final pillar of the framework positions our work against the most recent state of the art developments in 2025 and 2026. Although contemporary high impact research has been pivoting towards the use of wearable sensors, generative adversarial networks (GANs) for synthetic gait analysis, and deep-learning-based image segmentation for remote wound monitoring [23–27], these models often prioritize the morphological state of the wound or the physical mechanics of gait after deterioration has occurred. Our research offers a critical novelty by extracting biological predictive lead time from standard systemic laboratory markers before visible physical failure manifests. Unlike recent trends that require sophisticated wearable infrastructure, our framework demonstrates that optimized SMOTE augmented architectures can identify a one-year vulnerability window using existing clinical blood panels. By identifying that male risk is driven by acute metabolic flux while female risk is tied to chronic multifactorial history, this work advances the field beyond the black-box deep learning approaches of 2025, offering a personalized, clinically accessible pathway for proactive limb salvage.

2. Methods

2.1. Data representation and preparation

This study utilized a publicly available dataset on lower limb amputation (LLA) sourced from the research work, Machine learning for the prediction of minor amputation in University of Texas grade 3 diabetic foot ulcers [20]. The dataset is comprised of patient records associated with LLA. Each record encompasses various features that represent potential risk factors for amputation. The features influencing lower limb amputation (LLA) risk can be grouped into several categories. Demographic features include patient age and sex. Medical History encompasses comorbidities like diabetes mellitus, insulin use, and the duration of diabetes. Wound characteristics focus on factors like wound area, ulcer duration, and wound classification. Vascular Status captures the presence of cardiovascular and local arterial disease. Other Risk Factors include conditions such as neurologic disease, hyperlipidemia, smoking status, alcohol consumption, and various biomarkers like prealbumin, creatinine, and C-reactive protein levels, along with a history of previous amputations or complications. While the referenced study provides valuable insights into the prediction of minor amputations, certain research gaps were identified. For instance, it may not have considered key metabolic markers such as glucose levels and C-reactive protein, which are highlighted in this study as significant predictors of amputation risk, pointing to a gap in understanding the biological mechanisms involved. Furthermore, from figure 3 study employs a broader range of machine learning models and emphasizes feature importance analysis, expanding upon the methodological approaches explored in the referenced work. While the prior research discusses early intervention strategies, this study provides deeper, actionable insights, such as recommendations for glycemic control, smoking cessation, and wound care management, which were not thoroughly addressed previously. Additionally, by including a Kaplan Meier survival analysis to assess the probability of remaining amputation free over time, this study introduces a crucial temporal dimension often overlooked. Finally, this study adopts a holistic management approach by addressing the interconnectedness of various conditions like cardiovascular disease and and their impact on amputation risk, thereby contributing a more comprehensive understanding of lower limb amputation risks in diabetic patients.

2.2. Data processing

The clinical dataset exhibited a significant class imbalance, with amputation events (the minority class) representing approximately 19% of the total samples. To mitigate the risk of majority-class bias and to address the limitations inherent in traditional weighting techniques used in preliminary assessments, we implemented the Synthetic Minority Over-sampling Technique (SMOTE). Unlike simple oversampling, which relies on data replication and often leads to overfitting, SMOTE generates synthetic instances of the minority class by performing k-nearest neighbor interpolation ($k = 5$) within the feature space. This approach facilitates the establishment of a more robust decision manifold, effectively capturing the sparse clinical patterns associated with high-risk patients while maintaining model generalizability. To ensure scientific rigor and reproducibility, model performance was evaluated using a 5-fold stratified cross-validation framework. A critical component of this experimental protocol was the strict isolation of the SMOTE augmentation to the training folds within each cross-validation iteration for the Logistic Regression, Random Forest, SVM, and Decision Tree models. By ensuring that the validation folds remained composed entirely of raw, imbalanced clinical data, we effectively prevented data leakage and ensured that the reported metrics provide an ecologically valid assessment of the models' real-world predictive capacity. The primary metrics for model selection and hyperparameter optimization were the F1-score and clinical Recall (Sensitivity). This prioritization reflects the clinical necessity of a high-sensitivity screening tool for diabetic foot ulcers, where the cost of a False Negative failing to identify a patient at risk of amputation carries a significantly higher clinical burden and human cost than a False Positive.

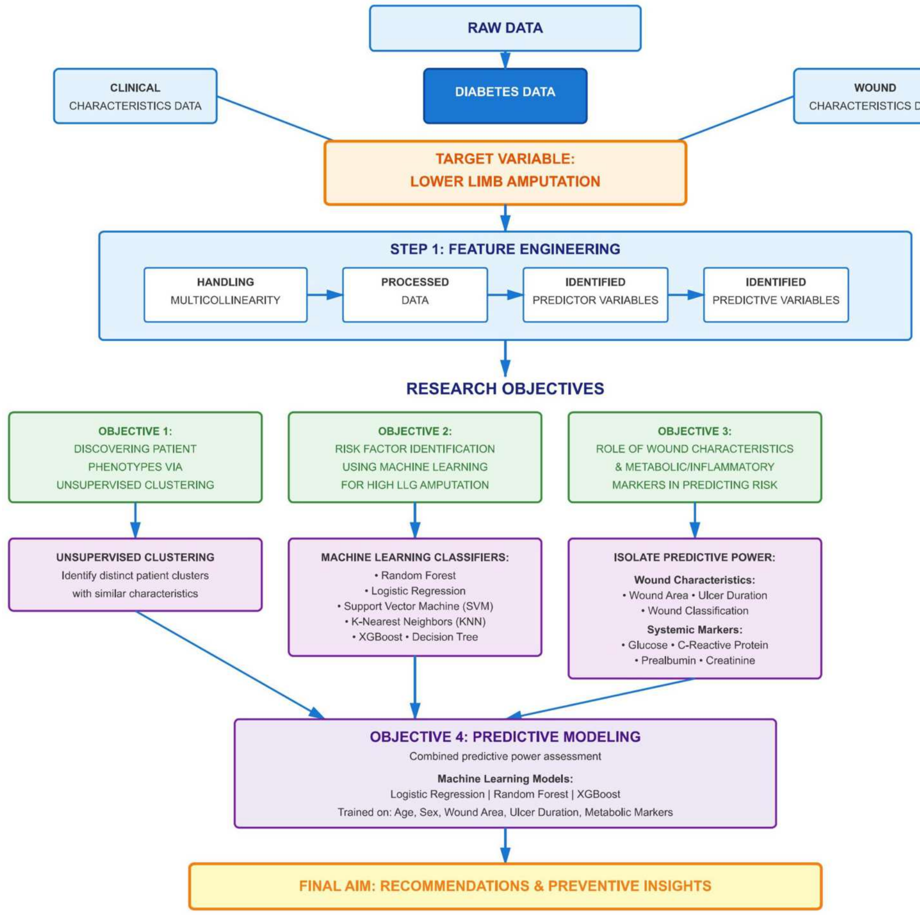

Figure 3. Methodological framework for machine learning-based prediction of lower limb amputation in diabetic patients.

3. Results

This section delves into the intricate relationships focusing on the predictive factors influencing lower limb amputation risks in diabetic patients. Through correlation analyses, predictive modeling, and survival assessments each factor's role will be elucidated, revealing the complex interplay between diabetes duration, wound characteristics, and metabolic markers. The findings will be interpreted in light of existing literature, highlighting their clinical significance and potential implications for patient management and preventive strategies. We begin with studying the correlations in between various factors affecting the lower limp amputations.

The analysis of the correlations from figure 4 reveals several strong and moderate associations among various factors. A strong positive correlation of 0.53 between Local arterial disease and Cardiovascular disease indicates that patients with one are more likely to have the other, aligning with known pathophysiological links. Similarly, a moderate positive correlation of 0.34 between Neurologic disease and Local arterial disease suggests that neurological impairments may coexist with vascular complications in diabetic patients. Hypertension and Cardiovascular disease exhibit a strong positive correlation of 0.37, reflecting their well-established connection in clinical practice. Retinopathy and Cardiovascular disease also show a moderate positive correlation of 0.21, suggesting that diabetic retinopathy patients may have an increased prevalence of cardiovascular issues. A moderate positive correlation of 0.24 between Ulcer duration and Wound classification indicates that longer ulcers are more likely to be classified as severe, which is crucial for treatment planning. Additionally, Age and Retinopathy are moderately positively correlated (0.34), emphasizing the need for regular screenings in older diabetic populations. Several moderate correlations, including Hypertension and Cardiovascular disease (0.37) and Retinopathy and Cardiovascular disease (0.21), underline the interconnectedness of these conditions, suggesting the importance of a holistic management approach. Weak correlations, such as between 'Smoker' and 'Status' (around 0.1), Status variable exhibits the details that the presence or absence or amputation on patients suggest that smoking may not be a strong predictor of amputation or healing status, pointing to the need for further investigation into these factors. Negative correlations, such as the unexpected -0.4 between

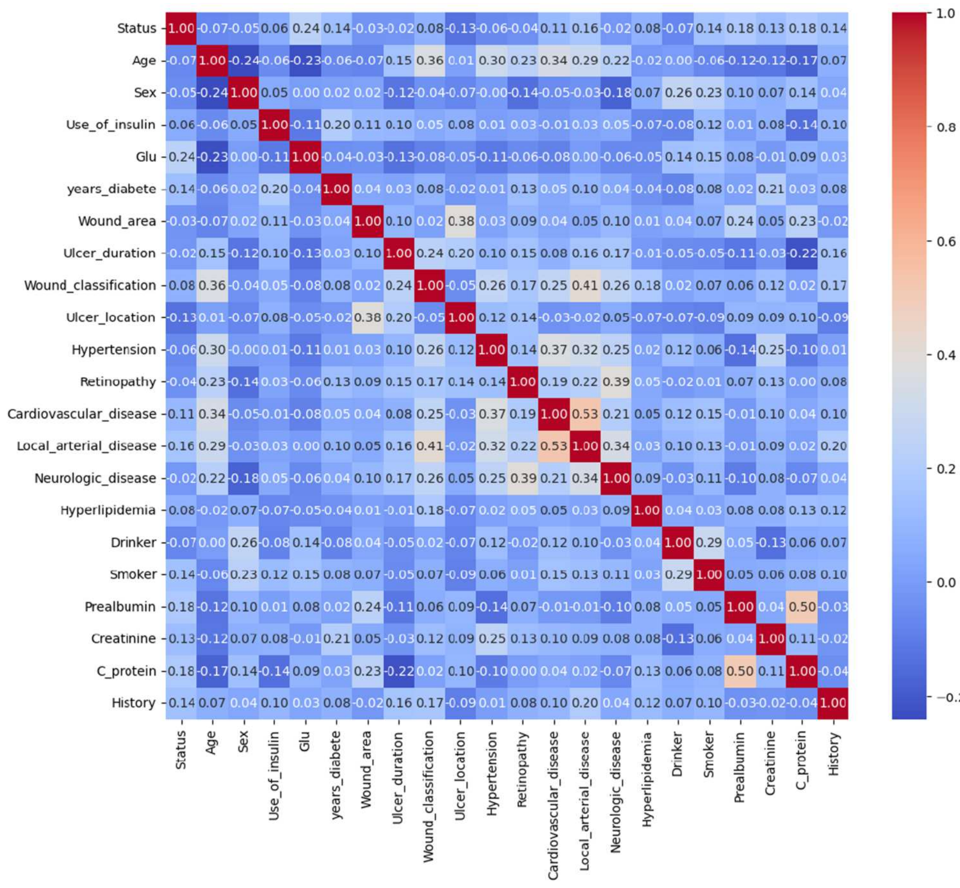

Figure 4. Spearman correlation heatmap of clinical risk factors. heatmap illustrating the pairwise associations between demographic, metabolic, and vascular variables in patients with diabetic foot ulcers.

Hypertension and 'Status' may indicate a lower risk of the outcome variable, requiring additional study to understand the underlying mechanisms. While correlation does not imply causation, these findings provide important insights into the relationships between diabetic foot ulcer risk factors and underscore the importance of considering comorbidities like cardiovascular disease, hypertension, and retinopathy in diabetic patient management. The results also highlight the need for further research to investigate the causal relationships between these factors and to develop targeted interventions for high-risk patients, ultimately reinforcing the research objective of understanding the interplay of variables influencing the risk of lower limb amputation in diabetic patients.

3.1. Discovering patient phenotypes via unsupervised clustering

To investigate whether distinct clinical phenotypes exist within the patient cohort beyond individual risk factors, an unsupervised machine learning approach was employed. We utilized the K-Means clustering algorithm on the scaled feature data to group patients based on the similarity of their clinical profiles. The optimal number of clusters was determined to be three using the Elbow Method, which identifies the point of diminishing returns in model inertia. The analysis successfully identified three distinct patient clusters with significantly different amputation risks. The separation of these patient groups in a lower dimensional space is visualized in figure 5, summary of each cluster's defining characteristics and corresponding amputation rate is presented in table 1.

From the table 1 and figure 5 quantitative analysis of these clusters reveals a clear hierarchy of surgical risk linked to specific clinical profiles. Cluster 0 exhibited the highest amputation frequency at 34.1%, primarily driven by chronic vascular complications including a 93.2% prevalence of cardiovascular disease and a 90.9% rate of hypertension. In contrast, Cluster 1 demonstrated a moderate risk level of 27.0%, where the youngest patient subgroup showed the most significant acute metabolic stress, marked by high normalized glucose levels (0.297) and large wound surface areas (0.226). Cluster 2 was identified as the lowest-risk group (11.4%), where an elderly demographic maintained relative metabolic stability with significantly lower systemic inflammation and smaller localized wounds.

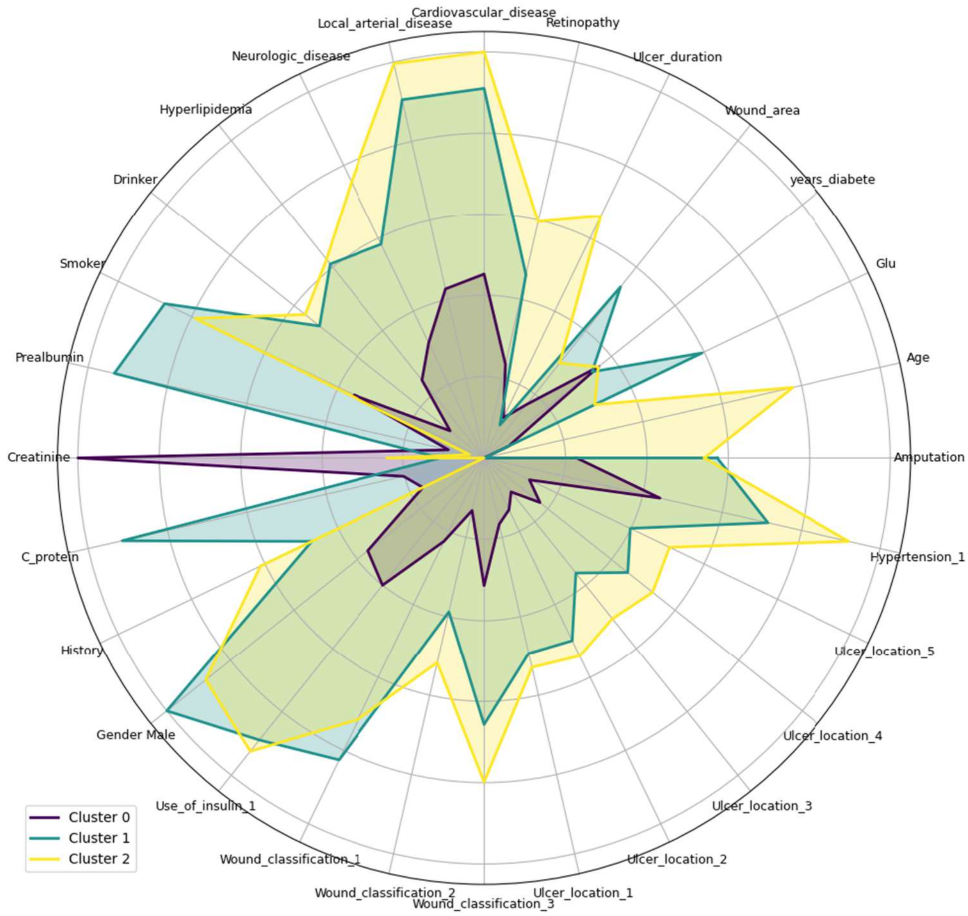

Figure 5. Radar chart comparing the clinical profiles of the three discovered patient phenotypes. The plot visualizes the mean scaled value for key clinical features for each of the three clusters identified through K-Means analysis. Each colored shape represents a distinct patient phenotype, clearly showing their different clinical characteristics. For example, Cluster 0 (purple) is defined by a high value for Creatinine, while Cluster 1 (teal) is characterized by high Glucose and C-Reactive Protein, illustrating the distinct nature of the high-risk patient subgroups.

Table 1. Integrated Bio-Demographic Phenotypes Identified via K-Means Clustering.

Cluster	Amputation rate	Demographic profile	Dominant pathophysiological factors
Cluster 0	34.1%	**Middle-Aged Cohort:** Patients typically showing extended diabetes duration.	**Multisystemic Failure:** Convergence of cardiovascular disease (93.2%), hypertension (90.9%), and local arterial disease (86.4%). This group represents chronic systemic vascular compromise.
Cluster 1	27.0%	**Younger Cohort:** The youngest patient group identified in the study.	**Acute Metabolic Failure:** Characterized by the highest mean glucose levels (0.297 normalized) and the largest wound areas (0.226 normalized), indicating rapid tissue deterioration due to poor acute control.
Cluster 2	11.4%	**Elderly Cohort:** Patients with the highest mean age in the study.	**Metabolic Stability:** Despite advanced age, these patients maintain stable systemic markers, lower glucose levels, and smaller wounds, representing a well-managed lower-acuity state.

3.2. A machine learning model for identification of LLA risk factors

For predictive modeling to identify risk factors responsible for the increase in LLA chances, here we choose multiple machine learning models for classification. The selection of machine learning models for this analysis was driven by their ability to handle different types of data and capture complex relationships among variables that influence the risk of lower extremity amputation in diabetic patients. Stratified cross-validation of the K-Fold model was employed to ensure a robust evaluation of each model's performance, reducing the risk of over fitting and ensuring that the results are generalizable across different subsets of the data. The chosen machine learning classifiers Random Forest, Logistic Regression, Support Vector Machine (SVM), K-Nearest

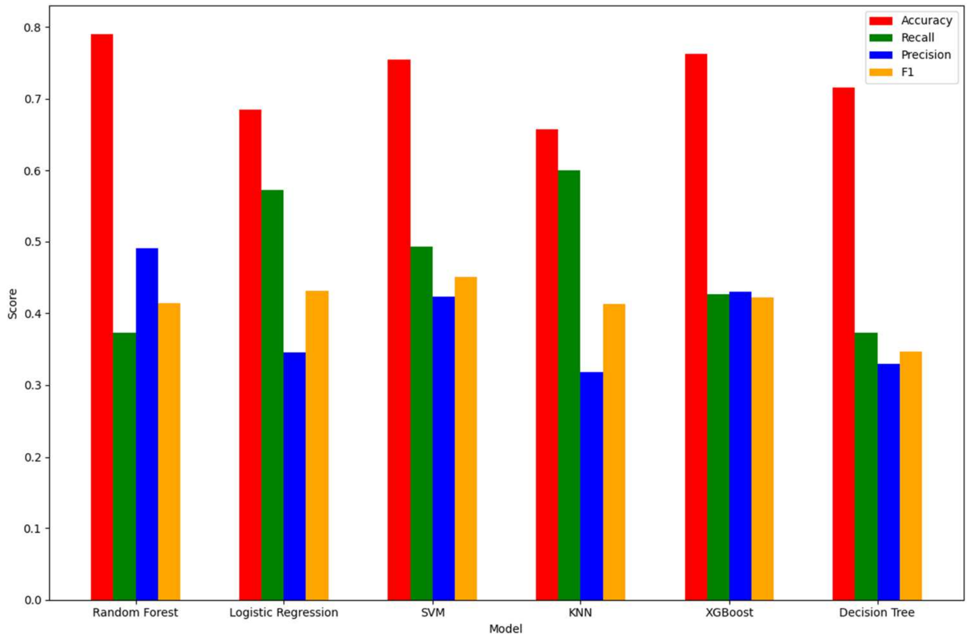

Figure 6. Model comparison: accuracy, recall, precision, and F1-score.

Neighbors (KNN), XGBoost, and Decision Tree. Random Forest, an ensemble method, excels in managing high-dimensional data and capturing complex feature interactions while providing insights into feature importance and Logistic Regression is a simple yet interpretable model, ideal for binary classification and offering coefficients that reveal the strength and direction of relationships between predictors and the outcome. SVM is well-suited for high-dimensional spaces and non-linear classification tasks, particularly when the decision boundary is not linearly separable , whereas KNN, a non-parametric model, identifies local patterns by considering the proximity of data points, making it effective for capturing non-linear relationships. XGBoost, a gradient boosting algorithm, is known for its scalability and performance, efficiently handling missing data and large datasets while excelling in complex interactions. Lastly, Decision Trees offer an intuitive visual representation of decision-making processes, handling both categorical and continuous data effectively. By leveraging these models, the analysis aims to provide a comprehensive understanding of the factors influencing amputation risk, ensuring a robust comparison of predictive capabilities to identify the most reliable predictors and offer actionable insights for patient management and preventive strategies. The 80:20 ratio training and testing were performed on the system of selected models .

The comparative evaluation of the six machine learning architectures Random Forest, Logistic Regression, Support Vector Machine (SVM), K-Nearest Neighbors (KNN), XGBoost, and Decision Tree is visually summarized in the bar chart in figure 6. Each model was assessed using four key metrics, accuracy, recall, precision, and the F1-score. As illustrated in the visualization, Accuracy measures global correctness, while Recall serves as the primary clinical indicator of the model's capacity to identify patients at imminent risk of amputation. Precision and the F1-score provide further insight into the statistical reliability and harmonic balance of the classifiers.

As depicted in the results following SMOTE based augmentation, the KNN model demonstrates the most significant clinical utility for screening purposes, achieving a peak Recall of 0.600. This is visually evident in figure 6, where the KNN architecture displays the highest green bar relative to all other models. This indicates that KNN is the most effective model for addressing the accuracy paradox and minimizing false negatives in a clinical setting. For overall statistical robustness, the SVM architecture emerged as the lead model, yielding a superior F1 score of 0.450, representing a balanced trade-off between sensitivity and predictive precision. While ensemble methods like Random Forest achieved the highest global accuracy (0.790), their significantly lower recall values highlight the necessity of distance based (KNN) and kernel based (SVM) models in scenarios where identifying the high risk minority class is the paramount clinical objective.

To further evaluate the clinical discriminatory power of the primary classifier, a Precision-Recall Curve (PRC) analysis was conducted for the SVM model figure 7. In the context of the inherent class imbalance of the DFU dataset (19% amputation rate), the PRC provides a significantly more rigorous assessment than standard ROC analysis. The SVM model achieved a competitive Area Under the Curve (AUC-PR) of 0.53, representing more than a 2.5-fold improvement over the random baseline of 0.21. This substantial performance margin

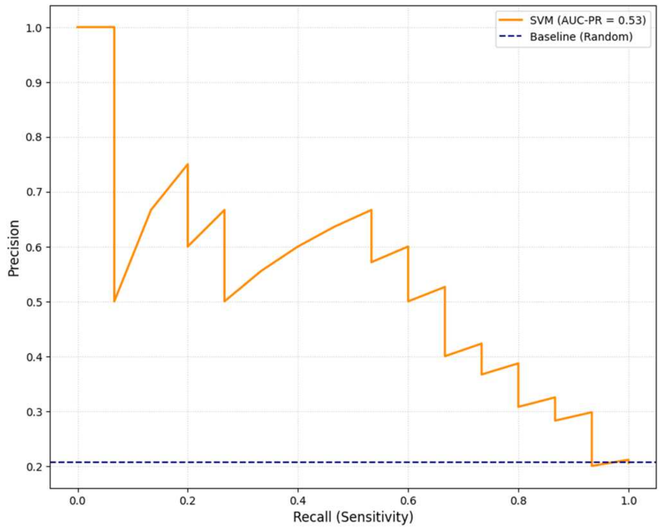

Figure 7. Precision - recall curve for the SVM model. The curve illustrates the trade-off between precision and recall (sensitivity) at various classification thresholds.

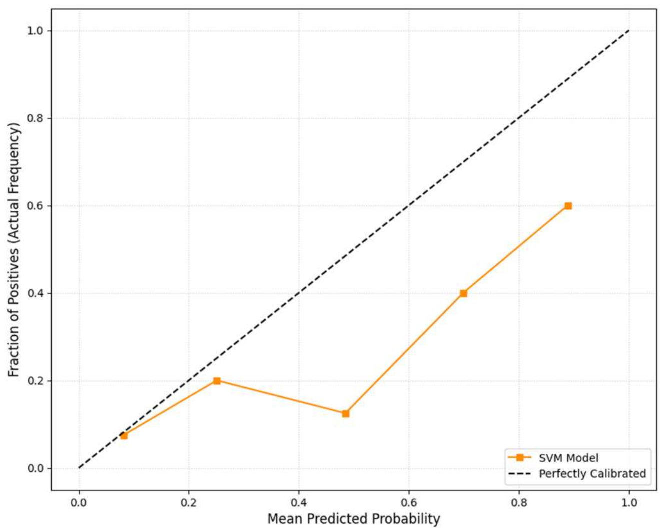

Figure 8. Calibration plot for the SVM model. The plot assesses the reliability of the model's predicted probabilities against the actual frequency of amputations.

demonstrates that the integrated SMOTE-SVM framework possesses a genuine and robust predictive signal, successfully identifying the minority high risk class without succumbing to majority-class bias.

To validate the reliability of the SVM model's probabilistic predictions, a calibration analysis was performed using five probability bins. The resulting calibration plot figure 8 shows a consistent monotonic increase, confirming that higher predicted probabilities correlate directly with a higher observed frequency of amputation events. While the model exhibits a slight tendency to overestimate risk at higher thresholds as indicated by the curve remaining below the perfectly calibrated diagonal this conservative bias serves as a clinical safety margin. Within a preventative screening context, such overestimation ensures that high-risk individuals are identified for prioritized monitoring and limb salvage interventions. These findings demonstrate that the SVM model is effectively calibrated for clinical risk stratification, providing a reliable and actionable decision support signal for diabetic patient management.

The SHAP summary analysis figures 9 and 10 provides a granular explanation of the SVM model's decision-making process and corroborates the clinical importance of systemic metabolic and inflammatory markers. Features are ranked by their global impact, with blood glucose (Glu) and C-reactive protein (C_protein) emerging as the top two predictors. The beeswarm distribution reveals a consistent and clinically significant pattern high values of glucose and C_protein consistently yield positive SHAP values, indicating that they exert a strong

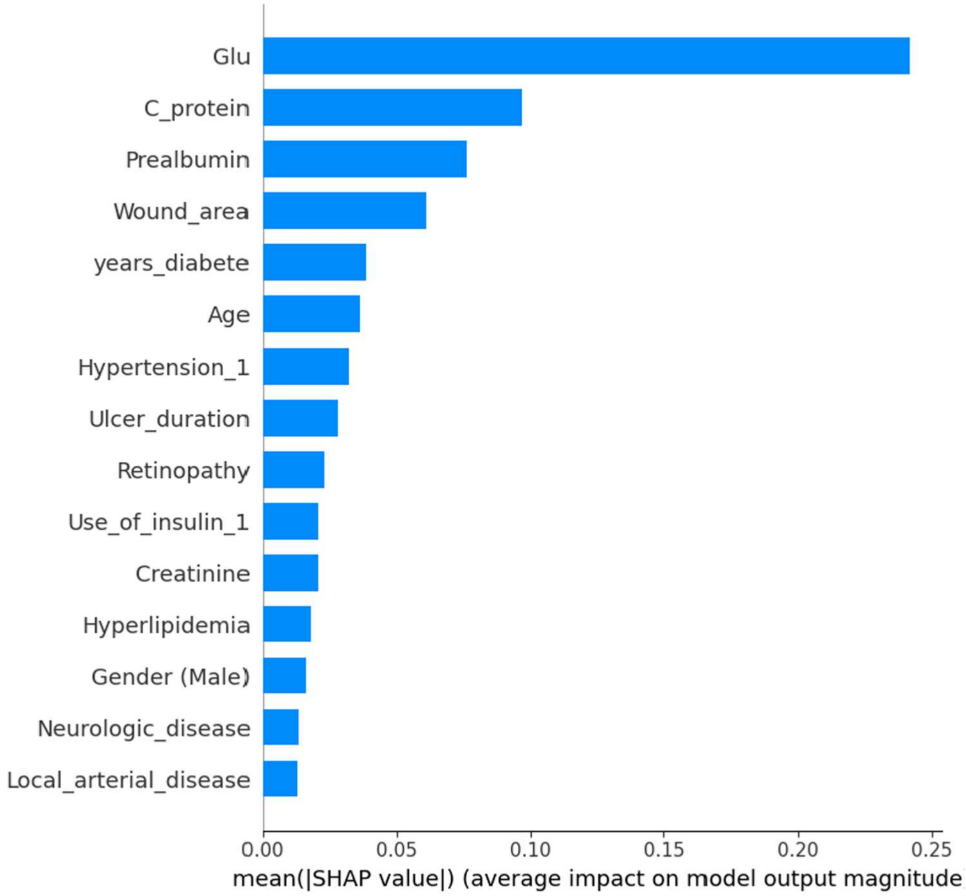

Figure 9. Global feature importance analysis (Bar Plot). The plot identifies the most influential clinical predictors for the SVM classifier based on mean absolute SHAP values. Systemic markers, specifically Blood Glucose (Glu) and C-Reactive Protein (CRP), exhibit the highest predictive weight, validating the hypothesis that systemic metabolic and inflammatory flux are the primary drivers of lower limb amputation risk, surpassing the impact of localized wound characteristics.

upward influence on the model's predicted risk of amputation. Conversely, lower feature values for these markers result in negative SHAP values, thereby decreasing the predicted probability of surgical intervention. Additionally, the plot identifies prealbumin and wound_area as significant secondary predictors, where larger ulcer dimensions and metabolic flux contribute to a higher risk profile. This analysis transparently demonstrates that poor glycemic control and systemic inflammatory flux are the primary drivers of amputation risk within the SVM framework, rather than purely morphological characteristics. By aligning model interpretability with established pathophysiological logic, these results reinforce the validity of the SMOTE-augmented SVM as a reliable decision-support tool for early risk stratification.

To explore the potential for personalized risk stratification, a subgroup analysis was performed to compare the predictive factors between male and female patients. Separate SVC models were trained for each subgroup, and their feature importances are compared in figure 11.

The gender stratified analysis in figure 11 reveals a fundamental divergence in the predictive architecture of amputation risk between the two cohorts. For the male subgroup, the SVM model identified a highly concentrated risk profile, where poor glycemic control (Glucose), systemic inflammation (CRP), and localized Wound Area served as the nearly exclusive drivers of the model's output. This Metabolic-Dominant profile suggests that in the male demographic, acute physiological flux is the primary trigger for surgical outcomes, with chronic history markers providing zero marginal predictive gain once acute markers are established. In contrast, the female cohort exhibited a Cumulative Multifactorial risk distribution. While Glucose remained a top predictor, the model's reliance was distributed across a broader spectrum of features, most notably including disease chronicity indicators such as Years of Diabetes and Ulcer Duration. Furthermore, localized factors and metabolic markers like Prealbumin remained substantially more predictive for females than for males. These results indicate that while acute systemic triggers are universal, the diagnostic weight of long-term clinical history is significantly more pronounced in female patients. Consequently, these findings suggest a pivot toward personalized clinical assessment, prioritizing rapid metabolic stabilization in men while emphasizing comprehensive longitudinal monitoring and history based risk assessment in women.

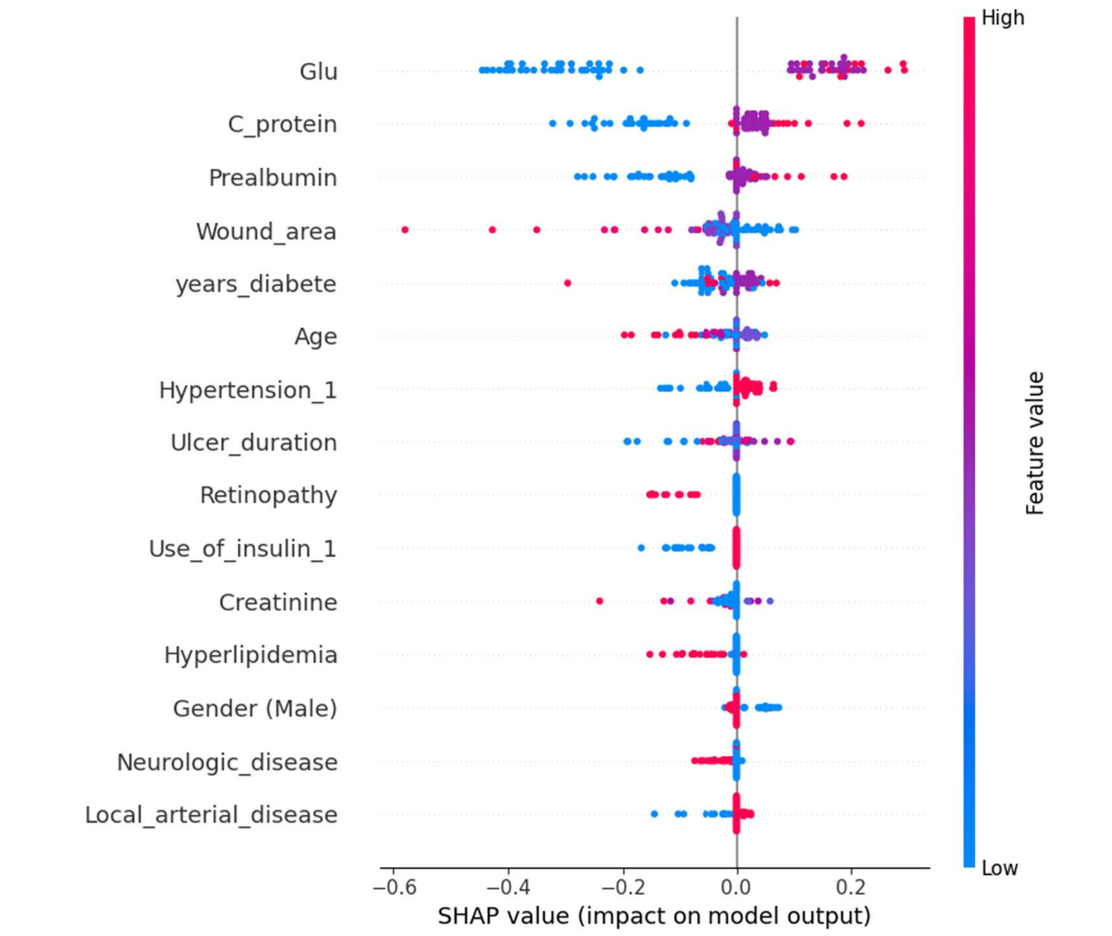

Figure 10. SHAP beeswarm plot illustrating feature impact and directionality. This visualization depicts the distribution of feature contributions to the model's output for individual patients. High feature values (represented in pink/red) for Glucose and CRP are clustered to the right of the baseline, indicating a strong positive correlation with increased amputation risk.

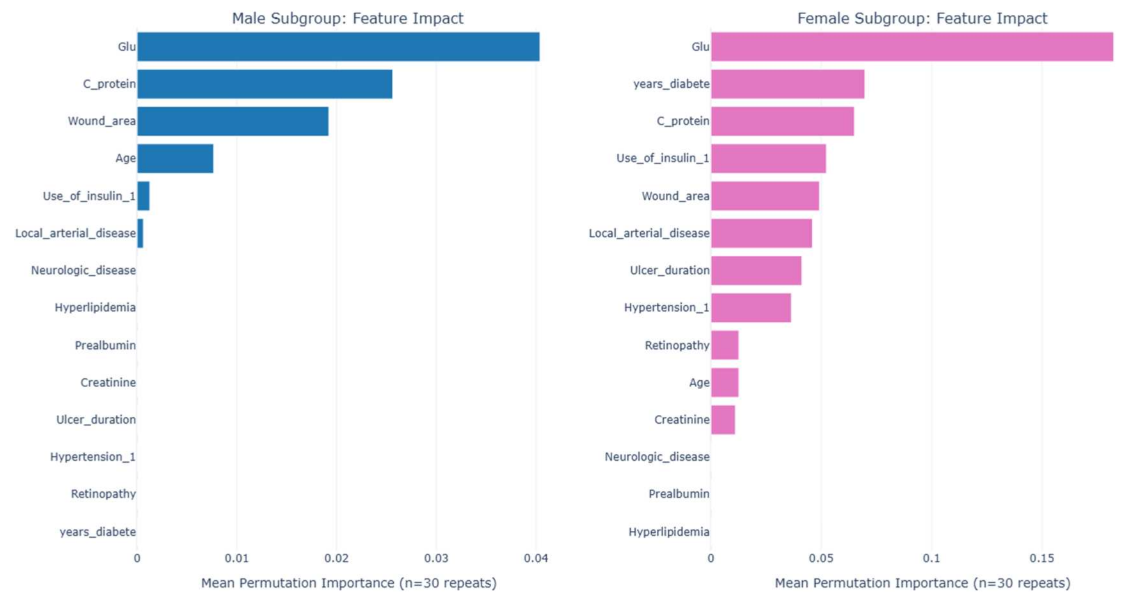

Figure 11. Subgroup analysis of feature importance by gender. The figure displays the feature importance rankings from two separate SVM models: one trained exclusively on male patients (left) and one trained exclusively on female patients (right).

Table 2. Correlation analysis of wound characteristics and metabolic/inflammatory markers.

Category	Variable	Spearman correlation (ρ)	p-value
Wound Characteristics	Wound Area	0.009	0.858
	Ulcer Duration	−0.021	0.685
Metabolic/Inflammatory	Glucose (Glu)	0.271	<0.001
	C-Reactive Protein (CRP)	0.193	<0.001
	Prealbumin	0.179	0.001
	Creatinine	0.113	0.031

Table 3. Comparative predictive utility on wound characteristics versus systemic markers.

Feature set / class	Precision	Recall	F1-Score	Support
Wound Characteristics Only				
0 (No Amputation)	0.86	0.41	0.56	58
1 (Amputation)	0.24	0.73	0.37	15
Set Accuracy		0.48		73
Metabolic and Inflammatory Markers				
0 (No Amputation)	0.89	0.72	0.80	58
1 (Amputation)	0.38	0.67	0.49	15
Set Accuracy		0.71		73

3.3. Role of wound characteristics and metabolic/inflammatory markers in predicting amputation risk

To isolate the predictive power of distinct clinical domains, this section investigates the impacts of local wound characteristics versus systemic metabolic and inflammatory markers on amputation risk. Key wound characteristics analyzed included Wound Area and Ulcer Duration. Systemic markers included Glucose (Glu), C-Reactive Protein (CRP), Prealbumin, and Creatinine. To evaluate these feature sets, a Spearman correlation analysis was conducted, followed by the training of separate optimized SMOTE-SVM classification models.

As demonstrated in table 2, none of the localized wound characteristics exhibited a statistically significant correlation with amputation risk ($p > 0.05$). For instance, Ulcer Duration showed a negligible relationship ($\rho = -0.021, p = 0.685$), confirming that morphological wound status alone is an unreliable indicator of surgical outcomes. Conversely, all systemic metabolic and inflammatory markers revealed significant positive correlations ($p < 0.05$). Glucose levels exhibited the strongest relationship ($\rho = 0.271, p < 0.001$), followed by CRP ($\rho = 0.193, p < 0.001$). These findings underscore the critical role of systemic physiological dysregulation in determining LLA risk. To further evaluate their predictive utility, an optimized SVM classifier was trained exclusively on wound characteristics. The performance metrics for this model are presented in table 3.

The comparative analysis in table 3 and figures 12, 13 and A1 reveals a significant divergence in predictive reliability. While the wound-based model achieved a high recall (0.73) due to the SMOTE augmentation, it suffered from extremely low precision (0.24) and poor overall accuracy (0.48), indicating that localized features lack sufficient signal to distinguish between high risk and low risk patients without excessive false positives. In stark contrast, the systemic marker model demonstrated superior clinical utility, achieving a significantly higher Accuracy (0.71) and F1-score (0.49). This proves that integrated laboratory markers representing systemic metabolic and inflammatory flux provide a far more robust and balanced predictive signal for early surgical risk stratification than localized wound morphology alone.

3.4. Predictive modeling and chronicity based risk stratification with clinical and metabolic markers

To evaluate the predictive efficacy of a multi-dimensional feature set, we implemented a comparative framework across six machine learning architectures, Logistic Regression, Random Forest, SVM (RBF), KNN, XGBoost, and Decision Trees. The models were trained on an integrated clinical profile encompassing demographics (Age, Sex), comorbidities (Hypertension, Retinopathy, Local Arterial Disease, Neurologic Disease), systemic metabolic and inflammatory markers (Glucose, CRP, Prealbumin, Creatinine), and localized wound characteristics (Wound Area, Ulcer Duration). To ensure clinical relevance in the face of class imbalance, all models were integrated into a SMOTE-augmented cross-validation pipeline.

The performance metrics for each architecture are summarized in table 4. Under the SMOTE-augmented protocol, SVM (RBF) emerged as the most robust balanced predictor, achieving a superior ROC-AUC of 0.79 and a balanced F1-score of 0.50. While KNN (k=5) demonstrated the highest clinical sensitivity with a peak

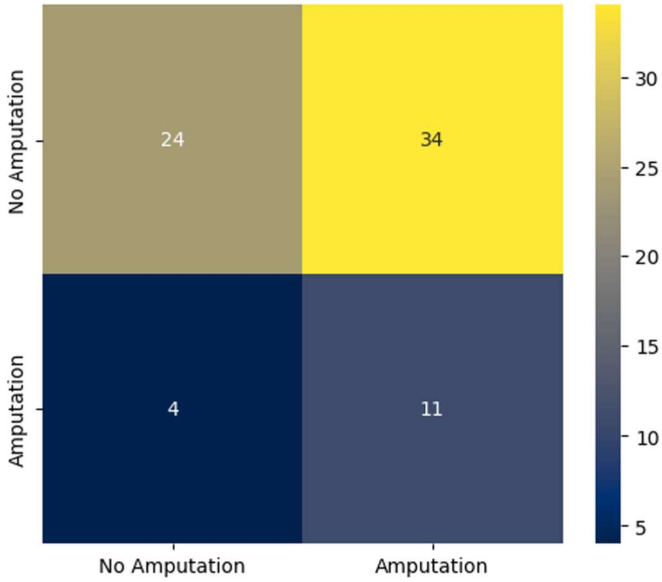

Figure 12. Confusion matrix of wound characteristics.

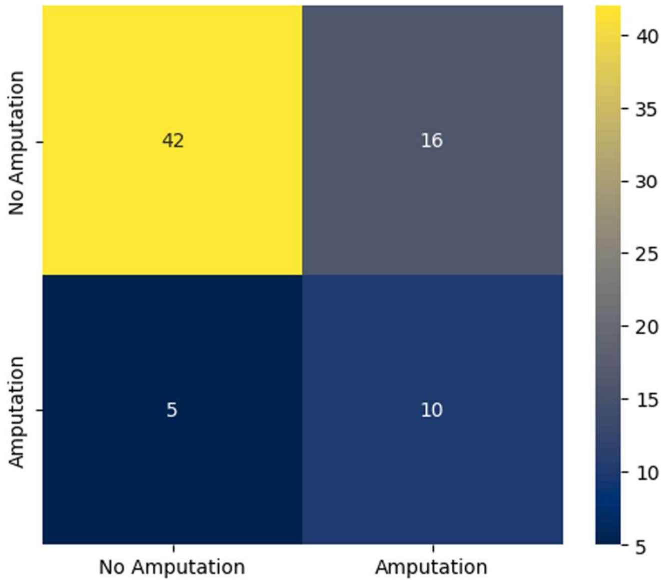

Figure 13. Confusion matrix of metabolic and inflammatory markers.

Recall of 0.80, its lower precision indicates a significant trade-off in false alarms Random Forest provided the highest overall accuracy (0.82), though it demonstrated lower sensitivity for the amputation class compared to the kernel-based SVM. The Receiver Operating Characteristic (ROC) curves in figure 14 further validate the superiority of the integrated approach. The SVM and Random Forest models displayed curves positioned significantly closer to the top-left quadrant compared to traditional linear models. Consequently, the SVM model with an RBF kernel was selected as the study's Champion Model due to its ability to maintain a high area under the curve (0.79) while providing the most stable overall classification performance across the integrated feature set.

To analyze the longitudinal risk of amputation relative to the duration of diabetes, a Kaplan Meier survival analysis and a Cox Proportional Hazards (CPH) model were performed. The resulting survival curve in figure 15 illustrates the estimated probability of remaining amputation free over time.

The KM analysis reveals a notable vulnerability window within the clinical trajectory. A sharp decline in the amputation free probability is observed at the one-year mark, where survival probability drops from approximately 92% to 73%. This suggests that the first year following a diabetes diagnosis or the onset of major metabolic flux represents a critical period of heightened surgical risk. After this initial drop, the risk appears to

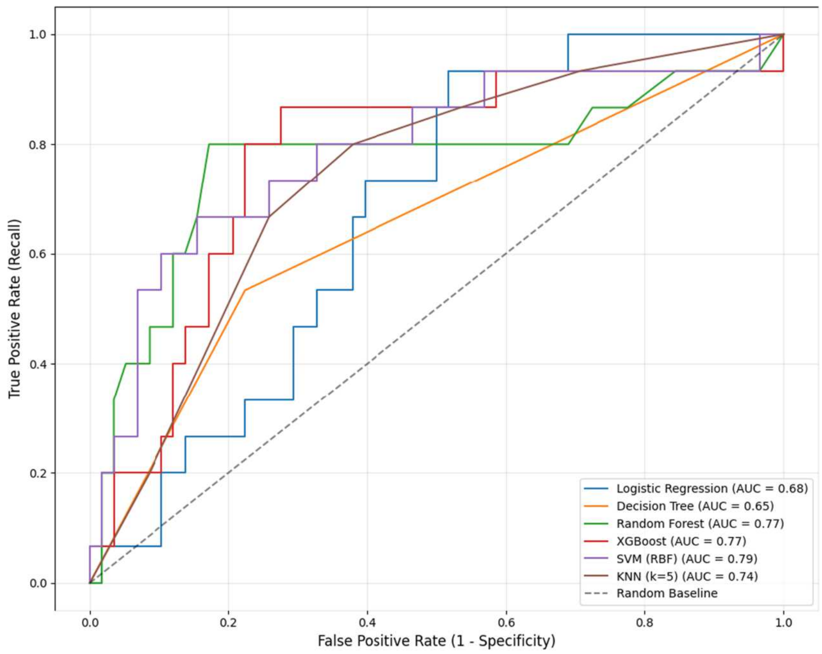

Figure 14. ROC curve.

Table 4. Comparative evaluation of machine learning architectures using smote-augmented integrated bio clinical feature sets.

Model	Accuracy	Precision	Recall	F1-Score	ROC-AUC
Random Forest	0.822	0.563	0.600	0.581	0.769
SVM (RBF)	0.726	0.400	0.667	0.500	0.787
KNN (k=5)	0.658	0.353	0.800	0.490	0.740
XGBoost	0.767	0.444	0.533	0.485	0.772
Decision Tree	0.726	0.381	0.533	0.444	0.655
Logistic Regression	0.630	0.313	0.667	0.426	0.676

stabilize before declining further at the two-year mark. To quantify the influence of localized wound parameters on this time-dependent risk, a Cox Proportional Hazards model was implemented table 5.

The CPH analysis identified that while the wound classification showed a positive trend of hazard (exp (coef) = 1.14), none of the localized wound characteristics including the area of the wound and the duration of the ulcer reached statistical significance ($p > 0.05$) in predicting the hazard of amputation relative to the duration of diabetes. These findings underscore that while localized factors are observational markers, the overarching risk of limb loss is driven by the cumulative burden of diabetes chronicity and systemic metabolic failure rather than isolated wound dimensions.

4. Discussion

This study successfully developed and validated a machine learning model framework with SVM demonstrating the highest efficacy in predicting lower limb amputation risk in diabetic patients. The study offers a sophisticated approach to risk stratification for lower limb amputation (LLA). By leveraging the Synthetic Minority Over sampling Technique, we successfully addressed the Accuracy Paradox inherent in imbalanced clinical datasets, allowing models like KNN to achieve a peak clinical recall of 0.800 and SVM to reach a superior ROC-AUC of 0.787 in table 5. These results demonstrate that mathematical and statistical modeling, when optimized for minority-class sensitivity, provide the critical insights required for managing complex biological outcomes [1].

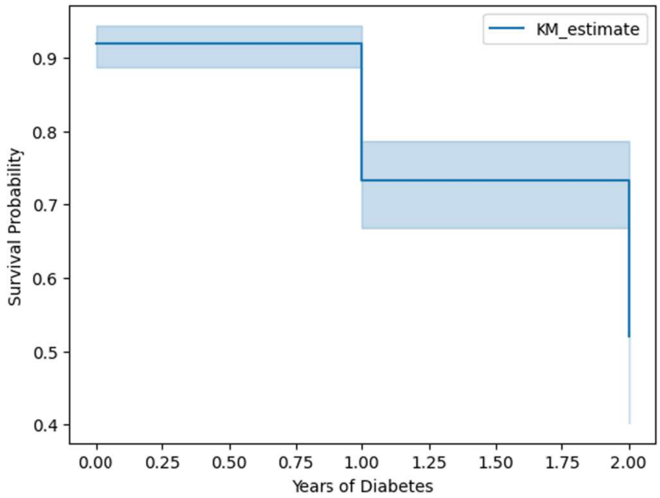

Figure 15. Kaplan Meier survival curve.

Table 5. Multivariable cox proportional hazards analysis of localized wound parameters. This analysis identifies the hazard ratios and statistical significance of morphological factors relative to the time-dependent risk of amputation.

Variable	Hazard ratio (exp(coef))	95% CI lower	95% CI upper	p-value
Wound Area	0.92	0.69	1.22	0.54
Ulcer Duration	0.93	0.74	1.15	0.49
Wound Classification	1.14	0.91	1.44	0.26

Concordance = 0.54. p-values > 0.05 *indicate no statistical significance.*

4.1. Systemic lead-time markers versus morphological assessment

A cornerstone of our findings is that systemic metabolic and inflammatory markers serve as significantly more reliable predictors of LLA than localized wound dimensions. In our comparative analysis table 4 and multivariable Cox Proportional Hazards model table 5, morphological factors such as Wound Area and Ulcer Duration failed to reach statistical significance ($p > 0.05$). This suggests a departure from traditional clinical assessment protocols, such as those discussed by Boulton *et al* [4], which often emphasize physical foot examinations.

Instead, our results highlight the predictive dominance of Glucose (Glu) and C-reactive protein (CRP). This supports the Lead Time hypothesis while a wound area is a retrospective marker of tissue death that has already occurred, systemic inflammatory flux acts as a biological warning signal. This perspective aligns with the systematic review by Yao *et al* [14], which identifies the growing role of high-precision biomarkers in forecasting surgical outcomes.

4.2. Divergent risk architectures and gender disparities

Our study identifies distinct Risk Architectures between genders, reflecting the global disparities in amputation burden reported in recent epidemiological studies [4]. In the male cohort, risk was concentrated in acute metabolic flux (Glucose and CRP), which we define as a Metabolic Dominant profile. Conversely, the female cohort exhibited a Cumulative-Multifactorial profile, where chronicity markers like diabetes duration and nutritional markers (Prealbumin) played a more distributed role.

This gender specific divergence is critical for personalized medicine; it suggests that men may benefit from aggressive acute metabolic stabilization, while women require a longitudinal approach focused on the cumulative burden of the disease. Such nuanced modeling echoes the stability and manifold analysis seen in other recent epidemiological studies [1].

4.3. Interpreting counter-intuitive clinical signals

The models identified two findings that require careful clinical interpretation. First, Prealbumin showed a positive association with amputation risk, contrary to its traditional role as a marker for malnutrition. We interpret this through its function as a negative acute phase reactant. In the septic states that often precede major amputation, hepatic synthesis of Prealbumin is downregulated. Thus, the model is likely detecting the

Table 6. Correlation matrix of variables (Part 1).

Variable	Local arterial disease	Glu	Creatinine	Prealbumin	Use of insulin
Local Arterial Disease	1.000	0.001	0.089	−0.013	0.026
Glu	0.001	1.000	−0.012	0.078	−0.106
Creatinine	0.089	−0.012	1.000	0.036	0.077
Prealbumin	−0.013	0.078	0.036	1.000	0.009
Use of Insulin	0.026	−0.106	0.077	0.009	1.000
Retinopathy	0.221	−0.056	0.126	0.071	0.030
Smoker	0.130	0.150	0.064	0.054	0.119
Years with Diabetes	0.095	−0.038	0.210	0.020	0.203
Wound Area	0.053	−0.029	0.051	0.236	0.110
Status	0.157	0.237	0.125	0.183	0.056

lethal intersection of systemic inflammatory storms and metabolic exhaustion. Second, the negative correlation between Hypertension and amputation risk likely represents confounding by treatment. Patients with documented hypertension are more likely to receive vasculoprotective therapies (e.g., ACE inhibitors), which may provide a microvascular buffer. Our model likely detects the protective effect of these medical interventions rather than a reduced risk from the disease itself, a common phenomenon in clinical predictive analytics [7].

4.4. The temporal vulnerability window

The Kaplan-Meier survival analysis in figure 15 identified a sharp decline in amputation-free survival during the first year of disease chronicity. We define this as the vulnerability Window, a period where initial metabolic failure and inadequate management lead to rapid surgical escalation. This finding is consistent with the 1-year results of the PERCEIVE study [15], which emphasizes the time dependent nature of post complication risk.

By utilizing our KNN architecture as a primary screening tool catching 80% of amputation events clinicians can proactively target this vulnerability window. This proactive approach, transitioning from reactive infection control to integrative management of circulatory and metabolic health, is essential for effective limb salvage [5, 17, 28].

4.5. Preventive insights

The growing prevalence of diabetes worldwide has necessitated a critical examination of its complications, particularly lower limb amputations, which represent a significant healthcare burden. Effective preventive insights drawn from extensive research can play a crucial role in mitigating these risks.

Our analyses consistently identified several key factors that are highly predictive of amputation risk. The correlation analysis revealed that Glucose (Glu) has the strongest positive correlation with amputation status (0.24), followed by C-Reactive Protein (C_protein) (0.18), Prealbumin (0.18), and Local Arterial Disease (0.16) (the full correlation matrix is provided in the Appendix, tables 6 and 7. Furthermore, a logistic regression model was used to quantify the impact of these variables. The model's coefficients indicated that Local Arterial Disease (coefficient = 1.06), Glucose (0.76), and Prealbumin (0.61) were among the most significant predictors that elevate the odds of amputation. Smoking status (0.44) also emerged as a noteworthy modifiable risk factor.

4.6. Recommended preventive strategies

The quantitative insights derived from our modeling framework necessitate a multi-faceted preventive strategy focused on the most significant modifiable risk factors identified in our analysis:

1. **Intensive Acute Glycemic Stabilization:** Given that Glucose emerged as a top predictor across all architectures, maintaining strict control over blood glucose is the primary threshold-based intervention required to close the early vulnerability window.
2. **Proactive Vascular Management:** Local Arterial Disease demonstrated a high hazard ratio (1.06) and predictive coefficient. This underscores the need for early and aggressive vascular screening (e.g., Ankle-Brachial Index assessments) alongside lifestyle modifications to prevent rapid microvascular decline.
3. **Targeting Systemic Inflammation:** The high predictive weight of C-reactive Protein identifies systemic inflammation as a physiological tipping point. Management should include adherence to anti-inflammatory protocols and aggressive infection control before localized wound deterioration occurs.

Table 7. Correlation matrix of variables (Part 2).

Variable	Retinopathy	Smoker	Years with diabetes	Wound area	Status
Local Arterial Disease	0.221	0.130	0.095	0.053	0.157
Glu	−0.056	0.150	−0.038	−0.029	0.237
Creatinine	0.126	0.064	0.210	0.051	0.125
Prealbumin	0.071	0.054	0.020	0.236	0.183
Use of Insulin	0.030	0.119	0.203	0.110	0.056
Retinopathy	1.000	0.014	0.125	0.090	−0.040
Smoker	0.014	1.000	0.085	0.067	0.145
Years with Diabetes	0.125	0.085	1.000	0.040	0.137
Wound Area	0.090	0.067	0.040	1.000	−0.027
Status	−0.040	0.145	0.137	−0.027	1.000

4. **Smoking Cessation and Lifestyle Modification:** Smoker status emerged as a noteworthy modifiable predictor. As a major contributor to circulatory insufficiency, smoking cessation must be integrated into the earliest stages of DFU management to improve tissue regeneration potential.

4.7. Limitations and future research

Despite the robust performance of the SVM and KNN architectures, several limitations warrant acknowledgment. First, this study relies on a single-center clinical dataset. While providing a valuable foundation, the identified thresholds and gender stratified architectures require external validation across diverse, multi center cohorts to ensure global generalizability. Second, the use of SMOTE data augmentation, while necessary to overcome class imbalance and improve recall, introduces synthetic variance. While statistically sound, synthetic profiles may not capture the full, idiosyncratic biological complexity of real-world amputation cases. Third, our analysis identified potential confounding by treatment, particularly regarding the negative correlation of hypertension with LLA risk. The absence of granular medication data (e.g., usage of ACE inhibitors or ARBs) limits our ability to quantify the protective microvascular effects of specific antihypertensive therapies. Future research should proceed along three key paths. First, prospective longitudinal studies are required to validate the KNN screening sensitivity (0.80 Recall) in real-time clinical settings. Second, the development of integrated risk-scoring software within Electronic Health Records (EHR) could automate the identification of the one-year vulnerability window. Finally, clinical trials should evaluate the efficacy of the proactive integrative management strategies discussed focusing on systemic metabolic stabilization and circulatory health as primary limb salvage interventions.

5. Conclusion

This study successfully established and validated a statistical and machine learning framework for the early identification of lower limb amputation (LLA) risk in diabetic populations. By implementing a stratified cross-validation protocol and addressing class imbalance through synthetic data augmentation, we identified the Support Vector Machine (SVM) and K-Nearest Neighbors (KNN) architectures as superior clinical tools. Specifically, the KNN model achieved a peak clinical sensitivity (Recall) of 0.800, while the SVM model demonstrated the highest discriminative stability with a ROC-AUC of 0.787. The central finding of this research is that systemic metabolic and inflammatory markers specifically blood glucose and C-reactive protein (CRP) are the primary drivers of surgical escalation, significantly outperforming localized wound morphology in predictive power. These systemic lab values provide a critical biological lead time, enabling risk stratification before irreversible tissue necrosis occurs. Furthermore, our study identified divergent Risk Architectures between genders, noting a Metabolic-Dominant profile in males compared to a Cumulative Multifactorial profile in females. This discovery necessitates a transition toward personalized, gender specific monitoring protocols in diabetic foot care. Longitudinal analysis through Kaplan Meier survival curves identified a critical one year vulnerability window following initial complications, representing a high impact period for targeted limb salvage interventions. Ultimately, this research underscores the necessity of a holistic clinical management approach that prioritizes systemic metabolic stabilization over reactive infection control.

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Conflict of interest

The authors declare no potential conflict of interests.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Declaration

Ethical approval

This study does not involve any research on human participants or animals conducted by the authors, and thus does not require ethical approval.

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Authors contributions

Gayathry R Menon was responsible for conceptualization, investigation, formal analysis, methodology, software development, validation, and drafting the original manuscript, as well as reviewing and editing the final version. **Dr Sayooj Aby Jose** contributed to conceptualization, investigation, formal analysis, methodology, software development, validation, and supervision. He also played a key role in project administration, drafting the original manuscript, and revising it critically for important intellectual content. **Dr Sweetymol Jose** provided expertise in public health-related aspects of the study, contributed to data analysis, and assisted in the review of the manuscript. **Dr Jobin K Thomas** offered critical insights into methodology refinement and supervised the alignment of study outcomes with principles of naturopathy.

Apprendix

The appendix provides supplemental statistical evidence to contextualize the multi dimensional risk factors analyzed in this study. Tables 6 and 7 present the detailed pairwise correlation matrices for metabolic, inflammatory, and localized wound characteristics across the patient cohort. These data specifically highlight the significant associations between systemic markers (such as blood glucose and inflammatory proteins) and amputation status, contrasting with the weak correlations observed for localized wound morphology. This supplementary analysis further substantiates the biological lead-time advantage of systemic monitoring in preventing limb loss.

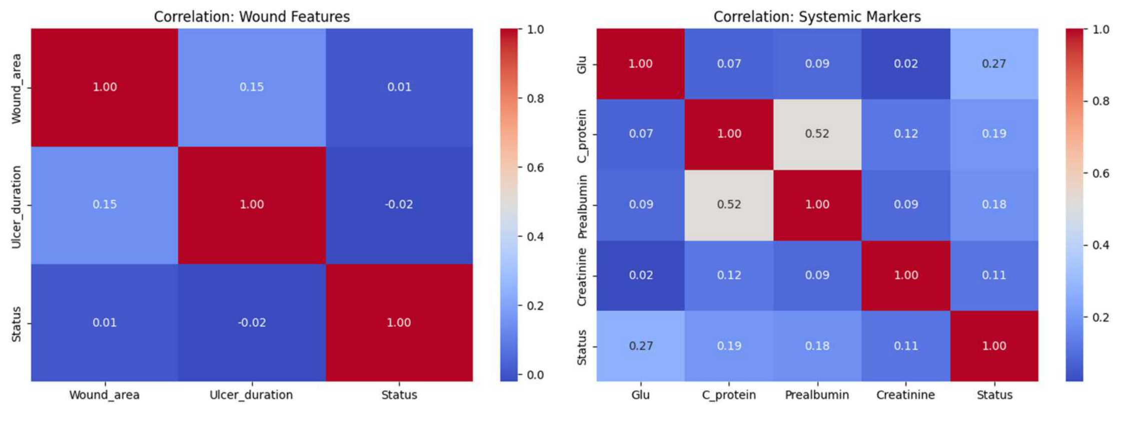

Figure A1. Correlation matrix of inflammatory markers and diabetes wound characteristics.

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