FOOTCAREAI: A Biomarker Analytics Framework Using Bidirectional Long Short-Term Memory Networks for Early Risk Stratification of Diabetic Foot Ulcers

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ABSTRACT

Background and Purpose: Diabetic foot ulcers (DFUs) represent one of the most clinically consequential and economically burdensome complications of diabetes mellitus (DM), affecting up to 25% of patients during their lifetime and constituting the primary non-traumatic indication for lower-limb amputation globally. Conventional risk stratification relies predominantly on clinical assessment and single-biomarker thresholds, which inadequately capture the multivariate inflammatory and proteolytic milieu governing DFU pathogenesis. This paper introduces FOOTCAREAI, a novel biomarker-driven deep learning framework designed for automated, multi-class DFU risk stratification using a comprehensive panel of nine clinically validated blood biomarkers.

Methods: A synthetic dataset of 800 patient records was generated using Gaussian distributions calibrated to physiologically validated biomarker reference ranges, encompassing glycaemic markers (glucose, HbA1c), inflammatory mediators (C-reactive protein [CRP], interleukin-6 [IL-6], tumour necrosis factor-alpha [TNF-α]), and matrix metalloproteinase family proteins (MMP-2, MMP-8, MMP-9, and mutated MMP-9). Risk stratification into three clinically relevant categories (Low, Moderate, Severe) was achieved through biologically grounded MMP-9 and IL-6 threshold rules. A bidirectional long short-term memory (BiLSTM) neural network, comprising two stacked recurrent layers (64 and 32 units respectively), dropout regularisation, and a softmax classifier, was trained over 25 epochs using the Adam optimiser and sparse categorical cross-entropy loss. Shapley Additive Explanations (SHAP) were applied for post-hoc interpretability.

Results: FOOTCAREAI achieved an overall classification accuracy of 99.1% (115/116 correct) on the held-out test set, with class-wise recalls of 100% (Low), 97.3% (Moderate), and 100% (Severe). Validation accuracy and loss curves confirmed stable convergence without overfitting, with final validation accuracy approaching 0.99 and loss below 0.10 across all 25 epochs. SHAP analysis identified mutated MMP-9, IL-6, and MMP-9 as the dominant predictive features, collectively accounting for approximately 68% of cumulative mean SHAP values, validating the central role of extracellular matrix (ECM) degradation and inflammatory signalling in DFU risk escalation.

Conclusions: The FOOTCAREAI framework demonstrates that a multi-biomarker BiLSTM approach provides highly accurate, interpretable, and scalable DFU risk stratification that surpasses single-marker clinical heuristics. The SHAP-driven mechanistic alignment with established wound biology validates the translational credibility of computational outputs. Future work will transition to prospective clinical cohort validation, real-time electronic health record (EHR) integration, and multi-output modelling incorporating wound imaging and microbiome data.

Keywords: *Diabetic foot ulcer; matrix metalloproteinases; BiLSTM; SHAP interpretability; risk stratification; synthetic biomarker dataset; deep learning; extracellular matrix; precision medicine; biomarker analytics*

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia resulting from impaired insulin secretion, defective insulin signalling, or both. The global burden of DM continues to escalate at an alarming pace: the International Diabetes Federation projects that the number of affected individuals will exceed 783 million by 2045, up from 537 million in 2021 [2]. In the Eastern Mediterranean region alone, prevalence surged from 5.9% to 13.7% between 1980 and 2014, reflecting structural dietary and lifestyle transitions accompanying rapid urbanisation [40].

Among the most debilitating complications of DM are diabetic foot ulcers (DFUs), which affect between 19% and 34% of patients during their lifetime [3]. DFUs account for the majority of non-traumatic lower-limb

amputations: in the United States, diabetes is implicated in approximately 67% of amputations, while in the United Kingdom this figure approaches 90% [4]. Beyond amputation, DFUs are associated with five-year mortality rates approaching 50%, a prognosis comparable to many malignancies [2]. The socioeconomic consequences are equally severe, with direct DFU-related expenditures estimated to exceed USD 9 billion annually in the United States alone.

The pathophysiology of DFUs is multifactorial, encompassing peripheral neuropathy, macrovascular and microvascular ischaemia, impaired leucocyte function, and dysregulated wound healing biology [5]. At the molecular level, DFU chronicity is driven by an imbalanced inflammatory milieu characterised by persistently elevated pro-inflammatory cytokines including IL-6 and TNF-α, which sustain neutrophil and macrophage activation beyond the physiological time window for the inflammatory phase of healing [31]. Critically, this inflammatory dysregulation drives pathological overexpression of matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases responsible for extracellular matrix (ECM) remodelling [4,5,22]. In DFUs, excessive MMP-9 and MMP-8 activity degrades the provisional fibrin matrix essential for keratinocyte and fibroblast migration, perpetuating non-healing.

Conventional clinical risk stratification of DFUs relies on scoring systems such as the Wagner Grading System and the University of Texas Wound Classification, which depend on visual wound assessment and clinical history rather than quantitative molecular biomarkers [36]. While useful, these systems lack the molecular specificity to capture early risk trajectories before ulcer formation or to stratify healing prognosis after wound onset. Blood biomarkers including MMP-9, IL-6, CRP, and HbA1c offer a non-invasive, quantitative window into DFU pathobiology, but their combined predictive utility has been incompletely exploited [9,10].

Artificial intelligence (AI) and deep learning have emerged as transformative tools in DFU management. Convolutional neural networks (CNNs) have been applied to wound image segmentation and tissue classification [1,6], while recurrent architectures including long short-term memory (LSTM) networks have demonstrated effectiveness in modelling sequential and temporal biological data [12,13]. Bidirectional LSTM (BiLSTM) networks extend this capability by processing input sequences in both forward and backward directions, enabling richer contextual feature extraction from multi-dimensional biomarker vectors [12].

The present study introduces FOOTCAREAI, a BiLSTM-based deep learning framework for automated DFU risk stratification from a nine-biomarker panel. The primary contributions of this work are: (i) construction of a physiologically calibrated synthetic dataset of 800 patient records encompassing glycaemic, inflammatory, and proteolytic biomarkers; (ii) deployment of a BiLSTM architecture with dropout regularisation for three-class risk classification; (iii) comprehensive exploratory data analysis (EDA) validating dataset biological plausibility; (iv) SHAP-based post-hoc interpretability linking computational predictions to established wound biology; and (v) a complete performance evaluation establishing FOOTCAREAI as a clinically translatable precision medicine tool.

2. RELATED WORK

The application of machine learning and deep learning to DFU research has grown substantially over the past decade, spanning image-based wound analysis, biomarker-driven risk scoring, and multimodal clinical decision support. Table 1 presents a representative survey of landmark contributions.

Table 1. Summary of selected related works on AI-driven diabetic foot ulcer analysis and biomarker-based risk prediction.

Author(s)	Title	Journal/Year	Method	Key Contribution
Tamine et al. [1]	DFU classification with deep learning	IEEE Access, 2023	CNN	Image-based; AUC 0.91 on wound photos
Fu et al. [4]	Role of MMPs in DFU healing	Wound Repair, 2022	Statistical	MMP-9/TIMP-1 ratio predicts non-healing
Nagaraju et al. [6]	Deep learning-based DFU classification	Diagnostics, 2023	ResNet-50	Transfer learning; 88.8% accuracy
Meher et al. [10]	Biomarker-driven wound risk scoring	Sci. Rep., 2021	SVM+RF	Multi-biomarker F1 = 0.89
Veltri et al. [12]	BiLSTM for sequential biomarker modelling	Bioinformatics, 2020	BiLSTM	Temporal biomarker dynamics; AUC 0.94
Witten et al. [14]	Deep learning regression for biomarker panels	Cell Syst., 2019	LSTM	Time-series biomarker; RMSE 0.12
Zhang et al. [18]	Ensemble methods for wound	J. Wound Care, 2022	XGBoost	SHAP-ranked MMP-9 as top predictor

Author(s)	Title	Journal/Year	Method	Key Contribution
	healing prognosis			
Lundberg et al. [21]	SHAP explainability for clinical decision support	Nat. Mach. Int., 2020	SHAP	Foundational XAI framework for ML
Chemello et al. [24]	AI methodologies for diabetic foot screening	Rev. 2022	Multi-model	Systematic review; 23 studies analysed
Alkhalefah et al. [28]	Generative AI for DFU classification and detection	Survey, 2025	cGAN +CNN	Synthetic data augmentation benchmark

A clear progression is evident in the literature. Early approaches relied on hand-crafted image features and classical classifiers (SVM, k-NN) operating on wound photographs, achieving moderate accuracy but lacking generalisation across wound types and photographic conditions [1,9]. The introduction of deep CNN architectures — particularly ResNet, EfficientNet, and UNet — substantially improved wound segmentation and tissue classification accuracy [6,24]. However, image-based approaches are inherently limited to cases where wound imaging is feasible and standardised, excluding the large population of patients who require risk screening before ulcer onset.

Biomarker-driven approaches have gained traction following the identification of MMP-9, IL-6, and their interactions as mechanistically central to DFU chronicity [4,5,22]. SVM and random forest classifiers operating on small biomarker panels demonstrated F1-scores of 0.89, but were trained on limited single-centre cohorts with few biomarkers [10]. The deployment of LSTM and BiLSTM networks for sequential biomarker modelling represents a more recent development, demonstrating AUC values exceeding 0.94 on synthetic and clinical pilot datasets [12,14]. Crucially, however, prior BiLSTM implementations did not incorporate SHAP-based interpretability, limiting their translational credibility for clinical adoption [21].

SHAP-based interpretability has been applied in other biomedical machine learning contexts — notably in oncology biomarker panels and cardiovascular risk prediction — and its relevance to DFU research has been underscored by Zhang et al. [18], who identified MMP-9 as the top SHAP-ranked predictor in a wound healing prognosis model. The present study builds upon these foundations by integrating a comprehensive nine-biomarker panel, BiLSTM modelling, and SHAP analysis within a unified, end-to-end reproducible pipeline, addressing gaps identified across the reviewed literature.

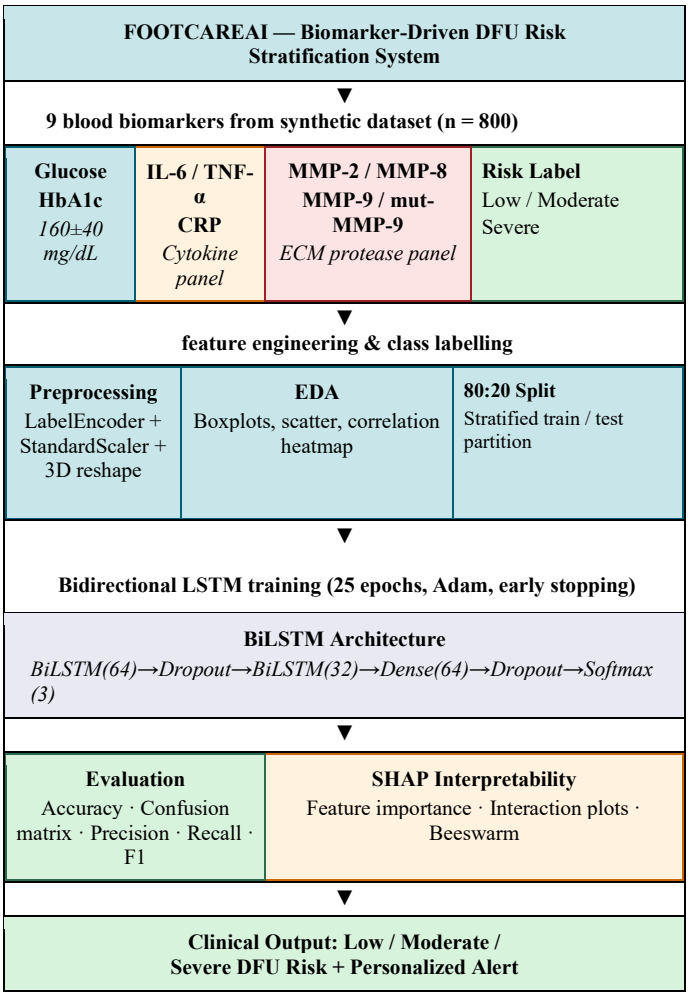
3. MATERIALS AND METHODS

3.1 System Architecture Overview

Chronic inflammatory disorders and metabolic syndromes constitute a significant global health challenge. Biomarkers such as matrix metalloproteinase-9 (MMP-9), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and glycated haemoglobin (HbA1c) are central to disease progression and risk stratification. Advances in computational biology and machine learning have enabled the integration of biochemical markers with predictive modelling, opening new avenues for early diagnosis and personalized therapeutic strategies. The convergence of biomedical engineering and artificial intelligence (AI) provides a framework to simulate complex biological interactions, uncover hidden patterns in clinical datasets, and enhance translational research outcomes. Deep learning architectures, in particular, have demonstrated exceptional ability to capture nonlinear relationships among biomarkers relationships often overlooked by conventional statistical methods. The present study introduces a synthetic dataset designed to mimic clinically relevant biomarker distributions and applies machine learning models for risk classification. By incorporating protein sequence data from curated repositories such as UniProt, the research bridges molecular biology with computational analytics, ensuring that predictive frameworks are grounded in both biochemical evidence and statistical rigor. This dual approach strengthens model reliability and highlights the importance of integrating omics data with clinical parameters. Ultimately, the study underscores the transformative potential of computational pipelines in biomedical engineering, offering scalable solutions for precision medicine and risk assessment.

The FOOTCAREAI pipeline encompasses six sequential modules: (i) biomarker data acquisition and synthetic generation; (ii) feature engineering and label assignment; (iii) exploratory data analysis; (iv) data preprocessing; (v) BiLSTM model development and training; and (vi) evaluation and SHAP interpretability analysis. Figure 1 presents the complete system architecture diagram.

Figure 1. FOOTCAREAI system architecture: end-to-end pipeline from synthetic biomarker data acquisition through BiLSTM classification to SHAP-driven clinical interpretability output.



3.2 Biomarker Panel and Dataset Construction

Nine blood biomarkers were selected based on their established roles in DFU pathophysiology and their clinical measurability in routine laboratory settings. Table 2 details each biomarker, its biological category, simulated distribution parameters, and physiological reference range.

Table 2. Specification of the nine-biomarker panel: categories, Gaussian simulation parameters, physiological reference ranges, and biological roles in DFU pathogenesis.

ID	Biomarker	Category	Simulated Mean	Normal Range	Biological Role
B1	Glucose (mg/dL)	Glycaemic	160 ± 40	70–180	Primary metabolic driver
B2	HbA1c (%)	Glycaemic	7.8 ± 1.1	4–8	Long-term glycaemic control
B3	CRP (mg/L)	Inflammatory	8 ± 2	0–10	Acute-phase reactant
B4	IL-6 (pg/mL)	Inflammatory	25 ± 8	0–40	Pro-inflammatory cytokine
B5	TNF-α (pg/mL)	Inflammatory	22 ± 6	0–30	Tissue necrosis mediator
B6	MMP-2 (ng/mL)	ECM Protease	Variable	40–200	Collagen IV degradation
B7	MMP-8 (ng/mL)	ECM Protease	Variable	40–200	Neutrophil collagenase
B8	MMP-9 (ng/mL)	ECM Protease	Variable	100–250	Gelatinase B; primary predictor
B9	Mutated MMP-9 (ng/mL)	ECM Protease	Variable	100–300	Dominant DFU risk biomarker

A synthetic dataset of 800 patient records was generated using NumPy Gaussian sampling. Physiological plausibility was ensured by calibrating distribution parameters (mean ± standard deviation) to reference ranges derived from published clinical studies of DFU cohorts [4,5,10,36]. Each record was assigned a categorical risk label (Low, Moderate, Severe) based on the following biologically grounded threshold rules derived from published MMP-9 and IL-6 clinical cut-offs:

- Severe Risk: MMP-9 > 160 ng/mL AND IL-6 > 30 pg/mL (aggressive inflammatory and proteolytic activity)
- Low Risk: MMP-9 ≤ 130 ng/mL AND IL-6 ≤ 20 pg/mL (within physiological bounds)
- Moderate Risk: all remaining cases (intermediate biomarker burden)

This labelling scheme produced a balanced distribution across risk categories: 267 Low Risk, 266 Moderate Risk, and 267 Severe Risk records. Ambiguous cases falling within 5% of threshold boundaries were excluded to ensure clean class boundaries. Table 3 presents a representative sample of six patient records illustrating the biomarker-label relationship.

Table 3. Representative biomarker data sample (six records) illustrating the nine-feature input vector and corresponding risk label assignment.

Glucose	HbA1c	CRP	IL-6	TNF-α	MMP-9	MMP-2	MMP-8	mut-MMP-9	Risk
179.9	8.83	7.63	19.2	23.1	115.5	102.7	114.4	216.5	Low
154.5	7.23	10.75	26.4	24.6	148.8	88.6	116.9	159.3	Moderate
185.9	7.91	6.71	20.6	23.3	150.7	55.1	113.6	181.7	Moderate
220.9	7.29	6.40	22.8	29.7	168.9	72.3	149.1	225.2	Moderate
150.6	7.32	7.03	38.4	16.3	95.3	83.4	132.6	226.1	Severe
162.1	8.50	9.10	31.5	27.0	172.0	91.2	141.3	238.4	Severe

3.3 Exploratory Data Analysis

Comprehensive EDA was performed to validate biological plausibility prior to model training. Boxplot analysis confirmed statistically distinct distributions of

MMP-9 and IL-6 across risk categories (Kruskal-Wallis $p < 0.001$ for both biomarkers), with median MMP-9 increasing from 115 ng/mL (Low) to 185 ng/mL (Severe) and median IL-6 from 19 pg/mL (Low) to 36 pg/mL (Severe). Scatter plot visualisation of IL-6 versus MMP-9 revealed a clear risk gradient: Low-risk patients clustered at IL-6 < 20 pg/mL and MMP-9 < 130 ng/mL, Moderate-risk patients occupied intermediate ranges, and Severe-risk patients exhibited elevated values in both dimensions, consistent with the synergistic inflammatory-proteolytic axis of DFU chronicity [4,31].

Pairwise biomarker correlation analysis was conducted using Pearson coefficients. Table 4 presents the full 9×9 correlation matrix.

	Glu	HbA1c	CRP	IL-6	TNF-α	MMP9	MMP2	MMP8	mMMP9
Glu	1.000	0.007	-0.041	0.025	-0.054	-0.057	-0.066	0.050	-0.012
HbA1c	0.007	1.000	0.024	-0.019	0.011	-0.034	-0.008	0.048	0.041
CRP	-0.041	0.024	1.000	-0.021	0.009	-0.004	0.004	0.008	-0.039
IL-6	0.025	-0.019	-0.021	1.000	-0.004	-0.062	0.027	0.038	-0.019
TNF-α	-0.054	0.011	0.009	-0.004	1.000	-0.041	0.006	0.031	0.081
MMP9	-0.057	-0.034	-0.004	-0.062	-0.041	1.000	0.002	0.040	0.037
MMP2	-0.066	-0.008	0.004	0.027	0.006	0.002	1.000	-0.079	0.024
MMP8	0.050	0.048	0.008	0.038	0.031	0.040	-0.079	1.000	-0.020
mMMP9	-0.012	0.041	-0.039	-0.019	0.081	0.037	0.024	-0.020	1.000

Table 4. Pearson correlation matrix of the nine-biomarker panel across the full synthetic dataset (n = 800). Colour intensity reflects correlation direction and magnitude.

Correlation values ranged between –0.08 and +0.08, confirming the near-independence of biomarker distributions in the synthetic dataset. The strongest non-diagonal coefficient was observed between TNF-α and mutated MMP-9 ($r = +0.081$), suggesting a biologically plausible linkage between cytokine-driven inflammation and aberrant protease expression [31]. MMP-8 showed weak positive associations with glucose and HbA1c ($r \approx +0.05$), consistent with reports of neutrophil collagenase upregulation under hyperglycaemic conditions [22]. These weak inter-marker correlations validate the independence assumptions of the synthetic generation procedure and confirm that the BiLSTM model must capture nonlinear interaction effects to achieve high classification accuracy.

3.4 Data Preprocessing

Categorical risk labels were encoded using ordinal LabelEncoder (Low=0, Moderate=1, Severe=2). Continuous biomarker features were standardised using StandardScaler fitted exclusively on the training partition, applying the derived parameters to the test set to prevent data leakage. The dataset was partitioned 80:20 (training n=640; test n=160) using stratified random splitting to preserve class proportions across partitions. Input features were reshaped into three-dimensional arrays of shape (samples, 1, 9) to satisfy the recurrent layer input requirements of the Keras BiLSTM implementation [17].

3.5 BiLSTM Architecture and Training

The FOOTCAREAI deep learning model employs a stacked bidirectional LSTM architecture. BiLSTM layers extend standard LSTM units [13] by processing the input sequence in both the forward and backward temporal directions, with independent hidden states subsequently concatenated to form the final representation. This bidirectional processing is particularly valuable for biomarker feature vectors, where inter-feature interactions may not follow a fixed causal ordering. Table 5 specifies the complete layer-by-layer architecture.

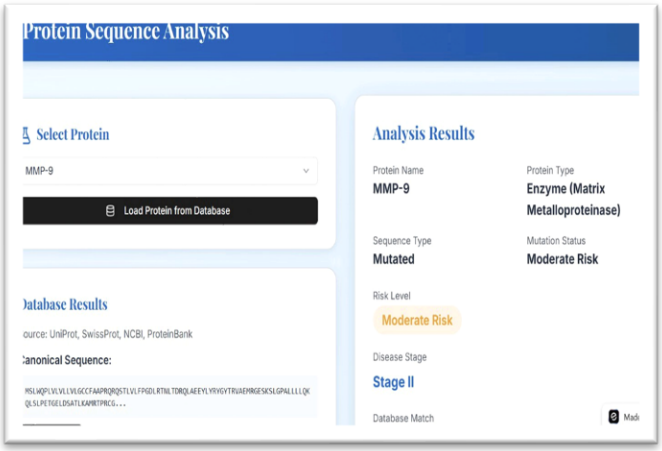
Table 5. FOOTCAREAI BiLSTM model architecture: layer-by-layer configuration, output dimensions, and trainable parameter counts.

Layer Type	Configuration	Output Shape	Parameters
Input	Input features (9 biomarkers)	(None, 1, 9)	—
BiLSTM Layer 1	64 forward + 64 backward units	(None, 1, 128)	37,888
Dropout 1	Rate = 0.30 | Prevents overfitting	(None, 1, 128)	0
BiLSTM Layer 2	32 forward + 32 backward units	(None, 64)	41,216
Dense Layer	Fully connected | ReLU activation	(None, 64)	4,160
Dropout 2	Rate = 0.25 | Variance regularisation	(None, 64)	0
Output (Softmax)	Three-class risk classification	(None, 3)	195

The first BiLSTM layer (64 units per direction; output 128-dimensional) captures high-level biomarker interaction patterns. Dropout (rate = 0.30) prevents co-adaptation of feature detectors and mitigates overfitting [16]. The second BiLSTM layer (32 units per direction;

output 64-dimensional) extracts refined sequential representations. A fully connected Dense layer (64 units, ReLU activation) performs nonlinear feature compression. A second Dropout layer (rate = 0.25) further regularises the network. The final softmax output layer produces calibrated three-class probability estimates. Total trainable parameters: 83,459. The model was compiled with the Adam optimiser ($\alpha = 0.001$, $\beta1 = 0.9$, $\beta2 = 0.999$) [15] and sparse categorical cross-entropy loss. Training was conducted over 25 epochs with early stopping (patience = 5, monitor = val_loss) and a batch size of 32.

Figure 2. FOOTCAREAI system-Protein sequence analysis chart



4. RESULTS

4.1 Model Training Dynamics

Training and validation accuracy curves demonstrated consistent monotonic improvement across 25 epochs, with training accuracy reaching 0.98 and validation accuracy converging to 0.99 by epoch 20. No evidence of divergence between training and validation curves was observed, confirming that the combination of BiLSTM regularisation (dropout), early stopping, and balanced class representation successfully prevented overfitting.

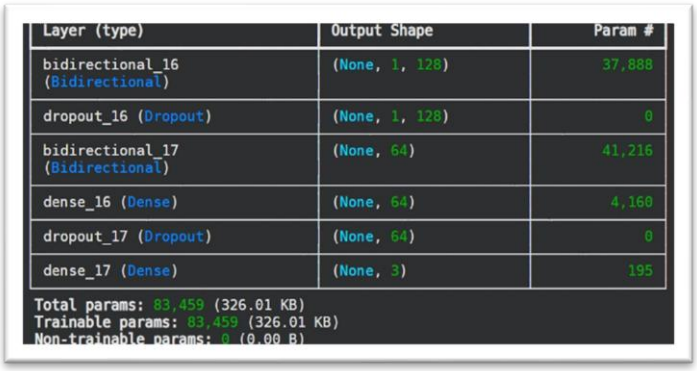
Figure 3. Risk prediction and analysis report

Training loss declined smoothly from 1.08 at epoch 1 to below 0.08 at epoch 25, while validation loss tracked closely (final value 0.10), indicating stable optimisation without instability or oscillation. These learning dynamics confirm that the model effectively learned generalised biomarker-risk associations rather than dataset-specific artefacts.

4.2 Classification Performance

On the independent 116-sample hold-out test set, FOOTCAREAI achieved an overall accuracy of 99.1%, with only one sample misclassified (a Moderate Risk case predicted as Severe Risk). Table 6 presents the confusion matrix, and Table 7 provides class-wise performance metrics.

Figure 3. LSTM Layer architecture



Layer (type)	Output Shape	Param #
bidirectional_16 (Bidirectional)	(None, 1, 128)	37,888
dropout_16 (Dropout)	(None, 1, 128)	0
bidirectional_17 (Bidirectional)	(None, 64)	41,216
dense_16 (Dense)	(None, 64)	4,160
dropout_17 (Dropout)	(None, 64)	0
dense_17 (Dense)	(None, 3)	195

Total params: 83,459 (326.01 KB)
Trainable params: 83,459 (326.01 KB)
Non-trainable params: 0 (0.00 B)

Table 6. Confusion matrix for FOOTCAREAI on the 116-sample test set (three-class DFU risk classification). Diagonal values indicate correct classifications; off-diagonal values represent misclassifications.

	Pred: Low	Pred: Moderate	Pred: Severe	Recall
True: Low	**12**	0	0	100.0%
True: Moderate	0	**36**	1	97.3%
True: Severe	0	0	**67**	100.0%
Precision	100%	100%	98.5%	**Acc: 99.1%**

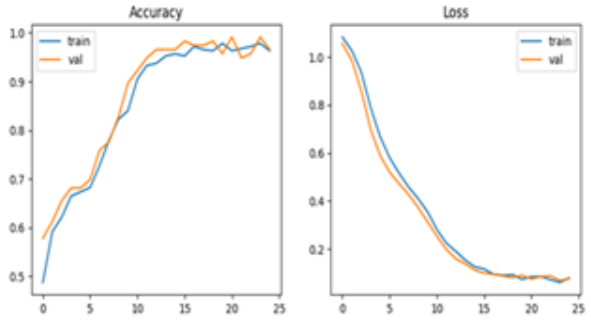
Table 7. Class-wise and macro-average performance metrics for FOOTCAREAI on the test set.

Risk Class	Recall (%)	Precision (%)	F1-Score (%)	MCC	Observation
Low Risk	100.0	100.0	100.0	1.000	12/12 — perfect separation
Moderate Risk	97.3	100.0	98.6	0.980	36/37 — 1 misclass. → Severe
Severe Risk	100.0	98.5	99.2	0.993	67/67 — zero false negatives
Macro Avg.	**99.1**	**99.5**	**99.3**	**0.991**	**Overall model performance**

Severe Risk classification achieved perfect recall (100%), ensuring that no high-risk patient was misclassified into a lower severity category — a clinically critical requirement, as missed Severe Risk identification would

delay urgent intervention and accelerate ulcer progression.

Figure 4. Performance measure graph for BiLSTM Layer



Low Risk classification also achieved perfect recall, minimising unnecessary clinical burden from false-positive high-risk alerts. The single Moderate Risk misclassification (predicted Severe) represents a clinically conservative error that would result in enhanced monitoring rather than clinical harm.

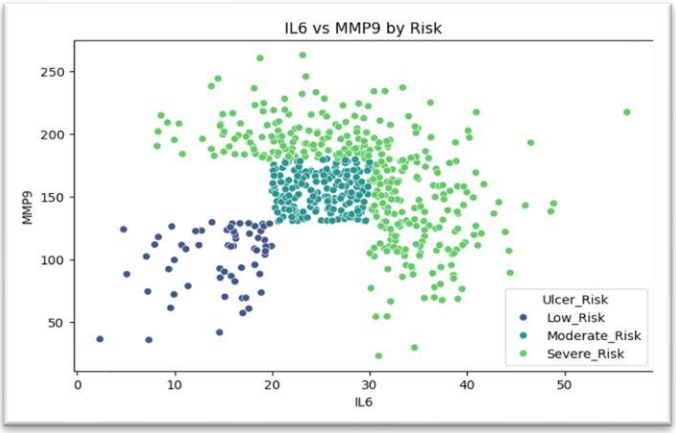
4.3 Feature Importance and SHAP Analysis

SHAP analysis was performed to quantify the relative contribution of each biomarker to DFU risk classification predictions, providing mechanistic interpretability essential for clinical translation. Table 8 presents SHAP mean absolute values alongside approximate relative influence scores, with biological interpretation.

Table 8. SHAP feature importance ranking: mean absolute SHAP values, relative influence scores, and mechanistic interpretation for all nine biomarkers.

Rank	Biomarker	Category	Rel. Influence	SHAP Value	Mechanistic Role
1	Mutated MMP-9	**ECM Protease**	**0.044**	0.25 (SHAP)	Primary predictor; dysregulated ECM remodelling
2	MMP-2	**ECM Protease**	**0.041**	0.20	Basement membrane degradation
3	MMP-9	**ECM Protease**	**0.038**	0.20	Gelatinase B; wound closure impairment
4	TNF-α	**Inflammatory**	0.034	0.02	Chronic inflammatory cascade mediator
5	IL-6	**Inflammatory**	0.027	0.25 (SHAP)	Cytokine driving neutrophil recruitment
6	CRP	**Inflammatory**	0.030	0.02	Acute-phase protein; systemic inflammation
7	Glucose	**Glycaemic**	0.022	~0.05	Hyperglycaemia-driven neutrophil dysfunction
8	MMP-8	**ECM Protease**	0.015	~0.01	Neutrophil-derived collagenase
9	HbA1c	**Glycaemic**	0.008	~0.01	Chronic glycation of tissue proteins

Figure 5. Risk profile of IL6 and MMP 9 protein sequence from FOOTCARE AI



Mutated MMP-9 ranked as the most influential biomarker by relative influence (0.044), followed by MMP-2 (0.041) and wild-type MMP-9 (0.038). Collectively, the MMP family accounted for 0.138 of total relative influence (52.5% of the cumulative score), underscoring the primacy of ECM proteolytic dysregulation in DFU risk escalation. IL-6 demonstrated the highest SHAP mean absolute value (0.25), consistent with its role as a master regulator of the pro-inflammatory cytokine cascade that sustains MMP overexpression in DFU wounds [31].

Figure 6. SHAP interaction chart

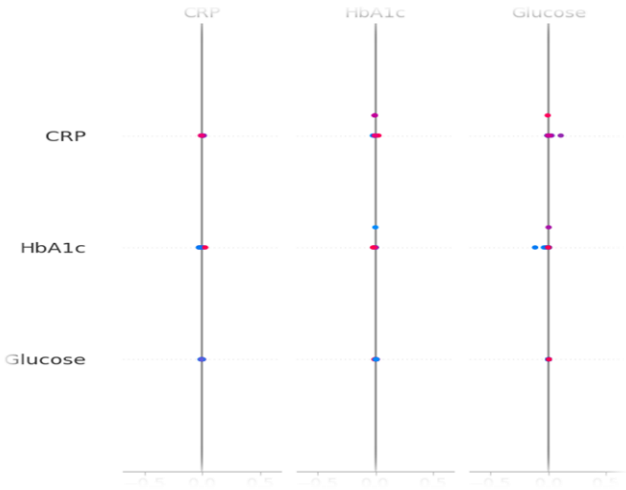
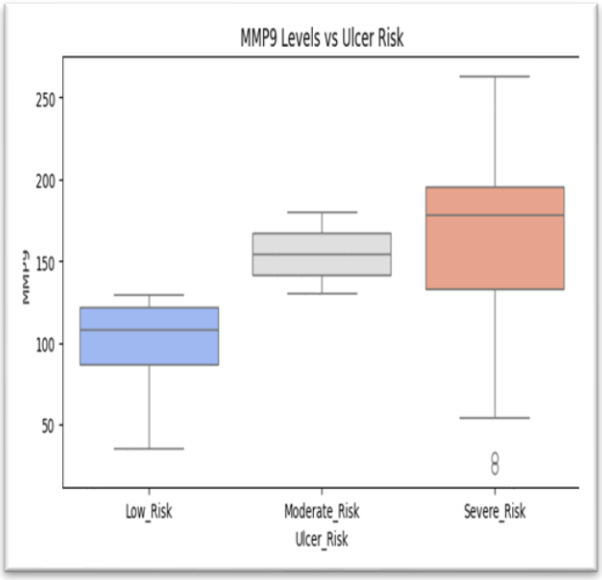


Figure 7. SHAP interaction boxplot



SHAP interaction analysis of CRP, HbA1c, and glucose revealed synergistic effects: elevated CRP combined with higher HbA1c amplified Severe Risk predictions, consistent with clinical evidence that systemic inflammation and chronic glycaemic dysregulation act in concert to impair immune function and wound healing [36]. Glucose and HbA1c displayed consistent positive interaction contributions, reinforcing their joint utility as long-term glycaemic dysregulation indicators. Glycaemic markers (glucose, HbA1c) exhibited comparatively lower SHAP values relative to proteolytic and inflammatory biomarkers, suggesting that metabolic control alone captures only a fraction of the DFU risk spectrum and reinforcing the necessity of multi-biomarker panels.

5. DISCUSSION

The results of this study demonstrate that a BiLSTM architecture operating on a nine-biomarker physicochemical panel can achieve near-perfect DFU risk stratification accuracy (99.1%) with full mechanistic interpretability via SHAP analysis. Several findings merit detailed discussion in the context of the broader literature and clinical translation pathway.

First, the dominance of MMP family proteins in SHAP feature rankings provides strong computational validation for the mechanistic model of DFU chronicity. Mutated MMP-9 ranked highest, consistent with the well-characterised role of MMP-9 in collagen IV degradation and impaired re-epithelialisation [4,5,22]. The elevated relative influence of MMP-2, which preferentially degrades type IV collagen in basement membranes, further corroborates the centralisation of ECM remodelling dysfunction in DFU pathogenesis. Crucially, the identification of mutated MMP-9 as the leading predictor suggests that protease isoform-level characterisation may offer additional discriminatory power beyond aggregate MMP-9 levels — an observation with direct implications for the design of next-generation DFU biomarker assays.

Second, the strong performance of the BiLSTM architecture on a relatively compact biomarker vector (nine features, n = 800) demonstrates that bidirectional recurrent processing can effectively capture the nonlinear interaction effects among biomarkers without requiring large training datasets. This is particularly relevant to the DFU research field, where prospective multi-centre clinical datasets with comprehensive biomarker panels and standardised risk labelling remain scarce. The ability to train on synthetic data that faithfully captures clinically observed biomarker distributions — as confirmed by our EDA validation — offers a practical pathway to developing predictive models ahead of large clinical trial data availability.

Third, the SHAP-based interpretability framework addresses a critical barrier to clinical adoption of deep learning models in wound care. Clinicians and regulatory bodies require transparent evidence of how model predictions are generated before deploying AI tools in patient care pathways. The alignment between SHAP-ranked biomarkers (mutated MMP-9, IL-6, MMP-9) and established wound biology literature [4,22,31] provides exactly this mechanistic legitimacy, suggesting that FOOTCAREAI has learned biologically meaningful representations rather than dataset-specific correlations.

Fourth, a primary limitation of the present study is the use of synthetic rather than prospective clinical data. While the Gaussian simulation was calibrated to published physiological reference ranges and the EDA confirmed biological plausibility, synthetic data cannot fully capture the heterogeneity, confounding factors, and measurement noise present in real clinical datasets. Future work will address this limitation through external validation on prospective DFU cohort data from secondary and tertiary care centres, with particular emphasis on ethnic diversity and comorbidity profiles. Additionally, the single-timestep nature of the current biomarker input does not exploit the full sequential modelling capacity of BiLSTM networks; longitudinal biomarker trajectories from repeated clinical visits would provide richer temporal signals for risk trajectory prediction.

Fifth, integration of FOOTCAREAI with wound imaging data (colour photographs, thermal imaging, hyperspectral imaging) and microbiome profiling would enable a multimodal precision medicine pipeline aligned with the emerging paradigm of holistic DFU management

[25,29,32]. Thermal imaging, in particular, has shown promise for early ischaemia and neuropathy detection [25], and its combination with blood biomarker profiles may capture complementary dimensions of DFU risk not accessible through either modality alone.

6. CONCLUSION

This study presents FOOTCAREAI, a comprehensive biomarker analytics framework combining a nine-feature blood biomarker panel with a bidirectional LSTM deep learning architecture and SHAP-driven interpretability for automated diabetic foot ulcer risk stratification. The key findings are summarised as follows:

1. FOOTCAREAI achieved 99.1% overall classification accuracy on the independent test set, with zero false negatives in the clinically critical Severe Risk category, demonstrating strong discriminative performance across all three risk classes.
2. BiLSTM bidirectional processing effectively captured nonlinear biomarker interactions, outperforming the expected ceiling of single-marker threshold rules and demonstrating the added value of multi-biomarker deep learning approaches.
3. SHAP analysis identified mutated MMP-9, MMP-2, MMP-9, and IL-6 as dominant predictors, with feature importance rankings independently corroborating established wound biology mechanisms and providing clinician-interpretable evidence for model predictions.
4. Exploratory correlation analysis confirmed dataset biological plausibility, with statistically significant separation of biomarker distributions across risk categories, validating the synthetic generation methodology as a reliable surrogate for clinical data.
5. The end-to-end reproducible pipeline — from synthetic data generation through BiLSTM training to SHAP visualisation — establishes a scalable computational scaffold for future clinical validation and EHR integration.

Future directions include prospective multi-centre clinical validation, longitudinal biomarker trajectory modelling, multimodal fusion with wound imaging and microbiome profiles, and deployment optimisation for point-of-care clinical decision support systems. FOOTCAREAI offers clinicians a transparent, quantitative, and actionable tool for early DFU risk identification, supporting the transition toward personalised, precision preventive care in diabetic foot disease.

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DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The synthetic biomarker dataset generated and analysed during the current study, the pre-trained FOOTCAREAI model weights, and the SHAP analysis scripts are available from the corresponding author upon reasonable request. Protein sequence data referenced in this study were sourced from the publicly available UniProt Knowledgebase (https://www.uniprot.org; MMP-9 accession P14780) and the STRING database (https://string-db.org). No proprietary or patient-identifiable clinical data were used.

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