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ORIGINAL RESEARCH

Association of Systemic Immune-Inflammatory Index with Risk of Foot Ulcer Amputation in Patients with Type 2 Diabetes Mellitus: Insights from a Cross-Sectional Study

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Objective: Diabetic foot ulcer (DFU) is one of the complications of diabetes, which can lead to amputation and death. The systemic immune-inflammatory index (SII), calculated based on platelet, neutrophil, and lymphocyte counts, serves as a cost-effective and practical biomarker. This study aimed to explore the relationship between SII and amputation risk in patients with DFU.

Methods: In this cross-sectional study, all eligible patients were divided into an amputation group and a non-amputation group based on their amputation status. Laboratory test data obtained on the first day of hospitalization were collected for all patients. SII was calculated from complete blood count parameters. Subgroup analysis, univariate analysis, and multivariate logistic regression were employed to assess the association between SII and amputation in patients with DFUs. Receiver operating characteristic (ROC) curves were used to evaluate the predictive accuracy of SII for amputation risk.

Results: The amputation group exhibited significantly higher SII levels compared to the non-amputation group ($p < 0.05$). Multivariate logistic regression analysis, after adjusting for all covariates, revealed that SII remained independently associated with DFU-related amputation (OR = 1.019; 95% CI: 1.007–1.031; $p = 0.002$). Subgroup analyses and interaction tests demonstrated that this positive association was not modified by age, sex, hypertension, smoking, or alcohol consumption (p for interaction > 0.05). In the ROC curve analysis, SII achieved an area under the curve (AUC) of 0.786 with a sensitivity of 77.70%. Reclassification based on propensity score matching showed that SII was significantly higher in the high-risk group than in the low-risk group($p < 0. 05$).

Conclusion: Higher SII levels in patients with type 2 DFU raise the risk of amputation. For assessing the risk of amputation in patients with DFUs, SII is likely to be a valuable biomarker for DFU amputation.

Keywords: systemic immune-inflammatory index, diabetic foot ulcer, amputation, biomarker, cross-sectional study

Introduction

Diabetes mellitus (DM) frequently results in diabetic foot ulcers (DFUs). DFUs, primarily caused by peripheral neuropathy and microangiopathy, frequently lead to localized or systemic infections and represent the leading cause of lower extremity amputations in patients with DM. Studies have shown that 19%–33% of patients with DFU ultimately progress to amputation, with some cases even threatening life.[1,2] This not only imposes a substantial economic, psychological, and emotional burden on patients but also generates significant financial strain on healthcare systems.[3–5] Consequently, identifying early warning indicators and risk factors that are easily accessible and associated with DFU-related amputations holds significant clinical value.

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In recent years, inflammatory biomarkers derived from routine blood tests, such as the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR), have gained increasing recognition in research across various diseases. SII is a relatively new biomarker that has been found to be associated with cardiovascular diseases, peripheral arterial disease, and autoimmune diseases.[6–10] Notably, no research has directly examined the association between SII and amputation in patients with DFU, just one study has examined the possible predictive usefulness of SII for amputation in this patient population.[11]

Thus, the main goal of this study was to explore the relationship between SII and lower limb amputations in patients with type 2 DFU, as well as to assess its predictive value for DFU-related amputations. To elucidate the relationship between SII and DFU-related amputations, we included a large sample size and employed comprehensive statistical methods for exploration. Our research findings contribute to the early identification of patients with high-risk DFU who are likely to require amputation, enabling timely interventions that can improve patient prognosis and potentially reduce amputation rates.

Materials and Methods

Study Design

This study was carried out at the Sixth Affiliated Hospital of Guangxi Medical University (First People's Hospital of Yulin) using a cross-sectional design from March 2022 to October 2024. This study has been thoroughly reviewed and approved by the hospital ethics committee, and all participants gave informed consent to this study. Cases were selected from patients diagnosed with type 2 DFUs who were hospitalized during this period and met predefined inclusion criteria (Figure 1). The patients were divided into two groups—the amputation group and the non-amputation group—according to the severity of the disease and the existence of inflammatory lesions. The following were the inclusion criteria for a DFU diagnosis: (1) a diagnosis of diabetes according to established criteria;[12] (2) a history of foot disease, peripheral neuropathy, lower limb vascular disease, foot ulcers, and/or deep tissue destruction, which may be healed, unresolved, or under treatment; and (3) exclusion of foot ulcers caused by other etiologies.[13]

Data Collection

The hospital's electronic medical record system provided the demographic, clinical, and laboratory data. The collected information included age, gender, smoking and alcohol consumption history, hypertension status, and the duration of DFU. Laboratory tests conducted within 24 h of admission included complete blood count, C-reactive protein (CRP), glycosylated hemoglobin a1c (HbA1c), and albumin (ALB). The complete blood count results were obtained through testing by the SYSMEX XN-10X automatic hematology analyzer, while the biochemical results were acquired through testing by the Roche cobas c701 automatic biochemical analyzer. The formula used to determine each patient's SII was SII = platelet count (PLT) × neutrophil count (NEU) / lymphocyte count (LYM). Accuracy and dependability were guaranteed by the ethical collection of all data.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. Data with a normal distribution were expressed as mean ± standard deviation EQN, and group comparisons were conducted using the independent samples *t*-test. Non-normally distributed data were expressed as the median and interquartile range [M (Q1, Q3)], and group comparisons were performed using the Mann–Whitney *U*-test. The chi-squared (χ^2) test was used to compare groups, and categorical variables were displayed as frequencies (n) and percentages (%). The association between SII and amputation in patients with DFU was investigated using univariate and multivariate logistic regression models. Amputation status (0 = non-amputation, 1 = amputation) was set as the dependent variable, whereas covariates included age, sex (0 = men, 1 = women), hypertension (0 = no, 1 = yes), smoking (0 = no, 1 = yes), alcohol use (0 = no, 1 = yes), ulcer duration, CRP, HbA1c, and ALB. To evaluate the influence of subgroup variables, including sex, age (less than 60 years, more than 60 years), hypertension, smoking, and alcohol consumption, on the association between SII and amputation, four regression models were created and subgroup analyses were carried out using multivariate logistic regression. The interaction between SII and each subgroup variable was also assessed. A receiver operating characteristic (ROC) curve was

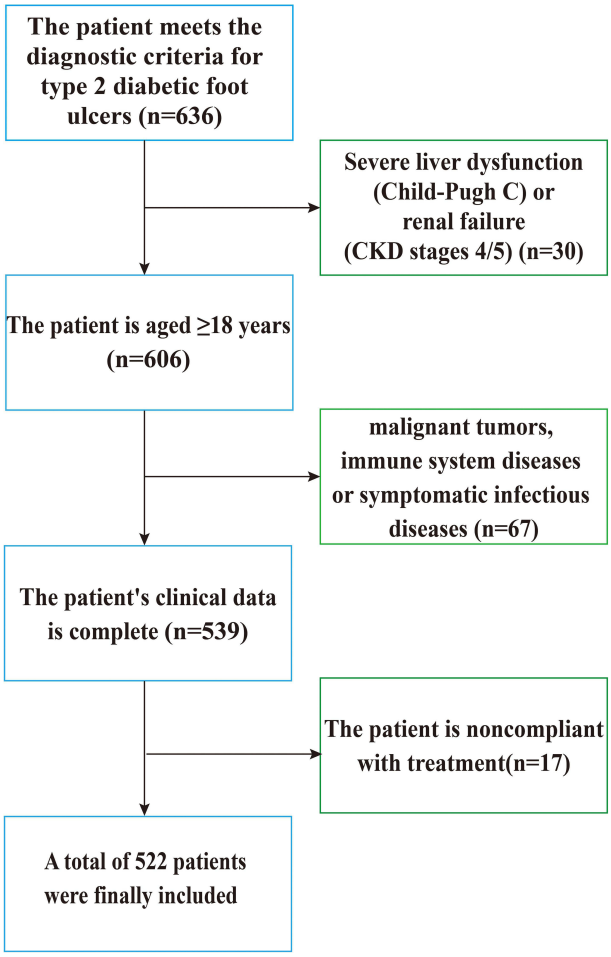

Figure 1 Study Flowchart.

generated for patients with DFU to evaluate the predictive accuracy of SII for amputation risk. On the basis of the optimal threshold of SII, patients were divided into groups at high and low risk for amputation. To ensure balance between these groups, we created a new dataset using propensity score matching, including covariates such as CRP, ALB, HbA1c, sex, age, smoking status, hypertension, drinking and ulcer duration. Matched groups were compared, and $p < 0.05$ was considered statistically significant.

Results

Comparison of the Two Groups' Clinical, Laboratory, and Demographic Features

A total of 522 patients participated in the study, of whom 121 underwent amputation, for an overall amputation rate of 23.18%. Age, history of hypertension, alcohol usage, and sexual orientation did not significantly differ between the two groups. In contrast to the non-amputation group, the amputation group had considerably lower ($p < 0.05$) ALB levels and significantly higher percentages of smoking, ulcer duration, CRP levels, HbA1c, and SII (Table 1).

Relationship Between SII and Amputation in Type 2 DFU

Among patients with type 2 DFU, univariate analysis revealed that smoking, SII, CRP, ALB, HbA1c, and ulcer duration were substantially linked to amputation ($p < 0.05$; Table 2). Multivariate logistic regression analyses of models 1–4 revealed that SII and amputation in type 2 DFUs were positively correlated (Tables 2 and 3). No significant nonlinear association between SII and DFU amputation was found when a restricted cubic spline curve was fitted to analyze the interaction (p for nonlinearity > 0.05; Figure 2).

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Table 1 Comparison of Baseline Characteristics and Laboratory Parameters Between the Amputation and Non-Amputation Groups

Variables	Amputation (n=121)	Non-Amputation (n=401)	p-value
Age (years)	64.000(56.500,72.000)	62.000(55.000,71.000)	0.473
Gender			0.887
Men, n (%)	76(62.810%)	249(52.095%)	
Women, n (%)	45(37.190%)	152(37.905%)	
Hypertension, n (%)	60(49.587%)	182(45.387%)	0.417
Smoking, n(%)	59(48.760%)	138(34.414%)	0.004
Drinking, n(%)	44(36.364%)	127(31.671%)	0.335
Ulcer duration (months)	1.200(0.800,3.200)	1.000(0.500,2.100)	0.002
CRP (mg/L)	113.410(45.200,184.575)	12.720(2.785,41.245)	<0.001
Albumin (mg/dl)	32.000(26.550,35.250)	35.600(31.550,38.600)	<0.001
HbA1c (%)	10.200(8.050,12.350)	9.300(7.400,11.250)	0.009
SII	2973.592(1538.842,6976.551)	1072.522(637.560,2015.608)	<0.001

Table 2 Univariate and Multivariate Analyses of Factors Associated with Amputation in Type 2 Diabetic Foot Ulcer

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.005 (0.987–1.023)	0.573	1.014(0.984–1.044)	0.362
Gender	0.970 (0.637–1.477)	0.887	1.385(0.738–2.600)	0.311
Hypertension, n (%)	1.184(0.788–1.778)	0.417	1.048(0.534–2.059)	0.891
Smoking, n(%)	1.814 (1.202–2.737)	0.005	2.261(1.263–4.049)	0.006
Drinking, n(%)	1.233 (0.805–1.888)	0.335	0.882(0.493–1.579)	0.673
Ulcer duration (months)	1.041(0.998–1.086)	0.061	1.049(1.008–1.091)	0.019
CRP (mg/L)	1.016 (1.013–1.020)	<0.001	1.019(1.007–1.016)	<0.001
Albumin (mg/dl)	0.900 (0.868–0.932)	<0.001	0.961(0.919–1.005)	0.083
HbA1c (%)	1.088 (1.015–1.165)	0.017	0.991(0.904–1.085)	0.839
SII per 100	1.043(1.033–1.054)	<0.001	1.019(1.007–1.031)	0.002

Subgroup Analysis of Variables Affecting the Relationship Between SII and Amputation in Type 2 DFU

The association between SII and DFU-related amputations is shown in Figure 3 for subgroups stratified by age (<60 years, ≥60 years), smoking, alcohol use, hypertension, and gender. Subgroup analysis indicated that the association between SII and type 2 DFU amputation remained significant across all subgroups ($p < 0.05$). Interaction tests revealed

Table 3 Relationship Between Systemic Immune-Inflammatory Index (SII) and Amputation in Type 2 Diabetic Foot Ulcer

	Model 1	**Model 2**	**Model 3**	**Model 4**
	OR (95% CI for OR) p-value	OR (95% CI for OR) p-value	OR (95% CI for OR) p-value	OR (95% CI for OR) p-value
SII per 100	1.043 (1.033–1.054) <0.001	1.044 (1.033–1.055) <0.001	1.045 (1.034–1.056) <0.001	1.019 (1.007–1.031) 0.002

Notes: Model 1: No adjustment for covariates.Model 2: Adjusted for age and gender.Model 3: Adjusted for age, gender, smoking, alcohol consumption, ulcer duration, and hypertension.Model 4: Adjusted for model 3 plus CRP, ALB, and HbA1c.

that the relationship between SII and DFU amputation did not significantly differ across the subgroups based on age, gender, hypertension, smoking, and alcohol consumption ($p > 0.05$).

Predictive Value of SII for Amputation in Type 2 DFU and Risk Stratification Analysis Based on Propensity Score Matching

The SII data was used to perform ROC analysis. The preoperative SII had an area under the curve (AUC) of 0.786, a sensitivity of 77.70%, and a specificity of 66.60%, as illustrated in Figure 4. A threshold of 1522.696 was found to be the ideal value for SII. Following the matching of propensity scores, 118 patients were split into two risk groups. SII levels were substantially greater in the high-risk group than in the low-risk group ($p < 0.05$) (Table 4).

Discussion

DFU is one of the most severe complications in patients with DM, primarily arising from peripheral vascular disease, peripheral neuropathy, and impaired immune function. Infections resulting from DFU can lead to fasciitis, osteomyelitis, and even systemic sepsis, with severe cases requiring amputation. The development and advancement of atherosclerosis are intimately associated with inflammation.[14] Inflammation and immunological reactions are important components of DFU pathophysiology.[4,15] The NLR and PLR have been found to be important prognostic indicators for diabetic foot in

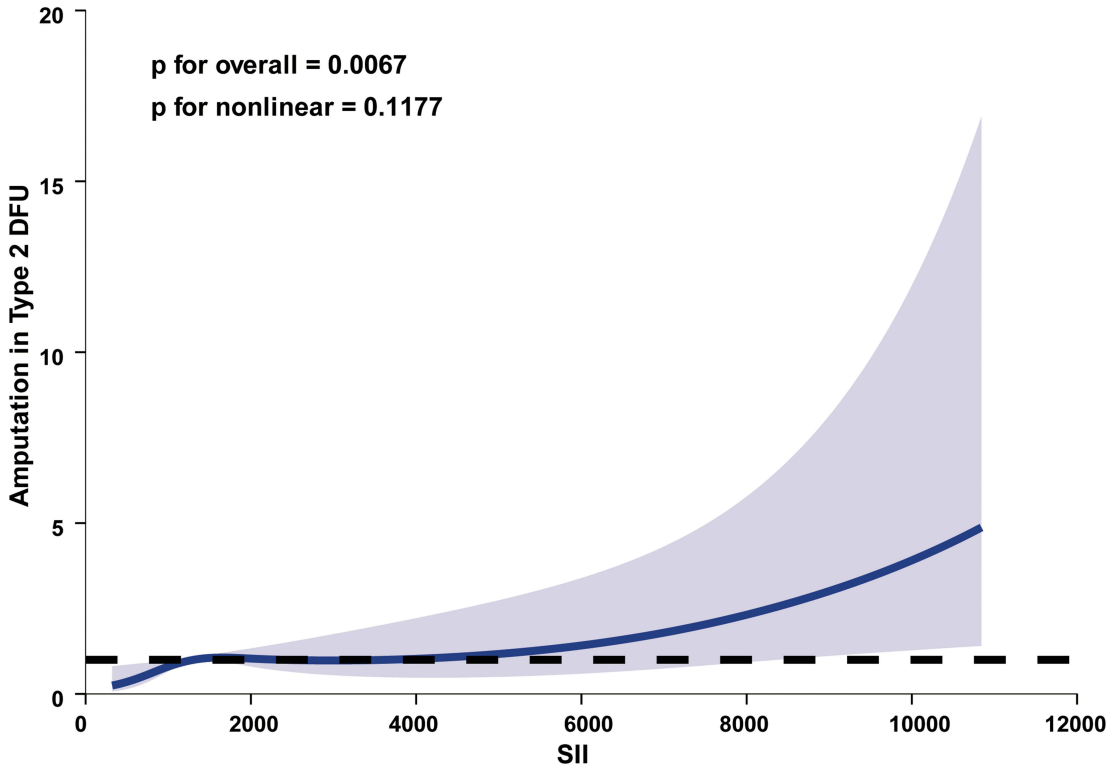

Figure 2 Restricted Cubic Spline for the Relationship between Systemic Immune-inflammatory Index (SII) and Type 2 DFU Amputation.

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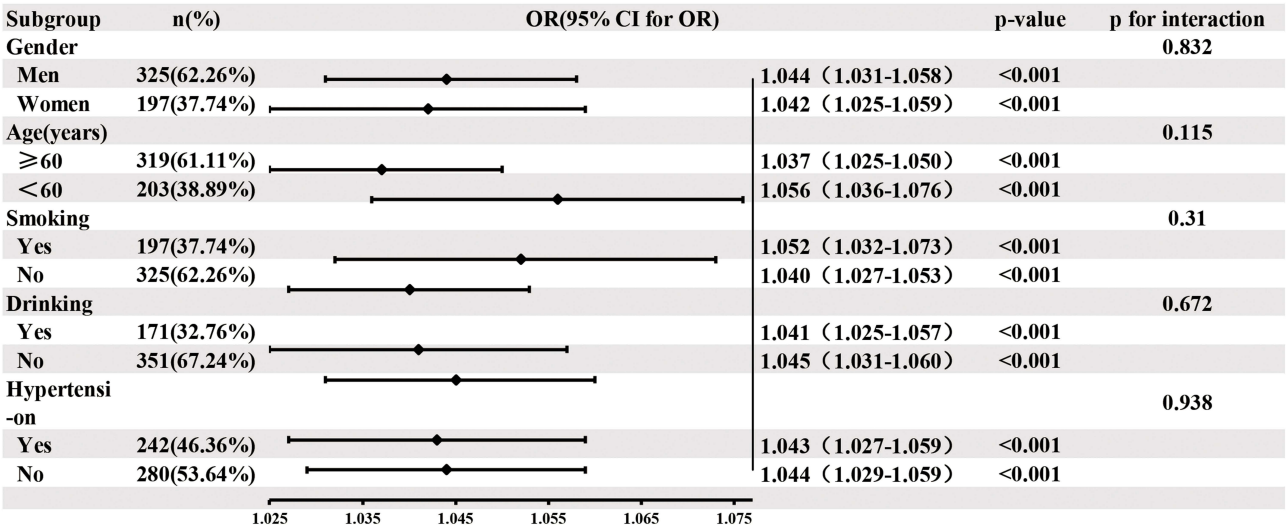

Figure 3 Subgroup Analysis of Variables Affecting the Relationship between Systemic Immune-inflammatory Index (SII) and Amputation in Type 2 Diabetic Foot Ulcer.

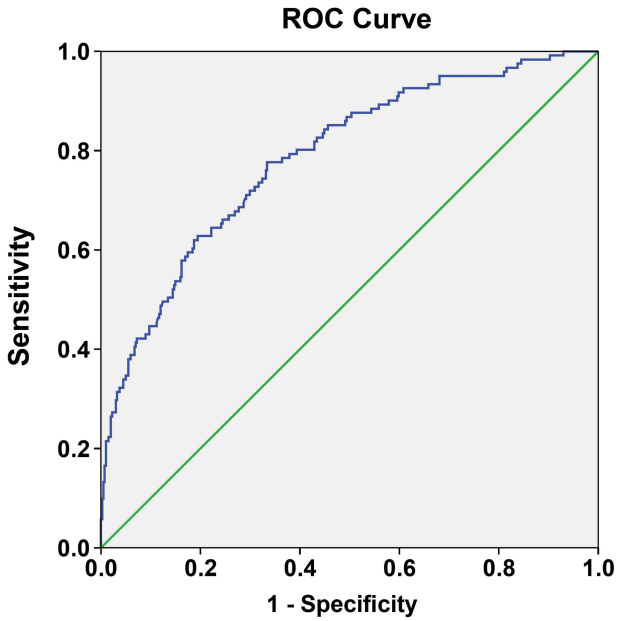

Figure 4 ROC Curve for Systemic Immune-inflammatory Index (SII) in Predicting Amputation in Type 2 Diabetic Foot Ulcer.

previous research. Furthermore, the diagnostic significance of the classical inflammatory marker CRP in evaluating DFU infections is well-established. For instance, Tuna Demirdal et al found that patients with DFU who required amputation had significantly higher levels of NLR and PLR compared with those who did not undergo amputation.[16] Nasibeh Vatankhah et al reported that NLR can predict the healing of DFU wounds.[17] According to a retrospective analysis, in patients with DFU, NLR, PLR, and CRP were independent risk factors for amputation.[18] NLR and PLR were found to predict mortality in 348 patients with DFU amputation in another retrospective observational analysis.[19] However, some studies suggest that the NLR may have limited diagnostic value in predicting amputation in patients with DFU, while CRP remains a valuable prognostic marker for DFU outcomes.[20] Our research found that SII was significantly higher in the amputation group compared to the non-amputation group among patients with DFU. The SII was considerably higher in the high-risk group than in the low-risk group in the propensity score-matched research. SII integrates platelets into NLR and neutrophils into PLR, both of which play critical roles in the inflammatory response.[21–23] Therefore, compared

Table 4 Comparison of Baseline Characteristics and Laboratory Parameters between High-Risk and Low-Risk Groups

Variables	Before Matching			After Matching		
	Low-Risk	High-Risk		Low-Risk	High-Risk	
	(n = 294)	(n =228)	p-value	(n = 118)	(n = 118)	p-value
Age (years)	63.000(56.000,71.000)	62.000(53.250,71.000)	0.473	61.000(54.000,70.000)	62.000(53.750,71.000)	0.452
Gender			0.710			0.894
Men, n (%)	181(61.565%)	144(63.158%)		72(61.017%)	73(61.864%)	
Women, n (%)	113(38.435%)	84(36.842%)		46(38.983%)	45(38.136%)	
Hypertension, n (%)	137(46.599%)	105(46.053%)	0.901	56(47.458%)	56(47.458%)	1
Smoking, n(%)	107(36.395%)	90(39.474%)	0.472	43(36.441%)	42(35.593%)	0.892
Drinking, n(%)	90(30.612%)	81(35.526%)	0.235	33(27.967%)	33(27.967%)	1
Ulcer duration (months)	1.100(0.500,2.200)	1.100(0.500,3.000)	0.762	1.000(0.500,2.125)	1.000(0.400,2.275)	0.862
CRP (mg/L)	5.780(2.233,21.740)	78.895(31.983,153.385)	<0.001	28.205(11.655,46.145)	32.575(16.645,55.220)	0.059
Albumin (mg/dl)	36.200(32.675,39.200)	32.300(28.100,36.300)	<0.001	33.950(30.225,37.425)	34.250(30.100,37.725)	0.635
HbA1c (%)	8.900(7.200,10.700)	10.200(8.200,12.400)	0.009	9.700(7.875,11.750)	9.800(7.775,12.300)	0.827
SII	768.743(536.978,1100.989)	2978.0588(2081.850,5128.218)	<0.001	870.789(667.315,1203.221)	2383.206(1874.522,3521.330)	0.009
Amputation, n (%)	27(9.184%)	94(41.228%)	<0.001	18 (15.254%)	30 (25.424%)	0.052

with NLR and PLR, SII is less affected by a single parameter and, theoretically, provides a more comprehensive reflection of the balance between inflammation and immune status in the body.

To the best of our knowledge, this work is the first thorough and in-depth study to examine the relationship between SII and amputation in patients with DFU. Prior research by Safak Ozer Balin et al showed a positive relationship between SII and indicators such as PCT, CRP, and ESR in diabetic foot infections.[24] Javier Aragón-Sánchez et al suggested that SII can serve as a biomarker for diabetic foot infections and observed a linear correlation between SII and white blood cell (WBC), CRP, and ESR.[25] A cross-sectional study identified SII as an independent risk factor for peripheral arterial disease (PAD) in patients with type 2 DM.[26] Similarly, a retrospective observational study involving 6,576 participants also confirmed SII as an independent risk factor for PAD. After controlling for age, sex, race, body mass index, DM, hypertension, and coronary artery disease, higher SII levels were linked to an increased risk of PAD.[27] Another study reported a significant positive correlation between SII and PAD severity, suggesting that elevated SII levels are linked to highly complex lower extremity arterial disease.[28] Our multivariate logistic regression model 4 demonstrated that SII remained an independent risk factor for amputation in patients with DFU, even after adjusting for age, sex, ulcer duration, hypertension, smoking, alcohol consumption, CRP, HbA1c, and albumin. For every 100-point increase in SII, the risk of amputation rose by 1.9%, suggesting that patients with DFU and elevated inflammation and/or reduced immune function are more likely to undergo amputation than their counterparts. Subgroup studies revealed that the correlation between SII and amputation risk was stronger in patients under 60, those with a history of smoking, and men compared with their counterparts. Notably, this association was also more significant in patients with no history of alcohol consumption. A possible explanation for the higher odds ratio (OR) in patients with no alcohol use could be attributed to gender-related factors. Our data revealed that a greater percentage of women in the amputation group than in the non-amputation group had a history of alcohol use. Nonetheless, there were more men and fewer women in the drinking group overall.

SII is a composite index derived from platelets, neutrophils, and lymphocytes, and it was first proposed by Hu Bo et al[29] as a novel systemic inflammatory biomarker. It is advantageous due to its ease of use and low cost. Elevated SII levels can result from increased neutrophils and/or platelets, or decreased lymphocytes, or a combination of these factors. We hypothesized the following mechanisms for high SII levels in patients with DFU requiring amputation: (1) Elevated systemic inflammatory

responses result in high serum levels of inflammatory cytokines, leading to an increase in neutrophils, which act as the body's second line of defense. Neutrophils rapidly proliferate and migrate toward the site of inflammation under chemotactic factors, where they phagocytize and kill pathogens, clear necrotic tissue, and stimulate megakaryocytes to induce platelet aggregation.[30] (2) In the intense inflammatory state, platelet activation manifests as increased adhesion, activation, aggregation, and the expression of receptors that promote immune cell recruitment, leading to an increased platelet count. Additionally, platelets are essential for the onset and advancement of atherosclerotic vascular disease.[22,23,31] (3) Inflammatory cytokines induce lymphocyte apoptosis and inhibit their proliferation, resulting in a reduction in peripheral blood lymphocyte count. (4) Chronic hyperglycemia and/or malnutrition may impair immune function, leading to decreased lymphocyte count and activity.[32] A cross-sectional study involving 231 patients with DFU found that SII can predict mortality following amputation in patients with DFU.[17] SII may be a potential marker for diabetic foot infection prediction, according to other studies.[24] A retrospective analysis was carried out by Mehmet Salih Aydın et al on 511 patients with DFU, and they found that SII has high predictive value for amputation in these patients.[11] Our study's ROC curve showed an AUC of 0.786 and a sensitivity of 77.70%. Following matching, the high-risk group still had significantly higher SII than the low-risk group, highlighting the strong predictive capability of SII and suggesting that elevated SII levels may indicate an increased risk of amputation in patients with DFU.

Although this study offers valuable insights, several limitations should be considered. (1) Given the small sample size and the single-center, cross-sectional design of this study, the results may have been subject to some degree of bias. (2) Although patients with clinically documented infectious diseases, immune system disorders, and malignancies were excluded, we could not fully rule out the potential impact of subclinical inflammatory conditions or other unidentified factors that may influence the study outcomes. (3) The association between SII and amputation of other forms of DFUs was not investigated in this work, which was restricted to individuals with type 2 DFU. These need to be improved and further validated by conducting more and more comprehensive studies in the future. We expect that SII may play a greater role in risk assessment, dynamic monitoring, and decision-making for foot ulcer amputation in diabetic patients in the future.

Conclusion

In conclusion, our findings suggested that elevated SII levels are associated with a heightened risk of amputation in patients with type 2 DFU. For patients with DFU, SII can be a crucial indicator for amputation prediction. SII can be used in primary care settings with limited resources because it is inexpensive and simple to use. It may help in the early detection of high-risk patients when paired with conventional diagnostic techniques, which would enable prompt interventions, enhance patient outcomes, and lower the rate of amputation.

Abbreviations

SII, Systemic Immune-Inflammation Index; DFU, Diabetic Foot Ulcer; NEU, Neutrophil; LYM, Lymphocyte; PLT, Platelet; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; ALB: Albumin; CRP, C-reactive Protein; CKD, Chronic Kidney Disease; PAD, Peripheral Arterial Disease; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; WBC, White Blood Cell; ESR, Erythrocyte Sedimentation Rate; PCT, Procalcitonin; OR, Odds Ratio; CI, Confidence Interval.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the first author.

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. It has been thoroughly reviewed and approved by the Ethics Committee of the Sixth Affiliated Hospital of Guangxi Medical University (The First People's Hospital of Yulin) (Approval No. YLSY-IRB-SR-2024137).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that the study was conducted without any potential conflicts of interest.

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