International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

The Role of Systemic Immune-Inflammation Index and Prognostic Nutritional Index in Predicting Outcomes of Chinese Patients with Diabetic Foot Ulcers After Moist Exposed Burn Ointment Treatment

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Objective: To evaluate the prognostic value of the systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) in predicting healing outcomes in patients with diabetic foot ulcers (DFUs) treated with Moist Exposed Burn Ointment (MeBo).

Methods: This retrospective study analyzed 273 DFU patients treated at the First Hospital of Qinhuangdao (January 2022–December 2024). Patients were categorized into complete healing (n=123) and non-healing (n=150) groups based on 12-week outcomes. Univariate and multivariate logistic regression analyses were conducted to identify predictors of healing. Receiver operating characteristic (ROC) curve analysis evaluated the discriminative abilities of SII and PNI.

Results: Compared to the non-healing group, the complete healing group exhibited significantly lower SII (1444.82±560.26 vs. 2979.88±1357.18, P<0.001) and higher PNI (38.17±5.20 vs. 31.65±5.54, P<0.001). ROC analysis indicated that SII had strong predictive ability (AUC=0.920, P<0.001; optimal threshold 1901.48), with 86.0% sensitivity and 83.7% specificity. PNI showed moderate predictive capacity (AUC=0.811, P<0.001). Notably, the combined model (SII+PNI) demonstrated superior predictive performance (AUC=0.940), achieving 89.3% sensitivity and 87.0% specificity.

Conclusion: SII and PNI are robust prognostic biomarkers for DFU patients treated with MeBo. Elevated SII acts as a risk factor for non-healing, while higher PNI serves as a protective factor. Integrating these indices into clinical practice may facilitate early risk assessment and guide therapeutic strategies to improve healing outcomes.

Keywords: diabetic foot ulcers, moist exposed burn ointment, systemic immune-inflammation index, prognostic nutritional index, predictive biomarkers

Introduction

Diabetic foot ulcer (DFU) is a serious and disabling drawback of diabetes mellitus (DM), typically developing in about 15% to 25% of cases with diabetes throughout their lifetime.[1,2] These ulcers significantly impair patients' quality of life and contribute substantially to the high rates of morbidity, disability, and mortality observed among this population.[1,2] DFUs are associated with prolonged hospitalization, increased healthcare costs, and a substantial risk of amputation.[3] It is estimated that about 15% of patients with DFUs may eventually require an amputation, and this risk increases with the duration of the ulcer and the presence of co-existing conditions, such as peripheral artery disease and neuropathy.[4] Hence, DFUs are a significant burden not only for individuals, but also for the healthcare system globally. The pathogenesis of DFUs is complex and multifactorial, with chronic hyperglycemia contributing to vascular damage, impaired immune function, and neuropathy.[5] These factors disrupt normal wound healing, leading to delayed or incomplete wound closure.

https://doi.org/10.2147/IJGM.S578889
Received: 20 November 2025
Accepted: 5 February 2026
Published: 11 March 2026

For numerous cases, DFUs progress to chronic wounds that resist conventional treatments, further increasing the likelihood of amputation and worsening the prognosis.[6] Given the chronic nature of DFUs and the complications associated with non-healing wounds, there is an urgent need for effective and reliable methods to predict healing outcomes. Timely recognition of individuals at elevated risk for poor healing could enable clinicians to personalize treatment strategies and improve patient outcomes by preventing unnecessary interventions, involving amputations and prolonged hospitalizations.

Moist exposed burn ointment has emerged as a widely used topical treatment for DFUs.[7–9] Moist exposed burn ointment creates a moist wound environment, accelerating the healing process by promoting autolysis, reducing inflammation, and enhancing tissue regeneration.[10] It has been demonstrated its effectiveness in promoting wound closure in DFU patients, especially when used in conjunction with other standard treatment modalities.[11] However, despite its clinical utility, the prediction of which patients may achieve complete wound healing remains challenging. Not all DFUs respond to moist exposed burn ointment treatment in the same way, and some patients experience delayed healing, recurrent infections, or the need for surgical interventions (eg, amputations). Therefore, it is essential to identify reliable prognostic markers that can predict healing outcomes and guide therapeutic decisions in DFU patients treated with moist exposed burn ointment.

Over the past few years, attention has shifted toward identifying biomarkers that can accurately predict the healing potential of DFUs. Recent investigations have increasingly underscored the superiority of composite immune-inflammatory biomarkers over single parameters in predicting chronic wound prognosis, highlighting their robustness in capturing the complex pathophysiology of diabetes complications.[12–14] Among them, the systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) have shown promise in various disease contexts, comprising chronic wounds[15,16] and cancer,[17] while their function in predicting DFU healing outcomes has not been thoroughly explored. The SII is a composite index that reflects systemic inflammation and immune status,[18] two critical factors in wound healing. The index is derived from platelet, leukocyte, and lymphocyte counts, parameters that collectively reflect the body's systemic inflammatory activity. Increased SII values have been reported to be linked with unfavorable clinical outcomes across multiple disease states,[19,20] reflecting that systemic inflammatory activity may contribute substantially to the underlying mechanisms involved in chronic wound development and persistence. In a similar manner, the PNI, which is derived from serum albumin concentration and lymphocyte count, has been dominantly noted as a comprehensive indicator that not only reflects the nutritional status of an individual, but also outlines insight into their immune competence.[21] Malnutrition and immune dysfunction may impair wound healing,[22,23] and the PNI has been used as a prognostic tool in several clinical settings, including cancer[24] and cardiovascular diseases.[25] In the setting of DFUs, immune-inflammatory activity and nutritional status are both crucial determinants of wound repair. Mechanistically, a synergistic interplay likely exists between these factors via the "inflammation-nutrition axis", wherein sustained systemic inflammation depletes metabolic reserves and poor nutritional status further compromises immune competence, collectively hindering the tissue repair microenvironment. Yet, the interaction between these indices and healing outcomes in DFU patients treated with MeBo has not been fully investigated.

Several studies have highlighted the need for personalized treatment strategies in managing DFUs, as not all patients respond similarly to the same therapeutic regimen.[26,27] Identifying patients at risk of poor healing can lead to more targeted and timely interventions, potentially reducing the incidence of amputations and chronic wounds. Despite the broad usage of MeBo in clinical practice, there is a lack of data on how immune-inflammatory and nutritional factors influence healing outcomes in DFU patients treated with this therapy. However, a notable knowledge gap remains regarding the specific prognostic utility of these indices within the context of MeBo treatment, leaving clinicians without tailored predictive tools for this patient population. Accordingly, the current investigation concentrated on the predictive significance of the SII and PNI in relation to wound healing outcomes among patients with DFUs receiving MeBo therapy. To the best of our knowledge, this is the first study to comprehensively evaluate the combined prognostic utility of SII and PNI specifically within a cohort of DFU patients treated with MeBo. Through this analysis, the study sought to update understanding of the biological processes underlying ulcer repair in diabetes and to identify potential prognostic indicators that may support clinicians in optimizing therapeutic decision-making.

Methods

Study Design

This retrospective observational investigation was carried out at First Hospital of Qinhuangdao from January 2022 to December 2024. During this period, 273 cases diagnosed with DFUs were consecutively included in the analysis. Based on ulcer healing outcomes following therapy with MeBo (Shantou Meibao Pharmaceutical Co., Ltd)., participants were categorized into two groups: the complete healing group (n = 123) and the non-healing group (n = 150). The diagnosis of DFU was made according to the criteria set by the American Diabetes Association (ADA),[28] with ulcers present for more than 4 weeks and associated with neuropathy and/or vascular insufficiency, after excluding other potential causes of foot wounds. The decision to categorize patients into the complete healing or non-healing groups was based on clinical assessment of wound closure within a 12-week period following MeBo treatment. The study was conducted at First Hospital of Qinhuangdao and the ethical approval was obtained by the Ethics Committee of First Hospital of Qinhuangdao (No.: FHQ-20250102). Declaration of Helsinki was followed. Written informed consent was obtained by all the participants.

Inclusion and Exclusion Criteria

The following conditions determine participants' involvement status: (1) were 18 years of age or older; (2) had a clinically confirmed diagnosis of DFU; (3) received treatment with MeBo; and (4) possessed complete baseline clinical and laboratory data necessary for the calculation of SII and PNI. Exclusion criteria included: (1) previous surgical interventions for DFUs; (2) active systemic infections or severe comorbidities unrelated to diabetes; (3) incomplete medical records, specifically defined as missing essential baseline laboratory parameters (neutrophils, lymphocytes, platelets, or albumin) or loss to follow-up preventing outcome assessment, which were systematically excluded to ensure statistical validity; (4) death within 30 days of initiating treatment; (5) ulcers caused by factors other than diabetes, such as trauma or non-diabetic infections; and (6) other significant complications that could interfere with wound healing, such as malignant diseases or severe liver and kidney dysfunction.

Outcome Assessment

The primary outcome of this investigation was the ulcer healing status assessed at 12 weeks after initiation of treatment with MeBo. Healing outcomes were categorized into four types: complete wound healing, minor amputation, major amputation, and chronic non-healing ulcers. Lesions that neither achieved full epithelialization nor required amputation within the observation period were defined as chronic wounds. Ulcers that attained complete closure without surgical removal were classified as completely healed and assigned to the complete healing group (n = 123). Conversely, wounds resulting in amputation or persisting without closure were designated as non-healing and included in the non-healing group (n = 150). Amputation procedures performed distal to the ankle joint were recorded as minor, whereas those proximal to this level were identified as major amputations.

Collecting Clinical Data

Clinical information was retrospectively extracted from the medical records of cases who received MeBo therapy for DFUs. Baseline characteristics comprised demographic variables such as age, sex, and body mass index (BMI), as well as diabetes type and ulcer-specific features, including wound duration and anatomical site. Hematologic and biochemical measurements included white blood cell (WBC) count, lymphocyte and monocyte counts, platelet count, C-reactive protein (CRP), and serum albumin (Alb) concentration. The SII was computed according to the formula: SII = platelet × count/ lymphocyte, with all parameters expressed as $\times 10^9$/L. The PNI was derived using the equation: PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (cells/μL). All data were obtained at the initial clinical assessment prior to commencement of MeBo treatment, and patients were observed for a 12-week period to evaluate wound healing outcomes. Data collection was performed by trained clinical staff, ensuring accuracy and completeness. Missing data were cross-checked, and patients with unavailable critical data were excluded. All data were anonymized and securely stored for analysis.

Statistical Analysis

Data analysis was performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables with a normal distribution are presented as mean ± standard deviation (SD), while those with a non-normal distribution are expressed as median (interquartile range [IQR]). Categorical variables are reported as frequencies and percentages (n, %). Differences between the complete healing and non-healing groups were evaluated using the independent Student's *t*-test or Mann–Whitney *U*-test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. To identify independent prognostic factors aligned with the study's objectives, univariate logistic regression analysis was first conducted to screen for variables that exhibited statistically significant differences ($P < 0.05$) in the baseline comparison. Variables with a $P < 0.05$ in the univariate analysis were subsequently included in the multivariate logistic regression model to adjust for potential confounders. Crucially, during the model construction, we deliberately included the composite SII and PNI indices while excluding their individual component parameters (ie, neutrophils, platelets, lymphocytes, and albumin) to avoid multicollinearity and mathematical redundancy. Although a formal a priori power calculation was not performed, the sample size was deemed sufficient based on the "events per variable" (EPV) guideline (ensuring at least 10 outcome events per predictor variable) to maintain the stability and reliability of the regression estimates. The strength of associations was reported as odds ratios (ORs) with 95% confidence intervals (CIs). Furthermore, to assess the robustness of the multivariate model, sensitivity analysis was performed using the Bootstrap method with 1000 resamples. To quantify and compare the predictive accuracy of the biomarkers, receiver operating characteristic (ROC) curve analysis was performed. The area under the curve (AUC) was calculated to evaluate the discriminative ability of the SII, PNI, and the combined model. The Youden index (maximum vertical distance between the ROC curve and the diagonal line) was used to determine the optimal cutoff values, along with their corresponding sensitivity and specificity. All statistical tests were two-tailed, and a P-value < 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics Between Complete Healing and Non-Healing Groups of DFUs Treated with MeBo

A total of 273 DFU patients were evaluated, consisting of 123 with complete healing and 150 without (Table 1). In the non-healing group, there were 23 patients who underwent minor amputation (15.33%), 6 who underwent major amputation (4.00%), and 121 who had chronic wounds (80.67%). Demographic characteristics were similar between the groups, with no significant differences in age (63.46 ± 4.29 vs. 64.41 ± 5.19 years, P = 0.103), sex distribution (male:

Table 1 Baseline Characteristics Between Complete Healing and Non-Healing Groups of DFUs Treated with MeBo

Indices	Complete Healing Group (n=123)	Non-Healing Group (n=150)	P value
Sex [n(%)]			0.793
Female	39 (31.71)	45 (30.00)	
Male	84 (68.29)	105 (70.00)	
Age (Years)	63.46±4.29	64.41±5.19	0.103
BMI (kg/m^2)	33.36±4.98	34.52±5.19	0.062
Types of DM [n(%)]			0.327
Type 1 DM	17 (13.82)	28 (18.67)	
Type 2 DM	106 (86.18)	122 (81.33)	
Wound age (d)	102.11±27.16	105.82±31.26	0.302
Affected side [n(%)]			0.227
Right	69 (56.10)	73 (48.67)	
Left	54 (43.90)	77 (51.33)	

(*Continued*)

Table 1 (Continued).

Indices	Complete Healing Group (n=123)	Non-Healing Group (n=150)	P value
Comorbidities [n(%)]			
Hypertension	70 (56.91)	97 (64.67)	0.213
Coronary heart disease	37 (30.08)	59 (39.33)	0.127
Cerebrovascular disease	26 (21.14)	26 (17.33)	0.442
Diabetic kidney disease	21 (17.07)	38 (25.33)	0.106
Laboratory parameter			
Neutrophil ($\times10^9$/L)	8.04±1.89	11.80±1.80	<0.001
Lymphocyte ($\times10^9$/L)	1.69±0.41	1.24±0.37	<0.001
Monocyte ($\times10^9$/L)	0.65±0.22	0.63±0.20	0.44
PLT ($\times10^9$/L)	284.95±39.34	280.27±37.31	0.316
CRP (mg/L)	74.91±30.13	287.61±51.15	<0.001
Blood glucose (mg/dL)	210.20±39.94	201.83±39.41	0.084
Alb (g/dL)	2.97±0.52	2.55±0.54	<0.001
Hb (g/dL)	11.66±1.46	11.32±1.54	0.062
SII	1444.82±560.26	2979.88±1357.18	<0.001
PNI	38.17±5.20	31.65±5.54	<0.001

Abbreviations: DFUs, Diabetic Foot Ulcers; ICU, Intensive Care Unit; GCS, Glasgow Coma Scale; BMI, Body Mass Index; DM, Diabetes Mellitus; PLT, Platelet count; CRP, C-Reactive Protein; Alb, Albumin; Hb, Hemoglobin; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

68.29% vs. 70.00%, P = 0.793), or BMI (33.36 ± 4.98 vs. 34.52 ± 5.19 kg/m^2, P = 0.062). The majority had type 2 DM (86.18% vs. 81.33%, P = 0.327). Regarding comorbidities, there were no statistically significant differences between the complete healing and non-healing groups in the prevalence of hypertension (56.91% vs. 64.67%, P = 0.213), coronary heart disease (30.08% vs. 39.33%, P = 0.127), cerebrovascular disease (21.14% vs. 17.33%, P = 0.442), or diabetic kidney disease (17.07% vs. 25.33%, P = 0.106). Wound age was similar (102.11 ± 27.16 vs. 105.82 ± 31.26 days, P = 0.302). The affected side of the ulcer did not significantly differ (P = 0.227). Laboratory parameters demonstrated significant differences. The complete healing group had lower neutrophil (8.04 ± 1.89 vs. 11.80 ± 1.80 $\times10^9$/L, P < 0.001) and CRP (74.91 ± 30.13 vs. 287.61 ± 51.15 mg/L, P < 0.001). Lymphocyte counts were higher in the complete healing group (1.69 ± 0.41 vs. 1.24 ± 0.37 $\times10^9$/L, P < 0.001), while monocyte counts were similar (P = 0.440). Platelet counts and hemoglobin level were comparable (P = 0.316 and 0.062, respectively). Blood glucose levels were similar (P = 0.084), whereas Alb concentration was higher in the complete healing group (2.97 ± 0.52 vs. 2.55 ± 0.54 g/dL, P < 0.001). SII was significantly lower in the complete healing group (1444.82 ± 560.26 vs. 2979.88 ± 1357.18, P < 0.001), while PNI was significantly higher (38.17 ± 5.20 vs. 31.65 ± 5.54, P < 0.001).

Logistic Regression Analyses of Risk Factors for Outcomes in DFU Patients Treated with MeBo

Following baseline comparisons, variables showing significant inter-group differences in the *t*-test were entered into univariate logistic regression. As outlined in Table 2, higher neutrophil (OR = 1.241, 95% CI: 2.593–4.616, P < 0.001) was associated with poor healing outcomes. Conversely, higher lymphocyte counts (OR = 0.054, 95% CI: 0.025–0.118, P < 0.001) were protective. Lower albumin level (OR = 0.226, 95% CI: 0.136–0.375, P < 0.001) was also strongly linked to poor healing. While CRP level did not exhibit a significant association (OR = 1.246, 95% CI: 0.915–1.697, P = 0.162), SII (OR = 1.003, 95% CI: 1.002–1.004, P < 0.001) was positively correlated with non-healing. PNI (OR = 0.794, 95% CI: 0.747–0.844, P < 0.001) was inversely associated with non-healing, indicating that better nutritional status promotes healing. Considering WBC and lymphocyte counts are components of SII, and lymphocyte count and albumin are components of PNI, to avoid collinearity and redundancy, only SII and PNI were retained in the final model for analysis of their associations with healing outcomes. In multivariate logistic regression (Table 3), SII (OR = 1.003, 95% CI: 1.002–1.003, P < 0.001) and PNI (OR = 0.823, 95% CI: 0.758–0.893, P < 0.001) continued to exhibit independent

Table 2 Univariate Logistic Regression Analysis Identifying Risk Factors Associated with Outcomes in Patients with DFUs Treated with MeBo

Variables	B	SE	Wald X2	P	OR	95% CI
Neutrophil	1.241	0.147	71.146	<0.001	3.46	2.593~4.616
Lymphocyte	−2.921	0.398	53.787	<0.001	0.054	0.025~0.118
CRP	0.22	0.158	1.952	0.162	1.246	0.915~1.697
Alb	−1.486	0.258	33.093	<0.001	0.226	0.136~0.375
SII	0.002	0	61.984	<0.001	1.002	1.002~1.003
PNI	−0.23	0.031	54.237	<0.001	0.794	0.747~0.844

Abbreviations: DFUs, Diabetic Foot Ulcers; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval; CRP, C-Reactive Protein; Alb, Albumin; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

Table 3 Multivariate Logistic Regression Analysis Identifying Independent Risk Factors Associated with Outcomes in Patients with DFUs Treated with MeBo

Variables	B	SE	Wald X2	P	OR	95% CI
SII	0.003	0	52.694	<0.001	1.003	1.002~1.003
PNI	−0.195	0.042	21.74	<0.001	0.823	0.758~0.893

Abbreviations: DFUs, Diabetic Foot Ulcers; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index; B, Regression Coefficient; SE, Standard Error; Wald X2, Wald Chi-Square; P, P-value; OR, Odds Ratio; CI, Confidence Interval.

associations with healing outcomes. Specifically, higher SII was linked to an increased risk of non-healing, whereas higher PNI remained a protective factor, remarkably diminishing the likelihood of non-healing.

ROC Analysis for Predicting Mortality in Patients with Non-Traumatic SAH in the ICU

Evaluating the predictive performance of the SII and PNI for wound healing outcomes particularly in cases with DFUs who managed with MeBo was through ROC curve analysis (Table 4 and Figure 1). The SII exhibited strong discriminatory capability, as reflected by an AUC of 0.920 (95% CI: 0.889–0.952, $P < 0.001$). The optimal threshold for SII was determined to be 1901.475, corresponding to 86.0% sensitivity and 83.7% specificity. In contrast, the PNI demonstrated a moderate level of prognostic accuracy, with an AUC of 0.811 (95% CI: 0.760–0.862, $P < 0.001$). The most appropriate cut-off point for PNI was 33.85, yielding 82.9% sensitivity and 68.7% specificity. When both indices were incorporated simultaneously into a composite predictive model, the discriminative performance remarkably improved, achieving an AUC of 0.940 (95% CI: 0.913–0.967, $P < 0.001$). This integrated model resulted in a sensitivity of 89.3% and a specificity of 87.0%, indicating enhanced accuracy in evaluating ulcer healing potential.

Discussion

In the current retrospective cohort of 273 Chinese patients with diabetic foot ulcers uniformly treated with moist exposed burn ointment and followed for 12 weeks, we evaluated the utility of the SII and the PNI as biomarkers for predicting

Table 4 ROC Analysis of Potential Predictors for Outcomes in Patients with DFUs Treated with MeBo

Variables	AUC	95% CI	Best Cut-Off Value	Sensitivity (%)	Specificity (%)	P value
SII	0.92	0.889~0.952	1901.475	86	83.7	<0.001
PNI	0.811	0.760~0.862	33.85	82.9	68.7	<0.001
Combined	0.94	0.913~0.967		89.3	87	<0.001

Abbreviations: DFUs, Diabetic Foot Ulcers; AUC, Area Under the Curve; CI, Confidence Interval; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

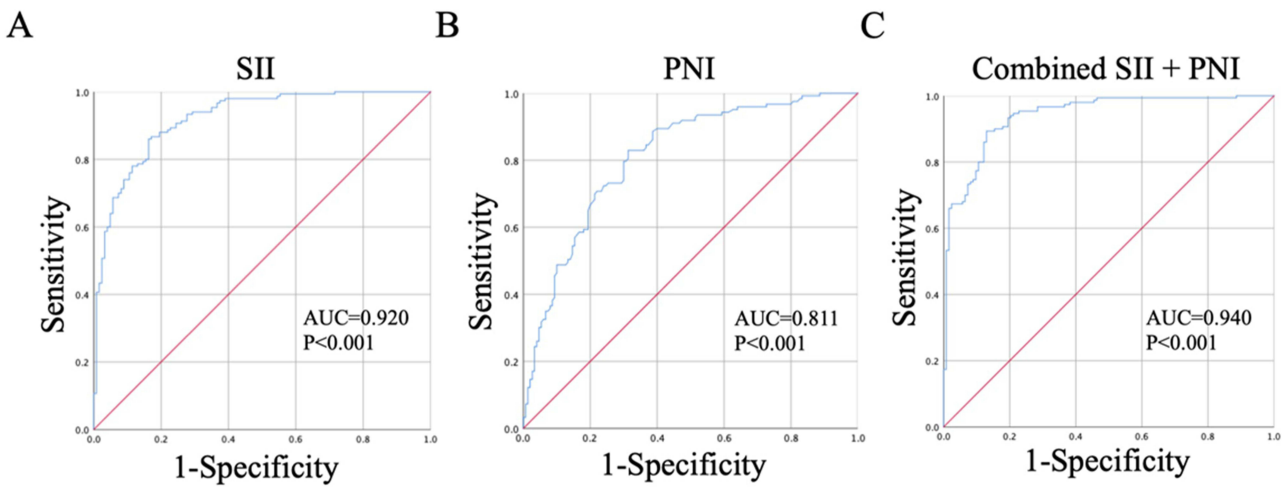

Figure 1 ROC Analysis of (**A**) SII, (**B**) PNI, and (**C**) Their Combination for Predicting Outcomes in Patients with Diabetic Foot Ulcers Treated with MeBo.
Abbreviations: SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index; AUC, Area Under the Curve; ROC, Receiver Operating Characteristic.

healing outcomes. The outcomes unveiled that SII was significantly higher and PNI significantly lower in the non-healing group compared with the complete-healing group, and both indices were independently associated with greater odds of non-healing. Moreover, ROC analyses demonstrated robust discriminative performance, with a combined SII–PNI model yielding improved classification.

With respect to MeBo, the findings of the current investigation unveiled that, even under a standardized moist-healing strategy, baseline host factors remain powerful determinants of outcome. MeBo is a topical formulation designed to maintain a physiologically moist wound environment, facilitate autolytic debridement, and support re-epithelialization.[29,30] Beyond its original indication for burns, MeBo has demonstrated therapeutic potential across a spectrum of cutaneous wounds and postoperative conditions, consistently exhibiting analgesic, granulation-promoting, and safety advantages in clinical and experimental contexts.[31–33] Li et al[31] demonstrated that MEBO markedly enhanced wound closure and pain relief in patients with pressure ulcers, achieving a significantly higher rate of complete healing and favorable tolerability relative to placebo. Expanding on these findings, Tang et al[32] revealed that MEBO facilitated excisional wound repair in rat models by stimulating granulation tissue development, neovascularization, and fibroblast proliferation through the upregulation of VEGF and bFGF expression levels. Complementarily, Al-Meshaan et al[33] pointed out that MEBO application following surgical debridement in Fournier's gangrene not only accelerated wound recovery but also mitigated pain, suppressed infection, and significantly reduced hospitalization duration. Within the context of DFUs, available clinical observations, though limited, have indicated that MEBO may contribute to improved exudate management, stimulation of granulation tissue formation, and satisfactory patient tolerability.[11] Preclinical investigations have further elucidated the mechanistic basis underlying these effects. Xu et al[34] demonstrated that MEBO facilitates wound repair in diabetic mice by dynamically modulating neovascularization and regulating plasma exosomal miR-31-5p expression through the upregulation of VPS4a and Rab27a during the early and intermediate stages of tissue regeneration. Consistently, Gong et al[7] revealed that MEBO accelerates diabetic wound closure by enhancing granulation tissue deposition, collagen remodeling, and epidermal regeneration, primarily through the promotion of re-epithelialization, without markedly altering keratinocyte differentiation. Expanding upon these findings, Zhang et al[8] provided further mechanistic insight, reporting that MEBO augments angiogenesis and expedites full-thickness wound healing in hyperglycemic rats via activation of the SDF-1/CXCR4 signaling axis and upregulation of HIF-1α. Collectively, these studies suggest that MEBO exerts a multifaceted pro-healing effect in diabetic wounds, involving the coordinated regulation of vascular, cellular, and molecular pathways. The present study does not quantify MeBo's absolute effect due to the absence of a comparator, yet it shows that baseline systemic inflammation and nutrition strongly influence healing outcomes. Thus, while MeBo and moist wound care are essential, optimizing host inflammatory and nutritional status is equally crucial to maximize therapeutic efficacy.

Regarding SII, it was uncovered that elevated baseline SII independently predicted non-healing DFUs at 12 weeks. Inflammation plays a complex role in the tissue repair of DFU. Excessive or insufficient levels of inflammation can impair wound healing. The pathological changes of patients with diabetes are characterized by excessive and prolonged inflammatory reaction, while the wound of diabetes is characterized by excessive inflammation.[35–37] Conceptually, SII captures the link of inflammatory activation with immune regulation by integrating platelet- and leukocyte-driven inflammation with lymphocyte-mediated immune competence. This construct is biologically plausible in DFUs, where persistent low-grade inflammation, microvascular dysfunction, and impaired cellular immunity impede orderly progression from inflammation to proliferation and remodeling.[38–40] In line with reports from other disease areas (eg, malignancy,[41–43] cardiovascular disease,[44,45] and infection[46,47]) showing that higher SII correlates with adverse outcomes, the current investigation's outcome unveiled that a heightened systemic inflammatory milieu, potentially reflecting platelet activation, leukocytosis, and relative lymphopenia, portends delayed closure or amputation in the diabetic foot. Recent evidence from DFU research consistently implicated elevated SII level in more severe disease manifestations, involving heightened amputation risk, infection burden, and delayed wound healing. Aydın et al[13] demonstrated that SII serves as a cost-effective and easily obtainable biomarker that correlates with an increased likelihood of amputation among DFU patients. Expanding upon these findings, Aragón-Sánchez et al[16] pointed out that SII values were markedly higher in individuals presenting with severe infections, tissue necrosis, or impending amputation, and moderately correlated with traditional inflammatory indices such as CRP and ESR. Similarly, Ozer Balin et al[48] identified significantly elevated SII level in diabetic patients with osteomyelitis relative to those with cellulitis, highlighting its diagnostic potential as a practical and reliable indicator of deep tissue infection. Further extending its prognostic relevance, Yilmaz et al[49] concluded that elevated preoperative SII independently predicted short-term (30-day) mortality following below-knee amputation, reflecting its value as an integrated marker of systemic inflammation and immune dysregulation in advanced DFU. Against this backdrop, the current study advanced the field by evaluating SII within a cohort uniformly managed with MeBo and by jointly assessing PNI while concentrating on 12-week healing rather than solely infection severity or amputation, provides pragmatic cut-offs and an actionable inflammation–nutrition framework. This design reduces confounding from heterogeneous local care and refines current evidence into a low-cost, bedside stratification approach that can guide early triage and inform prospective validation in DFU.

For PNI, lower baseline values were associated with non-healing, indicating that hypoalbuminemia and lymphopenia, markers of malnutrition and impaired immune competence, demonstrated poor tissue repair and delayed epithelialization. PNI was originally developed for perioperative risk estimation and has repeatedly predicted complications, length of stay, and mortality in surgical and oncologic populations.[50–52] In diabetes-related foot pathology, prior investigations have similarly documented a link of a low PNI with adverse clinical outcomes, involving elevated amputation rates, extended hospitalization durations, and slower wound closure,[53,54] aligning closely with our results. Coşkun et al[55] have pointed out that the PNI, reflecting nutritional and immune status, is noticeably lower in DFU patients who undergo amputation and serves as an excellent predictor of amputation risk with high sensitivity and specificity. Mechanistically, albumin reflects both nutritional reserve and the systemic inflammatory response (as a negative acute-phase reactant),[56,57] while lymphocyte counts index adaptive immune capacity essential for bacterial control and coordinated wound healing.[58,59] Clinically, PNI is attractive because its components are routinely available, inexpensive, and modifiable. Embedding structured nutritional assessment early, targeting adequate protein-energy intake, micronutrient repletion, and mitigation of inflammation-driven protein catabolism, may improve trajectories when paired with infection management and revascularization where indicated. Furthermore, interpretation of PNI should consider potential confounders, such as fluid status, hepatic or renal dysfunction, and acute inflammatory states that depress albumin independent of nutrition. Future prospective studies should explicate whether serial PNI monitoring adds incremental prognostic value over a single baseline measure and whether PNI-informed nutritional interventions can translate prognostic insight into tangible improvements in healing and limb salvage. Integrating PNI with SII may yield complementary information, capturing both systemic inflammatory load and host nutritional-immune fitness, and warrants evaluation in externally validated, decision-oriented prediction tools.

Mechanistically, the robust predictive utility of SII stems from its capacity to integrate the hyperactivity of innate immunity and coagulation with adaptive immune suppression. Emerging evidence suggests that systemic neutrophilia

drives an aberrant local immune response, where infiltrating neutrophils release excessive matrix metalloproteinases (MMPs), reactive oxygen species, and neutrophil extracellular traps, perpetuating a hostile proteolytic environment that actively degrades the extracellular matrix and impedes epithelial migration.[60,61] Concurrently, platelet hyperactivation not only facilitates microthrombosis but also releases pro-inflammatory cytokines, further exacerbating endothelial dysfunction and aggravating the local ischemia intrinsic to the diabetic foot.[62] Conversely, PNI serves as a critical surrogate for the host's nutritional and immunological functional reserve. Serum albumin is not only indispensable for collagen synthesis and reducing tissue edema but also functions as a vital antioxidant and transport vehicle for essential nutrients.[63] Furthermore, adequate lymphocyte levels are essential for counteracting the polymicrobial bioburden often found in chronic ulcers. Therefore, the convergence of a low PNI and a high SII depicts a pathological "perfect storm" characterized by systemic metabolic consumption and unchecked inflammatory destruction. This synergistic imbalance creates a severe catabolic state that arrests the wound healing cascade, effectively preventing the crucial transition from the inflammatory phase to the proliferative remodeling phase.

To address the complex pathophysiology of diabetic wounds, recent advances in regenerative medicine have increasingly focused on the development of functionalized biomaterials and nanotechnology. Emerging evidence highlights the pivotal role of novel nanomaterials and tetrahedral DNA frameworks (tFNAs) in modulating the wound microenvironment and enhancing structural stability for drug delivery.[64,65] Parallelly, biological scaffolds derived from decellularized extracellular matrix (dECM) continue to serve as a fundamental platform for tissue remodeling by mimicking the native cellular niche.[66] Building upon these scaffolding strategies, the integration of engineered exosomes into hydrogel systems has been demonstrated to overcome the limitations of rapid clearance, effectively regulating macrophage polarization and promoting angiogenesis through sustained release.[67,68] Furthermore, the latest generation of "smart" wound dressings has evolved to synergize therapeutic efficacy with real-time diagnostic capabilities. For instance, Xie et al[69] developed a self-healing injectable hydrogel capable of real-time pH monitoring and modulating MMP-9 expression, while Wang et al[70] engineered a conductive eutectogel that not only eradicates multidrug-resistant bacteria but also enables precise temperature sensing, offering a comprehensive theranostic solution for refractory diabetic ulcers.

From a clinical perspective, the integration of SII and PNI into routine workflows holds substantial promise for optimizing DFU management. As these indices are derived from standard, cost-effective complete blood counts, they can serve as accessible screening tools for early risk stratification immediately upon hospital admission. The identification of high-risk phenotypes, specifically those with elevated SII and diminished PNI, should trigger tailored therapeutic interventions. For instance, patients with low PNI scores may benefit from early, structured nutritional support, such as high-protein supplementation, to restore immune competence and tissue repair capacity. Conversely, an elevated SII suggests an excessive inflammatory burden, necessitating optimized anti-inflammatory strategies. These may include stricter glycemic control to reduce metabolic stress, more aggressive surgical debridement to remove bioburden, and targeted infection management to modulate the wound microenvironment, ultimately improving the likelihood of healing under MeBo treatment.

It is noteworthy that while CRP exhibited significant predictive value in the univariate analysis, it failed to retain significance in the multivariate logistic regression model. This phenomenon is likely attributable to the potential collinearity between CRP and the SII, as both serve as indicators of systemic inflammatory status. However, unlike CRP, the SII is a composite index integrating three distinct distinct cell lines, neutrophils, lymphocytes, and platelets, thereby capturing a more comprehensive landscape of the host immune-inflammatory, coagulation, and nutritional response. Consequently, the SII demonstrated superior independent discriminative power in the multivariate adjustment, rendering CRP redundant in the final predictive model for this specific cohort.

The current investigation's limitations are noteworthy. Firstly, the retrospective, single-center design inherently introduces potential selection bias and limits the generalizability of the findings to broader populations. Although the sample size was deemed sufficient for the analysis, a formal a priori power calculation was not performed. Furthermore, the absence of a non-MeBo control group limits causal inference regarding specific treatment efficacy and leaves residual confounding a possibility. Secondly, biomarker assessment was limited to a single baseline time point; we did not evaluate dynamic changes in SII or PNI, and the SII employed total leukocytes rather than neutrophils, influencing comparability with other studies. Thirdly, we lacked granular data on several determinants of healing, involving

standardized ischemia/neuropathy grading, detailed infection severity, glycemic variability, and structured nutritional interventions, refining risk estimates and model calibration. Fourthly, the study focused primarily on the internal validation of the SII and PNI; due to data availability constraints inherent to the retrospective design, we were unable to perform a direct comparative analysis against other established prognostic scores to benchmark predictive performance, warranting future prospective validation.

Conclusion

In summary, this retrospective study of Chinese patients with DFUs treated with moist exposed burn ointment found that higher SII was independently linked to an escalated risk of non-healing, while higher PNI served as a protective factor. ROC analysis confirmed meaningful discriminative ability for both indices, with SII demonstrating the strongest individual performance and the combined SII–PNI model achieving the highest overall accuracy. Beyond their prognostic value, these findings underscore the clinical utility of integrating inflammatory and nutritional profiling into routine risk stratification. Identifying high-risk phenotypes, specifically those with elevated inflammatory burden and nutritional deficits, can guide clinicians to implement intensified multidisciplinary care, such as targeted nutritional support and optimized anti-inflammatory strategies, to maximize the therapeutic efficacy of MeBo. Future research should focus on validating these findings in large-scale, multi-center prospective cohorts and investigating whether therapeutic modification of SII and PNI levels can directly improve healing outcomes.

Abbreviations

SII, systemic immune-inflammation index; PNI, prognostic nutritional index; DFUs, diabetic foot ulcers; MeBo, Moist Exposed Burn Ointment; DM, diabetes mellitus; ADA, American Diabetes Association; BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; Alb, albumin; ORs, odds ratios; CIs, confidence intervals; ROC, receiver operating characteristic.

Data Sharing Statement

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted at First Hospital of Qinhuangdao and the ethical approval was obtained by the Ethics Committee of First Hospital of Qinhuangdao. The procedures used in this study were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained by all the participants.

Author Contributions

All the authors read and approved the final manuscript.

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.

Specifically, Lianying Wang contributed to conceptualization, methodology, resources, supervision, and writing (review and editing). Yunyang Tang contributed to validation, investigation, formal analysis, and writing (original draft). Xiaofei Lin contributed to validation, investigation, formal analysis, and writing (review and editing).

Funding

This research did not receive any funding.

Disclosure

The authors declare that there is no conflict of interest in this work.

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