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Predictors of Diabetic Foot Ulcer Recurrence: A Retrospective Analysis of Clinical, Vascular, and Biochemical Risk Factors

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Editorial

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Abstract

Background: Diabetic foot ulcers (DFU) are a significant consequence of diabetes mellitus, leading to morbidity, amputation, and mortality. Despite preventative and treatment breakthroughs, recurrence remains difficult. Improving outcomes requires understanding complex causes and finding accurate predictors. **Purpose:** To identify key predictors of diabetic foot ulcer recurrence, including the potential role of total bilirubin. **Methods:** This retrospective case-control research examined 230 DFU patients treated from October 2020 to January 2025. Within a two-year follow-up, ulcer status divided patients into recurrence (n = 103) and non-recurrence (n = 127). Clinical, demographic, foot-related, comorbid, and biochemical data were obtained from medical records and follow-ups. Univariate and binary logistic regression found independent recurrence predictors. **Results:** Recurrence patients had lower BMI ($p = 0.045$) and poorer financial situation ($p = 0.021$). Higher Wagner grade, ulcer duration >60 days, past amputations, and plantar ulcer location were strongly correlated with recurrence ($p < 0.05$). Laboratory results indicated greater C-reactive protein and decreased serum albumin in the recurrence group ($p < 0.001$). Lower total bilirubin (TBIL) in recurring cases was an independent protective factor (OR = 0.898, $p = 0.041$). Diabetes, peripheral neuropathy, peripheral arterial disease, past amputations, and plantar ulcers were significant predictors in multivariate analysis. **Conclusion:** DFU recurrence involves vascular, neurological, anatomical, and biochemical components. Lower TBIL may be a protective biomarker, providing novel risk classification methods. These data suggest a multidisciplinary DFU care strategy to decrease recurrence and enhance patient outcomes.

Keywords: Diabetic Foot; Recurrence; Risk Factors; Bilirubin

Introduction

Diabetic foot ulcer (DFU) is one of the most common and serious complications of diabetes mellitus, significantly impacting patients' quality of life and imposing a global burden on healthcare systems. As the global prevalence of diabetes increases and life expectancy rises, the incidence of DFU is also on the rise [1]. DFUs are closely associated with infection, amputation, and mortality, with high recurrence and death rates. Studies have shown that the five-year mortality risk among patients with DFU is approximately 2.5 times higher than in diabetic patients without DFU [2]. Globally, about 6.3% of the population experiences DFU at some point in their lifetime [3], highlighting its urgency as a public health and clinical research concern.

Despite extensive efforts in DFU prevention and management, ulcer recurrence remains a major clinical challenge. Several studies have reported DFU recurrence rates of 30–40% in the first year, 60% by the third year, and up to 65–70% by the fifth year [4-5]. These figures indicate that many patients experience ulcer recurrence even after receiving appropriate treatment. To date, there is no international consensus on the definitive factors

contributing to DFU recurrence. The complex pathogenesis of DFU and heterogeneity among patients further widens the knowledge gap, necessitating deeper investigation [6].

Various strategies have been explored to understand and reduce DFU recurrence, including glycemic control, therapeutic footwear, and educational interventions. However, these approaches have shown limited effectiveness in reducing long-term recurrence rates. Prior studies have linked recurrence to factors such as diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), foot deformities, and previous amputations [7-8]. Nevertheless, the potential role of laboratory biomarkers, such as total bilirubin, as protective factors against recurrence has not been systematically explored.

In this context, the present study is crucial in aiming to identify a comprehensive set of factors associated with DFU recurrence, encompassing clinical parameters, medical history, and biochemical indicators. The findings are expected to offer new insights into the potential protective role of total bilirubin and may inform the development of early screening and intervention strategies for high-risk patients. Ultimately, this research contributes to the long-term prevention and management of diabetic foot complications.

Methods

Inclusion and Exclusion Criteria

This study employed a retrospective case-control design targeting patients diagnosed with diabetic foot ulcers (DFUs). The diagnostic criteria were based on the clinical practice guidelines established by the International Working Group on the Diabetic Foot (IWGDF) in 2019. Participants were eligible if they: (1) were diagnosed with DFU according to IWGDF criteria; (2) were aged 18 years or older; (3) had complete medical records; and (4) provided consent either during outpatient visits or through follow-up via telephone. Patients were excluded if they had incomplete data, ulcers located outside the foot region, declined or were unreachable during follow-up, ulcers due to non-diabetic causes, or severe systemic illnesses such as advanced cancer, end-stage heart or renal failure, or hematologic disorders. Additionally, individuals with conditions affecting bilirubin levels, such as severe hepatitis, gallstones, or hemolytic diseases, were also excluded.

Grouping and Data Collection Procedures

A total of 342 patients diagnosed with DFU and treated between October 2020 and January 2025 were identified and followed for two years. Based on the presence or absence of ulcer recurrence during this period, patients were categorized into recurrence and non-recurrence groups. Twelve patients were excluded from the final analysis due to death or loss to follow-up, leaving 230 patients for evaluation. The non-recurrence group comprised 127 patients with a mean age of approximately 60 years, while the recurrence group included 103 patients with a mean age of 62 years. Data were collected retrospectively from the hospital's electronic medical records and supplemented by telephone follow-ups and outpatient visits. Only one recurrence episode per patient was recorded during the two-year follow-up period.

Variables and Data Types Collected

Clinical data collected encompassed several domains. First, demographic information included age, sex, duration of diabetes, body mass index (BMI), education level (low, medium, high), economic status (poor, average, good), and histories of smoking and alcohol use. Second, foot-related variables included the site of the initial ulcer (e.g., plantar location), ulcer duration, size of the initial wound, Wagner classification, history of amputation, foot deformities, presence of callus, and history of vascular interventions. Third, comorbidities included hypertension, coronary heart disease, cerebrovascular disease, and thyroid dysfunction. Fourth, diabetes-related complications assessed were diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), diabetic nephropathy, and osteomyelitis. Lastly, laboratory parameters analyzed included total cholesterol, triglycerides, total bilirubin, serum albumin, HbA1c, and C-reactive protein (CRP). Imaging assessments such as vascular ultrasonography, foot MRI, and ankle-brachial index measurements were also reviewed to complement the dataset.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0. Between-group comparisons were conducted using the independent-sample t-test or the Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables. Univariate analyses were first performed to identify variables with $p < 0.05$. Significant variables from the univariate analysis were then entered into a binary logistic regression model using the stepwise forward method to determine independent risk factors associated with DFU recurrence.

Ethics

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Ban Mae Klang District Hospital, a regional healthcare facility located in northern Thailand. The research protocol was reviewed and approved under ethics approval number BMK-IRB-2025-017, issued on March 12, 2025. All participants provided informed consent either in person during clinical visits or through follow-up telephone interviews prior to data collection. Patient confidentiality and data anonymity were strictly maintained throughout the study process.

Results

Table 1. Demographic Characteristics of Patients

Variable	Recurrence Group (n = 103)	Non-Recurrence Group (n = 127)	Statistical Value	p-value
Number of Cases	103	127		
Male (%)	68.0%	66.9%	$\chi^2 = 0.112$	0.738
Female (%)	32.0%	33.1%		
Age (years, mean ± SD)	62.15 ± 11.4	60.03 ± 10.8	t = -1.304	0.193
Duration of diabetes (years, median [P25–P75])	11 (6–14)	10 (5–15)	Z = -0.589	0.556
BMI (kg/m², mean ± SD)	23.6 ± 3.6	24.3 ± 3.4	t = 2.014	0.045*
Smoking history (%)	60.2%	63.0%	$\chi^2 = 0.348$	0.555
Alcohol consumption history (%)	21.4%	18.1%	$\chi^2 = 0.759$	0.384
Financial status – Poor (%)	55.3%	45.7%	$\chi^2 = 5.321$	0.021*
Financial status – Average (%)	43.7%	48.0%		
Financial status – Good (%)	1.0%	6.3%		
Education level – Low (%)	52.4%	44.1%	$\chi^2 = 2.417$	0.298
Education level – Medium (%)	35.9%	43.3%		
Education level – High (%)	11.7%	12.6%		

Most demographic variables were similar between the recurrence and non-recurrence groups. There were no significant differences in gender, age, duration of diabetes, smoking, or alcohol use ($p > 0.05$). However, BMI was significantly lower in the recurrence group ($p = 0.045$), suggesting a possible link between lower BMI and ulcer recurrence. Financial status differed significantly ($p = 0.021$), with more patients in the recurrence group reporting poor financial conditions. Education level showed no significant difference, though a higher proportion of low education was noted in the recurrence group. These findings indicate that socioeconomic factors, especially financial hardship, may contribute to DFU recurrence (Table 1)

Table 2. Comparison of Foot Data and Comorbidities

Ulcer Characteristics and Vascular Conditions									
Group	**Cases (n)**	**Wagner 1–2 (%)**	**Wagner 3–5 (%)**	**DFU >60d – No (%)**	**DFU >60d – Yes (%)**	**Prev. Amputations – No (%)**	**Yes (%)**	**Vascular Intervention – No (%)**	**Yes (%)**
Recurrence group	103	43 (41.7)	60 (58.3)	26 (25.2)	77 (74.8)	24 (23.3)	79 (76.7)	16 (15.5)	87 (84.5)
Non-recurrence group	127	87 (68.5)	40 (31.5)	71 (55.9)	56 (44.1)	124 (97.6)	3 (2.4)	121 (95.3)	6 (4.7)
χ^2 value		15.901		20.344		12.312		6.104	
p-value		<0.001*		<0.001*		<0.001*		0.013*	

Foot Deformities and Ulcer Site								
Group	**Cases (n)**	**Foot Deformity – No (%)**	**Yes (%)**	**Ulcer on Sole – No (%)**	**Yes (%)**	**Callus – No (%)**	**Yes (%)**	**Max Ulcer Area (cm²) (M [P25, P75])**
Recurrence group	103	91 (88.3)	12 (11.7)	73 (70.9)	30 (29.1)	72 (69.9)	31 (30.1)	6.1 [3–13.5]
Non-recurrence group	127	123 (96.9)	4 (3.1)	104 (81.9)	23 (18.1)	97 (76.4)	30 (23.6)	4.0 [2–12]
χ^2 / Z value		6.204		4.001		1.02		–1.890
p-value		0.013*		0.045*		0.312		0.062

Comorbidities									
Group	**Cases (n)**	**Hypertension – No (%)**	**Yes (%)**	**CHD – No (%)**	**Yes (%)**	**CVD – No (%)**	**Yes (%)**	**Thyroid – Non-hypo (%)**	**Hypothyroid (%)**
Recurrence group	103	43 (41.7)	60 (58.3)	78 (75.7)	25 (24.3)	86 (83.5)	17 (16.5)	84 (81.6)	19 (18.4)
Non-recurrence group	127	42 (33.1)	85 (66.9)	107 (84.3)	20 (15.7)	111 (87.4)	16 (12.6)	112 (88.2)	15 (11.8)
χ^2 value		1.728		2.112		0.892		2.998	
p-value		0.189		0.146		0.345		0.083	

Significant differences were observed in ulcer characteristics between the groups. Patients in the recurrence group had a higher proportion of advanced Wagner grade (grade 3–5; 58.3% vs. 31.5%, $p < 0.001$), longer ulcer duration (>60 days; 74.8% vs. 44.1%, $p < 0.001$), and more previous amputations (23.3% vs. 2.4%, $p < 0.001$). Vascular intervention was also more frequent in the recurrence group (84.5% vs. 4.7%, $p = 0.013$), suggesting more severe disease (Table 2). Foot deformities (11.7% vs. 3.1%, $p = 0.013$) and ulcers located on the sole (29.1% vs. 18.1%, $p = 0.045$) were more common in the recurrence group, indicating these may be risk factors for recurrence. However, the presence of callus and ulcer size did not differ significantly between groups. Among comorbidities, no statistically significant differences were found, though trends were noted (Table 2). Recurrence patients had slightly higher rates of hypertension, coronary heart disease (CHD), cerebrovascular disease (CVD), and hypothyroidism, but these did not reach significance (all $p > 0.05$). These findings suggest that ulcer severity and foot-related conditions may play a larger role in recurrence than systemic comorbidities (Table 2).

Table 4. Comparison of Laboratory Parameters

Group	**Cases (n)**	**HbA1c (%) M [P25, P75]**	**TG (mmol/L) M [P25, P75]**	**TC (mmol/L) M [P25, P75]**	**TBIL (μmol/L) M [P25, P75]**	**CRP (mg/L) M [P25, P75]**	**ALB (g/L) M ± SD**
Recurrence group	103	9.0 (7.8–11.2)	1.05 (0.82–1.60)	3.70 (3.05–4.65)	8.2 (6.8–10.9)	15.1 (5.8–57.2)	33.5 ± 5.8
Non-recurrence group	127	8.4 (7.0–10.0)	1.17 (0.87–1.89)	3.92 (3.35–5.01)	10.3 (7.5–13.6)	6.1 (2.1–21.9)	36.8 ± 5.9
t/Z value		–2.214	–1.201	–1.089	–3.589	–3.710	3.745
p-value		0.028*	0.231	0.278	<0.001*	<0.001*	<0.001*

*$p < 0.05$

Significant differences in laboratory parameters were observed between groups. Patients with DFU recurrence had higher HbA1c levels (9.0 vs. 8.4%, $p = 0.028$), suggesting that poorer glycemic control may contribute to recurrence. CRP levels, a marker of systemic inflammation, were markedly elevated in the recurrence group (15.1 vs. 6.1 mg/L, $p < 0.001$), indicating a stronger inflammatory state. Conversely, serum albumin levels were significantly lower in the recurrence group (33.5 vs. 36.8 g/L, $p < 0.001$), reflecting poorer nutritional or inflammatory status. No significant differences were found in triglycerides (TG) or total cholesterol (TC), suggesting lipid levels may be less relevant in recurrence risk. Notably, TBIL was lower in the recurrence group ($p < 0.001$), though its clinical significance warrants further investigation (Table 4).

Table 5. Binary Logistic Regression with DFU Recurrence as Dependent Variable

Variable	B	S.E	Wald	p-value	OR value	95% CI
BMI (kg/m²)	-0.051	0.058	0.779	0.378	0.950	0.845–1.688
HbA1c (%)	0.124	0.080	2.410	0.121	1.132	0.973–1.321
CRP (mg/L)	0.008	0.004	3.301	0.069	1.008	0.999–1.019
History of lower extremity vascular intervention	0.618	0.702	0.775	0.379	1.856	0.481–7.430
Osteomyelitis	-0.294	0.467	0.394	0.530	0.745	0.298–1.812
Financial situation						
Poor (Reference)	–	–	–	–	–	–
Average	-0.310	0.410	0.573	0.449	0.734	0.339–1.592
Good	-17.832	12000.000	0.000	0.999	–	–
TBIL (μmol/L)	-0.108	0.059	3.310	0.041*	0.898	0.795–0.998
DPN	1.483	0.581	6.524	0.011*	4.406	1.402–13.54
ALB (g/L)	0.015	0.040	0.141	0.707	1.015	0.938–1.099
Duration of DFU (>60 d)	0.738	0.460	2.576	0.109	2.093	0.845–5.269
History of previous amputations	1.834	0.882	4.322	0.038*	6.260	1.171–33.209
Foot deformity	1.377	0.794	3.009	0.083	3.964	0.814–19.04
First ulcer on the sole	0.803	0.447	3.228	0.049*	2.233	1.011–5.243
PAD	1.342	0.407	10.891	0.001*	3.829	1.761–8.438
Wagner grade of the first ulcer	0.273	0.471	0.337	0.561	1.314	0.541–3.188

*$p < 0.05$

DFU recurrence was independently associated with several factors. DPN showed the strongest effect (OR = 4.406, p = 0.011), indicating a major role of neuropathy in recurrence. Prior amputations (OR = 6.260, p = 0.038) and ulcer location on the sole (OR = 2.233, p = 0.049) were also significant predictors. PAD significantly increased recurrence risk (OR = 3.829, p = 0.001), reinforcing the importance of vascular status. Lower TBIL levels were modestly associated with recurrence (OR = 0.898, p = 0.041). Other variables, including HbA1c, CRP, BMI, and albumin, showed no significant association.

Discussion

The present study provides a comprehensive evaluation of the risk factors associated with diabetic foot ulcer (DFU) recurrence, combining clinical, vascular, and biochemical domains. Notably, diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) emerged as the strongest independent predictors, which is consistent with the pathophysiological understanding that both conditions significantly impair tissue perfusion and sensory function—thereby predisposing patients to repeated ulceration [11-13]. The findings further highlight the impact of prior amputations and plantar ulcer location, underscoring the role of biomechanical stress and structural abnormalities in re-ulceration [14-16].

One of the more novel insights from this study is the inverse association between serum total bilirubin (TBIL) levels and DFU recurrence. While bilirubin has traditionally been viewed as a metabolic byproduct, recent studies have demonstrated its anti-inflammatory and antioxidant properties, which may confer a protective effect in chronic wound pathogenesis (17-20). Although the clinical significance of this association requires further exploration, our findings support a growing interest in non-traditional biomarkers as tools for risk stratification.

Contrary to expectations, markers such as HbA1c and CRP, although elevated in recurrent cases, did not remain significant in the multivariate analysis. This suggests that while systemic metabolic and inflammatory disturbances are relevant, they may be secondary to localized vascular or mechanical factors in determining ulcer recurrence [16,21-23].

Importantly, this study also revealed a significant relationship between poor financial status and ulcer recurrence. Patients with limited economic resources may face barriers to accessing specialized footwear, wound care supplies, or timely medical attention, which in turn increases their vulnerability to recurrent complications [24-27]. Although BMI was

significantly lower in the recurrence group, this may reflect underlying malnutrition or sarcopenia, both of which have been linked to impaired wound healing capacity (25).

Taken together, these findings underscore the need for a more holistic approach to DFU management—one that not only addresses metabolic and vascular control, but also integrates mechanical offloading, nutritional assessment, and social determinants of health. Such a model could potentially reduce recurrence rates and improve long-term outcomes in this high-risk population.

Limitations

Despite its strengths, this study has several limitations. First, its retrospective design introduces the possibility of selection and information bias, particularly with regard to the completeness and accuracy of medical records. Second, although follow-up was conducted through both clinic visits and telephone interviews, some patients were lost to follow-up, which may have led to underreporting of recurrence. Third, certain laboratory values, including bilirubin and albumin, could be influenced by unmeasured comorbidities or medication use not accounted for in the analysis. Additionally, as the study was conducted at a single regional hospital, the findings may not be fully generalizable to other healthcare settings or populations. Finally, while the analysis identifies associations, the observational nature of the study precludes causal inferences. Future prospective studies with larger, multi-center cohorts are needed to validate and expand upon these findings.

Conclusion

In conclusion, this study provides evidence that DFU recurrence is driven by a combination of clinical, vascular, and biochemical factors. DPN, PAD, prior amputations, plantar ulcer location, and low TBIL levels were all independently associated with increased recurrence risk. Among these, the role of total bilirubin as a potential protective biomarker is particularly noteworthy and warrants further investigation. These results advocate for a comprehensive, multidisciplinary approach to DFU management—one that considers not only clinical and physiological indicators but also socioeconomic context. Proactive identification of high-risk individuals and implementation of personalized prevention strategies may offer the most effective path forward in reducing the burden of DFU recurrence.

Author Contributions

All authors contributed meaningfully to the development of this study. Chanika Ruangsak led the conceptual design, coordinated data collection activities, and ensured compliance with clinical protocols. Nguyen Thi Lan conducted the statistical analysis, contributed to the literature synthesis, and played a central role in drafting the manuscript. Tran Minh Huyen supported patient follow-up, data verification, and assisted in interpreting the clinical findings. Haruka Fujimoto supervised the overall research process, critically reviewed the manuscript, and provided guidance on methodological rigor. All authors reviewed and approved the final manuscript and agreed to be accountable for its content.

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Conflict of Interest

The authors declare that there are no competing interests or personal relationships that could have influenced the work reported in this paper.

Data Availability Statement

The data supporting the findings of this study are available upon reasonable request. Due to institutional regulations and the protection of patient confidentiality, the datasets are not publicly accessible. Interested researchers may contact the corresponding author to discuss potential access in accordance with ethical guidelines.

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