Received: 13 April 2022 | Accepted: 27 May 2022

DOI: 10.1111/iwj.13861

IWJ WILEY

ORIGINAL ARTICLE

Risk factors for foot ulcer recurrence in patients with comorbid diabetic foot osteomyelitis and diabetic nephropathy: A 3-year follow-up study

Li Zhang[1] | **Guifen Fu**[2] | **Yongqing Deng**[3] | **Yuechou Nong**[1] | **Jianhao Huang**[1] | **Xiulu Huang**[1] | **Fenglian Wei**[1] | **Yanqing Yu**[1] | **Litian Huang**[1] | **Wenjiao Zhang**[1] | **Meizhu Tang**[1] | **Licai Deng**[1] | **Jiaxia Han**[1] | **Xing Zhou**[1] | **Qiu Wang**[1] | **Wensheng Lu**[1]

[1]The Department of Endocrinology and Metabolism, Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, P.R. China

[2]The Nursing Department of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, P.R. China

[3]The Family Planning Office of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, P.R. China

Correspondence
Wensheng Lu, The Department of Endocrinology and Metabolism, Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi 530021, P.R. China.
Email: lws2613676@sohu.com

Funding information
Guangxi Medical and Health Appropriate Technology Research and Development Project, Grant/Award Numbers: S201315-03, S201422-01; Guangxi Zhuang Autonomous Region Health Committee Project, Grant/Award Numbers: Z20190209, Z2016765; National Natural

Abstract

This study aimed to explore the risk factors for foot ulcer recurrence in patients with comorbid diabetic foot osteomyelitis (DFO) and diabetic nephropathy (DN). This is a prospective cohort study. Between May 2018 and May 2021, we selected 120 inpatients with comorbid severe diabetic foot infection (PEDIS Grade 3 or above) and DN for inclusion in our study. All cases were followed up for 36 months. The study outcomes were whether foot ulcer recurred and the time to recurrence. The risk factors of ulcer recurrence were analysed by comparing the data of the three groups. According to the recurrence of foot ulcer, the participants were divided into three groups: Group A (no foot ulcer recurrence, n = 89), Group B (foot ulcer recurrence within 12-36 months, n = 19) and Group C (foot ulcer recurrence within 6-12 months, n = 12). The multivariate Cox regression analysis showed that urine albumin-creatinine ratio (UACR) (HR: 1.008, 95% CI: 1.005-1.011, $P < .001$) and vibration perception threshold (VPT) (HR: 1.064, 95% CI: 1.032-1.096, $P < .001$) were identified as independent risk factors. Kaplan-Meier curves showed a significant positive association between UACR or VPT and the risk of foot ulcer recurrence (log rank, all $P < .05$). Areas under the ROC curves for UACR, VPT and the combination of UACR and VPT were 0.802, 0.799 and 0.842, respectively. The best cut-off values of UACR and VPT were 281.51 mg/g and 25.12 V, respectively. In summary, elevated UACR and VPT were independent risk factors. The best clinical cut-off values of UACR and VPT for prediction of foot ulcer recurrence were 281.51 mg/g and 25.12 V, respectively. Besides, our results suggested that microcirculation disorders rather than macrovascular

Li Zhang, Guifen Fu, Yongqing Deng and Yuechou Nong contributed equally to this work.

Science Foundation of China, Grant/Award Numbers: 81560044, 30860113, 82160052; Shanxi Health Research Project, Grant/Award Number: 2019165

complications play a major role in the recurrence of foot ulcer in patients with comorbid DFO and DN.

KEYWORDS

diabetic foot, diabetic nephropathy, foot ulcer recurrence, influencing factors

Key Messages

- elevated UACR and VPT were independent risk factors in patients with comorbid diabetic foot osteomyelitis (DFO) and diabetic nephropathy (DN)
- microcirculation disorders rather than macrovascular complications play a major role in the recurrence of foot ulcer in patients with comorbid DFO and DN

1 | INTRODUCTION

At present, diabetes mellitus (DM) has increasingly become a common and chronic intractable disease, seriously threatening human health worldwide. The prevalence of DM in adults is approximately 11.2%[1] in China. Diabetic nephropathy (DN) and diabetic foot disease, especially diabetic foot ulcers (DFU), are clinically common and chronic complications of DM. It is estimated that approximately 20% to 40% of patients with DM develop DN[2,3] and the proportion of chronic kidney disease was as high as 39.3%[4] in patients with diabetic foot disease. About one in four patients with DM suffer from diabetic foot disease or DFU.

DN is manifested as increased urine protein excretion and a decline in the glomerular filtration rate. Renal insufficiency was recognised as a risk factor for cardiovascular events. It has been reported that more than 20% of patients with DFU suffered from one or more cardiovascular disease events. Albuminuria was an independent predictor for cardiovascular disease events[5,6] and also associated with foot ulcer, amputation and mortality.[7,8] However, the relationship between albuminuria and foot ulcer recurrence is still unknown. Approximately 85% of DM patients with amputations have a history of DFU and the 5-year mortality rate is nearly 80% after amputations.[2] Diabetic foot osteomyelitis (DFO) is a complex and serve complication of DFU. It usually occurs after DFU and needs surgical intervention. DFO is an independent risk factor for foot ulcer recurrence. It has been reported that the recurrence rate of DFO within 1 year was about 40% after DFU recurrence, which increased the risk of amputation, especially major amputations.[9,10]

In recent decades, numerous studies have reported that DFU is associated with a greater risk of cardiovascular events or death and all-cause mortality.[11-13] Cardiovascular events are believed to be a major cause of mortality.[14,15] Remarkably, in these predictive factors, the history of cardiovascular disease (CVD) has a negative impact in DFU progression, and cerebrovascular disease is also closely related to the progression or recurrence of DFU and amputation.[16] In particular, the patients with comorbid kidney disease and CVD have a poor prognosis.[17,18]

Taken together, patients with comorbid DFO and DN have a significantly higher risk of ulcer recurrence, amputation, cardiovascular mortality and all-cause mortality than patients with diabetic foot disease alone. It is clinically important to investigate influencing factors and predictors of DFU recurrence. Therefore, we aimed to explore the risk factors of foot ulcer recurrence in patients with comorbid DFO and DN in 120 patients with comorbid severe diabetic foot infection (PEDIS Grade 3 or above) and DN. As far as we know, our study is the first to investigate the factors of ulcer recurrence in patients with comorbid DFO and DN.

2 | METHODS

2.1 | Subjects

Between May 2018 and May 2021, we selected 120 inpatients with comorbid severe diabetic foot infection (PEDIS Grade 3 or above) and DN. The inclusion criteria for the study enrolment were as follows: (a) DM was diagnosed according to the 1999 World Health Organization (WHO) criteria[19]; (b) all participants met the International Working Group on the Diabetic foot and the Infectious Diseases Society of Americas[20] for the diagnosis and grade of diabetic foot infection and were diagnosed as PEDIS Grade 3 or above. The exclusion criteria included: (a) foot ulcers and infections caused by non-diabetics such as tophus ulcers and venous ulcers; (b) chronic kidney disease caused by other diseases; (c) patients complicated with other malignancies; (d) patients were treated with immunosuppressants or glucocorticoids; (e) patients with incomplete follow-up

data, lost to follow-up, less than 1 year of follow-up and death.

The wound condition was assessed by two professional clinicians in the management of diabetic foot. The wound characteristics such as size, depth, sinus tract and fistula formation were evaluated (Figure 1A). The wounds were treated with wound dressing change and negative pressure pump wound therapy for 14 days (Figure 1B). The dynamics of wound healing during the treatment were assessed daily (Figure 1C). Then the dressing changes were performed twice per week until wound healing (Figure 1D). During hospitalisation, all patients were given the same standardised and effective treatment measures, such as antibiotic use intensity, ultrasonic debridement, biatain alginate/adhesive wound dressings and negative pressure pump treatment technology, etc. During home life, the same standardised foot care guidance, such as pressure relief shoes and foot bath in warm water with traditional Chinese medicine after the wound healing, were recommended to prevent the recurrence of foot ulcer.

The follow-up data were required by outpatient service, WeChat app, telephone and reviewing medical records. Patients were followed up every 6 months for 36 months and the recurrence of the foot ulcer was assessed. All participants agreed to participate in this study and written informed consent was obtained. The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region.

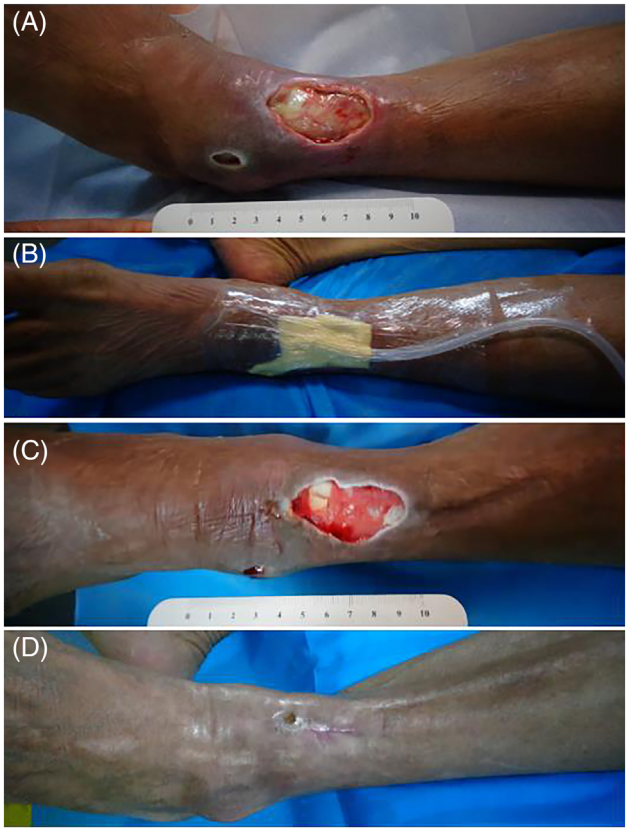

FIGURE 1 The dynamics of foot ulcer healing during the treatment. (A) Foot ulcer before treatment. (B) The wounds were treated with wound dressing change and negative pressure wound therapy. (C) The wounds after 14 days treatment. (D) The healing of the ulcer after treatment

2.2 | The grouping criteria

The patients were divided into three groups based on the presence or absence of recurrence and the time to recurrence: Group A had no foot ulcer recurrence, Group B occurred foot ulcer recurrence within 12 to 36 months and Group C occurred foot ulcer recurrence within 6-12 months. The standard of foot ulcer healing was that foot ulcer was completely covered by the skin for 6 months and the standard of foot ulcer recurrence was that a new ulcer occurred in the same location after the ulcer had healed.

Regarding the diagnosis of urine albumin-creatinine ratio (UACR), microalbuminuria and macroalbuminuria were defined if the UACR was 30 to 299 mg/g and ≥300 mg/g, respectively. Regarding the general criterion of vibration perception threshold (VPT), VPT was stratified as normal (VPT 0-15 V), decreased (VPT 16-25 V) and lost (VPT > 25 V).

2.3 | Data collection

Participants' demographics include age, gender, duration of diabetes, smoking status and comorbidities (hypertension, CHD and CVD). Glycosylated haemoglobin (HbA1c), white blood cells (WBC), haemoglobin (Hb), albumin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), urine albumin and creatinine were analysed at the Central Chemistry Laboratory of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region. UACR was expressed as urinary albumin/urinary creatinine. Ankle-brachial index (ABI) was defined as the ratio of ankle to brachial systolic blood pressure. ABI was measured using Summit Ultrasonic Doppler Blood Flow Analyzer (Vista AVS, Cooper Surgical Inc. USA). VPT was measured using vibratory sensory tester (Sensiometer A200, Beijing Laxons Technology Co., Ltd) following the provided protocols. All measurements were performed by experienced technicians.

2.4 | Statistical analyses

Data analyses were performed using the SPSS statistical software, version 23.0 (SPSS Inc., Chicago, IL, USA). For normally distributed variables, data were described as mean ± SD. One-way ANOVA was used for multi-group comparison and then LSD-*t* test was applied for pairwise comparison. Bonferroni adjustment of α level was used to control for pairwise comparisons. For non-normally distributed variables, data were described as median (quartiles). Kruskal-Wallis *H* test was used for multi-group comparison, and then the Mann-Whitney *U* test was applied for pairwise comparison. Counting data were expressed as cases (percentage) and analysed by χ^2 test. To identify the risk factors for foot ulcer recurrence, the univariate Cox regression analysis was initially used and then the factors with $P < .1$ in the univariate analysis were enrolled into the multivariate Cox regression analysis. Survival analysis was analysed by the Kaplan-Meier method and the log-rank statistic was used to compare the risk of foot ulcer recurrence between groups. Receiver operating characteristic (ROC) curve was used to determine the prognostic value of different factors in ulcer recurrence assessment and was plotted based on the logistic regression model. *P*-values <.05 were considered statistically significant.

TABLE 1 Clinical characteristics

Clinical data	Group A (n = 89)	Group B (n = 19)	Group C (n = 12)	*P* value
Age, years	59.17 ± 13.46	61.39 ± 15.93	64.25 ± 11.84	.113
Gender, n (%)				.907
Female	36 (40.4%)	7 (36.8%)	4 (33.3%)	
Male	53 (59.6%)	12 (63.2%)	8 (66.7%)	
Duration of diabetes, year	7.55 ± 3.19	8.96 ± 3.80	9.24 ± 3.60	.114
Smoke, n (%)	35 (39.3%)	8 (42.1%)	6 (50.0%)	.785
Comorbidities				
Hypertension, n (%)	37 (41.6%)	9 (47.4%)	6 (50.0%)	.796
CHD, n (%)	13 (14.6%)	2 (10.5%)	4 (33.3%)	.210
Cerebrovascular disease, n (%)	17 (19.1%)	2 (10.5%)	2 (16.7%)	.787
HbA1c, %	8.29 ± 1.84	8.32 ± 2.76	7.49 ± 1.73	.270
WBC, $\times 10^9$/L	10.50 ± 2.56	11.50 ± 2.76	12.30 ± 2.17	.407
Hb, g/L	121.07 ± 21.24	119.55 ± 23.35	119.45 ± 17.59	.916
Albumin, g/L	38.82 (35.08, 42.10)	38.20 (34.03, 40.29)	40.88 (37.87, 41.88)	.535
TC, mmol/L	4.84 ± 1.80	5.06 ± 2.02	4.92 ± 1.45	.885
TG, mmol/L	2.00 ± 0.65	2.08 ± 0.77	2.30 ± 0.88	.801
HDL-C, mmol/L	1.13 ± 0.37	0.95 ± 0.38	0.93 ± 0.36	.076
LDL-C, mmol/L	3.01 ± 0.93	3.14 ± 1.14	3.43 ± 0.95	.235
eGFR, mL/min/1.73 m^2	81.83 (59.71, 106.78)	86.79 (51.19, 108.71)	47.90 (36.86, 68.24)	.003*
UACR, mg/g	175.96 (107.01, 238.85)	306.61 (163.09, 387.46)	416.63 (290.93, 469.95)	<.001*
ABI	0.90 ± 0.29	0.82 ± 0.24	0.92 ± 0.42	.620
VPT, V	17.29 ± 7.41	23.15 ± 9.55	29.08 ± 6.79	<.001*
Infection severity (n, %)				.371
PEDIS 3 Grade/moderate	56 (62.9%)	9 (47.4%)	6 (50.0%)	
PEDIS 4 Grade/severe	33 (37.1%)	10 (52.6%)	6 (50.0%)	

Note: Mean ± SD and median (inter-quartile range) for continuous variables. Percentage (%) for categorical variables.
Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UACR, urinary albumin-to-creatinine ratio; VPT, vibration perception threshold; WBC, white blood cells.
*$P < .05$.

3 | RESULTS

3.1 | Clinical characteristics of the study cohort

A total of 120 eligible subjects were enrolled in this study. The clinical characteristics of the subjects are shown in Table 1. Of the 120 subjects, 89 (59.6% male; mean age 59.17 ± 13.46 years) had no foot ulcer recurrence (Group A), 19 had (63.2% male; mean age 61.39 ± 15.93 years) foot ulcer recurrence within 12 to 36 months (Group B) and 12 (66.7% male; mean age 64.25 ± 11.84 years) had foot ulcer recurrence within 6-12 months (Group C). There were no significant differences in age, gender, duration of diabetes, smoke, hypertension, CHD, cerebrovascular disease, HbA1c, WBC, Hb, albumin, TC, TG, HDL-C, LDL-C, ABI and infection of severity among the three group (all $P > .05$). However, there were significant differences in eGFR, UACR and VPT among the three groups (all P-values $< .05$).

3.2 | Factors associated with ulcer recurrence

Univariate and multivariate analyses were used to reveal the factors that influenced the recurrence of foot ulcer, and the results are shown in Table 2. Univariate Cox

TABLE 2 Cox regression analyses for the recurrence of foot ulcer

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Duration of diabetes	1.131	1.012-1.264	.030*	—	—	—
WBC, $\times 10^9$/L	1.204	1.036-1.399	.015*	—	—	—
HDL-C	0.328	0.128-0.841	.020*	—	—	—
eGFR	0.988	0.976-0.999	.039*	—	—	—
UACR	1.009	1.006-1.012	<.001*	1.008	1.005-1.011	<.001*
VPT	1.090	1.053-1.128	<.001*	1.064	1.032-1.096	<.001*

Abbreviations: HR, hazard ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; VPT, vibration perception threshold.
*$P < .05$.

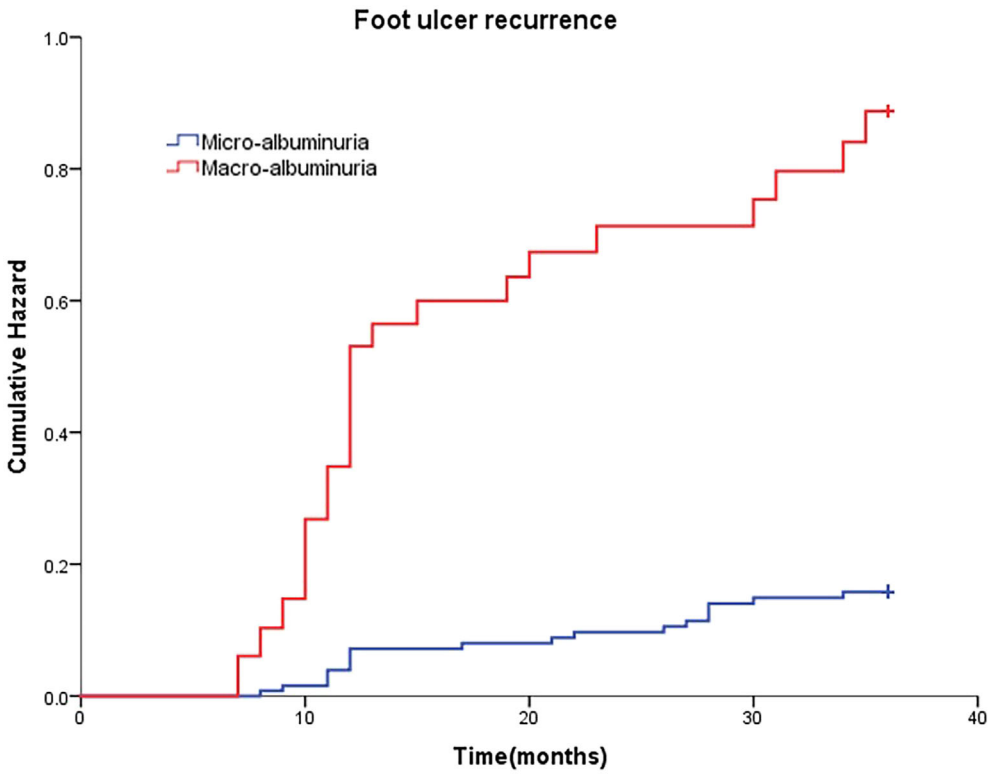

FIGURE 2 Kaplan-Meier curves of the cumulative incidence of ulcer recurrence stratified by urine albumin-creatinine ratio (UACR) levels

analysis showed that duration of diabetes (HR: 1.131, 95% CI: 1.012-1.264, $P = .030$), WBC (HR: 1.204, 95% CI: 1.036-1.399, $P = .015$), HDL-C (HR: 0.328, 95% CI: 0.128-0.841, $P = .020$), eGFR (HR: 0.988, 95% CI: 0.976-0.999, $P = .039$), UACR (HR: 1.009, 95% CI: 1.006-1.012, $P < .001$), VPT (HR: 1.090, 95% CI: 1.053-1.128,

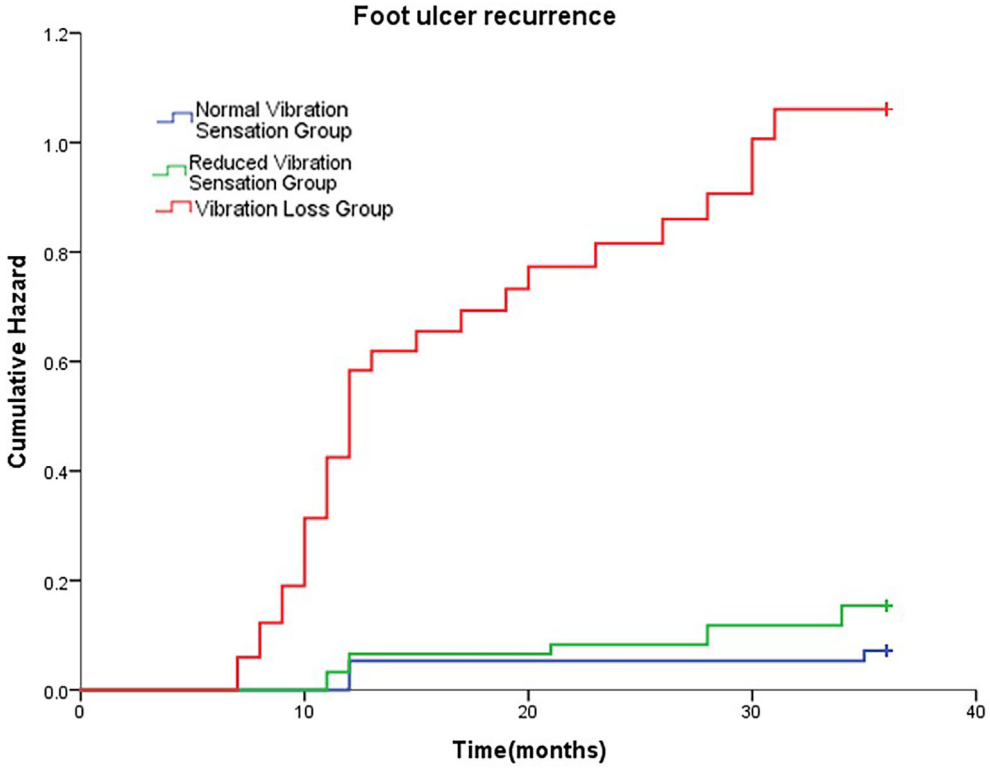

FIGURE 3 Kaplan-Meier curves of the cumulative incidence of ulcer recurrence stratified by vibration perception threshold (VPT) levels

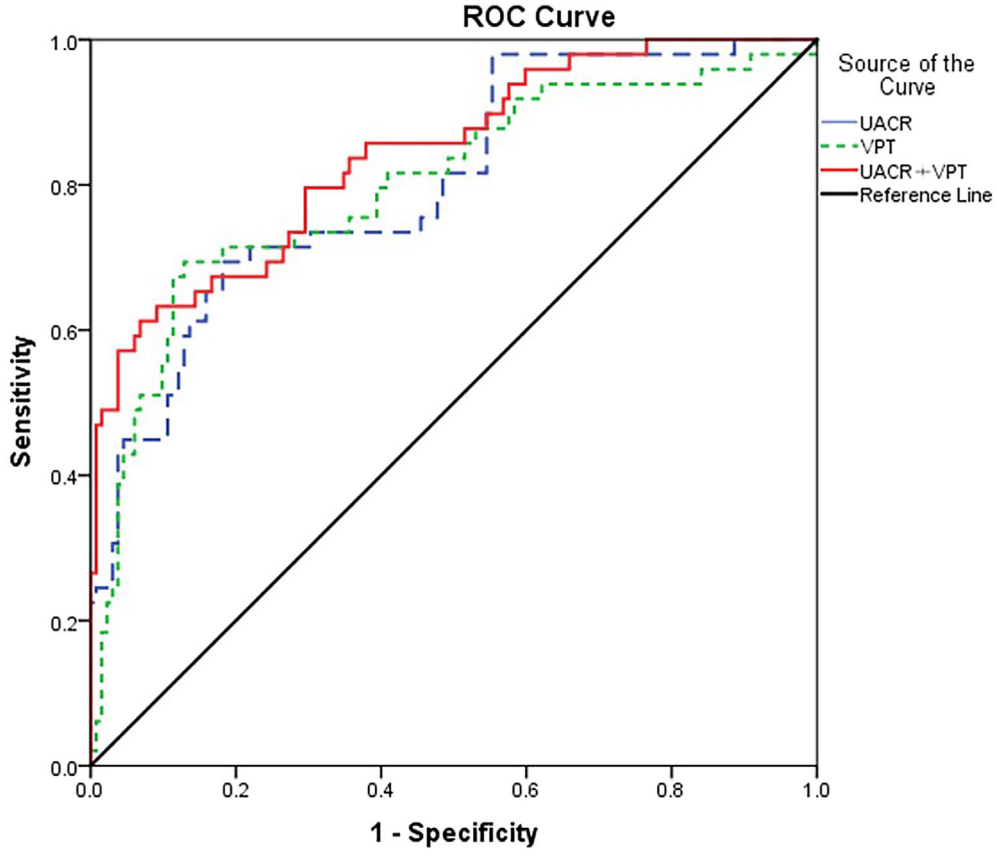

FIGURE 4 Receiver-operator characteristic (ROC) curve of urine albumin-creatinine ratio (UACR) and vibration perception threshold (VPT) for the risk prediction of foot ulcer recurrence

$P < .001$) were significantly associated with foot ulcer recurrence. Next, the significant factors identified by the univariate analysis were included in multivariate Cox analysis. We found that UACR (HR: 1.008, 95% CI: 1.005-1.011, $P < .001$) and VPT (HR: 1.064, 95% CI: 1.032-1.096, $P < .001$) were identified as independent risk factors in patients with comorbid diabetic foot infection and DN.

3.3 | Comparison of foot ulcer recurrence risk in different UACR and VPT levels

We next explored the influence of different UACR and VPT levels on risk of foot ulcer recurrence. The Kaplan-Meier estimates of the cumulative risk of foot ulcer recurrence stratified by the UACR and VPT levels are depicted in Figures 2 and 3. The results showed a significant positive association between UACR or VPT and the risk of foot ulcer recurrence (log rank, all $P < .05$).

3.4 | ROC analysis of UCAR and VPT for the risk prediction of foot ulcer recurrence

In ROC analysis, areas under the curves for UACR, VPT and the combination of UACR and VPT were 0.802, 0.799 and 0.842, respectively (all P-values $< .05$) (Figure 4). According to the Youden index calculation, the best cut-off values of UACR and VPT were 281.51 mg/g (sensitivity 69.4%; specificity 81.8%) and 25.12 V (sensitivity 69.4%; specificity 87.1%), respectively.

4 | DISCUSSION

DFU is a late and severe complication of DM and is a highly prevalent disease in China and worldwide.[21,22] Foot ulcer recurrence is more prevalent in DFU patients with DFO or DN. Past research studies have mainly focused on amputation and mortality in DFU patients.[23-25] However, there are few studies to explore the factors related to ulcer recurrence in DFU patients. To our knowledge, this is the first study that aimed to investigate the factors affecting foot ulcer recurrence in patients with comorbid DFO and DN.

In our study, among the patients, 89 individuals (Group A) had no foot ulcer recurrence, 19 individuals (Group B) had foot ulcer recurrence within 12 to 36 months and 12 individuals (Group C) had foot ulcer recurrence within 6 to 12 months. There were significant differences in eGFR, UACR and VPT among the three groups. Next, we found UACR and VPT were identified as independent risk factors in patients with comorbid diabetic foot infection and DN. There was a significant positive association between UACR or VPT and the risk of foot ulcer recurrence. Areas under the ROC curves for UACR, VPT and the combination of UACR and VPT were 0.802, 0.799 and 0.842, respectively. Besides, the best cut-off values of UACR and VPT were 281.51 mg/g and 25.12 V, respectively.

UACR and VPT reflect the severity of DN and diabetic peripheral neuropathy, respectively, and play important roles in the occurrence and development of ulcers. In this study, multivariate Cox analysis showed that UACR and VPT were found to be the independent risk factors in patients with comorbid DFO and DN. The survival analysis also suggested elevated urinary protein levels and VPT increased the cumulative risk of foot ulcer recurrence. Elevated UACR is a marker of kidney injury that can be used for the diagnosis and stage of chronic kidney disease[26,27] and also represents a hallmark of DN.[28] Elevated UACR levels usually imply the presence of vascular endothelial dysfunction, increased capillary permeability, thickened capillary basement membrane, luminal stenosis and then lead to ischaemia and hypoxia in neural and muscle tissues.[29] These pathological changes are important factors in the recurrence of foot ulcer. Our previous study[30] has found that UACR was associated with prognosis in patients with DFO, and elevated UACR levels increased the risk of all-cause mortality, major cardiovascular adverse events and mixed endpoint events. Therefore, there is a need for UACR screening in these patients and reducing UACR is a therapeutic target.[31] VPT is an effective and convenient diabetic peripheral neuropathy (DPN) screening by the vibration sensation detection in functional nerve fibres to assess the risk of foot ulcers.[32,33] Based on this, we thought that elevated VPT indicated the loss of protective sensation and recurrent ulcer was more likely to occur after DFU healing. The areas under the curves for the combination of UACR and VPT in ROC curve were higher, which fully illustrated the importance of microcirculation for foot ulcer recurrence. In addition, ABI mainly reflects the severity of obstructive atherosclerotic disease in large vessels, especially lower extremity artery.[34,35] In our study, we found that ABI was not different among the three groups, which also suggested that microvasculopathy is a major cause of foot ulcer recurrence in these patients. Hence, we found not only the factors affecting foot ulcer recurrence, but also the important role of nerve and kidney protection in the treatment of DFU. Furthermore, we also found that the best cut-off values of UACR and VPT were 281.51 mg/g and 25.12 V, respectively. Both UACR and VPT are widely

used in clinical screening for diabetes complications. As a result, our study provides a theoretical basis for treatment modalities and prognosis judgement of DFO with DN.

Thus, this study has shown that microcirculation disorders play a major role in the recurrence of ulcers in patients with DFO and DN, which is different from the previous general belief that macrovascular disease plays a major role.[36-38] UACR and VPT respectively reflect the severity of DN and DPN,[39,40] which are both complications of diabetic microangiopathy. This suggests that lower extremity microvascular disease may be the main reason for the recurrence of ulcers in patients with DFO and DN.

There are still some shortcomings in our study. First, the use of insulin and low BMI also are related to DFU recurrence. Second, our results might be limited by the relatively small sample size and short follow-up period; therefore, further study with larger sample size is needed. Moreover, we focused our analysis on the foot ulcer recurrence, and patients with loss to follow-up or death were excluded. The long-term clinical outcomes were not investigated in this population. The subsequent study should enrol more cases, extend follow-up time and observe clinical outcomes including cardiovascular events and all-cause death.

5 | CONCLUSION

In conclusion, elevated UACR and VPT are risk factors for foot ulcer recurrence in patients with comorbid severe diabetic foot infection and DN. Besides, our results suggested that microcirculation disorders rather than macrovascular complications play a major role in the recurrence of foot ulcer in patients with comorbid DFO and DN. That would help clinical doctors adopt the appropriate therapeutic measures for the prevention of foot ulcer recurrence.

AUTHOR CONTRIBUTIONS

Wensheng Lu, Li Zhang, Guifen Fu, Yongqing Deng and Yuechou Nong drafted the manuscript. Jianhao Huang, Xiulu Huang, Fenglian Wei and Yanqing Yu performed the statistical analysis and results interpretation, and contributed to the study concept and design. Litian Huang, Wenjiao Zhang, Meizhu Tang and Licai Deng performed the statistical analysis and results interpretation and performed critical revision of the manuscript. Wensheng Lu, Jiaxia Han, Xing Zhou and Qiu Wang performed critical revision of the manuscript and supervised the study. Wensheng Lu is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

The authors thank the Diabetic Foot Disease Studio of the Department of Endocrinology and metabolism, Information Network Center and Medical Record Information Quality Control Center of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region for assisting in retrieving medical records. The authors also thank all the diabetic foot patients, medical staff, volunteers and the sponsors of scientific research funds involved in this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in the published article.

ETHICS STATEMENT

All patients agreed to participate in this study and signed written informed consent. The guidelines outlined in the Declaration of Helsinki were followed. All experiments were performed with approval from the Ethics Committee of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region.

ORCID

Wensheng Lu https://orcid.org/0000-0003-4179-1171

REFERENCES

1. Li Y, Teng D, Shi X, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. *BMJ*. 2020;369:m997. doi:10.1136/bmj.m997
2. Zhang L, Long J, Jiang W, et al. Trends in chronic kidney disease in China. *N Engl J Med*. 2016;375(9):905-906. doi:10.1056/NEJMc1602469
3. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S135-S151. doi:10.2337/dc20-S011
4. He Y, Qian H, Xu L, et al. Association between estimated glomerular filtration rate and outcomes in patients with diabetic foot ulcers: a 3-year follow-up study. *Eur J Endocrinol*. 2017;177(1):41-50. doi:10.1530/EJE-17-0070
5. Ninomiya T, Perkovic V, de Galan BE, et al; ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol*. 2009;20(8):1813-1821. doi:10.1681/ASN.2008121270

6. Konta T, Kudo K, Sato H, et al. Albuminuria is an independent predictor of all-cause and cardiovascular mortality in the Japanese population: the Takahata study. *Clin Exp Nephrol*. 2013;17(6):805-810. doi:10.1007/s10157-013-0770-3
7. Uccioli L, Izzo V, Meloni M, Vainieri E, Ruotolo V, Giurato L. Non-healing foot ulcers in diabetic patients: general and local interfering conditions and management options with advanced wound dressings. *J Wound Care*. 2015;24(4 Suppl):35-42. doi:10.12968/jowc.2015.24.Sup4b.35
8. Anyanwagu U, Donnelly R, Idris I. Albuminuria regression and all-cause mortality among insulin-treated patients with type 2 diabetes: analysis of a large UK primary care cohort. *Am J Nephrol*. 2019;49(2):146-155. doi:10.1159/000496276
9. Li X, Xiao T, Wang Y, et al. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a Chinese tertiary hospital. *Diabetes Res Clin Pract*. 2011;93(1):26-30. doi:10.1016/j.diabres.2011.03.014
10. Dutra LMA, Melo MC, Moura MC, et al. Prognosis of the outcome of severe diabetic foot ulcers with multidisciplinary care. *J Multidiscip Healthc*. 2019;12:349-359. doi:10.2147/JMDH.S194969
11. Brownrigg JR, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. *Diabetologia*. 2012;55(11):2906-2912. doi:10.1007/s00125-012-2673-3
12. Ricci L, Scatena A, Tacconi D, et al. All-cause and cardiovascular mortality in a consecutive series of patients with diabetic foot osteomyelitis. *Diabetes Res Clin Pract*. 2017;131:12-17. doi:10.1016/j.diabres.2017.06.006
13. Rubio JA, Jimenez S, Alvarez J. Clinical characteristics and mortality in patients treated in a Multidisciplinary Diabetic Foot Unit. [Caracteristicas clinicas y mortalidad de los pacientes atendidos en una Unidad Multidisciplinar de Pie Diabetico]. *Endocrinol Diabetes Nutr*. 2017;64(5):241-249. doi:10.1016/j.endinu.2017.02.012
14. Morbach S, Furchert H, Groblinghoff U, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care*. 2012;35(10):2021-2027. doi:10.2337/dc12-0200
15. Dietrich I, Braga GA, de Melo FG, da Costa Silva Silva ACC. The diabetic foot as a proxy for cardiovascular events and mortality review. *Curr Atheroscler Rep*. 2017;19(11):44. doi:10.1007/s11883-017-0680-z
16. Young MJ, McCardle JE, Randall LE, Barclay JI. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. *Diabetes Care*. 2008;31(11):2143-2147. doi:10.2337/dc08-1242
17. Yotsu RR, Pham NM, Oe M, et al. Comparison of characteristics and healing course of diabetic foot ulcers by etiological classification: neuropathic, ischemic, and neuro-ischemic type. *J Diabetes Complications*. 2014;28(4):528-535. doi:10.1016/j.jdiacomp.2014.03.013
18. Meloni M, Izzo V, Giurato L, Lazaro-Martinez JL, Uccioli L. Prevalence, clinical aspects and outcomes in a large cohort of persons with diabetic foot disease: comparison between neuropathic and ischemic ulcers. *J Clin Med*. 2020;9(6):1780. doi:10.3390/jcm9061780
19. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553. doi:10.1002/(SICI)1096-9136(199807)15:73.0.CO;2-S
20. Lipsky BA, Berendt AR, Cornia PB, et al; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):e132-e173. doi:10.1093/cid/cis346
21. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet*. 2005;366(9498):1719-1724. doi:10.1016/S0140-6736(05)67698-2
22. Bus SA, van Netten JJ, Monteiro-Soares M, Lipsky BA, Schaper NC. Diabetic foot disease: "the times they are a Changin'". *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3249. doi:10.1002/dmrr.3249
23. Jiang Y, Wang X, Xia L, et al. A cohort study of diabetic patients and diabetic foot ulceration patients in China. *Wound Repair Regen*. 2015;23(2):222-230. doi:10.1111/wrr.12263
24. Ugwu E, Adeleye O, Gezawa I, Okpe I, Enamino M, Ezeani I. Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study. *J Foot Ankle Res*. 2019;12:34. doi:10.1186/s13047-019-0345-y
25. Van GH, Amouyal C, Bourron O, et al. Diabetic foot ulcer management in a multidisciplinary foot centre: one-year healing, amputation and mortality rate. *J Wound Care*. 2021;30(Sup6):S34-S41. doi:10.12968/jowc.2021.30.Sup6.S34
26. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713-735. doi:10.1053/j.ajkd.2014.01.416
27. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes Management in Chronic Kidney Disease: synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med*. 2021;174(3):385-394. doi:10.7326/M20-5938
28. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. *Am J Kidney Dis*. 2014;64(4):510-533. doi:10.1053/j.ajkd.2014.08.001
29. Huang MJ, Wei RB, Zhao J, et al. Albuminuria and endothelial dysfunction in patients with non-diabetic chronic kidney disease. *Med Sci Monit*. 2017;23:4447-4453. doi:10.12659/msm.903660
30. Yang J, Huang J, Wei S, et al. Urine albumin-creatinine ratio is associated with prognosis in patients with diabetic foot osteomyelitis. *Diabetes Res Clin Pract*. 2021;180:109043. doi:10.1016/j.diabres.2021.109043
31. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation*. 2004;110(8):921-927. doi:10.1161/01.CIR.0000139860.33974.28
32. Rathur HM, Boulton AJ. The diabetic foot. *Clin Dermatol*. 2007;25(1):109-120. doi:10.1016/j.clindermatol.2006.09.015
33. Dyck PJ, Albers JW, Andersen H, et al; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. *Diabetes Metab Res Rev*. 2011;27(7):620-628. doi:10.1002/dmrr.1226
34. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham risk

score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300(2):197-208. doi:10.1001/jama.300.2.197

35. Polonsky TS, McDermott MM. Lower extremity peripheral artery disease without chronic limb-threatening ischemia: a review. *JAMA*. 2021;325(21):2188-2198. doi:10.1001/jama.2021.2126
36. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev*. 2012;28(7):574-600. doi:10.1002/dmrr.2319
37. Bus SA, van Deursen RW, Armstrong DG, et al; International Working Group on the Diabetic Foot (IWGDF). Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):99-118. doi:10.1002/dmrr.2702
38. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375. doi:10.1056/NEJMra1615439
39. Vileikyte L, Leventhal H, Gonzalez JS, et al. Diabetic peripheral neuropathy and depressive symptoms: the association revisited. *Diabetes Care*. 2005;28(10):2378-2383. doi:10.2337/diacare.28.10.2378
40. Bakris GL, Agarwal R, Chan JC, et al; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group.Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA*. 2015;314(9):884-894. doi:10.1001/jama.2015.10081

How to cite this article: Zhang L, Fu G, Deng Y, et al. Risk factors for foot ulcer recurrence in patients with comorbid diabetic foot osteomyelitis and diabetic nephropathy: A 3-year follow-up study. *Int Wound J*. 2023;20(1):173-182. doi:10.1111/iwj.13861