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The association between estimated glomerular filtration rate and prognosis in patients with diabetic foot osteomyelitis

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Abstract

We aimed to explore the association between estimated glomerular filtration rate (eGFR) and prognosis in patients with diabetic foot osteomyelitis (DFO). Three hundred twenty-one DFO inpatients were enrolled and classified into four groups according to the eGFRs as follows: normal (≥90), mildly reduced (60-89), moderately reduced (30-59) and severely reduced (<30). These patients were followed-up for 6 months to observe the outcomes, including ulcer healing and amputation. The associations between eGFR and the outcomes were analysed by univariate and multivariate logistic regression models. Compared with patients with normal eGFR, patients with severely reduced eGFR group had higher risk of healing failure (OR = 4.72, 95% CI: 1.44-15.48), total amputation (OR = 4.50, 95% CI: 1.18-17.13) and minor amputation (OR = 4.05, 95% CI: (1.04-15.87). Severely reduced eGFR in patients with DFO was an independent predictor for amputation and healing failure.

KEYWORDS

diabetic foot osteomyelitis, estimated glomerular filtration rate, prognosis

Key Messages

- previous studies suggest diabetic foot ulcer (DFU) patients may have adverse outcomes when combined with renal insufficiency. However, the association between estimated glomerular filtration rate (eGFR) and clinical outcomes of diabetic foot osteomyelitis (DFO) patients has not been described before
- three hundred twenty-one DFO inpatients were enrolled in this study. In multivariate logistic regression, severely reduced eGFR in patients with DFO was an independent predictor for amputation and healing failure
- our study highlights the importance of protecting renal function in the management of DFO patients

1 | INTRODUCTION

The diabetes population is increasing in China and worldwide, which has become a global public health problem.[1]The global prevalence of diabetes is estimated to be 9.3% in 2019 and will rise to 10.9% in 2045.[2] In China, the prevalence of diabetes in adults has reached 11.2%.[3] People with diabetes are more likely to foot infection, and about 20% of them will develop diabetic foot ulcer (DFU)[4,5] . Furthermore, a lower limb amputation due to a DFU is carried out every 30 seconds worldwide, with rates being 30 to 40 times higher for diabetic patients than the individuals without diabetes.[6,7]

Diabetic foot osteomyelitis (DFO) is a moderate to severe infection phase of DFU and has a high amputation and mortality rate.[8,9] The annual mortality rate of DFU is as high as 11%, while the mortality of amputated patients is even higher than 22%.[10] It has become a hot and difficult point about how to avoid amputation for DFO patients.

Diabetes is also frequently complicated by chronic kidney disease (CKD). Individuals with CKD have an increased risk for DFU.[11] Among patients with DFU, the proportion of CKD is as high as 39.3%.[12] Estimated glomerular filtration rate (eGFR) is a clinically identifiable and intervenable prognostic indicator, which is widely used to evaluate prognosis in patients with DFU.[12,13] However, there is still no research to observe the association between eGFR and clinical outcomes of DFO patients. Therefore, this study aims to explore the impact of CKD on prognosis of DFO patients according to eGFR.

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 321 DFO patients (224 men and 97 women) diagnosed at Tianjin Medical University Chu Hsien-I Memorial Hospital between December 2019 and January 2021 were prospectively enrolled. All participants provided written informed consent to use their data for research purposes. The research protocol was approved by the ethics committee of Tianjin Medical University Chu Hsien-I Memorial Hospital [DXBYYhMEC2021-26]. This prospective cohort study was conducted in accordance with the Helsinki Declaration. They met the International Working Group on the Diabetic Foot (IWGDF) diagnostic criteria for DFO and have the data of eGFR. Patients were followed up for 6 months from enrollment or until death. Characteristics and the laboratory data were recorded at presentation including gender, age, diabetes duration, coronary heart disease (CHD), stroke, HbA1c, albumin (ALB) and other biochemical data. The outcome information was collected from the medical records of inpatients in our department. If the patient cannot be contacted due to foot treatment elsewhere, it is obtained by calling him. All the treatments are based on the guidelines for diabetic foot treatments recommended by the International Working Group on the Diabetic Foot (IWGDF).[14] Exclusion criteria included previous occurrence of DFUs or major amputations, type 1 diabetic foot and acute kidney injury patients. The flow chart is shown in Figure 1.

2.2 | Definition and measurement of exposure, outcomes and impact factors

eGFR was calculated following the EPI[15] equation. Patients were divided into four groups as follows: normal eGFR: ≥90 mL/min/1.73 m^2, mildly reduced eGFR: 60 to 89 mL/ min/1.73 m^2, moderately reduced eGFR: 30 to 59 mL/min/1.73m^2 and severely reduced eGFR: <30 mL/ min/1.73 m^2. DFO was based on probing-to-bone test positive, abnormal plain x-ray and abnormal laboratory testing (including erythrocyte sedimentation rate, high-sensitivity C-reactive protein and procalcitonin).[16] Peripheral arterial disease (PAD)[17] was defined as the presence of stenosis or occlusion of lower limb arteries indicated by Doppler ultrasound. Infection degree was defined according to the classification system of Infectious Diseases Society of America (IDSA).[16] If osteomyelitis is demonstrated in the absence of ≥2 signs/symptoms of local or systemic inflammation, classify the foot as either moderate infection (if <2 systemic inflammatory response syndrome criteria) or severe infection (if ≥2 systemic inflammatory response syndrome criteria) (including: temperature, >38°C or <36°C; heart rate, >90 beats/min; respiratory rate, >20 breaths/min or $PaCO_2$ < 4.3 kPa; white blood cell count >12 000/mm^3). DFO healing was determined by complete epithelialisation on the wound without major amputation. The definition of amputations as follows: a minor amputation was defined as any amputation distal to the ankle joint; a major amputation was defined as any amputation up to or proximal to the ankle joint, and a toe amputation was defined as the level of amputation lower than the metatarsophalangeal joint. Other impacted factors, including demographic data, duration of diabetes, HbA1c, blood pressure (BP), ALB, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), medication records and microvascular or macrovascular complications of patients, were recorded and assessed at admission. The following factors were measured in all study

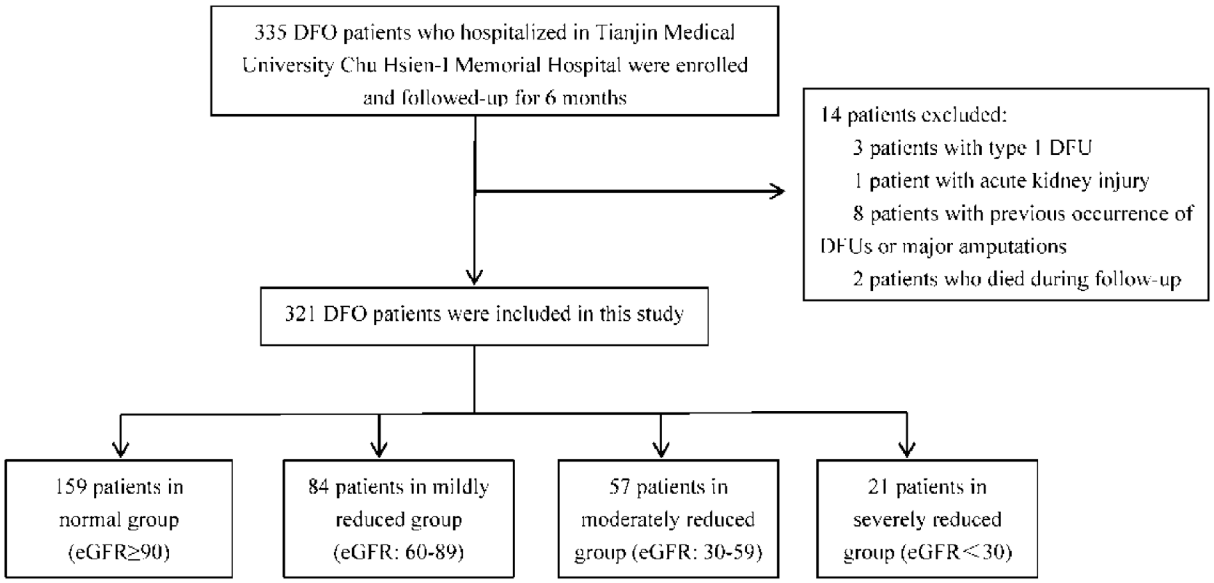

FIGURE 1 Flow diagram of processing for the selection of patients

subjects after a 10-hours overnight fast: HbA1c, BP, ALB, TC, TG, LDL-C and HDL-C. HbA1c was measured using high-performance liquid chromatography. BP was measured after 15 minutes of rest. Smoker was identified as having smoked more than 100 cigarettes in their lifetime. History of CHD was confirmed by medical records or defined by history of angina or myocardial infarction, any positive cardiac stress test result or pathological signs on coronary angiography.[18] History of stroke was defined as any event of neurological deficit with or without sequelae.[18]

2.3 | Statistical analysis

All clinical and laboratory data were analysed using the Statistical Package for Social Sciences (SPSS) statistical software version 23.0. Quantitative variables were expressed as means ± SD or median (range) according to their distribution, and the one-way ANOVA or Kruskal-Wallis test was used to make comparisons among groups. Qualitative variables were expressed as percentages, and comparisons were made using the $\chi 2$ test. To analyse the association between reduced eGFR and healing and amputation, odd ratios (OR) with 95% confidence intervals were first calculated using logistic univariate models. Then, the following factors: age, sex, HbA1c, duration of diabetes, CHDs, SBP, TG, PAD and infection degree were included as confounders to ascertain OR for healing and amputation in multivariate logistic regression models step by step. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics of the 321 patients with DFO stratified by eGFR are summarised in the Table 1. Two patients who died during follow-up were excluded. Overall, the mean age was 63.10 ± 11.64 years, and 69.8% of the patients were male. The median diabetes duration was 15 (IQR =10-20) years. HbA1c level averaged 8.80 ± 2.05%. Two hundred thirty-seven (73.8%) patients received insulin therapy to control blood glucose. Eighty-six (26.8%) patients received angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB) agents treatment. Among them, 159 individuals (49.5%) had normal eGFR, 84 individuals (26.2%) had mildly reduced eGFR, 57 individuals (17.8%) had moderately reduced eGFR and 21 individuals (6.5%) had severely reduced eGFR. There were significant differences in age, HbA1c, stroke, CHD, SBP, TG, PAD and infection degree among the four groups ($P < .05$).

3.2 | Wound healing

A total of 293 patients without major amputation were followed up. Two hundred twenty-four (76.5%) attained ulcer healing by the end of the follow-up. At the end of follow-up, the healing rate of the normal group was 81.5% (123/151), the healing rate was lower in reduced eGFR group, with78.4% (58/74), 70.6% (36/51) and 41.2% (7/17) in the mildly, moderately and severely reduced

TABLE 1 Baseline clinical characteristics and treatments of the study grouped by estimated glomerular filtration rate (eGFR)

		eGFR (mL/min/1.73 m^2)				
	Total	**≥90**	**60-89**	**30-59**	**<30**	***P***
n	321	159	84	57	21	
Male (%)	224 (69.8)	105 (66)	61 (72.6)	43 (75.4)	15 (71.4)	.52
Age (y)	63.1 ± 11.65	60.29 ± 11.66	67.71 ± 10.74	65.26 ± 10.98	60 ± 10.19	<.01
Diabetes duration (y)	15 (10,20)	14 (10,22)	20 (10,25)	20 (10,22)	20 (11,26.5)	.09
HbA1c (%)	8.81 ± 2.05	9.14 ± 2.19	8.67 ± 1.92	8.39 ± 1.64	8.08 ± 2.09	<.05
PAD (%)	247 (76.9)	112 (70.4)	62 (73.8)	54 (94.7)	19 (90.5)	<.01
Infection degree (%)						<.01
Moderate infection	203 (63.2)	119 (74.8)	48 (57.1)	27 (47.4)	9 (42.9)	
Severe infection	118 (36.8)	40 (25.2)	36 (42.9)	30 (52.6)	12 (57.1)	
CHD (%)	129 (40.2)	41 (25.8)	39 (46.4)	32 (56.1)	17 (81)	<.01
Stroke (%)	83 (25.9)	27 (17.0)	27 (32.1)	23 (40.4)	6 (28.6)	<.01
SBP (mmHg)	136.6 ± 18.58	133.34 ± 17.16	137.02 ± 19.07	144.39 ± 18.89	138.71 ± 20.55	<.01
DBP (mmHg)	77.44 ± 11.87	77.66 ± 11.62	76.62 ± 11.78	78.46 ± 13.38	76.29 ± 10.10	.78
Smoking (%)	140 (43.6)	70 (44.0)	35 (41.7)	28 (49.1)	7 (33.3)	.63
ALB (g/L)	33.72 ± 5.24	34.25 ± 5.04	34 ± 4.64	32.52 ± 6.11	32.15 ± 6.02	.08
TC (mmol/L)	4.35 ± 1.25	4.42 ± 1.28	4.17 ± 1.18	4.53 ± 1.25	4.1 ± 1.20	.24
TG (mmol/L)	1.26 (0.98,1.73)	1.20 (0.94,1.68)	1.14 (0.89,1.46)	1.63 (1.14,1.98)	1.45 (1.19,2.09)	<.01
LDL (mmol/L)	3.02 ± 0.97	3.06 ± 0.98	2.87 ± 0.97	3.16 ± 0.95	2.89 ± 0.91	.27
HDL (mmol/L)	0.86 ± 0.24	0.88 ± 0.26	0.87 ± 0.25	0.84 ± 0.21	0.74 ± 0.19	.08
ACEI/ARB (%)	86 (26.8)	40 (25.2)	29 (34.5)	15 (26.3)	2 (9.52)	.11
Insulin use (%)	237 (73.8)	113 (71.1)	64 (76.2)	44 (77.2)	16 (76.2)	.74

Abbreviations: ALB, albumin; CHD, coronary heart disease; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

group respectively ($\chi 2 = 14.98$; $P < .01$). Furthermore, comparing the mildly, moderately and severely reduced group with the normal group, the risk ratio (RR) of healing in the severely reduced eGFR group was 0.505 (95% CI: 0.29-0.90) ($\chi 2 = 14.16$; $P < .01$). However, there was no significant difference between the mildly/moderately reduced eGFR group and the normal eGFR group (Detailed in Figure 2A).

The results of the univariate and multivariate logistic regression models for estimating the relationship between eGFR and ulcer healing failure in patients with DFO are listed in Table 2. In univariate regression model (model 1), the risk of healing failure was higher in the severely reduced eGFR group, with OR of 6.28 (95% CI: 2.2-17.92), but there was no significant difference in the mild to moderate decreased eGFR group ($P < .05$). After further adjusting gender and age, there was still no significant difference in the mildly and moderately reduced eGFR group. Further adjusting for HbA1c, diabetes duration, CHD, stroke, SBP, TG, PAD and infection degree, the difference was still statistically significant in the severely reduced eGFR group ($P = .01$) (shown in Table 2).

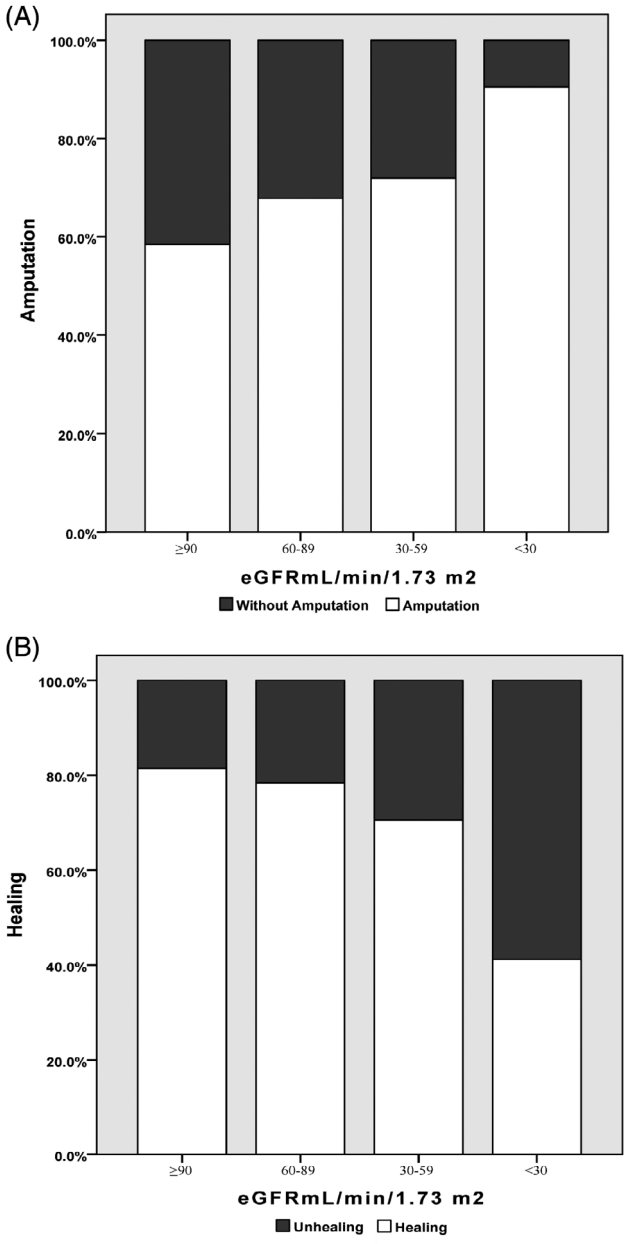

FIGURE 2 The comparisons of healing and amputation rate at 6 months between estimated glomerular filtration rate (eGFR) groups. (A) The healing rate at 6 months among eGFR groups. (B) The amputation rate at 6 months among eGFR groups

3.3 | Total amputation

During the follow-up, 65.1% (209/321) patients underwent amputations. The total amputation rate of the normal group was 58.5% (93/159), the total amputation rate was higher in reduced eGFR group, with 67.9% (57/84), 71.9% (41/57) and 85.7% (19/21) in the mildly, moderately and severely reduced group, respectively ($\chi 2 = 8.44$; $P = .04$). Furthermore, comparing the mildly, moderately and severely reduced group with the normal group, the RR of total amputation in the severely reduced eGFR group was 1.47 (95%CI:1.18-1.82) ($\chi 2 = 5.82$; $P = .02$). No significant difference was found between the mildly/moderately reduced eGFR group and the normal eGFR group (Figure 2B).

Whether in univariate regression analysis or the model after adjusting gender and age, we can see patients with severely reduced eGFR have a higher risk of amputation, and the difference is statistically significant. There was no significant difference between the mildly/moderately reduced eGFR group and the normal eGFR group. By adjusting the confounding factors of diabetes duration and HbA1c, we found that moderately and severely reduced eGFR were all associated with the risk of total amputation, and the difference was statistically significant. Finally, after adjusting all the confounding factors, we found that severely reduced eGFR was independently associated with total amputation rate, and the OR was 4.50 (95% CI: 1.18-17.13, $P = .03$). (Table 3).

3.4 | Minor amputation

Of all patients who underwent amputation, 187 (89.5%) underwent minor amputation and 22 (10.5%) underwent major amputation. Because of the small major amputation population, in order to avoid statistical bias, we further conducted the regression analysis for minor

TABLE 2 Univariate and multivariate logistic regression models assessing the association between healing failure and estimated glomerular filtration rate (eGFR)

	eGFR (mL/min/1.73 m^2)						
		60-89 (n = 84)		30-59 (n = 57)		<30 (n = 21)	
Outcomes	**≥90 (n = 159)**	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Healing failure							
Model 1	Reference	1.21 (0.61-2.41)	.59	1.83 (0.88-3.79)	.10	6.28 (2.20-17.92)	<.01
Model 2	Reference	1.06 (0.52-2.17)	.87	1.67 (0.79-3.53)	.18	6.19 (2.15-17.85)	<.01
Model 3	Reference	1.02 (0.50-2.11)	.96	1.56 (0.73-3.32)	.25	5.21 (1.78-15.25)	<.01
Model 4	Reference	0.97 (0.46-2.03)	.92	1.11 (0.49-2.50)	.81	3.98 (1.28-12.42)	.02
Model 5	Reference	1.06 (0.50-2.27)	.88	1.26 (0.542.95)	.59	4.72 (1.44-15.48)	.01

Abbreviations: CI, confidence intervals; Model 1, univariate analysis; Model 2, adjusted for age, sex; Model 3, adjusted for age, sex, HbA1c, diabetes duration; Model 4, adjusted for age, sex, HbA1c, diabetes duration, CVD, stroke, SBP, TG; Model 5, adjusted for age, sex, HbA1c, diabetes duration, CVD, stroke, SBP, TG, PAD, infection degree; OR, odd ratio.

TABLE 3 Univariate and multivariate logistic regression models assessing the association between amputation/minor amputation and estimated glomerular filtration rate (eGFR)

	eGFR (mL/min/1.73 m^2)						
		60-89 (n = 84)		30-59 (n = 57)		<30 (n = 21)	
Outcomes	**≥90 (n = 159)**	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Total amputation							
Model 1	Reference	1.50 (0.86-2.61)	.15	1.82 (0.94-3.51)	.08	4.26 (1.21-15.05)	.02
Model 2	Reference	1.66 (0.93-2.97)	.09	1.94 (0.99-3.80)	.05	4.25 (1.20-15.05)	.03
Model 3	Reference	1.70 (0.95-3.05)	.08	2.02 (1.03-3.98)	.04	4.59 (1.28-16.41)	.02
Model 4	Reference	1.74 (0.96-3.16)	.07	2.46 (1.18-5.13)	.02	5.17 (1.38-19.32)	.02
Model 5	Reference	1.64 (0.89-3.02)	.12	2.18 (1.02-4.66)	.04	4.50 (1.18-17.13)	.03
Minor amputation							
Model 1	Reference	1.35 (0.76-2.38)	.31	1.62 (0.83-3.18)	.16	3.46 (0.96-12.53)	.06
Model 2	Reference	1.52 (0.84-2.75)	.17	1.78 (0.89-3.53)	.1	3.61 (0.99-13.13)	.05
Model 3	Reference	1.56 (0.86-2.83)	.15	1.85 (0.93-3.70)	.08	3.96 (1.08-14.55)	.04
Model 4	Reference	1.61 (0.88-2.97)	.13	2.11 (0.99-4.51)	.05	4.43 (1.15-17.04)	.03
Model 5	Reference	1.55 (0.83-2.91)	.17	2.07 (0.95-4.51)	.07	4.05 (1.04-15.87)	.04

Abbreviations: CI, confidence intervals; Model 1, univariate analysis; Model 2, adjusted for age, sex; Model 3, adjusted for age, sex, HbA1c, diabetes duration; Model 4, adjusted for age, sex, HbA1c, diabetes duration, CVD, stroke, SBP, TG; Model 5, adjusted for age, sex, HbA1c, diabetes duration, CVD, stroke, SBP, TG, PAD, infection degree; OR, odd ratio.

amputation. No matter in univariate regression analysis or the model after adjusting gender and age (model 2), reduced eGFR did not correlate with the minor amputation. After further adjusting all other confounding factors, we found that the severely reduced eGFR was independently associated with minor amputation, and the OR was 4.05 (95% CI: 1.04-15.87, $P = .04$). This is consistent with the result of total amputation (Table 3).

4 | DISCUSSION

A large number of studies have revealed that DFU patients may have adverse outcomes when combined with renal insufficiency, especially in patients with severe renal dysfunction or dialysis.[19-21] A retrospective study[22] about the long-term diabetic complications as predictors of foot ulcers healing failure revealed that eGFR <60 mL/min/1.73 m^2 was an independent risk factor for

poor wound healing. However, among patients with DFUs, patients with DFO are more complicated and worse prognosis than those without osteomyelitis.[23,24]

At present, there are few studies on renal function and prognosis of DFO. Some research[25] found that high urine albumin-creatinine ratio was associated with poor clinical outcomes in patients with DFO. However, there is no research on eGFR and prognosis of DFO patients.

The current study analysed the association between eGFR and healing/amputation of DFO patients. The results demonstrated that severely reduced eGFR was an independent predictor of healing failure in DFO patients. In our study, 23.5% of patients failed to heal, and the healing rate gradually decreased with the decline of eGFR. The present study found that DFO patients who had a severely reduced eGFR (<30 mL/min/1.73 m^2) had a high risk for healing failure (OR = 4.72, $P = .01$). This was consistent with the previous studies.[12,26] Zubair et al[26] reported that wound healing was associated with the decrease in creatinine clearance rate in patients with DFUs. He et al[12] revealed that a moderate or severe decrease in eGFR was an independent predictor of poor outcomes in DFU patients.

DFU healing is a complex and multi-factor process. Infection and limb ischemia are common factors affecting wound healing. In this study, we demonstrated that severely reduced eGFR was an independent predictor of healing failure in DFO patients. The increased albumin excretion rate could induce peripheral edema, tissue oxygenation and inflammation may be worsened by tissue edema in eGFR-reduced patients.[27,28] Anaemia is the most common complication of CKD, which is another factor involved in the healing failure of DFU, as it can also reduce the tissues' oxygen supply.[29] Hypertension caused by renal insufficiency may lead to endothelial dysfunction, worsening of the lower limb ischemia, which harms the process of wound healing.[29]

Several studies[19,21,30,31] revealed that renal insufficiency (eGFR <60 mL/min/1.73 m^2) was a risk factor for amputation in DFU patients. Our study confirms that severe reduced eGFR is associated with amputation risk after adjusting the confounders, including the PAD and infection degree (OR = 4.50, $P = .03$). Different from previous studies, this study further analysed the association between eGFR and the risk of minor amputation in DFU patients. The results revealed that the risk of minor amputation increased by 4.05 times when the eGFR <30 mL/min/1.73 m^2, which was consistent with the overall amputation. Impaired immune defences of patients with renal failure make the wound more likely to infection, especially the infection of bone tissue. Antibiotic treatment is important for DFO patients. The decline of renal function may represent a limiting factor for antibiotic treatment. This leads to the failure of antibiotic treatment and increases the risk of amputation.[32]

There were several limitations in our study. First, the sample size was small. Second, the follow-up was short, so we cannot observe the long-term adverse outcomes.

In conclusion, severely reduced eGFR is strongly associated with poor prognoses in DFO patients. The results from this study highlight the need for clinician to protect the renal function in the management of DFU patients.

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CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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