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ORIGINAL RESEARCH

Associations of Estimated Glomerular Filtration Rate with All-Cause Mortality and Cardiovascular Mortality in Patients with Diabetic Foot Osteomyelitis

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Aim: The purpose of this study was to explore the association between estimated glomerular filtration rate (eGFR) and clinical outcomes in patients with diabetic foot osteomyelitis (DFO).

Methods: This was a retrospective observational study. A total of 199 patients with DFO were recruited and divided into three groups by eGFR: normal kidney function group (eGFR ≥ 90), mildly decreased kidney function group (eGFR 60–89) and moderately to severely decreased kidney function group (eGFR < 60). The patients were followed-up for a median of 36 months, and the study outcomes were all-cause mortality and major cardiovascular adverse events (MACE). Cox proportional hazard models were used to assess the association between eGFR and the outcomes, and a stratified analysis by sex was conducted.

Results: During follow-up, all-cause mortality occurred in 51 (25.63%) patients among 199 participants, 54 (28.72%) had MACE in 188 participants and 26 (48.15%) of them died. After fully adjusting for potential confounders, compared to eGFR < 90 mL/min/1.73 m^2, eGFR ≥ 90 mL/min/1.73 m^2 had lower incidence of all-cause mortality (HR = 0.43, 95% CI: 0.22–0.85; $P = 0.015$) and MACE (HR = 0.51, 95% CI: 0.27–0.96; $P = 0.038$). Additionally, compared to eGFR < 90 mL/min/1.73 m^2, eGFR ≥ 90 mL/min/1.73 m^2 was independently associated with decreased risk of all-cause mortality (HR = 0.33; 95% CI 0.14–0.76, $P = 0.010$) and MACE (HR = 0.27; 95% CI 0.11–0.65, $P = 0.004$) in male, but not in female.

Conclusion: In conclusion, decreased eGFR is a risk factor for all-cause mortality and MACE in individuals with DFO. Additionally, male with decreased eGFR had a higher risk of all-cause mortality and MACE, but female did not.

Keywords: diabetic foot osteomyelitis, estimated glomerular filtration rate, prognosis

Introduction

Diabetic foot osteomyelitis (DFO) is mostly caused by the contiguous spread of foot infection to adjacent soft tissue and eventually to bone.[1] At present, the number of diabetes is increasing yearly worldwide and the prevalence of diabetes in China increased to 11.2%.[2] About 15–25% of diabetic patients develop diabetic foot disease during the progression of the disease.[3] Even though the prevalence and mortality differ between countries,[4] recent studies, which come from China have shown that the annual mortality rate of Chinese patients with diabetic foot disease is 14.40%,[5] and the 5-year mortality rate is about 50%.[6] Among patients with diabetic

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foot disease, more than 60% have ulcer with infection and DFO patients often have more complicated ulcers and more extensive infection.[7]

Chronic complications of diabetes include microvascular and macrovascular complications. The occurrence and development of diabetic foot disease are closely related to diabetic lower extremity arterial disease and diabetic peripheral vascular disease (PVD).[8] Therefore, clinically, diabetic foot disease usually does not exist in a single form. Diabetic foot disease is complicated with multiple complications and multiple target organ damage can result in increased medical expenditures, decline in quality of life,[9] difficulty in wound healing and recurrence of foot ulcers, so it has become a problem[10] and a research hotspot in the medical field.

Diabetic nephropathy is a common chronic complication combined with diabetic foot disease. Studies[11] have shown that chronic kidney disease is related to the risk of cardiovascular events and all-cause mortality in diabetic patients. The decline in estimated glomerular filtration rate (eGFR) and end-stage renal disease (ESRD) is related to the survival time of diabetic foot disease.[12] Among patients with diabetic foot ulcers, patients with DFO tend to have more severe infections and more complicated conditions than those without osteomyelitis. However, few studies have reported on the prognosis of DFO and the value of eGFR as an evaluation index of kidney function in DFO patients. Moreover, there is also no research to observe the relationship between eGFR and the prognosis of DFO and further investigate the difference between male and female in clinical outcomes by eGFR in DFO patients. To this end, we propose a hypothesis: eGFR levels are associated with the clinical outcomes of DFO patients, and decreased eGFR may be a risk factor for all-cause mortality and major cardiovascular adverse events (MACE) in DFO patients. We aim to investigate the associations of eGFR with all-cause mortality and MACE in 199 DFO patients and explore the differences between sexes.

Methods

Subjects

From June 2015 to June 2017, a total of 199 patients with DFO who were hospitalized in the Department of Endocrinology, Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region were selected. The following inclusion criteria were utilized: (1) diabetes was diagnosed in accordance with criteria established by the World Health Organization (WHO) in 1999;[13] (2) DFO was diagnosed according to the criteria established by the World Health Organization International Working Group on Diabetic Foot (IWGDF).[14] The exclusion criteria were as follows: (1) non-diabetic foot ulcers such as venous ulcers caused by varicose veins,[15] tophus ulcers and bedsores caused by prolonged bed rest; (2) patients with long-term use of glucocorticoids or immunosuppressants; (3) patients were lost to follow-up and had incomplete medical records or insufficient follow-up time. Written informed consent was provided by all patients prior to undergoing any study-related procedures. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region.

Definitions and Impact Factors

Venous blood samples were taken after 8 hours of overnight fasting. According to the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines,[16] baseline eGFR was categorized into three groups: normal kidney function (eGFR $\geq$ 90 mL/min/1.73 m^2), mildly decreased kidney function (eGFR = 60 to 89 mL/min/1.73 m^2) and moderately-to-severely decreased kidney function (eGFR < 60 mL/min/1.73 m^2). Meanwhile, for survival analysis, eGFR was grouped into two categories: normal kidney function (eGFR $\geq$ 90 mL/min/1.73 m^2) and abnormal kidney function (eGFR < 90 mL/min/1.73 m^2). The eGFR was calculated through MDRD equation for Chinese adults: eGFR = 175 $\times$ (serum creatinine [mg/dL])$^{-1.234}$ $\times$age$^{-0.179}$ $\times$ 0.79 (if female).[17]

According to the guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update),[14] we used a combination of the probe bone (PTB), inflammatory biomarkers including erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), procalcitonin (PCT), and plain X-rays to diagnose DFO and confirmed through histopathology of bone biopsy. The severity of DFO infection was classified according to the Guidelines of The International Working group on the Diabetic Foot/Infectious Diseases Society of America system (IWGDF/IDSA).[18] Ischemic or non-ischemic infected wounds were classified according to the University of Texas Diabetic Wound Classification (UTDWC).[19]

Also, we collected other information about impact factors. The demographics include age, sex, body mass index (BMI) and smoking status. Laboratory parameters

collected included: serum creatinine (SCr), urinary albumin-to-creatinine ratio (UCAR), glycosylated hemoglobin (HbA1c), white blood cells (WBC), hemoglobin (Hb), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (apoA1), apolipoprotein B (apoB). The medical histories of the patients were collected, including type and duration of diabetes, hypertension, coronary heart disease (CHD), cardiovascular diseases (CVD), sepsis, peripheral arterial diseases (PVD) and foot examinations (neuropathy, the degree and location of infection).

Outcomes

The outcomes of the study were all-cause mortality and MACE within three years after DFO diagnosis. Clinical outcome occurrences were obtained by the medical files in our department for outpatient or inpatient and by telephone to contact the patients or patients' families using online questionnaires. MACE was defined as cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke.[11]

Statistical Analyses

Data were expressed as mean ± SD or as median (quartiles) as appropriate. Categorical variables were expressed using percentages (%). For comparisons between multiple groups, one-way ANOVA and Kruskal–Wallis rank sum tests were applied. Pearson χ^2 test was used for categorical variables. The cumulative incidence of all-cause mortality and MACE was estimated between eGFR < 90 mL/min/1.73 m^2 group and eGFR ≥ 90 mL/min/1.73 m^2 group by using Kaplan–Meier analysis and compared by the Log rank test. Univariate Cox proportional hazard analysis was used to identify the statistically significant variables for all-cause mortality and MACE. Multivariate Cox proportional hazard analysis was then used with these statistically significant and clinically meaningful variables to investigate whether different eGFR levels are associated with all-cause mortality and MACE in patients with DFO. The results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Cox proportional hazard analysis was performed with three different models as follows: crude model: no adjustment; model I: adjustment for age, sex, smoke and duration of diabetes; model II: adjustment for model I + SCR, CHD, hindfoot, infection, sepsis and ABI. Besides, the analyses were repeated after stratification by sex. Data analyses were performed using the SPSS 18 statistical software package (IBM Corp., Armonk, NY, USA). P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Cohort

A total of 199 patients with DFO were enrolled in this study. The average age was 60.19 ± 12.50, 62.81% were male. The baseline characteristics of the patients according to the baseline eGFR categories are shown in Table 1. Among the patients, 39 individuals (71.79% male; mean age 62.62 ± 13.18 years) had moderately to severely decreased kidney function, 48 individuals (62.50% male; mean age 62.35 ± 10.86 years) had mildly decreased kidney function and 112 individuals (59.82% male; mean age 58.41 ± 12.73 years) had normal kidney function. At the initiation of the study, individuals with higher eGFR had lower SCr and lower UACR and were more likely to have a history of CHD. Other characteristics at baseline were similar among the three groups.

The Associations Between Normal Kidney Function and Abnormal Kidney Function with the Outcomes All-Cause Mortality and MACE

The patients were followed up for a median of 36 months (range, 2–36 months). During the follow-up period, 51 (25.63%) individuals died in 199 patients. Data on MACE were available from 188 patients due to missing data such as early death with other causes. There were 54 (28.72%) individuals had MACE and 26 of them died (data not shown). Among them, 18 (35.29%) and 33 (64.71%) patients died in eGFR ≥ 90 mL/min/1.73 m^2 group and eGFR < 90 mL/min/1.73 m^2 group, respectively; 20 (37.04%) and 34 (62.96%) patients had MACE in eGFR ≥ 90 mL/min/1.73 m^2 group and eGFR < 90 mL/min/1.73 m^2 group, respectively. The eGFR ≥ 90 mL/min/1.73 m^2 group had lower rates of all-cause mortality and MACE compared to eGFR < 90 mL/min/1.73 m^2 (P < 0.05 for both). Kaplan–Meier analysis demonstrated that eGFR < 90 mL/min/1.73 m^2 group showed higher incidence of the 3-year all-cause mortality and MACE than the eGFR ≥ 90 mL/min/1.73 m^2 group (log rank, both P < 0.01) (Figure 1). In the univariate Cox proportional-hazard analysis, 26 variables were identified that were

Table 1 Baseline Characteristics of the Study Population Based on eGFR (mL/Min/1.73m^2)

Characteristics	All (N = 199)	<60 (N=39)	60–89 (N = 48)	≥ 90 (N = 112)	*P*
Age, years	60.19 ± 12.50	62.62 ± 13.18	62.35 ± 10.86	58.41 ± 12.73	0.075
Sex, n (%)					0.411
Female	74 (37.19%)	11 (28.21%)	18 (37.50%)	45 (40.18%)	
Male	125 (62.81%)	28 (71.79%)	30 (62.50%)	67 (59.82%)	
Smoke, n (%)					0.373
No	91 (45.73%)	15 (38.46%)	20 (41.67%)	56 (50.00%)	
Yes	108 (54.27%)	24 (61.54%)	28 (58.33%)	56 (50.00%)	
Duration of diabetes (years)	11.31 ± 6.16	10.38 ± 6.46	11.48 ± 6.15	11.56 ± 6.08	0.578
TEXAS, n (%)					0.787
3B	96 (48.24%)	17 (43.59%)	23 (47.92%)	56 (50.00%)	
3D	103 (51.76%)	22 (56.41%)	25 (52.08%)	56 (50.00%)	
Laboratory parameters					
SCr, umol/L	78.71 ± 38.69	122.40 ± 59.73	83.97 ± 17.82	61.25 ± 18.00	< 0.001
eGFR, mL/min ·1.73m^2	92.43 ± 32.03	48.56 ± 7.20	76.27 ± 7.10	114.64 ± 22.46	< 0.001
UACR, mg/g	26.79 (17.56–106.73)	353.26 (26.49–434.93)	28.99 (18.29–109.75)	25.05 (16.69–61.40)	< 0.001
HbA1c, %	8.88 ± 2.05	8.88 ± 1.96	8.41 ± 2.26	9.08 ± 1.97	0.171
WBC, ×10^9/L	11.41 ± 2.84	11.82 ± 2.67	10.79 ± 2.98	11.53 ± 2.83	0.195
Hb, g/L	117.21 ± 20.37	119.63 ± 17.11	117.83 ± 19.56	116.10 ± 21.78	0.631
TC, mmol/L	4.69 ± 1.76	4.57 ± 1.86	4.47 ± 1.90	4.82 ± 1.66	0.451
TG, mmol/L	2.06 ± 0.56	2.22 ± 0.57	2.03 ± 0.50	2.01 ± 0.57	0.119
HDL-C, mmol/L	1.16 ± 0.38	1.19 ± 0.34	1.13 ± 0.41	1.17 ± 0.38	0.780
LDL-C, mmol/L	2.77 ± 0.93	2.77 ± 0.88	2.71 ± 1.01	2.80 ± 0.93	0.859
apoA1, g/L	1.20 ± 0.26	1.17 ± 0.24	1.23 ± 0.28	1.19 ± 0.26	0.606
apoB, g/L	0.96 ± 0.25	1.02 ± 0.22	0.94 ± 0.28	0.94 ± 0.24	0.228
ABI	0.87 ± 0.36	0.80 ± 0.40	0.84 ± 0.31	0.90 ± 0.36	0.244
Comorbidities					
T2DM, n (%)					0.561
No	9 (4.52%)	3 (7.69%)	2 (4.17%)	4 (3.57%)	
Yes	190 (95.48%)	36 (92.31%)	46 (95.83%)	108 (96.43%)	
Hypertension, n (%)					0.746
No	36 (18.09%)	8 (20.51%)	7 (14.58%)	21 (18.75%)	
Yes	163 (81.91%)	31 (79.49%)	41 (85.42%)	91 (81.25%)	
CHD, n (%)					0.022
No	126 (63.32%)	18 (46.15%)	29 (60.42%)	79 (70.54%)	
Yes	73 (36.68%)	21 (53.85%)	19 (39.58%)	33 (29.46%)	
CVD, n (%)					0.309
No	152 (76.38%)	32 (82.05%)	33 (68.75%)	87 (77.68%)	
Yes	47 (23.62%)	7 (17.95%)	15 (31.25%)	25 (22.32%)	
Sepsis, n (%)					0.386
No	171 (85.93%)	32 (82.05%)	44 (91.67%)	95 (84.82%)	
Yes	28 (14.07%)	7 (17.95%)	4 (8.33%)	17 (15.18%)	
PVD, n (%)					0.646
No	98 (49.25%)	19 (48.72%)	21 (43.75%)	58 (51.79%)	
Yes	101 (50.75%)	20 (51.28%)	27 (56.25%)	54 (48.21%)	

(*Continued*)

Table 1 (Continued).

Characteristics	All (N = 199)	<60 (N=39)	60–89 (N = 48)	≥ 90 (N = 112)	*P*
Neuropathy, n (%)					0.642
No	86 (43.22%)	17 (43.59%)	18 (37.50%)	51 (45.54%)	
Yes	113 (56.78%)	22 (56.41%)	30 (62.50%)	61 (54.46%)	
Infection, n (%)					0.159
Moderate	118 (59.30%)	20 (51.28%)	25 (52.08%)	73 (65.18%)	
Severe	81 (40.70%)	19 (48.72%)	23 (47.92%)	39 (34.82%)	
Location					
Forefoot, n (%)					0.312
No	19 (9.55%)	6 (15.38%)	5 (10.42%)	8 (7.14%)	
Yes	180 (90.45%)	33 (84.62%)	43 (89.58%)	104 (92.86%)	
Midfoot, n (%)					0.082
No	184 (92.46%)	33 (84.62%)	44 (91.67%)	107 (95.54%)	
Yes	15 (7.54%)	6 (15.38%)	4 (8.33%)	5 (4.46%)	
Hindfoot, n (%)					0.792
No	183 (91.96%)	35 (89.74%)	45 (93.75%)	103 (91.96%)	
Yes	16 (8.04%)	4 (10.26%)	3 (6.25%)	9 (8.04%)	
All-cause mortality n (%)					0.002
Survival	148 (74.37%)	24 (61.54%)	30 (62.50%)	94 (83.93%)	
Dead	51 (25.63%)	15 (38.46%)	18 (37.50%)	18 (16.07%)	
MACE, n (%)					0.002
No	134(71.28%)	19 (54.29%)	28 (60.87%)	87 (81.31%)	
Yes	54 (28.72%)	16 (45.71%)	18 (39.13%)	20 (18.69%)	

Notes: Mean ± standard deviation (SD) and Median (Inter Quartile Range) for continuous variables. Percentage (%) for categorical variables.
Abbreviations: SCr, serum creatinine; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; HbA1c, glycosylated hemoglobin; WBC, white blood cells; Hb, hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; ABI, ankle brachial index; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CVD, cardiovascular diseases; PVD, peripheral arterial diseases; MACE, major cardiovascular adverse events.

associated with 3-year all-cause mortality and MACE (Tables 2 and 3). Then, we established three models in order to explore the associations between eGFR levels and all-cause mortality or MACE (Table 4). In the crude model, compared patients with abnormal kidney function, patients with normal kidney function exhibited lower incidence of all-cause mortality (HR 0.36; 95% CI: 0.20–0.64; $P < 0.01$) and MACE (HR 0.37; 95% CI: 0.22–0.65; $P < 0.01$). Model I (adjustment for age, sex, smoke and duration of diabetes) and Model II (adjustment for Model I, SCR, CHD, hindfoot, infection, sepsis and ABI) also showed that patients with normal kidney function had lower incidence of all-cause mortality with HRs of 0.42 (95% CI: 0.24–0.75; $P < 0.01$) and 0.43 (95% CI: 0.22–0.85; $P < 0.01$), respectively and MACE with HRs of 0.43 (95% CI: 0.33–0.75; $P < 0.01$) and 0.51 (95% CI: 0.27–0.96; $P < 0.05$), respectively.

Stratified Analysis by Sex

To explore the influence of sex on the association of eGFR with the clinical outcomes, Table 5 shows the stratified analysis by sex for HRs of all-cause mortality and MACE by eGFR. Our results suggested that in both the unadjusted and adjusted models, compared to eGFR < 90 mL/min/1.73 m^2, eGFR ≥ 90 mL/min/1.73 m^2 was independently associated with decreased risk of all-cause mortality (crude model: HR 0.29, 95% CI 0.14–0.60, $P < 0.01$; Model I: HR 0.29; 95% CI 0.14–0.61, $P < 0.01$; Model II: HR 0.33; 95% CI 0.14–0.76, $P < 0.01$) and MACE (crude model: HR 0.28, 95% CI 0.13–0.60, $P < 0.01$; Model I: HR 0.25; 95% CI 0.12–0.56, $P < 0.01$; Model II: HR 0.27; 95% CI 0.11–0.65, $P < 0.01$) in male, but not in female (crude model: HR 0.56, 95% CI 0.22–1.55, $P > 0.05$; Model I: HR 0.72; 95% CI 0.26–2.02, $P > 0.05$; Model II: HR 0.35; 95% CI 0.09–1.40, $P > 0.05$) and

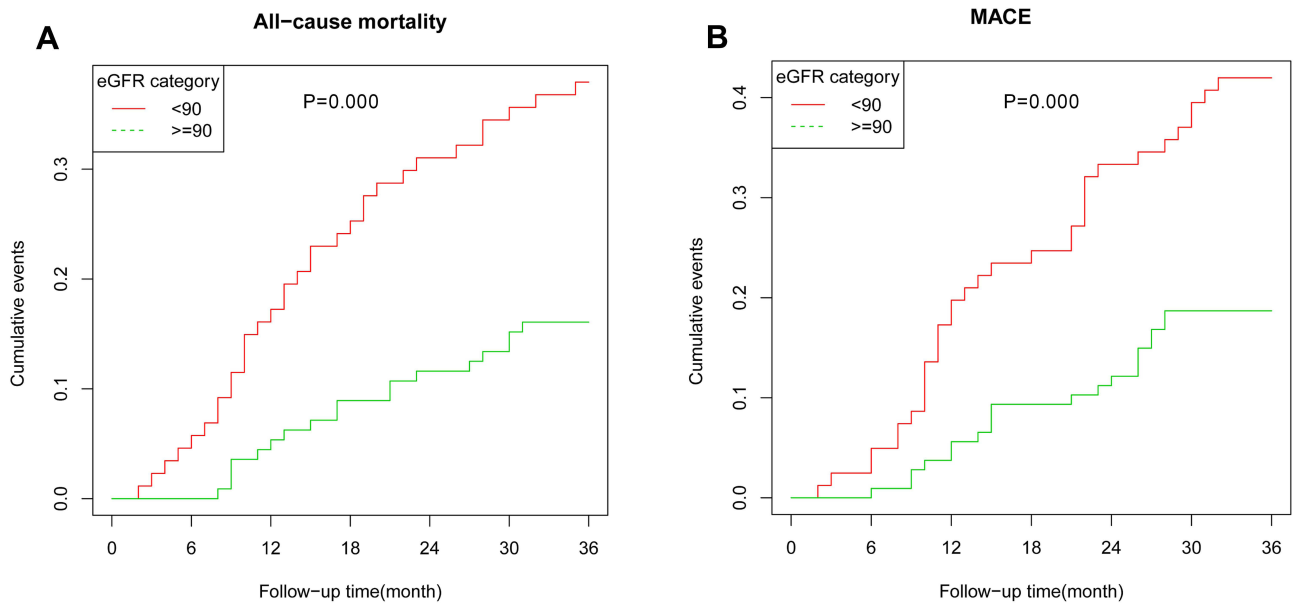

Figure 1 Kaplan-Meier curves of the cumulative incidence of all-cause mortality (**A**) and MACE (**B**) stratified by eGFR groups.

MACE (crude model: HR 0.57, 95% CI 0.24–1.33, $P > 0.05$; Model I: HR 0.78; 95% CI 0.32–1.93, $P > 0.05$; Model II: HR 1.27; 95% CI 0.33–4.87, $P > 0.05$), which implied that the association of eGFR with the clinical outcomes may be confounded by sex.

Discussion

In this study, among the patients, 39 individuals had moderately to severely decreased kidney function, 48 individuals had mildly decreased kidney function and 112 individuals had normal kidney function. At study initiation, patients with higher eGFR had lower SCr and lower UACR and were more likely to have a history of CHD. During a 3-year follow-up, all-cause mortality occurred in 51 patients among 199 participants, 54 had MACE in 188 participants and 26 of them died. After fully adjusting for potential confounders, compared to eGFR < 90 mL/min/1.73 m^2, eGFR ≥ 90 mL/min/1.73 m^2 had lower incidence of all-cause mortality and MACE. Additionally, when compared to eGFR < 90 mL/min/1.73 m^2, eGFR ≥ 90 mL/min/1.73 m^2 was independently associated with decreased risk of all-cause mortality and MACE in male, but not in female.

In our study, 43.72% of the patients with DFO showed eGFR < 90 mL/min/1.73 m^2. Of these, 19.60% was eGFR < 60 mL/min/1.73 m^2 and 24.12% was eGFR 60 to 89 mL/min/1.73 m^2. It is not only higher than the proportion of diabetic patients with chronic kidney disease (20–40%),[20] but also higher than the proportion of patients with diabetic foot disease complicated with chronic kidney disease (39.3%).[21] There were significant differences in the prevalence of CHD among the three groups, which suggests that DFO with poorer kidney function was more likely to have CHD. CHD is one of the main causes of death in patients with diabetic foot disease.[22] There is evidence that the survival rate of CHD patients with renal insufficiency is lower,[23] which is closely related to renal insufficiency.[24,25] Inflammation and atherosclerosis are involved in the common pathogenesis of chronic kidney disease and CHD, so they may be the underlying causes of the above findings.[26,27] There was no significant difference in HbA1c between the three groups. However, glucose metabolism and insulin action in diabetic patients are profoundly altered by a decrease in eGFR. Glycemic assessment by HbA1c is hampered by a variety of CKD-associated conditions, which makes the measured value either low or high. Alternative glycemic biomarkers, such as glycated albumin or fructosamine, are not fully validated.[28] Therefore, whether salivary amylase and salivary glucose concentration, relatively novel blood glucose indicators,[29] can effectively reflect the actual blood glucose level of CKD is worthy of further study. There was no significant difference between the three groups regarding the location of the diabetic foot wound. The location of the diabetic foot wound should be related to the Foot Posture Index.[30]

Table 2 Univariate Cox Proportional Hazard Model of eGFR Levels for All-Cause Mortality (n = 199)

Characteristics	HR	95% CI	-*P*-value
Sex			
Female	1.00	—	—
Male	1.36	(0.75–2.46)	0.3090
Age	1.05	(1.03–1.07)	< 0.0001
BMI	0.95	(0.88–1.02)	0.1253
Duration of diabetes	0.97	(0.93–1.02)	0.2483
Smoke			
No	1.00	—	—
Yes	1.25	(0.71–2.18)	0.4393
Hypertension			
No	1.00	—	—
Yes	1.29	(0.61–2.75)	0.5049
CHD			
No	1.00	—	—
Yes	2.07	(1.20–3.59)	0.0095
CVD			
No	1.00	—	—
Yes	1.31	(0.72–2.39)	0.3838
Sepsis			
No	1.00	—	—
Yes	2.49	(1.32–4.67)	0.0046
Infection			
Moderate	1.00	—	—
Severe	3.26	(1.83–5.79)	< 0.0001
Neuropathy			
No	1.00	—	—
Yes	1.61	(0.90–2.88)	0.1091
TEXAS			
3B	1.00	—	—
3D	1.16	(0.67–2.02)	0.5964
Forefoot			
No	1.00	—	—
Yes	1.33	(0.48–3.69)	0.5831
Midfoot			
No	1.00	—	—
Yes	1.69	(0.72–3.97)	0.2268
Hindfoot			
No	1.00	—	—
Yes	4.92	(2.56–9.48)	< 0.0001
HbA1c	0.95	(0.83–1.08)	0.45570
WBC	1.02	(0.92–1.12)	0.7133
Hb	1.01	(0.99–1.02)	0.3347
TC	1.08	(0.92–1.27)	0.3317
TG	1.34	(0.83–2.18)	0.2310
HDL	0.59	(0.28–1.21)	0.1505
LDL	1.05	(0.78–1.41)	0.7378
apoA1	1.07	(0.38–2.99)	0.8941
apoB	1.02	(0.34–3.11)	0.9678
SCr	1.01	(1.00–1.01)	0.0037
ABI	0.36	(0.16–0.81)	0.0133

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular diseases; MACE, major cardiovascular adverse events; HbA1c, glycosylated hemoglobin; WBC, white blood cells; Hb, hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; SCr, serum creatinine; ABI, ankle brachial index.

At present, there are still few studies on MACE of diabetic foot disease. In this study, 54 cases (28.72%) had MACE, 26 of them died, and the mortality rate of MACE was 48.15%. A recent study by Hung et al[31] showed that the incidence of MACE in patients with diabetic foot disease during hospitalization was 1.86% and the mortality rate of MACE patients was 47.62%. Their results were similar to ours, but the incidence of MACE in their study is different from our study. There are two reasons for consideration: one is that our observation is 3-year cumulative occurrence of MACE, while Hung's observation time was only 30.0 ± 25.0 days, and they only observed what happened during the patient's hospitalization; secondly, they assessed diabetic foot disease using Wagner grade 1–5 ulcers; however, we assessed DFO using Wagner grade 3 and above only.[32] Hence, our patients had more complicated conditions and more severe infections. The survival analysis showed that there was a significant difference in the cumulative risk of MACE between the decreased eGFR group and the normal eGFR group, and the decreased eGFR group had a higher risk of MACE as the observation time extended. He et al[21] followed up with patients for 3 years and explored the association between eGFR and cardiovascular events. They showed about 50% of patients with diabetic foot ulcers (DFU) in the decreased eGFR group had cardiovascular events, but less than 30% of the DFU patients in the normal eGFR group had cardiovascular events, which is similar to the results in our study. Previous studies[33] have shown that moderately and severely decreased kidney function (eGFR ≤ 60 mL/min/1.73 m^2) is an independent predictor of cardiovascular events in diabetic patients. Our

Table 3 Univariate Cox Proportional Hazard Model of eGFR Levels for MACE (n = 188)

Characteristics	HR	95% CI	*P*-value
Sex			
Female	1.00	—	—
Male	0.98	(0.57–1.70)	0.9477
Age	1.05	(1.03–1.08)	< 0.0001
BMI	0.95	(0.89–1.02)	0.1674
Duration of diabetes	0.98	(0.94–1.03)	0.5070
Smoke			
No	1.00	—	—
Yes	1.74	(0.99–3.07)	0.0539
Hypertension			
No	1.00	—	—
Yes	1.48	(0.70–3.14)	0.3059
CHD			
No	1.00	—	—
Yes	3.3	(1.90–5.74)	< 0.0001
CVD			
No	1.00	—	—
Yes	1.31	(0.73–2.35)	0.3665
Sepsis			
No	1.00	—	—
Yes	0.7	(0.25–1.95)	0.5006
Infection			
Moderate	1.00	—	—
Severe	2.52	(1.47–4.31)	0.0008
Neuropathy			
No	1.00	—	—
Yes	1.24	(0.71–2.14)	0.4489
TEXAS			
3B	1.00	—	—
3D	0.97	(0.57–1.65)	0.9015
Forefoot			
No	1.00	—	—
Yes	1.5	(0.54–4.15)	0.4349
Midfoot			
No	1.00	—	—
Yes	1.51	(0.64–3.52)	0.3435
Hindfoot			
No	1.00	—	—
Yes	4.48	(2.34–8.57)	< 0.0001
HbA1c	0.97	(0.86–1.10)	0.6341
WBC	1.06	(0.96–1.16)	0.2595
Hb	0.99	(0.98–1.01)	0.3766
TC	1.12	(0.96–1.30)	0.1669
TG	1.15	(0.72–1.82)	0.5683
HDL	0.73	(0.36–1.47)	0.3720
LDL	1.02	(0.76–1.35)	0.9176
apoA1	1.17	(0.43–3.18)	0.7529
apoB	1.41	(0.48–4.15)	0.5334
SCR	1.01	(1.00–1.01)	0.0046
ABI	0.38	(0.17–0.84)	0.0162

Abbreviations: MACE, major cardiovascular adverse events; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular diseases; MACE, major cardiovascular adverse events; HbA1c, glycosylated hemoglobin; WBC, white blood cells; Hb, hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; SCr, serum creatinine; ABI, ankle brachial index.

Table 4 Multivariate Cox Proportional Hazard Model of Association of eGFR Levels with All-Cause Mortality and MACE

Clinical Outcome	eGFR Category	HR	95% CI	*P*-value
All-cause mortality				
Crude model	eGFR < 90	1.00	—	—
	eGFR ≥ 90	0.36	(0.20–0.64)	0.001
Model I	eGFR < 90	1.00	—	—
	eGFR ≥ 90	0.42	(0.24–0.75)	0.004
Model II	eGFR < 90	1.00	—	—
	eGFR ≥ 90	0.43	(0.22–0.85)	0.015
MACE				
Crude model	eGFR < 90	1.00	—	—
	eGFR ≥ 90	0.37	(0.22–0.65)	0.001
Model I	eGFR < 90	1.00	—	—
	eGFR ≥ 90	0.43	(0.33–0.75)	0.003
Model II	eGFR < 90	1.00	—	—
	eGFR ≥ 90	0.51	(0.27–0.96)	0.038

Notes: Crude model adjust for none. Model I: adjust for age, sex, smoke, duration of diabetes. Model II: adjust for age, sex, smoke, duration of diabetes, SCR, CHD, hindfoot, infection, sepsis and ABI. Models for all-cause mortality (n = 199); models for MACE (n = 188).
Abbreviations: HR, hazard ratio; CI, confidence interval.

study further suggested that decreased GFR is a risk factor for MACE in patients with DFO compared with the normal eGFR. We also found that there was a significant difference in the cumulative risk rate of all-cause mortality between the decreased eGFR group and the normal eGFR group. With the extension of the observation time, patients in the decreased eGFR group had a higher risk of all-cause

Table 5 Stratified Analysis by Sex of eGFR Levels with All-Cause Mortality and MACE by Sex

Sex	Clinical Outcome	eGFR Category	HR	95% CI	*P*-value
Female	**All-cause mortality**				
	Crude model	eGFR < 90 eGFR ≥ 90	1.00 0.56	— (0.22–1.55)	— 0.276
	Model I	eGFR < 90 eGFR ≥ 90	1.00 0.72	— (0.26–2.02)	— 0.532
	Model II	eGFR <90 eGFR ≥ 90	1.00 0.35	— (0.09–1.40)	— 0.136
	MACE				
	Crude model	eGFR < 90 eGFR ≥ 90	1.00 0.57	— (0.24–1.33)	— 0.192
	Model I	eGFR < 90 eGFR ≥ 90	1.00 0.78	— (0.32–1.93)	— 0.59
	Model II	eGFR < 90 eGFR ≥ 90	1.00 1.27	— (0.33–4.87)	— 0.727
Male	**All-cause mortality**				
	Crude model	eGFR < 90 eGFR ≥ 90	1.00 0.29	— (0.14–0.60)	— 0.001
	Model I	eGFR < 90 eGFR ≥ 90	1.00 0.29	— (0.14–0.61)	— 0.001
	Model II	eGFR < 90 eGFR ≥ 90	1.00 0.33	— (0.14–0.76)	— 0.010
	MACE				
	Crude model	eGFR < 90 eGFR ≥ 90	1.00 0.28	— (0.13–0.60)	— 0.001
	Model I	eGFR < 90 eGFR ≥ 90	1.00 0.25	— (0.12–0.56)	— 0.001
	Model II	eGFR < 90 eGFR ≥ 90	1.00 0.27	— (0.11–0.65)	— 0.004

Notes: Crude model adjust for none. Model I: adjust for age, smoke, duration of diabetes. Model II: adjust for age, smoke, duration, SCR, CHD, hindfoot, infection, sepsis and ABI. Models for all-cause mortality (n = 199); models for MACE (n = 188).
Abbreviations: HR, hazard ratio; CI, confidence interval.

mortality, suggesting that renal insufficiency increases the risk of all-cause mortality in DFO patients. Previous studies[22,34] suggested that decreased eGFR was a risk factor for death in patients with diabetic foot disease, which was further confirmed in this study.

However, few studies estimated this association between male and female. In the present work, we found that in male with DFO, the decreased eGFR is closely associated with all-cause mortality and MACE only, but the results were absent in female. Male sex is a known risk factor associated with the incidence of cardiovascular events. Previous related research studies support this result. Orozco-Beltrán et al[35] found that in older diabetic patients, male had a higher risk of MACE than female. Pilote et al[36] also reported that females have a lower mortality rate of cardiovascular disease (CVD) than male. The possible reason may be due to cardiovascular protective effects of estrogen. Estrogen has the endothelium-dependent vasodilation, anti-inflammatory effects and antioxidant properties that can enhance vasodilation, improve lipid metabolism, atherosclerosis and CVD.[37] Besides, estrogen also exerts protective effects on the kidney. Clinical studies[38] reported that female have a lower incidence of chronic renal disease than male across the lifespan. Animal study[39] found that male mice are more commonly affected than female mice in the mouse models of renal injury, and estrogen therapy can effectively increase tolerance to ischemia-reperfusion injury. The mechanism may be because estrogen has proliferative and antiapoptotic effects on proximal tubular cells. In our study, female were mostly middle-aged to elderly and were in menopause status, but estrogen exerts the long-term protective effect on cardiovascular systems and kidney in premenopausal women, so the relevant studies all confirmed that our data and conclusions are credible.

There are still some shortcomings in this research. First, the patients who were not followed up and lost to follow-up were excluded. The outcomes of these patients are unknown, and the true mortality rate may be underestimated. Second, patients with malignant tumors were not excluded when the patients were enrolled, and the cause of death of some patients may be related to malignant tumors. Third, more basic trials are needed to clarify the mechanism behind the relationship between eGFR levels and the clinical outcomes of patients with DFO; further, clinical trials are needed to determine whether the treatment of renal dysfunction is beneficial to improve the clinical outcomes of patients with DFO.

Conclusions

In summary, decreased eGFR is a risk factor for all-cause mortality and MACE in individuals with DFO. Additionally, male with decreased eGFR had a higher risk of all-cause mortality and MACE, but female did not.

Ethics Approval and Consent to Participate

Written informed consent were provided by all participants prior to undergoing any study-related procedures. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region.

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Author Contributions

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

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Disclosure

The authors declare that they have no competing interests.

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