Association between estimated glomerular filtration rate and outcomes in patients with diabetic foot ulcers: a 3-year follow-up study

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Abstract

Objective: End-stage renal disease and dialysis have been proven to be associated with poor prognoses in diabetic foot ulcers (DFUs). However, it has rarely been reported whether and to what extent milder renal insufficiency affects the prognosis. The purpose of this study was to investigate the categorized impact of estimated glomerular filtration (eGFR) on the outcomes of patients with DFU.

Design and methods: Three hundred and sixty-six DFU patients hospitalized in a Chinese tertiary hospital were recruited and classified into 4 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 an average of 37 months to observe the outcomes, including ulcer healing, amputation, ulcer recurrence, cardiac or cerebrovascular events and death. The associations between eGFR and the outcomes were analysed by Cox proportional-hazards models.

Results: Compared to patients with normal eGFR, patients with moderately reduced eGFR had higher risk of healing failure (hazard ratio (HR) = 2.08, 95% confidence interval (CI): 1.13–3.82), cardiac events (HR = 5.25, 95% CI: 2.17–12.89) and death (HR = 3.54, 95% CI: 1.36–9.20). Severely reduced eGFR was associated with higher incidence of healing failure (HR = 2.84, 95% CI: 1.25–6.49) and death (HR = 4.45, 95% CI: 1.23–16.07). The impact of eGFR on ulcer recurrence and cerebrovascular events was not observed in all groups.

Conclusions: Moderately and severely reduced eGFR in patients with DFU were independent predictors for poor prognoses of both the limbs and the patients.

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Introduction

Diabetic foot ulcer (DFU), which is a highly prevalent condition in China and worldwide (1), is an advanced complication of diabetes with unfavorable outcomes (2, 3).

Diabetes is known to be a leading cause of chronic kidney disease, resulting in renal insufficiency of varying degrees complicated with DFU (4). End-stage renal disease or dialysis was previously suggested to be associated with poor prognoses of DFU (5, 6). However, the impact of milder renal insufficiency on DFU outcomes has rarely been reported. Although Ghanassia *et al.* (3) and Morbach *et al.* (7) noticed the adverse effects of chronic renal insufficiency in the long-term prognosis of DFU patients, renal insufficiency in these reports was defined based on serum creatinine or creatinine clearance (calculated from the Cockcroft–Gault formula), both of

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which are less accurate (8, 9) in assessing renal function compared with eGFR calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula. Furthermore, none of these studies made a stratification analysis and categorized the impact of each stage of renal insufficiency.

The aim of this study was to investigate the association between renal insufficiency, which was defined and classified based on eGFR, and the outcomes in patients with DFU.

Subjects and methods

Patient population and selection

From April 2009 to March 2012, patients hospitalized in our department for DFU were consecutively recruited into the cohort. Those patients with a previous occurrence of DFUs or major amputations were excluded. Patients were followed-up every 6 months from enrolment until March 2014, or until death. The outcomes information was obtained by conducting questionnaire surveys on patients in our department for inpatient or outpatient foot care or by calling their family members over the phone if patients could not be reached because they were receiving foot care elsewhere. All the foot care and outcome assessments in our department were performed by the same treatment team according to the guidelines for diabetic foot treatments recommended by the International Working Group on the Diabetic Foot (IWGDF) (10, 11, 12).

All patients gave consent for participation in this study. This study protocol was approved by the ethics committee of the Ruijin Hospital affiliated to the Shanghai Jiao Tong University of Medicine.

Definition and measurement of exposure, outcomes and impact factors

Renal function was assessed based on eGFR. Blood samples for serum creatinine test were taken from venous blood after patients were fasted for at least 8 hours. EGFR was calculated using the following MDRD equation for Chinese adults (13): $eGFR = 175 \times (\text{serum creatinine (mg/dL)})^{-1.234} \times \text{age}^{-0.179} \times 0.79$ (if female). Patients were categorized into 4 groups as follows: normal eGFR: ≥90 mL/min per 1.73 m^2, mildly reduced eGFR: 60–89 mL/min per 1.73 m^2, moderately reduced eGFR: 30–59 mL/min per 1.73 m^2, and severely reduced eGFR: <30 mL/min per 1.73 m^2.

The ulcer-related outcomes included primary ulcer healing, ulcer recurrence and amputations, whereas the patient-related outcomes included cardiac events, cerebrovascular events and death. Primary ulcer healing was determined by the full coverage of skin or crusts on the primary wound without major amputation of the limb. Ulcer recurrence was defined as the reappearance of the ulcer after primary wound healing was achieved. An amputation was considered major when it was performed above the tarsometatarsal articulation level (14); otherwise, it was viewed as a minor one. The cardiac events included acute heart failure, acute coronary syndrome and sudden cardiac death. The cerebrovascular events included fatal and non-fatal stroke. The outcome occurrences were recorded in the medical files and death records in our department, or they were obtained through telephonic interviews with patients or their relatives using questionnaires.

Other impact factors, including demographic data, BMI, type and duration of diabetes, HbA1c, severity of DFUs and microvascular or macrovascular comorbidities of the patients were recorded and assessed on admission. HbA1c was measured using high-performance liquid chromatography. DFUs were assessed using the Wagner classification system (15). Wounds at Wagner Grade 1 or 2 were further categorized as mild foot ulcers, whereas the remaining (Wagner 3, 4 and 5) ulcers were regarded as critical ulcers. Diabetic peripheral neuropathy (DPN) was diagnosed when 2 of the following criteria were met (3, 16): (1) neuropathic pain, anesthesia or other symptoms of paresthesia; (2) abnormal pinprick sensation of the lower limbs or altered 10-g Semmes–Weinstein monofilament test; or (3) diminished ankle reflexes. Peripheral artery disease (PAD) was diagnosed if one or more lower limb artery occlusions were spotted by Doppler ultrasound and/or ankle-brachial pressure index (ABI) < 0.9 in either of the limbs (7). History of coronary heart disease was confirmed by medical records or defined by the presence of a history of angina pectoris or myocardial infarction, any positive cardiac stress test result, or pathological signs on coronary angiography (17). History of stroke was defined as the presence of any neurologic deficiency event with or without sequelae (17). Hypertension was determined by BP ≥ 140/90 mmHg or the current use of antihypertensive medicine.

Statistical analysis

Quantitative variables were described by the mean ± S.D. or median (range) according to their distribution,

and one-way ANOVA was used to make comparisons among groups. Discontinuous variables were expressed using frequency, and comparisons were made using the χ^2 test. To analyze the association between reduced eGFR categories and outcomes, hazard ratios with 95% confidence intervals were first calculated using univariate Cox proportional-hazards models. Then, the following factors were included as confounders to ascertain hazard ratios for ulcer-related outcomes in multiple Cox regression models: age, sex, Wagner grade, PAD, DPN, HbA1c and treatment at baseline. Regarding patient-related outcomes, disease history, including duration of diabetes, history of coronary heart disease, history of stroke and cardiac treatment at baseline were further added to the multiple Cox proportional hazards models. The accumulated survival rates in the different groups were graphed by the Kaplan–Meier curve, and the log-rank test was performed to make comparisons among groups. All the statistical analyses were performed using the SAS statistical system (version 8.0; SAS Institute Inc., Cary, NC). A P value <0.05 was considered statistically significant.

Results

Population assessment and validation

A total of 366 hospitalized patients with DFU were enrolled in this study. The median age was 69 (range 31–96) years, 62% were male and 99.2% had type 2 diabetes. The baseline characteristics of the categorized eGFR groups are given in Table 1. At the initiation of the study, patients with lower eGFR tended to be older, had lower HbA1c values and were more likely to have DPN, history of coronary heart disease, stroke and hypertension. Other characteristics at baseline were similar among study groups.

The treatment information is listed in Table 2. More than 90% of patients received insulin therapy to control blood glucose. Antiplatelet agents were taken by approximately 50% of patients. An increasing trend in the use of diuretics and angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB) agents was seen with the decrease of eGFR. Only 14 patients received revascularization therapy in other hospitals prior to this study. No revascularization therapy was performed in this study.

The mean length of follow-up was 37 months (range 0.1–60 months). Follow-up data were obtained for 333 (91.0%) participants. The distribution of patients among eGFR categories was not significantly different in the total participant population and in those who had been followed-up (total, 60.7, 25.1, 9.3 and 4.9%; followed-up, 60.4, 24.9, 9.3 and 5.4%, respectively; $P=0.99$).

Primary ulcer healing

Of the 317 participants without major amputation and with available follow-up data, 259 (81.7%) attained primary ulcer healing by the end of the study.

Table 1 Characteristics of the study patients at baseline stratified by eGFR. Values are presented as *n* (%) or means ± S.D.s or median (range); Further analysis were done after LOG transition if the quantitative data does not conform to normal distribution.

		eGFR (mL/min per 1.73 m²)				
	Total	≥90	60–89	30–59	<30	‖*P* for trend
n	366	222 (60.7)	92 (25.1)	34 (9.3)	18 (4.9)	
Male	227 (62.0)	138 (62.2)	56 (60.9)	22 (64.7)	11 (61.1)	0.97
Age (y)	69 (31, 96)	66 (31, 95)	74.5 (40, 96)*	73.5 (50, 90)*	67 (53, 85)	<0.01
Type 2 diabetes	363 (99.2)	219 (98.7)	92 (100)	34 (100)	18 (100)	0.72^
Diabetes duration (y)	10 (0.01, 42)	10 (0.01, 30)	10 (0.08, 42)	16.5 (2, 30)	12 (0.5, 30)	0.10
Critical wounds (Wagner ≥3)	227 (62.0)	138 (62.2)	50 (54.4)	23 (67.7)	16 (88.9)	0.15
HbA1C (%)	8.5 (5.1, 15.1)	8.8 (5.1, 15.1)	8.2 (5.3, 14.5)	8.3 (5.6, 12.9)	7.5 (6.4, 13.6)	0.03
PAD†	202 (55.2)	121 (54.5)	47 (51.2)	22 (64.7)	12 (66.7)	0.27
DPN‡	175 (47.8)	97 (43.7)	47 (51.1)	20 (58.8)	11 (61.1)*	0.02
History of CHD§	91 (24.9)	39 (17.6)	27 (29.4)	17 (50.0)*	8 (44.4)*	<0.01
History of stroke	83 (22.7)	39 (17.6)	26 (28.3)	13 (38.2)*	5 (27.8)	0.01
SBP#	140 (80, 200)	135 (85, 200)	140 (96, 200)	141 (96, 200)	150 (96, 180)	0.12
DBP&	80 (40, 120)	80 (40, 120)	80 (50, 110)	70 (60, 100)	80 (60, 100)	0.93
Hypertension	224 (61.2)	124 (55.9)	63 (68.5)	23 (67.7)	14 (77.8)	0.01
BMI (kg/m²)	22.2 (15.0, 41.5)	22.3 (15.0, 39.1)	22.5 (16.4, 41.5)	21.0 (15.2, 26.3)	22.3 (21.6, 24.2)	0.53

*$P<0.05$ vs eGFR ≥ 90 mL/min/1.73 m²; †PAD: peripheral artery disease; ‡DPN, diabetic peripheral neuropathy; §CHD, coronary heart disease; ‖*P* for trend through eGFR categories. #SBP, systolic blood pressure; DBP, diastolic blood pressure; ^Calculated from Fish exact probability.

Table 2 Treatment at baseline Data are presented as *n* (%).

		eGFR (mL/min per 1.73 m²)				
	Total	≥90	60–89	30–59	<30	‖*P* for trend
n	366	222 (60.7)	92 (25.1)	34 (9.3)	18 (4.9)	
β-blocker	14 (3.8)	5 (2.3)	7 (7.6)	0	2 (11.1)	0.04
ACEI/ARB	147 (40.2)	76 (34.2)	44 (47.8)	18 (52.9)	9 (50.0)	<0.01
Diuretics	115 (31.4)	50 (22.5)	36 (39.1)*	20 (58.8)*	9 (50.0)	<0.01
Antiplatelet	186 (50.8)	113 (50.9)	44 (47.8)	18 (52.9)	11 (61.1)	0.60
Insulin use	339 (92.6)	208 (93.7)	82 (89.1)	32 (94.1)	17 (94.4)	0.78
Dialysis	6 (1.8)	0	0	0	6 (33.33)*	<0.01
History of revascularization	14 (3.8)	9 (4.05)	4 (4.35)	1 (2.94)	0	0.48

*$P<0.05$ vs eGFR ≥ 90mL/min per 1.73 m²; ‖*P* for trend through eGFR categories; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; History of revascularization: revascularization done in an other hospital before enrolment, which included balloon valvuloplasty, vascular Stent, vascular bypass and (or) blood vessel prosthesis.

The accumulated healing rates at 3, 6 and 12 months were 60.1, 73.3 and 90.0%, respectively. The median time from initial treatment to healing was 2 months.

In the first six months, the healing rate of the normal group was 77.1% (145 out of 188 alive patients gained primary healing) whereas the rate was much lower in reduced eGFR group, with 64.7% (44/68), 45.5% (10/22) and 30.8% (4/13) in the mildly, moderately and severely reduced group respectively ($P<0.01$ in χ^2 test, Fig. 1A).

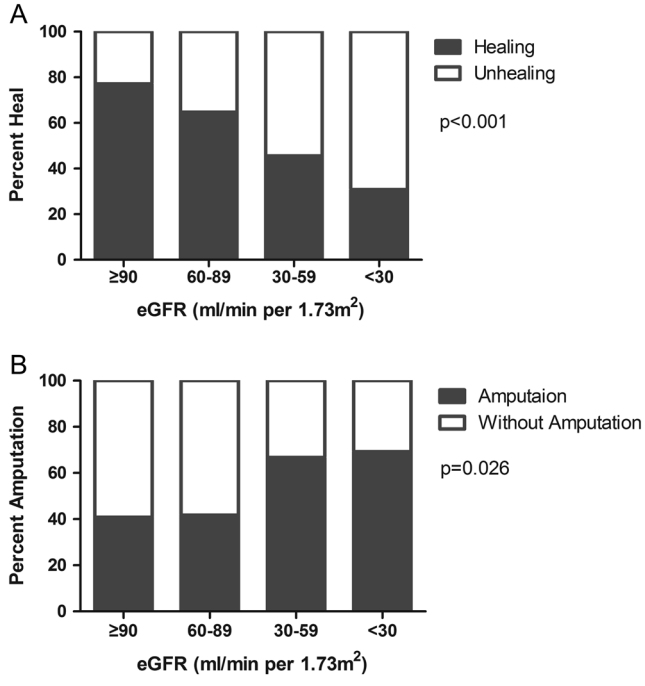

Figure 1

The comparisons of healing and amputation rate at 6 months between eGFR groups. (A) The healing rate at 6 months among eGFR groups. (B) The amputation rate at 6 months among eGFR groups. χ^2 tests were performed to make comparisons among groups.

Similarly, the Log-rank test and Cox proportional-hazards models also showed that patients with reduced eGFR exhibited a higher prevalence of ulcer healing failure (Fig. 2A, Table 3), with hazard ratios of 2.13 (95% CI: 1.18–3.83, $P=0.01$) and 2.85 (95% CI: 1.46–5.59, $P=0.002$) for moderately and severely reduced eGFR groups, respectively. Further adjustments for age, sex, Wagner grade, DPN, PAD, HbA1c and treatment confirmed the results, with the risk of healing failure increased by 108% and 184% for the moderately and severely reduced groups respectively, compared with that of the normal group. A decreasing healing trend across eGFR categories was also evident in both univariate and multiple analyses (Table 3).

Amputation

During the follow-up, 48.6% (162/333) of patients underwent amputations, of which 146 had minor ones and 16 had major amputations. In the first six months, approximately 40% of patients in the normal (40.8%, 80 out of 196 alive patients) and mildly (41.7%, 30/72) reduced eGFR groups underwent amputation, while the rate was above 60% in the moderately (66.7%, 16/24) and severely (69.2%, 9/13) reduced eGFR groups ($P=0.026$ in χ^2 test, Fig. 1B). In COX regression models, those with moderately reduced eGFR had a nearly two-fold higher risk of total amputation than patients with normal eGFR, even after adjusting for age, sex, Wagner grade, DPN, and PAD (hazard ratios (HRs) were 1.96 and 1.70 in Model 1 and Model 3, respectively, Table 3). Further adjustment of HbA1c and treatment showed moderately reduced eGFR was marginally associated with higher risk of total amputation (Model 4, Table 3). For patients with severely reduced eGFR, although their amputation rate was higher than that in the normal group (Fig. 2B), the results from Cox proportional-hazards models failed to show

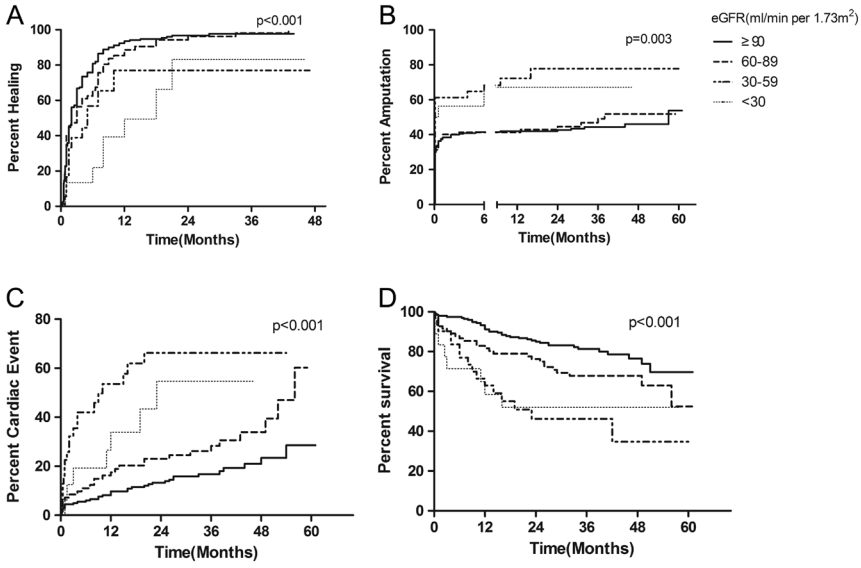

Figure 2
Kaplan–Meier curves of ulcer-related and patients-related outcomes stratified by eGFR groups. (A) The Kaplan–Meier curve of ucer healing in patients without major amputation among eGFR groups. (B) The Kaplan–Meier curve of total amputation among eGFR groups. (C) The Kaplan–Meier curve of cardiac event among eGFR groups. (D) The Kaplan–Meier curve of survival among eGFR groups. Log-rank tests were performed to make comparisons among groups.

statistically higher risk for amputation (Table 3). The risk for major amputation was not significantly different among all four groups (all $P>0.05$, Table 3).

Ulcer recurrence

Re-emerging ulcers were observed in 144 (52.9%) patients of the 272 patients who attained ulcer healing. The accumulated recurrence rates at 1, 2 and 3 years were 20.4, 35.5 and 47.1%, respectively. Reduced eGFR did not significantly correlate with the recurrence of ulcers either in univariate or in multivariate analysis (All $P>0.05$, Table 3).

Cardiac and cerebrovascular events

During the follow-up period, 131 (39.3%) patients suffered from one or more cardiac and (or) cerebrovascular events. Among them, cardiac events occurred in 84 (acute heart

Table 3 Unadjusted and adjusted HRs (95% CI) of the association between eGFR and ulcer-related outcomes.

	eGFR (mL/min per 1.73 m²)						
		60–89 (*n*=83)		30–59 (*n*=31)		<30 (*n*=18)	
Outcome	≥90 (*n*=201)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	***P* trend**
Healing failure								
Model 1	Ref	1.20 (0.90, 1.60)	0.20	2.13 (1.18, 3.83)	0.01	2.85 (1.46, 5.59)	<0.01	<0.01
Model 2	Ref	1.12 (0.83, 1.51)	0.46	2.02 (1.14, 3.66)	0.02	2.96 (1.51, 5.81)	<0.01	<0.01
Model 3	Ref	1.20 (0.88, 1.64)	0.24	2.13 (1.17, 3.89)	0.01	2.60 (1.32, 5.13)	<0.01	<0.01
Model 4	Ref	1.08 (0.78, 1.51)	0.63	2.08 (1.13, 3.82)	0.02	2.84 (1.25, 6.49)	0.01	<0.01
Total amputation								
Model 1	Ref	1.07 (0.73, 1.56)	0.73	1.96 (1.23, 3.10)	<0.01	1.63 (0.87, 3.06)	0.13	<0.01
Model 2	Ref	1.07 (0.73, 1.59)	0.72	1.97 (1.22, 3.16)	<0.01	1.63 (0.87, 3.06)	0.13	0.01
Model 3	Ref	1.15 (0.77, 1.70)	0.50	1.70 (1.06, 2.73)	0.03	1.00 (0.53, 1.89)	0.99	0.24
Model 4	Ref	1.19 (0.78, 1.82)	0.41	1.60 (0.97, 2.65)	0.06	0.64 (0.26, 1.61)	0.35	0.57
Major amputation								
Model 1	Ref	1.21 (0.36, 4.02)	0.76	1.79 (0.38, 8.47)	0.46	3.20 (0.68, 15.12)	0.14	0.15
Model 2	Ref	1.44 (0.41, 5.05)	0.57	2.12 (0.43, 10.40)	0.36	3.30 (0.70, 15.68)	0.13	0.11
Model 3	Ref	1.82 (0.49, 6.69)	0.37	2.22 (0.45, 11.08)	0.33	2.20 (0.44, 10.87)	0.33	0.21
Model 4	Ref	2.19 (0.53, 8.94)	0.28	3.38 (0.64, 17.99)	0.15	2.40 (0.25, 23.42)	0.45	0.16
Recurrence								
Model 1	Ref	1.00 (0.66, 1.52)	0.99	0.62 (0.25, 1.54)	0.31	0.72 (0.23, 2.29)	0.58	0.37
Model 2	Ref	1.04 (0.67, 1.60)	0.87	0.65 (0.26, 1.61)	0.35	0.71 (0.22, 2.26)	0.56	0.42
Model 3	Ref	1.07 (0.69, 1.65)	0.77	0.66 (0.26, 1.64)	0.37	0.74 (0.23, 2.36)	0.61	0.49
Model 4	Ref	1.11 (0.70, 1.78)	0.66	0.51 (0.19, 1.43)	0.20	1.15 (0.35, 3.74)	0.82	0.65

Model 1: univariate analysis; Model 2: adjusted for age, sex; Model 3: adjusted for age, sex, Wagner grade, DPN, PAD; Model 4: adjusted for age, sex, Wagner grade, DPN, PAD, HbA1c, history of revascularization, Dialysis, insulin use.

failure, 57; acute coronary syndrome, 12; acute coronary syndrome combined with acute heart failure, 9; sudden cardiac death, 6), stroke in 42 and both occurred in 5 patients.

The accumulated rates of cardiac events at 1, 2 and 3 years were 16.9%, 22.3% and 27.5% respectively. Over 50% of the patients with reduced eGFR suffered cardiac events, whereas only less than 30% of patients in the normal eGFR group had cardiac events (Fig. 2C). Of note, even those patients in the mildly reduced eGFR group had a nearly two-fold higher risk of cardiac events than those in the normal group (HR=1.88, 95% CI: 1.13–3.13), though further adjustments attenuated the results (Table 4). Moderately reduced eGFR was an independent predictor of cardiac events with HRs of 5.25 in the multivariate regression model. Severely reduced eGFR was associated with higher incidence of cardiac events independent of age, sex, Wagner grade and other diabetic complications, but the result was attenuated by further adjustment of HbA1c and treatment (Table 4).

A total of 47 participants were observed to have one or more cerebrovascular events. The accumulated incidences at 1, 2 and 3 years were 8.8%, 13.3% and 15.9% respectively. Even in the patients with normal eGFR, over 15% of participants had a stroke during the 3-year follow-up period. However, only five of the total 33 patients in the moderate group, and two of 18 patients in the severe group suffered a stroke. In the COX regression model, there was no significant correlation between the occurrence of cerebrovascular events and eGFR (all $P>0.05$, Table 4).

Mortality

Eighty-nine (26.7%) of the participants died during this study, including 44 (13.2%) from cardiovascular disease (32 from acute heart failure, 6 from sudden cardiac death, and 6 from myocardial infarction), 10 (3.0%) from stroke, 9 (2.7%) from renal failure, 8 (2.4%) from infection, 3 (0.9%) from malignancies, and 6 (1.8%) from other causes. The exact causes of the remaining 9 (2.7%) deaths were unknown, because these patients died at home without the presence of doctors and (or) an autopsy. The survival rates at 1, 3 and 5 years were 84.5%, 73.0% and 60.8%, respectively.

EGFR was a positive predictor for survival (Fig. 2D, Table 4), with HRs that increased from 1.78 (95% CI: 1.09–2.91, $P=0.02$) in the mildly reduced eGFR group to 3.78 (95% CI: 1.76–8.12, $P=0.0007$) in the severely reduced eGFR group. After adjustment by the complicated confounders and treatment variables, moderately and severely reduced eGFR were found to be independently associated with mortality, with risks of death three and four times higher than those in the normal eGFR group (Table 4). Nonetheless, this correlation was not observed in the mildly reduced eGFR group after adjustment (HR: 1.49, 95% CI: 0.66–3.34, $P=0.34$, Table 4).

Table 4 Unadjusted and adjusted HRs (95% CI) of the association between eGFR and patients-related outcomes.

	eGFR (mL/min per 1.73 m²)							
		60–89 (*n*=83)		30–59 (*n*=31)		<30 (*n*=18)		
Outcome	≥90 (*n*=201)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR(95% CI)	*P*	***P* trend**
Cardiac event								
Model 1	Ref	1.88 (1.13–3.13)	0.02	6.43 (3.64–11.34)	<0.01	3.80 (1.68–8.62)	<0.01	<0.01
Model 2	Ref	1.43 (0.84–2.43)	0.19	5.12 (2.87–9.15)	<0.01	3.77 (1.66–8.55)	<0.01	<0.01
Model 3	Ref	1.31 (0.75–2.29)	0.34	3.77 (2.01–7.05)	<0.01	2.51 (1.09–5.80)	0.03	<0.01
Model 4	Ref	1.55 (0.69–3.52)	0.29	5.25 (2.17–12.89)	<0.01	2.99 (0.89–10.09)	0.08	<0.01
Cerebrovascular event								
Model 1	Ref	1.20 (0.62–2.32)	0.60	1.82 (0.70–4.74)	0.22	1.24 (0.29–5.21)	0.77	0.32
Model 2	Ref	0.93 (0.47–1.87)	0.85	1.50 (0.57–3.97)	0.41	1.17 (0.28–4.96)	0.83	0.61
Model 3	Ref	0.78 (0.37–1.64)	0.52	1.51 (0.52–4.36)	0.45	1.25 (0.28–5.56)	0.77	0.73
Model 4	Ref	0.63 (0.17–2.30)	0.49	1.93 (0.41–9.16)	0.41	0.89 (0.07–12.32)	0.93	0.79
Death								
Model 1	Ref	1.78 (1.09–2.91)	0.02	3.98 (2.21–7.16)	<0.01	3.78 (1.76–8.12)	<0.01	<0.01
Model 2	Ref	1.20 (0.72–1.99)	0.49	2.88 (1.58–5.23)	<0.01	3.61 (1.68–7.78)	<0.01	<0.01
Model 3	Ref	1.13 (0.66–1.93)	0.67	2.24 (1.15–4.38)	0.02	3.27 (1.47–7.27)	<0.01	<0.01
Model 4	Ref	1.49 (0.66–3.34)	0.34	3.54 (1.36–9.20)	0.01	4.45 (1.23–16.07)	0.02	<0.01

Model 1: univariate analysis; Model 2: adjusted for age, and sex; Model 3: adjusted for age, sex, Wagner grade, DPN, PAD, CHD, Stroke, SBP, and diabetes duration; Model 4: adjusted for age, sex, Wagner grade, DPN, PAD, CHD, Stroke, SBP, diabetes duration, HbA1c, revascularization, dialysis, insulin use, antiplatelet, ACEI/ARB, diuretic.

Discussion

In this cohort study, we found that a moderate or severe decrease in eGFR was an independent predictor of poor outcomes in DFU patients, with higher rates of healing failure, a higher risk of cardiac events(significant in moderately group and marginally significant in the severely one), and higher all-cause mortality compared with the normal group. Meanwhile, moderately reduced eGFR was marginally associated with an increased need for amputation. Patients with mildly reduced eGFR exhibited a higher prevalence of cardiac events and death in univariate analysis, although no significant correlation was shown with ulcer-related and patient-related outcomes in multivariate analysis.

This study clarified how different levels of decreased eGFR impacted the foot, cardiovascular system and survival when a foot ulcer has already occurred in patients with diabetes. These results might help doctors realize the detrimental role of renal insufficiency in the progress of DFU even with proper foot treatment.

Renal insufficiency, regardless of whether it is defined as eGFR<60 mL/min per 1.73 m^2 (3, 18) or as serum creatinine above 1.5 mg/dL (19, 20), has been reported to affect ulcer healing in patients with diabetes. Our stratified analysis reconfirmed these results and further illustrated no statistically significant impact of mildly reduced eGFR on ulcer healing. Wound healing, included the phases of inflammation, proliferation and remodeling, is a complex process that requires a well-organized immune response, adequate blood or nutrition supply and normal innervation (21). Immune dysregulation in patients with renal insufficiency depletes the defences against infection and delays ulcer healing (22). Meanwhile, chronic kidney disease is commonly complicated with PAD and uremic neuropathy, which harm the process of wound healing (23, 24). Hypoalbuminemia, anemia and edema caused by renal failure may also explain the effect of moderately or severely decreased eGFR on poor ulcer healing in DFU (25, 26, 27).

Attention has been drawn to the remarkably high rate of amputations, and particularly major amputations, in patients with diabetes on either dialysis (7, 28, 29, 30) or with renal insufficiency (7, 31, 32). The present study found that the adverse impact of moderately reduced eGFR on amputation was marginally significant in DFU patients. However, the results from our study did not support the inclusion of eGFR <30 mL/min per 1.73 m^2 as a risk factor. The likely explanation might be our subjective determination of amputation. In our clinical practice, indications for amputation in patients with eGFR of <30 mL/min or dialysis were handled strictly, because these patients had relatively higher rates of postoperative complications or mortality (33, 34) and lower rates of wound healing after amputation (3). Therefore, amputations were performed only in patients with life-threatening ulcers. Other patients lived with ulcers that were carefully protected from infection. Therefore, the subjective determination of amputation might cover the true association between severely reduced eGFR and the need for amputation. For major amputations, the results were similar to those of total amputation but did not reach statistical significance. This result might be due to the limited number of major amputations (only 16) performed in our study.

A limited number of studies have concentrated on ulcer recurrence and its risk factors (35). Although Waaijman R carefully discussed the re-emerging ulcers in 171 patients with diabetes with recently healed ulcers, the impact of renal function was not mentioned in that study (36). Data from several other published studies did not support the correlation between renal insufficiency and recurrence. Connor & Mahdi reported that serum creatinine and proteinuria were similar between those who have a high risk of repetitive ulceration and their low risk counterparts (37). In another 3-year follow-up study on 79 patients with diabetes with healed ulcers, the proportion of end-stage renal disease was not markedly different in patients with and without recurrence. Furthermore, no renal-related index could be selected into the multivariate stepwise logistic regression model for re-ulceration (38). Consistent with these published data, our stratified study found none of the reduced eGFR groups to be associated with recurrence. Based on the discussion above regarding the detrimental role of renal insufficiency on blood supply, nutrition status, innervation and immune response, one may speculate that reduced eGFR is also a risk factor for re-emerging ulcers. However, the results were negative both in other studies and in ours; the reasons remain unknown. One likely explanation is that most of the studies were conducted in diabetes or foot care centers, where proper treatment for blood supply and peripheral nerves were given both in the hospital and during the follow-up period once a foot ulcer occurred, and therefore partially offsetting the adverse role of renal insufficiency in the re-emergence of foot ulcers. Another reason might be the decrease in the ability, intensity and duration of patients' activity with the deterioration of renal function, which, to some extent, protected patients from excessive plantar pressure and trauma.

Unlike amputation and mortality, cardiac events have rarely been considered important endpoints in follow-up studies of DFU. Indeed, diabetic foot disease has been observed to be a marker for cardiac events in recent decades (39). Our previous study (40) and several other reports (41, 42, 43) observed that patients with diabetes with foot ulcers were more likely to be complicated with cardiac disease and had a higher incidence of new cardiac events than those without foot ulcers. Additionally, cardiovascular events were suggested to be the leading cause of death in most long-term follow-up studies of DFU (3, 7), and the mortality of DFU might be decreased by aggressive cardiovascular risk management (44). Therefore, we regarded cardiac events as one of the observed endpoints in our study. Data from our study once again supported the high incidence of cardiac events in DFU, since over 20% of DFU patients experienced one or more cardiac events, even in the normal eGFR group. Moderately and severely reduced eGFR, which were previously proven to be independent predictors for cardiac events in patients with diabetes (45, 46), made matters worse in DFU, as the relative risk was increased five times higher (in the moderate group) and three times higher (in the severe group) than those with normal eGFR.

The independent impact of mildly reduced eGFR on cardiovascular disease remains unclear (47, 48). Wang found that patients with diabetes with eGFR of 60–89 (mL/min per 1.73 m^2) were at a significantly higher risk of coronary heart disease and stroke in a follow-up study containing 11 940 Caucasian and 16 451 African-American patients with diabetes (49). However, in another study of 6233 subjects in the US general population during an average of 15 years of follow-up, the association between mild renal insufficiency and cardiovascular disease was not independent (50). In our present study, mildly decreased eGFR was found to be associated with a higher risk of cardiac events in univariate analysis. However, this association seemed to be attributed to the concurrence of critical ulcers, PAD, DPN, cardiovascular disease, stroke and hypertension in the mildly decreased eGFR group at baseline.

Conflicting results regarding the impact of eGFR on stroke were reported in previous studies in both the general population (51, 52) and in patients with diabetes (53, 54). Little was previously known about this association in patients with DFU. In the present study, whether adjusted or not, eGFR was not significantly associated with cerebrovascular events in DFU patients. However, the limited number of strokes observed in the moderately and severely reduced eGFR groups might impact the accuracy of this statistic. Thus, the divergent impact of eGFR on cardiac events and cerebrovascular events, which share many risk factors in common, found in our study remains to be ascertained, and the underlying mechanism needs further investigation.

It is well established that foot ulcers increase the risk of mortality in patients with diabetes (55). Data from our present study showed that renal insufficiency may increase this risk further still, with progressively increased HRs for all-cause mortality in DFU patients from the onset of renal impairment to end-stage renal disease. Nevertheless, the correlation between mildly reduced eGFR and mortality was not independent. Older age and the co-occurrence of more cardiovascular disease, stroke and critical foot ulcers at baseline seemed to be the confounders between mildly reduced eGFR and increased risk of death. Consistent with our results, a previous 6.5 year follow-up study in 84 DFU patients reported creatinine clearance ≤60 mL/min to be an independent predictor for mortality (3). Similarly, serum creatinine concentration ≥1.5 mg/dL was found to be associated with mortality in another study of 247 DFU patients (7). These findings from our study and other published articles provide information on strategies that may further attenuate mortality in this group of patients.

There were several limitations in our study. First, the study cohort was recruited in one hospital, inevitably including selection bias. Second, the association between eGFR and specific-mortality was not analysed, because that incidence of subdivided death was relatively low and might cause insufficient statistical power. Finally, 33 (9.0%) patients were lost from the cohort. However, the rate of drop-out was low, and the baseline characteristics were similar between the total and drop-out patients. Therefore, the impact of this factor on the overall result is minimal and will not change the conclusion.

In conclusion, moderately and severely reduced eGFR is closely associated with unfavorable outcomes in patients with DFU. This study indicates that renal protection is crucial in the management of diabetic foot ulcers.

Declaration of Interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

Zhengyi Tang designed the study, reviewed the data and manuscript and was the guarantor of the work. Yang He researched data, performed statistical analysis and wrote the manuscript. Hongjie Qian, Lei Xu and Shanshan Zhang researched data and performed statistical analysis. Xueming Gu, Junyi Gu, Jianyuan Shi and Yaping Shen researched data. Jianmin Liu reviewed the manuscript.

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