The dose-response association between estimated glomerular filtration rate and prognosis of patients with ST-segment elevation myocardial infarction from rural areas of China’s Liaoning province

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Abstract
We aimed to investigate the dose-response associations between chronic kidney disease (CKD), and short and long-term cardiovascular outcomes, to characterize these associations by drawing dose-response curves based on a Chinese rural ST-segment elevation myocardial infarction (STEMI) population.

In all, 1067 patients with STEMI were consecutively enrolled from 12 secondary hospitals of China’s Liaoning province (from June 2009 to June 2010 and January 2015 to December 2015). The follow-up was regularly performed by telephone. Patients were grouped by estimated glomerular filtration rate (eGFR): normal, eGFR ≥90 mL/min/1.73 m²; mild CKD, 60 to 90 mL/min/1.73 m²; CKD, <60 mL/min/1.73 m². Adjusted logistic or Cox regression models were employed to compare short and long-term cardiovascular outcomes across different eGFR groups. Dose-response curves were plotted using restricted cubic spline functions.

About 18.46% of the STEMI patients had CKD. Patients with CKD were more likely to suffer from other comorbidities, but less likely to receive evidence-based therapies. CKD was independently associated with in-hospital mortality and major adverse cardiac events (MACE) as compared with patients with normal renal function (for in-hospital mortality, adjusted odds ratio [OR] 2.39, 95% confidence interval [CI] 1.18–4.85, P = .02; for in-hospital MACE, adjusted OR 2.01, 95% CI 1.09–3.70, P < .01). Likewise, CKD was significantly associated with long-term mortality as well (CKD vs normal, adjusted hazard ratio 2.55, 95% CI 1.17–5.57, P < .01). The dose-response associations between eGFR, and short and long-term cardiovascular outcomes were found to be linear (all with P values for nonlinear associations >.05).

CKD is an independent predictor of worse in-hospital and long-term clinical outcomes. The assessment of eGFR is essential to enable risk stratification, tailored therapy, and early and aggressive management.

Abbreviations: AIC = Akaike information criterion, AMI = acute myocardial infarction, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, CKD-EPI = the Chronic Kidney Disease Epidemiology Collaboration equation, CK-MB = creatine kinase isoenzyme MB, eGFR = estimated glomerular filtration rate, HR = hazard ratio, MACE = major adverse cardiac events, MI = myocardial infarction, OR = odds ratio, PCI = percutaneous coronary intervention, RCS = restricted cubic spline, STEMI = ST-segment elevation myocardial infarction.

Keywords: chronic kidney disease, estimated glomerular filtration rate, major cardiac adverse events, mortality, ST-segment elevation myocardial infarction.
1. Introduction

Acute myocardial infarction (AMI) caused tremendous medical, social, and economic burden all over the world.[1,2] In China, with the rapid economic growth and transition of lifestyles, the incidence of AMI and AMI-related mortality has dramatically increased over the past few decades. According to the Chinese cardiovascular report in 2015,[3] the mortality rate for AMI in urban areas was 55.32/100,000, whereas the mortality rate for AMI in rural areas was 68.60/100,000. Hence, AMI has become a major public health problem in China, particularly in rural areas. ST-segment elevation myocardial infarction (STEMI), known for its acute onset and high fatality rate, accounted for more than 80% of all AMI patients in China.[4,5]

Clinical evidence showed that chronic kidney disease (CKD) frequently coexisted among patients with coronary artery disease (CAD), which might result from accelerated atherosclerosis and underlying risk factors.[6] According to 2 previous nationwide cross-sectional studies in China,[7,8] the prevalence of renal insufficiency was 24.8% among CAD patients, as compared with 1.7% among the general population. Furthermore, patients with CKD at baseline usually have an increased cardiovascular risk and a poor prognosis after an AMI attack.[6,9-12] A glomerular filtration rate (GFR) formula is superior to single creatinine value in evaluating kidney function. Since an estimated GFR (eGFR) using specific formula combines creatinine level together with age, sex, race and BMI, it is less susceptible to confounding factors in predicting cardiovascular outcomes.[13] The prognostic significance of eGFR could last for more than 10 years after MI, even without accounting for changing values of serum creatinine.[14] Therefore, risk stratification using the eGFR-based kidney function estimates was preferred.

The majority of studies which investigated the association between CKD and clinical outcome of STEMI were limited to patients subjected to primary percutaneous coronary intervention (PCI).[12,15-19] However, little is known about the influence of CKD on the early and late outcomes of STEMI patients from rural areas where primary PCI is barely available. In addition, dose-response analyses in previous studies were usually carried out by converting eGFR into 2 or more categories.[9,15,20] As noted by Royston et al,[21] categorizing continuous exposure into groups would lead to loss of information and reduction in statistical power. An alternative to categorization is the application of spline functions.[22]

Therefore, the current study was conducted to investigate the associations between CKD, and short and long-term clinical outcomes among STEMI patients admitted to rural hospitals of China’s Liaoning province in a real world situation. Because we were especially interested in the continuous dose-response relationships, the spline functions were employed to plot the dose-response curves representing the associations between eGFR, and short and long-term clinical outcomes, to test the linear assumption of the associations, and to provide risk prediction of specific values of eGFR.

2. Materials and methods

2.1. Study subjects

In this multicenter study, STEMI patients were recruited by 2 stages. As previously described elsewhere,[23] 12 secondary hospitals located in rural areas of China’s Liaoning province were randomly sampled in the first stage (June 2009 to June 2010). All patients presenting with STEMI at those hospitals were consecutively enrolled. A purpose-designed questionnaire was completed by the local physicians after the achievement of written informed consent from patients or their families. In the second stage, all STEMI patients who were admitted to 8 secondary hospitals (chosen from the initial 12 secondary hospitals) were recruited by retrospectively reviewing medical records during January 2015 and December 2015. Data extraction was conducted by trained physicians using a minimally modified version questionnaire. All diagnoses and treatments were at the discretion of the local physicians without additional intervention from researchers.

We have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals. And the study protocol was approved by the ethics committee of the first affiliated hospital of China Medical University. Ethics approvals were also obtained from all the 12 participating secondary hospitals.

2.2. Inclusion and exclusion criteria for patient selection

Patients who fulfilled the following diagnostic criteria for STEMI were enrolled: symptoms of chest pain or chest discomfort that persisted over half an hour; ST-segment elevation was shown in at least 2 contiguous leads of a standard 12-lead electrocardiography (≥0.2 mm in precordial leads or ≥0.1 mm in limb leads); CK and creatine kinase isoenzyme MB (CK-MB) levels were twice above the decision limit or troponin level was high enough to be diagnosed with MI; and new emerging left bundle branch block was considered as a STEMI equivalent.

Patients were excluded according to the following criteria: the symptom-to-door time exceeded 24 hours; STEMI resulted from invasive operation; patients who had other coexisted life-threatening malignant diseases (such as cancers); patients whose serum creatinine on admission were unavailable were excluded as well; and patients with eGFR lower than 15 and greater than 150 would be excluded, being the former representative of a special group of patient (advanced kidney failure) and the latter possible outliers of the distribution.

2.3. Data collection

Data collection was performed using a standardized questionnaire. Information on demographics, cardiovascular risk factors, medical history, clinical characteristics on admission, reperfusion strategies, drugs used, laboratory tests, and cardiovascular outcomes were recorded.

2.4. GFR estimation and categorization

Serum creatinine measurements were carried out locally at the central laboratory of each collaborating hospital. Therefore, a dummy variable identifying the different laboratories was introduced in the subsequent statistical analysis. The eGFR estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation on the basis of baseline serum creatinine.[24] Of the 2 most widely used equations over the past decade, the CKD-EPI equation provided more accurate GFR estimation and translated to better performance of risk stratification than the Modification of Diet in Renal Disease equation did.[25-28]

The patients were stratified into 3 groups according to their baseline eGFR: the normal group (eGFR ≥90 mL/min/1.73 m²), the mild CKD group (eGFR ≥60 mL/min/1.73 m² and eGFR <90  

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mL/min/1.73 m²), and the CKD group (eGFR < 60 mL/min/1.73 m²). The definition of CKD was in accordance with the classification of stage 3 or higher CKD by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).

2.5. Definitions

We defined hyperlipidemia as having a history of hyperlipidemia or positive laboratory test reports (low-density lipoprotein ≥ 4.1 mmol/L, triglyceride ≥ 2.3 mmol/L, or total cholesterol ≥ 6.2 mmol/L). Diagnosis of recurrent MI depended entirely on the local physicians, based on indicators of new ischemia on electrocardiography, new emerging chest pain, and a significant elevation in CK, CK-MB, or troponin level. Major adverse cardiac events (MACE) were defined as the composite of cumulative all-cause mortality, recurrent MI, stroke and target vessel revascularization.

2.6. Follow-up

The follow-up was regularly performed by research assistants through telephoning the patients or their families after discharge. A dedicated questionnaire was completed for each of them. Data on medication usage, and also cardiovascular outcomes (such as all-cause mortality, stroke, recurrent MI, target vessel revascularization, bleeding, and rehospitalization) were obtained. The National Death Registration System serves as a supplemental strategy for follow-up when patients could not be contacted by telephone.

The primary endpoint was all-cause mortality. The secondary endpoint was the cumulative MACE during follow-up. The follow-up deadlines were November 30, 2010 and September 15, 2016 for the first and second study periods, respectively. For the primary endpoint, follow-up time was from discharge to death or deadline (if censored). As for the secondary endpoint, follow-up time was from discharge to the first occurrence of any MACE or deadline (if censored).

2.7. Statistical analysis

Data entry was independently conducted by 2 researchers using Epidata 3.1 software. Continuous variables were summarized as means ± standard deviation or as medians with interquartile range (25th, 75th), where appropriate. Categorical variables were summarized as counts and percentages. We examined patient demographic, cardiovascular risk factors, medical history, clinical characteristics, reperfusion therapies, drugs used, and clinical outcomes across different degrees of renal function using the Cochran-Armitage trend test for the trend of binary variables, and generalized linear model for the trend of continuous variables. All trend tests were based on 3 eGFR groups (normal, mild CKD, and CKD).

Crude and multivariable adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using logistic regression models so as to evaluate the impact of eGFR on in-hospital mortality and MACE. Similarly, univariate and multivariate Cox regression models were sequentially conducted to assess the prognostic value of eGFR on long-term mortality and MACE by providing hazard ratios (HRs) and their corresponding 95% CIs. The entry level for univariate analyses was P value less than .05. All significant variables would serve as covariates in the subsequent multivariate analyses. Cumulative event-free rates were calculated using the Kaplan-Meier curves and then compared across different groups using the log-rank test. The logistic regression analyses for 30-day clinical outcomes were not performed due to the relatively scarce data.

Since restricted cubic spline (RCS) allows easy visualization and flexible associations between an exposure and outcome, it was employed to characterize the dose-response relationships between eGFR, and short and long-term clinical outcomes, while adjusting for age, sex, and other significant covariates in the multivariate analyses. The reference value was set at 90 mL/min/1.73 m² for eGFR. The spline knots were chosen based on Akaike information criterion (AIC), an index to evaluate goodness of fit of a model. The risks of short and long-term outcomes for patients with specific eGFR values were predicted using the constructed dose-response curves. This analysis was conducted using the SAS macro provided by Desquilbet and Mariotti.

All statistical analyses were conducted with SAS software (version 9.3, SAS institute, Cary, NC). Missing data were handled using multiple imputation method (the details of missing data were shown in Supplemental Table 1, http://links.lww.com/MD/C48). Logistic regression models were used to impute binary variables, whereas linear regression models were used to impute continuous variables. A 2-tail P value < .05 was considered statistically significant.

3. Results

3.1. Population

As shown in the flowchart (Fig. 1), a total of 1244 STEMI patients were enrolled during the study period. After the exclusion of 177 patients whose creatinine level was unavailable or extremely low or high, there were 1067 patients left to evaluate the relationships between eGFR and in-hospital outcomes. The numbers of STEMI patients with an eGFR (mL/min/1.73 m²) of ≥ 90, 60 to 90, and <60 on presentation were 465 (43.58%), 405 (37.96%), and 197 (18.46%), respectively. Among those patients, 92 (8.62%) died during hospitalization. During the follow-up period, 920 patients completed the follow-up successfully and 55 patients (5.64%) lost to follow-up. The median follow-up time was 335 (233, 430) days.

3.2. Baseline characteristics

Table 1 compares demographic, cardiovascular risk factors, medical history, clinical characteristics, reperfusion therapies, and drugs used across different CKD degrees. Patients with mild CKD or CKD were older and more likely to be female, to present with hypertension, prior MI, previous stroke, and less likely to be smokers (all with P trend < .05). But the prevalence of diabetes, hyperlipidemia, history of CAD, and PCI was comparable among the 3 groups. The proportion of anterior MI, systolic blood pressure, and length of hospital stay declined gradually with decreasing values of eGFR. Conversely, patients with advanced CKD were more likely to have more advanced Killip class, higher heart rate, and serum creatinine level. No difference was observed in the symptom-to-door time.

3.3. Reperfusion therapies and drugs used

Patients with lower eGFR were less often treated with emergency reperfusion (P trend < .001). Meanwhile, the percentages of patients who received primary PCI or thrombolytic therapy concurrently decreased with the decrement of eGFR (P trend = .03
Significant differences were also noted in drugs used during hospitalization based on different renal function. Aspirin, low-molecular-weight heparin, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins were less frequently prescribed to those patients with lower renal function (all with $P_{\text{trend}} < .05$). By contrast, the prescription of clopidogrel, calcium antagonists, and traditional Chinese medicine were similar among normal, mild CKD, and CKD groups.

3.4. In-hospital, 30-day, and long-term clinical outcomes

Table 2 lists the in-hospital, 30-day, and long-term outcomes according to different degree of renal function. A significant stepwise increase in in-hospital mortality (3.66% vs 8.15% vs 21.32%; $P_{\text{trend}} < .0001$), stroke (1.72% vs 1.48% vs 5.08%; $P_{\text{trend}} = .03$), and the composite of mortality, stroke, recurrent MI (5.38% vs 10.12% vs 24.87%; $P_{\text{trend}} < .0001$) was observed in the transition from normal (eGFR $\geq 90\text{mL/min/1.73m}^2$) to CKD (eGFR $<60\text{mL/min/1.73m}^2$). However, there were no differences in the rates of in-hospital recurrent MI and bleeding ($P_{\text{trend}} = .63$ and .43, respectively).

Renal function was inversely associated with all-cause 30-day mortality. The mortality rate was 0.95% (normal group), 3.13% (mild CKD group), and 4.08% (CKD group) at 30-day postdischarge. Likewise, the 30-day MACE rates were significantly higher in STEMI patients with CKD, compared with patients in mild CKD or preserved kidney function groups (2.33% vs 4.29% vs 6.11%; $P_{\text{trend}} = .03$).

The worse degrees of renal function were significantly related to higher incidences of cumulative all-cause death and MACE. The cumulative mortality rates of STEMs in the normal, mild CKD, and CKD groups were 2.38%, 7.95%, and 16.33% during the entire follow-up period, respectively. Correspondingly, decline in the eGFR was significantly associated with progressive elevation of risk for cumulative MACE (from 9.82% to 23.66%; $P_{\text{trend}} < .001$). Kaplan-Meier survival analysis also indicated that lower eGFR was significantly associated with higher incidences of
long-term mortality and MACE (both with log-rank test \(P < .0001\)) (Fig. 2). During the follow-up visits, we found no significant differences with regard to any single components of MACE, except for mortality across eGFR groups.

3.5. Logistic regression analysis for in-hospital clinical outcomes

Table 3 demonstrates the crude ORs associated with in-hospital mortality and MACE. Of the significant covariates, CKD (eGFR <60 mL/min/1.73 m\(^3\)), advanced age, diabetes, prior stroke, increasing Killip class, and higher heart rate were associated with an elevated rates of in-hospital mortality and MACE. In contrast, male sex, current smoker, and higher systolic blood pressure were associated with a lower in-hospital mortality and MACE.

After adjustment for potential confounders (see Table 2), CKD, sex, prior stroke, Killip class, and systolic blood pressure were found to be significantly related to in-hospital mortality and MACE. For patients with CKD (eGFR <60 mL/min/1.73 m\(^3\)), the adjusted ORs of in-hospital and MACE were 2.39 (95% CI 1.18–4.85, \(P = .02\)) and 2.01 (95% CI 1.09–3.70, \(P < .01\)) as compared with those with preserved renal function (eGFR ≥90 mL/min/1.73 m\(^3\)).

3.6. Cox regression analysis for long-term clinical outcomes

After adjustment for baseline characteristics in the multivariate Cox regression model, eGFR less than 60 mL/min/1.73 m\(^3\) was independently associated with an increased risk of long-term mortality when compared with normal renal function (adjusted HR 2.55, 95% CI 1.17–5.57, \(P = .02\)) (Table 4). Other independent predictors of long-term mortality included age, symptom-to-door time, Killip class, and heart rate. However, the multiple Cox regression model failed to replicate the significant association between lower eGFR and long-term MACE after the
adjustment of age, current smoker, prior MI, prior PCI, Killip class, heart rate, and emergency reperfusion (mild CKD vs normal, adjusted HR 0.96, 95% CI 0.61–1.53, P = .87; CKD vs normal, adjusted HR 1.46, 95% CI 0.87–2.44, P = .15).

3.7. Dose-response analyses for the associations between eGFR, and short and long-term clinical outcomes using RCS functions

Dose-response association (adjusted for age, sex, and other significant covariates in multivariate analyses) between eGFR and in-hospital mortality was shown in Fig. 3A. The dose-response curve revealed a linear association for in-hospital mortality (test for overall association: P < .01; test for nonlinear association: P = .79, AIC = 487.55). Similarly, a statistically significant linear dose-response curve between eGFR and in-hospital MACE was plotted using RCS functions (test for overall association: P < .01, test for nonlinear association: P = .77, AIC = 590.50) (Fig. 3B).

Dose-response analyses for long-term mortality and MACE were illustrated in Fig. 4A and B. Since the graphic results did not reveal major deviations from linearity, the null hypothesis of linearity cannot be rejected. That is to say, the relationships between eGFR and long-term mortality and MACE were also linear (for long-term mortality, test for overall association: P = .02, test for nonlinear association: P = .36, AIC = 740.66; as

Table 2
Incidence of in-hospital, 30-day, and long-term outcomes according to different degrees of renal function.

| Outcomes          | Normal events (%) | Mild CKD events (%) | CKD events (%) | Z    | P*
|-------------------|-------------------|---------------------|---------------|------|------
| In-hospital outcomes | n=465             | n=405               | n=197         |      |      |
| Mortality         | 17 (3.66)         | 33 (8.15)           | 42 (21.32)    | −7.03| <.0001 |
| Stroke            | 8 (1.72)          | 6 (1.48)            | 10 (5.00)     | −2.22| .03   |
| Recurrent MI      | 1 (0.22)          | 7 (1.73)            | 0 (0.00)      | −0.48| .63   |
| TVR               | 0 (0)             | 0 (0)               | 0 (0)         | NA   | NA    |
| Bleeding          | 8 (1.72)          | 10 (2.47)           | 5 (2.54)      | −0.78| .43   |
| MACE              | 27 (5.38)         | 41 (10.12)          | 49 (24.67)    | −7.00| <.0001 |
| 30-d outcomes     | n=421             | n=352               | n=147         |      |      |
| Mortality         | 4 (0.95)          | 11 (3.13)           | 6 (4.00)      | −2.51| .01   |
| Stroke            | 0 (0)             | 0 (0)               | 0 (0)         | NA   | NA    |
| Recurrent MI      | 2 (0.52)          | 2 (0.66)            | 1 (0.76)      | −0.34| .73   |
| TVR               | 4 (1.03)          | 0 (0)               | 3 (2.29)      | −0.61| .54   |
| Bleeding          | 0 (0)             | 1 (0.33)            | 0 (0)         | −0.43| .67   |
| MACE              | 81 (20.90)        | 65 (21.45)          | 18 (13.74)    | 1.42 | .16   |
| Long-term outcomes| n=421             | n=352               | n=147         |      |      |
| Mortality         | 10 (2.38)         | 26 (7.95)           | 24 (16.33)    | −5.87| <.0001 |
| Stroke            | 9 (2.33)          | 5 (1.65)            | 3 (2.29)      | 0.23 | .81   |
| Recurrent MI      | 18 (4.65)         | 12 (3.96)           | 10 (7.63)     | −0.99| .32   |
| TVR               | 10 (2.58)         | 6 (1.98)            | 3 (2.29)      | 0.34 | .73   |
| Bleeding          | 1 (0.26)          | 3 (0.99)            | 0 (0)         | −0.17| .67   |
| MACE              | 121 (31.27)       | 109 (30.97)         | 47 (35.68)    | −1.25| .21   |

MACE = major adverse cardiac events, MI = myocardial infarction, TVR = target vessel revascularization.

Exclusively available in 821 patients who were followed up using telephone.

Bold texts indicated that P values for the linear trend among the three groups were statistically significant.

Figure 2. Kaplan-Meier estimates of the long-term mortality (A) and long-term major adverse cardiac events (B) by admission eGFR category. eGFR = estimated glomerular filtration rate.
Table 3
Logistic regression analysis for prediction of in-hospital mortality and MACE.

|                      | Univariate | Multivariate |
|----------------------|------------|--------------|
|                      | Crude OR   | 95% CI       | P     | Adjusted OR | 95% CI       | P     |
| In-hospital mortality|            |              |       |             |              |       |
| eGFR (mL/min/1.73 m²) |            |              |       |             |              |       |
| ≥90                  | Ref        | —            | —     | Ref         | —            | —     |
| 60–90                | 2.24       | 1.28–4.26    | <.01  | 1.30        | 0.66–2.57    | .45   |
| <60                  | 7.14       | 3.05–12.91   | <.0001| 2.39        | 1.18–4.85    | .02   |
| Age ≥60 y            | 2.70       | 1.57–4.64    | <.0001| 0.93        | 0.48–1.80    | .83   |
| Sex (male vs female) | 0.29       | 0.19–0.45    | <.0001| 0.44        | 0.26–0.75    | <.01  |
| Diabetes             | 1.82       | 1.15–2.88    | .01   | 1.09        | 0.64–1.88    | .75   |
| Current smoker       | 0.39       | 0.24–0.64    | <.0001| 0.68        | 0.38–1.23    | .21   |
| Prior stroke         | 2.06       | 1.24–3.41    | <.01  | 1.71        | 0.96–3.06    | .07   |
| Killip class ≥2      | 12.47      | 7.14–21.76   | <.0001| 8.42        | 4.68–15.18   | <.0001|
| Heart rate (bpm) ≥100| 3.13       | 1.94–5.05    | <.0001| 1.57        | 0.90–2.75    | .11   |
| SBP (mm Hg) ≥140     | 0.42       | 0.26–0.68    | <.0001| 0.41        | 0.24–0.70    | <.01  |
| Long-term MACE       |            |              |       |             |              |       |
| eGFR (mL/min/1.73 m²) |            |              |       |             |              |       |
| ≥90                  | Ref        | —            | —     | Ref         | —            | —     |
| 60–90                | 1.98       | 1.18–3.32    | <.01  | 1.12        | 0.63–2.00    | .30   |
| <60                  | 5.83       | 3.48–9.77    | <.0001| 2.01        | 1.00–3.70    | <.01  |
| Age ≥60 y            | 3.18       | 1.91–5.30    | <.0001| 1.41        | 0.78–2.56    | .25   |
| Sex (male vs female) | 0.33       | 0.22–0.49    | <.0001| 0.47        | 0.20–0.76    | <.01  |
| Diabetes             | 1.71       | 1.12–2.60    | .01   | 1.12        | 0.63–1.82    | .66   |
| Killip class ≥2      | 2.25       | 1.43–3.55    | <.0001| 1.92        | 1.15–3.21    | <.01  |
| Heart rate (bpm) ≥100| 2.76       | 1.77–4.32    | <.0001| 1.43        | 0.86–2.39    | .17   |
| SBP (mm Hg) ≥140     | 0.54       | 0.36–0.82    | <.01  | 0.55        | 0.35–0.87    | <.01  |

CI = confidence interval, eGFR = estimated glomerular filtration rate, MACE = major adverse cardiac events, MI = myocardial infarction, OR = odds ratio, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, STEM = ST-segment elevation myocardial infarction.

Bold tests indicated that P values for multivariate regression analyses were statistically significant.

Table 4
Cox regression analysis for prediction of long-term mortality and MACE.

|                      | Univariate | Multivariate |
|----------------------|------------|--------------|
|                      | Crude HR   | 95% CI       | P     | Adjusted HR | 95% CI       | P     |
| Long-term mortality  |            |              |       |             |              |       |
| eGFR (mL/min/1.73 m²) |            |              |       |             |              |       |
| ≥90                  | Ref        | —            | —     | Ref         | —            | —     |
| 60–90                | 3.32       | 1.61–6.83    | <.01  | 1.80        | 0.86–3.76    | .12   |
| <60                  | 7.51       | 3.59–15.72   | <.0001| 2.55        | 1.17–5.57    | .02   |
| Age ≥60 y            | 7.38       | 2.96–18.42   | <.0001| 3.17        | 1.22–8.27    | .02   |
| Current smoker       | 0.34       | 0.18–0.62    | <.0001| 0.69        | 0.36–1.30    | .24   |
| Prior MI             | 3.03       | 1.58–5.81    | <.0001| 1.58        | 0.80–3.15    | .19   |
| Prior stroke         | 2.19       | 1.25–3.82    | <.01  | 1.39        | 0.70–2.46    | .26   |
| Symptom-to-door time (min) ≥180 | 2.05 | 1.20–3.49 | <.01 | 1.76 | 1.02–3.03 | .04 |
| Killip class ≥2      | 5.23       | 3.11–8.80    | <.0001| 2.92        | 1.67–5.10    | <.001 |
| Heart rate (bpm) ≥100| 5.16       | 3.10–8.61    | <.0001| 2.43        | 1.41–4.20    | <.01  |
| Emergency reperfusion| 0.37       | 0.21–0.64    | <.001 | 0.58        | 0.33–1.03    | .06   |
| Long-term MACEb      |            |              |       |             |              |       |
| eGFR (mL/min/1.73 m²) |            |              |       |             |              |       |
| ≥90                  | Ref        | —            | —     | Ref         | —            | —     |
| 60–90                | 1.41       | 0.91–2.18    | .13   | 0.96        | 0.61–1.53    | .87   |
| <60                  | 2.77       | 1.72–4.45    | <.0001| 1.46        | 0.87–2.44    | .15   |
| Age ≥60 y            | 2.45       | 1.56–3.86    | <.0001| 1.88        | 1.14–3.09    | .01   |
| Current smoker       | 0.65       | 0.44–0.95    | .03   | 0.93        | 0.62–1.40    | .73   |
| Prior MI             | 2.81       | 1.63–4.84    | <.0001| 1.59        | 0.84–2.99    | .15   |
| Prior PCI            | 2.63       | 1.16–6.02    | .02   | 2.06        | 0.81–5.25    | .13   |
| Killip class ≥2      | 2.38       | 1.64–3.47    | <.0001| 1.55        | 1.03–2.32    | .04   |
| Heart rate (bpm) ≥100| 0.96       | 0.66–1.40    | .04   | 2.45        | 1.58–3.81    | <.0001|
| Emergency reperfusion| 0.50       | 0.40–0.65    | <.01  | 0.73        | 0.40–1.08    | .11   |

CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, MACE = major adverse cardiac events, MI = myocardial infarction, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, STEM = ST-segment elevation myocardial infarction.

b Exclusively available in 821 patients who were followed up by telephone.

Bold tests indicated that P values for multivariate regression analyses were statistically significant.
for long-term MACE, test for overall association: \( P = .01 \), test for nonlinear association: \( P = .29 \), AIC = 1384.26).

3.8. Risk predictions according the constructed dose-response curves

Risk predictions were conducted according to the dose-response curves previously constructed. The ORs/HRs and their corresponding 95% CIs for any given eGFR values within the variation ranges could be achieved from the dose-response curves, with a reference value of 90 mL/min/1.73 m² for eGFR. Tables 5 and 6 showed the risk predictions of every 10 unit increase in eGFR for in-hospital and long-term clinical outcomes. For instance, STEMI patients with a baseline eGFR of 60 mL/min/1.73 m² were 1.86 (95% CI 1.31–2.65) and 1.70 (95% CI 1.23–2.33) times more likely to suffer from in-hospital mortality and MACE, when compared with patients with a baseline eGFR of 90 mL/min/1.73 m². Likewise, the incidences of long-term mortality and MACE were 1.80 (95% CI 1.18–2.73) and 1.41 (95% CI 1.09–1.82) folds higher in patients with an on admission eGFR of 60 mL/min/1.73 m² as compared with those with an eGFR of 90 mL/min/1.73 m².

4. Discussion

Our study aimed at exploring the associations between CKD, and short and long-term clinical outcomes among STEMI patients from China’s rural areas. Our results demonstrated that in-hospital, 30-day, and long-term mortality and MACE significantly increased with the decreasing eGFR (all with \( P \text{ trend} < .05 \)). Multivariate logistic regression analyses indicated that CKD (eGFR less than 60 mL/min/1.73 m²) was an independent predictor of in-hospital mortality and MACE. There was a 2.39-fold increase in risk of in-hospital mortality, and 2.01-fold increase in risk of in-hospital MACE for STEMI patients with CKD, as compared with those with normal renal function (eGFR higher than 90 mL/min/1.73 m²). Similarly, multivariate Cox regression analyses revealed that CKD was an independent prognostic indicator for long-term mortality as well (CKD group vs normal group, adjusted HR 2.55, 95% CI 1.17–5.57, \( P = .02 \)). The prognostic values of eGFR were further confirmed by dose-response analyses using RCS functions. Since nonlinear tests did not reveal any major deviations from linearity, the associations between eGFR, and in-hospital and long-term outcomes were considered to be linear.

About 1 out of 5 STEMI patients (18.46%) were found to have CKD in our study, which was far higher than that in the general population (1.7%) and quite close to a previous study based on Chinese STEMI patients (18.5%).[8,37] The prevalence of CKD was also similar to other studies conducted in Korea (22.6%),[16] the United Kingdom (20.3%),[10] and Denmark (21.8%).[12] However, the in-hospital mortality rate in the CKD group was higher than that previously reported (21.32% vs 8.7%).[11] This might be because our study population was enrolled from real-world setting without preselection. In contrast, patients with severe renal dysfunction were excluded from the study conducted.
In addition, all patients in the previous study had received primary PCI treatment, compared with 6.09% in our study. Our findings, in accordance with earlier observations based on various populations, highlight the prognostic value of CKD as a strong and robust indicator of excess short and long-term risk in patients from China’s rural areas. Several possible explanations for the detrimental clinical outcomes are coexisting coronary risk factors (including advanced age, high percentage of female, diabetes mellitus, and hypertension), advanced Killip class, high burden of coronary atherosclerosis, low left ventricular ejection fraction, inadequate reperfusion.

**Table 5**

| eGFR (mL/min/1.73 m²) | In-hospital mortality OR² 95% CI | In-hospital MACE OR² 95% CI |
|-----------------------|---------------------------------|----------------------------|
| 30                    | 3.19, 1.54–6.61                | 2.65, 1.34–5.22            |
| 40                    | 2.67, 1.52–4.69                | 2.29, 1.36–3.86            |
| 50                    | 2.23, 1.45–3.45                | 1.97, 1.33–2.94            |
| 60                    | 1.86, 1.32–2.65                | 1.70, 1.23–2.33            |
| 70                    | 1.53, 1.14–2.06                | 1.44, 1.10–1.89            |
| 80                    | 1.25, 1.02–1.53                | 1.21, 1.01–1.45            |
| 90                    | 1.00                           | —                           |
| 100                   | 0.79, 0.58–1.08                | 0.81, 0.61–1.08            |
| 110                   | 0.61, 0.3–1.23                 | 0.65, 0.34–1.23            |
| 120                   | 0.48, 0.16–1.44                | 0.52, 0.19–1.42            |
| 130                   | 0.37, 0.08–1.68                | 0.42, 0.10–1.65            |

CI = confidence interval, eGFR = estimated glomerular filtration rate, MACE = major adverse cardiac events, OR = odds ratio.

*Adjusted factors include age, sex, and other significant covariates in multivariate analyses.

**Table 6**

| eGFR (mL/min/1.73 m²) | Long-term mortality HR² 95% CI | Long-term MACE HR² 95% CI |
|-----------------------|--------------------------------|----------------------------|
| 30                    | 2.32, 1.06–5.11                | 2.50, 1.33–4.70            |
| 40                    | 2.15, 1.15–3.99                | 2.05, 1.27–3.33            |
| 50                    | 1.98, 1.21–3.24                | 1.69, 1.19–2.41            |
| 60                    | 1.80, 1.16–2.73                | 1.41, 1.09–1.82            |
| 70                    | 1.57, 1.00–2.26                | 1.20, 0.90–1.47            |
| 80                    | 1.30, 1.02–1.67                | 1.07, 0.94–1.22            |
| 90                    | 1.00                           | —                           |
| 100                   | 0.71, 0.48–1.06                | 0.99, 0.80–1.22            |
| 110                   | 0.46, 0.20–1.18                | 1.00, 0.62–1.62            |
| 120                   | 0.32, 0.08–1.34                | 1.03, 0.46–2.22            |
| 130                   | 0.22, 0.03–1.52                | 1.06, 0.37–3.05            |

CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, MACE = major adverse cardiac events.

*Adjusted factors include age, sex and other significant covariates in multivariate analyses.
therapy, insufficient guideline recommended pharmacotherapy treatment, increased oxidative stress, and decreased nitric oxide activity.[6,18,20,39,40] Furthermore, as compared with patients with preserved renal function, CKD patients tend to have larger infarct size and left ventricular remodeling that result from excessive inflammatory response, oxidative stress, and activation of sympathetic nervous and rennin-angiotensin systems.[41,42] These factors may act synergistically to increase the risk of adverse cardiovascular events among CKD patients.

Consistent with the results from previous observational studies,[18,42] our study demonstrated a stepwise increase in the proportions of hypertension, prior MI, prior stroke, and advanced Killip class with the worsening renal function (Table 1). STEMI patients were less likely to be male and current smoker with decreasing eGFR. Despite the proven benefits,[43] the guideline recommended therapies, particularly the use of emergency reperfusion and antiremodeling drugs, were under use. Our findings suggest that there is a “treatment-risk-paradox” that patients with higher calculated risk scores are less likely to receive aggressive therapeutic procedures.[44] The insufficient use of therapies may partially be explained by clinicians’ concerns regarding side effects from medications, and the fact that few randomized controlled trials were specifically designed for MI patients with CKD and they were generally excluded from randomized trials.[45,46]

4.1. Limitations
One strength of this multicenter study is that STEM patients are unselected, all-comer, and consecutive. It provides valuable real-world data on the current practices of STEMI in China’s rural areas. Furthermore, dose-response curves were drawn using RCS functions to visually characterize the associations between eGFR, and in-hospital and long-term cardiovascular outcomes. Nevertheless, several limitations should be noted. Firstly, this was an observational and nonrandomized study with a relatively small size. Inherent biases related to unmeasured confounders could not be completely eliminated, though we tried to minimize this by conducting multivariate analyses. Secondly, serum creatinine level was not measured during follow-up, which can potentially be useful in adding predictive information to baseline 1-time measurement.[10] Despite this limitation, 1 previously published study pointed out that the predictive value of eGFR could last for more than 1 decade even without taking changing level of serum creatinine into account.[14] Thirdly, we did not collect information concerning urinary albumin or protein excretion, and other unmeasured factors that might have the same effects on cardiovascular outcomes as baseline eGFR did. Fourthly, as a longitudinal cohort study, loss of follow-up was unavoidably. Nonresponse analysis in Supplemental Table 2 (http://links.lww.com/MD/C48) showed that the majority of the basic characteristics were comparable between the successful follow-up group and loss of follow-up group, except for 4 variables (anterior MI, Killip class ≥2, heart rate, and serum creatinine). This indicated that the severity of the disease between the successful follow-up group and loss of follow-up group might be different. Thus, possible selection bias should be taken into consideration. However, considering the relatively low percentage of loss follow-up rate (5.64%), the differences in nonresponse analysis were unlikely to overturn our findings.

5. Conclusions
In this real-world multicenter study, we found that CKD (eGFR <60 mL/min/1.73 m²) is highly prevalent among China’s rural STEMI patients. Lower eGFR is an independent predictor of worse inhospital and long-term clinical outcomes. The dose-response associations between eGFR, and in-hospital and long-term clinical outcomes were both linear. Therefore, estimation of eGFR is of paramount importance and should be routinely conducted at baseline so as to enable risk stratification, tailored therapy, and early and aggressive management. Subsequent randomized controlled trials with large sample sizes are warranted to verify our findings.

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