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Renal insufficiency is an independent predictor of in-hospital mortality for patients with acute myocardial infarction receiving primary percutaneous coronary intervention

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Abstract: Objective: To investigate the relationship between renal function and clinical outcomes among patients with acute ST-segment elevation myocardial infarction (ASTEMI), who were treated with emergency percutaneous coronary intervention (PCI). Methods: 420 patients hospitalized in Peking University First Hospital, diagnosed with ASTEMI treated with emergency (PCI) from January 2001 to June 2011 were enrolled in this study. Estimated glomerular filtration rate (eGFR) was used as a measure of renal function. We compared the clinical parameters and outcomes between ASTEMI patients combined renal insufficiency and the patients with normal renal function. Results: There was a significant increase in the concentrations of fibrinogen and D-Dimer (P<0.05) and a much higher morbidity of diabetes mellitus in the group of patients with chronic kidney disease (CKD; eGFR<60 ml/(min·1.73 m^2)) (P<0.01). CKD (eGFR<60 ml/(min·1.73 m^2)) was an independent predictor of in-hospital mortality for patients hospitalized with ASTEMI receiving PCI therapy rapidly (P=0.032, odds ratio (OR) 4.159, 95% confidence interval (CI) 1.127–15.346). Conclusions: Renal insufficiency is an independent predictor of in-hospital mortality for patients hospitalized with ASTEMI treated with primary PCI.

Key words: Acute myocardial infarction (AMI), Percutaneous coronary intervention (PCI), Renal function, Estimated glomerular filtration rate (eGFR), Mortality

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1 Introduction

Acute myocardial infarction (AMI) is a life-threatening event with high mortality. It has been estimated that there are approximately half a million newly diagnosed AMI patients in China every year (National Center for Cardiovascular Disease, 2008). In patients with AMI, mortality is significantly decreased with rapid and successful reperfusion therapy. Primary percutaneous coronary intervention (PCI) has been recommended for all patients with ST-segment elevation myocardial infarction when PCI can be rapidly performed. In addition, epidemiologic data showed that a high percentage of AMI patients have kidney disease (National Center for Cardiovascular Disease, 2008). The relationship between renal dysfunction and outcomes in patients with myocardial infarction has been extensively investigated. Recent studies show that the association of decreased kidney function and mortality is strongest in patients with end-stage renal disease (Levy *et al*., 1999). This association has also been consistently shown in patients with moderate kidney disease (Anavekar *et al*., 2004; Schiele *et al*., 2006; Pitsavos *et al*., 2007). In addition, patients with renal

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dysfunction have an elevated risk of thrombosis and bleeding (Rabelink *et al*., 1994; Zachee *et al*., 1994; Berrocal *et al*., 2003), and are less likely to receive reperfusion therapy, antithrombotic drugs, and other conventional cardio protective therapy, which aggravate the outcomes of AMI patients.

Most research has focused on the short or long-term outcomes of AMI patients with chronic kidney disease (CKD). However, there are limited data about this relationship in acute ST-segment-elevation myocardial infarction (ASTEMI) patients who have received PCI therapy rapidly and effectively. Will the impact of renal insufficiency on short-term outcomes of AMI patients be attenuated when PCI is performed timely? The result is less clear. Therefore, the current retrospective study aimed to investigate the relationship between renal insufficiency and clinical outcomes in ASTEMI patients receiving primary PCI.

2 Materials and methods

2.1 Study subjects

A total of 420 patients with ASTEMI, hospitalized in Peking University First Hospital from Jan. 2001 to June 2011, received primary PCI following the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines (Kushner *et al*., 2009). Data were recorded on all patients, including demographics, electrocardiogram (ECG) findings, coronary angiographic findings, as well as detailed time line parameters defined as "symptom-onset-to-balloon time (SOTB)" (time between chest pain onset and first balloon inflation from the angioplasty procedure), and "door-to-balloon time (DTB)" (time between arrival at hospital and first balloon inflation). The glomerular filtration rate (GFR) was estimated from serum creatinine using the modification of diet in renal disease equation developed by Levy *et al*. (1999; 2002). Serum creatinine was tested when patients were admitted. Subjects with an estimated GFR (eGFR) below 60 ml/(min·1.73 m^2) were regarded as having CKD (National Kidney Foundation, 2002), and acute renal failure caused by all reasons and contrast associated nephropathy are excluded in this study. Multivessel disease was defined as those with >50% stenosis on more than two major epicardial coronary arteries or their main branch. No re-flow was defined as thrombolysis in myocardial infarction (TIMI) myocardial perfusion grades 0 to 2 flow after PCI (Chesebro *et al*., 1987). Fall back of ST-segment indicated that the downfall voltage of elevated ST-segment was over 50% of the highest level. Left ventricular ejection fraction (LVEF) was obtained on the 2nd or 3rd day after hospitalization. The concentration of cardiac troponin I (cTNI) was measured every 4 h after hospitalization until returning to normal.

2.2 Statistical analysis

Statistical analysis was performed with SPSS 13.0 statistical package. Continuous data were expressed as mean±standard deviation (SD) and categorical data as percentages. Analysis of variance was used for continuous variables. The χ^2 test or the Fisher exact test (in case the expected value of the variable was <5 in at least one group) was used for categorical variables. A P value <0.05 was considered statistically significant. Multivariate linear regression and Logistic regression analyses were used for multivariate analysis.

3 Results

3.1 Basic parameters

A total of 420 consecutive patients with ASTEMI undergoing primary PCI were evaluated. Mean age was (62.87±12.06) years, and 76.2% of patients were men. Cardiovascular history showed prior coronary heart disease in 20.4%, arterial hypertension in 55.2%, and hyperlipidemia in 49.8% of patients. Patients with diabetes mellitus made up 37.9% of the population, and 62.8% were smokers.

3.2 Baseline renal function of the study patients

At baseline, mean serum creatinine level was (86.07±28.79) μg/ml and mean eGFR was (87.77±24.48) ml/(min·1.73 m^2). After using the modification of diet in renal disease equation, we found that 234 (55.8%) patients had different levels of renal insufficiency (eGFR<90 ml/(min·1.73 m^2)), in which 172 (41.0%) patients had mild renal insufficiency, 57 (13.6%) had moderate renal function, and 5 (1.2%)

had severe renal function. Higher proportions of moderate and severe renal insufficiencies were observed in older age groups. Only six patients were aware of their renal disease history (Table 1; Fig. 1).

3.3 Demographic characteristics comparison of CKD and non-CKD groups

An eGFR <60 ml/(min·1.73 m^2) is classified as having CKD. We divided the subjects into two groups based on eGFR (eGFR≥60 ml/(min·1.73 m^2) (non-CKD group) and eGFR<60 ml/(min·1.73 m^2) group (CKD group)), and compared demographic characteristics of the two groups. There was a significant trend of increased impairment of kidney function in patients who were older, female, with diabetes mellitus, with a prior myocardial infarction, and with prior chronic renal disease. Patients with lower eGFR levels had multivessel diseases and were more likely to smoke. We also evaluated the influence of renal insufficiency on platelets and coagulation function. Compared to non-CKD subjects, subjects with CKD had significantly higher levels of fibrinogen and D-Dimer. In addition, the CKD group had significantly longer SOTB and DTB compared with the non-CKD group (Table 2).

Table 1 eGFR distribution of the study population

Renal function	eGFR (ml/(min·1.73 m^2))	Number of patients
Normal renal function	≥90	186 (44.2%)
Mild renal dysfunction	60~	172 (41.0%)
Moderate renal dysfunction	30~	57 (13.6%)
Severe renal dysfunction	<30	5 (1.2%)

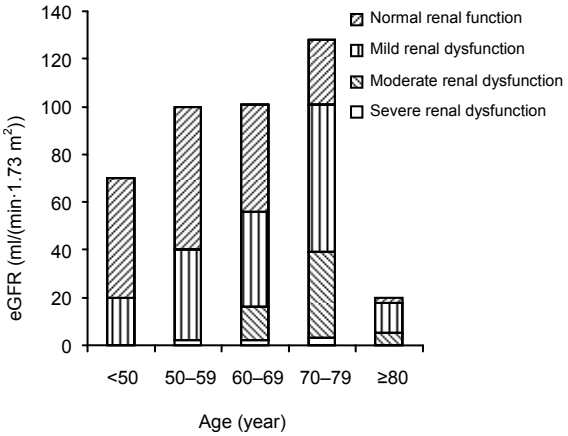

Fig. 1 Distribution of eGFR across different age groups

Table 2 Patient characteristics

Parameter	Value[#]		
	eGFR≥60 ml/(min·1.73 m^2) (*n*=359)	eGFR<60 ml/(min·1.73 m^2) (*n*=61)	*P*
Age (year)	61.26±12.02	72.34±6.86	0.000*
BMI (kg/m^2)	25.38±3.40	24.77±4.04	0.273
SOTB (min)	327.51±391.67	508.98±674.99	0.004*
DTB (min)	118.00±195.37	238.42±438.06	0.000*
Platelet count (10^9/L)	228.67±78.73	222.41±52.60	0.550
PT (s)	11.46±1.38	11.43±1.21	0.892
APTT (s)	33.04±9.69	31.55±7.71	0.254
Fibrinogen (g/L)	3.68±1.00	4.19±1.11	0.000*
D-Dimer (μg/L)	0.23±0.33	0.41±0.55	0.001*
Patient number			
Male	287 (72.66%)	33 (54.10%)	0.000*
Hypertesion	195 (54.32%)	37 (60.66%)	0.357
Diabetes mellitus	127 (35.38%)	32 (52.46%)	0.011*
Hyperlipidemia	184 (51.25%)	25 (40.98%)	0.138
Prior coronery heart diease	66 (18.54%)	19 (31.67%)	0.018*
Chronic renal diease	2 (0.56%)	4 (6.56%)	0.005*
Multivessel disease	234 (65.18%)	52 (85.25%)	0.002*
No reflow (TIMI 0–2)	30 (8.36%)	8 (13.11%)	0.237

[#] Data were expressed as mean±SD or *n* (%); BMI: body weight index; SOTB: symptom-onset-to-balloon time; DTB: door-to-balloon time; PT: prothrombin time; APTT: activated partial thromboplastin time; TIMI: thrombolysis in myocardial infarction grade; * $P<0.05$

3.4 Correlation between renal insufficiency and clinical outcomes

3.4.1 Clinical data comparison of CKD group and non-CKD group

To study the relationship between renal insufficiency and clinical outcomes of ASTEMI patients after primary PCI, we compared clinical data after PCI of the two groups, including creatine kinase-MB (CK-MB), cTNI peak values, and highly sensitive C-reactive protein (HS-CRP), ST-segment fall rate, Q wave formed, and IIIBIIA antiplatelet drag using in-hospital after PCI. LVEF, Killip class, and in-hospital mortality were taken into account. It revealed that patients with lower eGFR had higher HS-CRP levels. A tendency of decreased LVEF and Killip class in the CKD group was also observed. There were 231 (55%) patients that received glycoprotein (GP) IIb/IIIa receptor antagonists. The use of GP IIb/IIIa receptor antagonists decreased from 58.50% usage in the non-CKD group to 34.43% in CKD group (P=0.001). Importantly, patients with a lower eGFR were marginally less likely to implicate glycoprotein IIb/IIIa receptor inhibitors after PCI (Table 3).

3.4.2 Comparison of in-hospital mortality of CKD group and non-CKD group

Death from any cause was strongly associated to kidney function. In-hospital mortality of the CKD group was 8.2%, which was significantly higher compared to the non-CKD group (P=0.003) (Table 4). In addition, in-hospital mortality increased with the aggravation of the kidney impairment.

3.4.3 Results of multivariate analyses for in-hospital mortality

To further investigate the relationship between renal insufficiency and in-hospital mortality, a multivariate logistic regression analysis was performed, which revealed that eGFR <60 ml/(min·1.73 m^2) was an independent predictor for in-hospital mortality among patients with ASTEMI (P=0.032, odds ratio (OR) 4.159, 95% confidence interval (CI) 1.127–15.346), after adjusting for age and diabetes (Table 5). Additional independent variables for mortality included LVEF (P=0.005, OR 1.003, 95% CI 0.862–0.974), and TIMI flow after PCI (P=0.004, OR 0.916, 95% CI 1.891–26.493).

Table 3 Clinical outcomes of CKD and non-CKD groups

Parameter	Value[#]		
	eGFR≥60 ml/(min·1.73 m^2) (n=359)	eGFR<60 ml/(min·1.73 m^2) (n=61)	P
CTNI peak value	91.33±125.45	110.99±130.32	0.265
CK-MB	277.79±222.13	292.88±307.11	0.647
HS-CRP	16.65±28.16	32.04±52.44	0.019*
LVEF	53.08±10.85	48.59±10.79	0.004*
Patient number			
Q wave	284 (79.11)	49 (80.33)	0.828
ST-segment fall	285 (79.39)	44 (72.13)	0.203
Killip class >I	59 (16.43)	22 (36.07)	0.000*

[#] Data were expressed as mean±SD or number (%); * P<0.05; CTNI: cardiac troponin I; CK-MB: creatine kinase-MB; HS-CRP: highly sensitive C-reactive protein; LVEF: left ventricular ejection fraction

Table 4 In-hospital mortality

eGFR (ml/(min·1.73 m^2))	Death	P
≥60 (n=359)	6 (1.67%)	0.003
<60 (n=61)	5 (8.20%)	
<30 (n=5)	1 (20%)	<0.001

Data were expressed as number (%)

Table 5 Multivariate analysis for in-hospital mortality

Parameter	P	OR	95% CI
CKD	0.032	4.159	1.127–15.346
LVEF	0.005	1.003	0.862–0.974
No reflow (TIMI 0–2)	0.004	0.916	1.891–26.493

CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; TIMI: thrombolysis in myocardial infarction grade; OR: odds ratio; CI: confidence interval

4 Discussion

Among the 420 patients included in this study, 14.8% (62) had CKD; however, only 1.4% (6) were aware of their declined renal function. Our results were consistent with the results of a multicenter research which assessed the renal status of acute coronary syndrome (ACS) patients undergoing PCI (Huo and Ho, 2007), which revealed that about 472 (13.10%) patients reached the level of moderate renal insufficiency (eGFR <60 ml/(min·1.73 m^2)), but only 90 patients (2.51%) were known to have CKD at the time of admission. Higher proportions of moderate and severe renal insufficiency are found in older age groups, which are also more likely to have other established risk factors of cardiovascular disease. Considering the relationship of renal function with cardiovascular events and death, serum creatinine and eGFR of every AMI patient should be measured upon admission and post-PCI to evaluate risks.

Given the aspects mentioned above, patients in our study were grouped based on eGFR, which classifies patients with eGFR<60 ml/(min·1.73 m^2) as having CKD. Baseline characteristics and in-hospital mortality were examined across this renal function category. Our results showed that there was a significant increase in the activated coagulation markers (fibrinogen, D-Dimer) and higher levels of inflammatory markers (HS-CRP) in the group of patients with CKD than those without CKD. Multivariable linear regression model showed a significant association between D-Dimer and eGFR (P=0.012), even after adjusting potential confounders like age, diabetes mellitus, and smoking. These results are consistent with findings from a larger study conducted by Shlipak *et al*. (2003). They found that after adjusting for baseline differences, levels of C-reactive protein, fibrinogen, interleukin-6, factor VIIc, factor VIIIc, plasmin-antiplasmin complex, and D-Dimer were significantly higher among patients with renal insufficiency (P<0.001). Another trial led by Sjøland *et al*. (2007) indicated the unique characteristics of fibrin clots from patients with renal disease, which revealed that fibrin clots made from patients with end stage renal disease were found to be less permeable, less compactable, and less susceptible to fibrinolysis (P<0.001) than clots from healthy controls; furthermore, scanning electron microscopy revealed higher clot density of fibrin fibers in clots from patients than in clots from controls (P<0.001). These changes of coagulation in CKD patients can increase the risks of myocardial infarction, and make it harder to use reperfusion therapy.

Renal insufficiency is associated with short- and long-term mortalities of AMI patients. The study performed by Schiele *et al*. (2006) showed a significant association between one-year mortality and eGFR (OR 0.97, 95% CI 0.95–0.98 per additional GFR unit). Pitsavos *et al*. (2007) suggested that creatinine clearance rate is an important independent predictor of in-hospital mortality and should be taken into account, and patients with ACS complicated by renal dysfunction should receive more aggressive medical care. Shlipak *et al*. (2002) has associated renal insufficiency with significantly lower use of PCI and β-blocker, aspirin, and antiplatelet therapy both during hospitalization for AMI and after discharge. A multi-center research in China (Huo and Ho, 2007) of 2250 AMI patients showed that after adjusting with other variables, renal insufficiency (eGFR per 10 ml/min decrease, OR=1.133, 95% CI 1.011–1.270, P=0.032) and age (>65 years, OR=1.907, 95% CI 1.107–3.280, P=0.020) were proved to be the risk factors of in-hospital mortality. However, prior studies evaluated the prognostic value of kidney function and excluded patients with advanced age and patients with increased serum creatinine level at baseline, thereby limiting extrapolation of these studies to a general population of patients. In addition, survival of CKD patients after AMI is linked to less use of effective intervention therapy. To distinguish between the effects of kidney function and lower use of reperfusion, the present study focused on the predictive value of eGFR in patients treated with primary PCI as the standard procedure, and especially to ASTEMI patients. In our trial we found out that ASTEMI patients with CKD had poorer clinical outcomes, including a higher incidence of multivessel lesion, decreased LVEF, higher Killip classification, and higher in-hospital mortality. After adjustment for baseline differences, eGFR <60 ml/(min·1.73 m^2) was an independent predictor for in-hospital mortality among all patients. These results are consistent with the prior studies above. The short-term mortality rate of ASTEMI patients was significantly higher even after receiving

effective reperfusion therapy. This result can be partly explained by the increased prevalence of established risk factors, such as older age, diabetes mellitus, and hypertension. This relation remained strong after adjustment for the level of risks at admission; we can presume that this clinical intersection presents unique risks to the patients.

The mechanism of increased mortality risk in ACS patients with renal insufficiency is not entirely clear, but recognition of the increased mortality risk burden of patients with renal dysfunction is crucial. Several larger scale studies have revealed the significant relationship between CKD and cardiovascular disease (CVD) (Szczech *et al*., 2001; Wannamethee *et al*., 2006). Furthermore, Freeman *et al*. (2003) has summarized several of the leading explanations for the significant relationship between CKD and CVD: (1) Excess comorbidities in patients with CKD, such as hypertension, diabetes mellitus, congestive heart failure (systolic and diastolic), and older age may contribute. These higher prevalence of established risks may aggravate the outcomes. (2) Excess toxicities from conventional therapies and abnormal drug pharmacokinetics in these patients may further contribute to increased risk, like bleeding after utilization of antiplatelet drugs. (3) It shows that these patients receive fewer effective therapies (less reperfusion, GP IIb/IIIa receptor inhibitors, early angiography, β-blockers, and statins), and the assessment of risk and benefit of therapy is much more complicated in AMI patients combined with CKD. (4) The unique pathobiology of the CKD state, including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, hypoalbuminemia, which lead to accelerated and more severe CVD (McCullough, 2002), and may explain the results we presented above. The association between the aforementioned factors and increased risk of morbidity and mortality needs to be addressed in future studies. Although studies have suggested that the benefit-to-risk ratio of various therapeutic interventions is increased for patients with the highest risk to adverse events, this needs to be further investigated in future studies. Until such data are available, physicians should continue to use their best judgment in patient management while at the same time not depriving appropriate patients of newer treatment strategies.

We found no significant relationship between status of renal function and biomarkers of myocardium necrosis in our study. We can presume that ASTEMI caused such a severe damage to the myocardium, and therefore eliminated the effects of renal function in the patients.

Renal insufficiency is not simply the complication of the ACS patients, it is an independent factor of mortality of these patients, and impacts the clinical outcomes and treatment in many aspects. Therefore, the renal function of ACS patients should be attached importance to. In addition, the established risk factors of these patients, like diabetes mellitus, hypertension, and hyperlipidemia, should be more stringently controlled, clinician should value the risk and benefit to make a more rational therapeutic scheme. The treatment for ACS patients with CKD is still a controversial issue and a challenge for clinician. For this special group, further researches are needed to assess the benefits of different therapeutic plans. The future study should lay emphasis on the pharmacokinetics and pharmacodynamics of cardiovascular drugs in ACS patients with renal dysfunction, and more rigorous clinical trials should be developed to provide clinical evidence for therapeutic decisions.

There are limitations in our research. Our sample size was small, and more patients should be recruited to eliminate the latent bias in the further study. More detailed follow-ups are needed in order to appropriately assess the effects of renal function on the long-term prognosis in ASTEMI patients treated with primary PCI. In addition, in-hospital mortality should be further analyzed to assess impacts of renal insufficiency on ASTEMI.

6 Conclusions

The results of our study reveal that there was a significant increase in the concentrations of fibrinogen and D-Dimer and a much higher morbidity of diabetes mellitus in the group of CKD patients receiving primary PCI in the setting of ASTEMI. Moreover, CKD (eGFR<60 ml/(min·1.73 m^2))is an independent predictor of in-hospital mortality for patients hospitalized with ASTEMI after receiving PCI therapy rapidly (P=0.032, OR 4.159, 95% CI 1.127–15.346). Therefore, for ASTEMI patients,

clinicians should take into account the presence of renal dysfunction before and after PCI, and evaluate and use comprehensive therapy to reduce their risks of short- and long-term mortalities.

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