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Decreased Glomerular Filtration Rate is an Independent Predictor of In-Hospital Mortality in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Background and Objectives: Patients with renal dysfunction (RD) experience worse prognosis after myocardial infarction (MI). The aim of the present study was to investigate the impact of admission estimated glomerular filtration rate (eGFR) on clinical outcomes of patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation MI (STEMI). **Subjects and Methods:** We retrospectively evaluated 4,542 eligible patients from the Korea Acute Myocardial Infarction Registry (KAMIR). Patients were divided into three groups according to eGFR (mL/min/1.73 m²): normal renal function (RF) group (eGFR ≥60, n=3,515), moderate RD group (eGFR between 30 to 59, n=894) and severe RD group (eGFR <30, n=133). Baseline characteristics, angiographic and procedural results, and in-hospital outcomes between the three groups were compared. **Results:** Age, gender, Killip class ≥3, hypertension, diabetes, congestive heart failure, peak creatine kinase-MB, high sensitivity C-reactive protein, B-type natriuretic peptide, left ventricle ejection fraction, multivessel disease, infarct-related artery and rate of successful PCI were significantly different between the 3 groups (p<0.05). With decline in RF, in-hospital complications developed with an increasing frequency (14.1% vs. 31.8% vs. 45.5%, p<0.0001). In-hospital mortality rate was significantly higher in the moderate and severe RD groups as compared to the normal RF group (2.3% vs. 13.9% vs. 25.6%, p<0.0001). Using multivariate logistic regression analysis, adjusted odds ratio for in-hospital mortality was 2.67 {95% confidence interval (CI) 1.44-4.93, p=0.002} in the moderate RD group, and 4.09 (95% CI 1.48-11.28, p=0.006) in the severe RD group as compared to the normal RF group. **Conclusion:** Decreased admission eGFR was associated with worse clinical courses and it was an independent predictor of in-hospital mortality in STEMI patients undergoing primary PCI. (**Korean Circ J 2011;41:184-190**)

KEY WORDS: Glomerular filtration rate; Acute myocardial infarction; Mortality; Percutaneous coronary intervention.

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Introduction

Renal dysfunction is a strong risk factor for cardiovascular disease in the general population,¹⁾ and it is associated with an increased risk of death and cardiovascular events in patients with a broad range of cardiovascular diseases, including heart failure,²⁾ stable coronary artery disease undergoing percutaneous coronary intervention (PCI)^{3,4)} and acute coronary syndromes.^{5,6)}

In the setting of acute myocardial infarction (AMI), mortality risk is increased in patients with renal dysfunction (RD) of any degree of severity.⁷⁻⁹⁾ Primary PCI is the best reperfusion strategy for AMI patients and its mortality benefit has been shown in randomized trials.¹⁰⁻¹²⁾ However, most of these trials frequently excluded patients with RD, and few studies examining the outcomes of AMI patients with RD undergoing primary PCI have been reported.

To date, several studies evaluating the in-hospital prognostic significance of RD in patients undergoing primary PCI for AMI have reported that RD is an independent predictor of in-hospital mortality,¹³⁻¹⁵⁾ even in the case of a successful PCI.^{13,14)} However, one of these studies¹³⁾ used serum creatinine level to determine RD despite the fact that serum creatinine level can be unreliable as an estimate of renal function (RF), while the other studies^{14,15)} included a small number of patients and divided patients according to their RF into merely 2 groups which is insufficient for RD risk stratification. The aim of the present study was to investigate the impact of admission estimated glomerular filtration rate (GFR) on in-hospital outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI using data from the Korea Acute Myocardial Infarction Registry (KAMIR).

Subjects and Methods

Korea Acute Myocardial Infarction Registry

KAMIR is a Korean prospective multicenter online registry designed to reflect “real-world” practice trends for patients presenting with AMI in the recent reperfusion era; the registry has been supported by the Korean Circulation Society since November 2005. Online registry of AMI cases (www.kamir.or.kr) has been performed at 41 universities or community hospitals that are high-volume centers with facilities for primary PCI and onsite cardiac surgery. Data were collected at each site by a trained study coordinator using a standardized case report form, and registered and submitted from individual institutions via password-protected internet-based electronic case report forms. The study protocol was approved by the ethics committee at each participating institution.

Study population

From January 2006 to December 2007, a total of 7,895 ST-

EMI patients were registered in KAMIR. Of these, 864 patients were excluded from this study because they had received fibrinolytic therapy and 2,407 patients were excluded because they did not undergo PCI as the primary treatment strategy; an additional 82 patients were excluded due to missing data needed to calculate estimated GFR. The remaining 4,542 patients were eligible for the present study (Fig. 1). Data on clinical, angiographic and in-hospital outcomes were collected.

The mean age of the study patients was 62.2 ± 12.8 years, and 3,355 (73.8%) patients were males. The mean estimated GFR was $78.3 \text{ mL/min/1.73 m}^2$. The angiographic success rate was 91.8%, and the overall in-hospital mortality rate was 5.3%.

Definitions

STEMI was defined by the presence of new ST-segment elevation of at least 1 mm (0.1 mV) in 2 contiguous leads or new left bundle-branch block on the index or subsequent electrocardiogram with at least 1 positive cardiac biochemical marker of necrosis. Presence of left main coronary artery stenosis was defined as a luminal stenosis $\geq 50\%$. Primary PCI was defined as percutaneous coronary revascularization within 24 hours of symptom onset without antecedent treatment with a fibrinolytic agent as the initial therapy. Successful PCI was defined as thrombolysis in myocardial infarction 3 flow with residual stenosis $\leq 50\%$ in the infarct-related artery. Major bleeding was defined as intracranial bleeding, bleeding associated with the need for blood transfusion, or any other clinically relevant bleeding as judged by the investigator.

Assessment of renal function

RF was defined by estimated GFR, which was calculated by

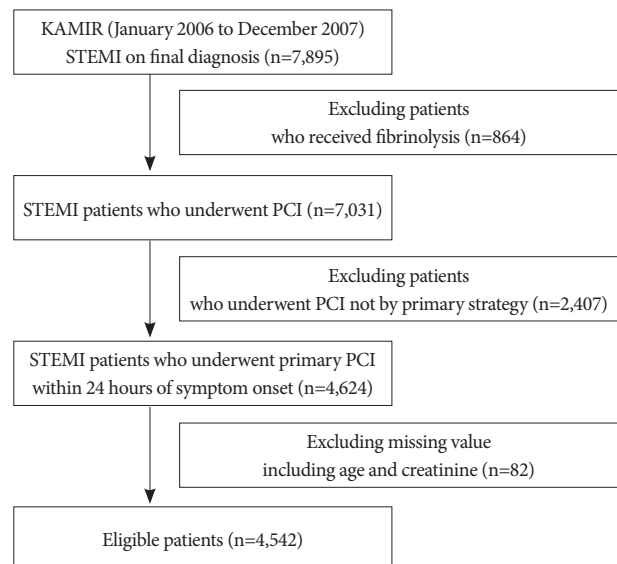


Fig. 1. Study flow chart. STEMI: ST-segment elevation myocardial infarction, KAMIR: Korea Acute Myocardial Infarction Registry, PCI: percutaneous coronary intervention.

the Modification of Diet in Renal Disease equation (MDRD)¹⁶⁾ from the serum creatinine level measured on admission. The patients were classified into 3 groups according to the estimated GFR. Normal RF, moderate and severe RD were defined as estimated GFR ≥ 60 mL/min/1.73 m², between 30 to 59 mL/min/1.73 m² and < 30 mL/min/1.73 m², respectively.

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Inc,

Chicago, IL, USA). Data are presented as mean \pm standard deviation or median with interquartiles for continuous variables, and as frequency for categorical variables. Comparisons between continuous variables were done using one-way analysis of variance or the Kruskal-Wallis test, while the Pearson's chi-square test was used for categorical variables. Logistic regression analyses were performed to determine predictors of in-hospital mortality. A probability value of $p < 0.05$ was considered significant.

Table 1. Baseline clinical characteristics

	Estimated GFR			p
	≥ 60 mL/min/1.73 m ² (n=3,515)	30-60 mL/min/1.73 m ² (n=894)	< 30 mL/min/1.73 m ² (n=133)	
Demographic characteristics				
Age (years)	59.9 \pm 12.4	70.1 \pm 10.3	69.6 \pm 12.7	<0.001
Male gender (%)	79.0	56.8	52.6	<0.001
BMI (kg/m ²)	24.1 \pm 3.1	23.7 \pm 3.1	23.5 \pm 3.5	0.005
Admission characteristics				
SBP (mmHg)	127.4 \pm 28.7	114.8 \pm 34.7	109.7 \pm 33.5	<0.001
HR (beats/min)	75.7 \pm 18.7	73.3 \pm 24.7	76.9 \pm 27.5	0.005
Killip class (%)				<0.001
1	77.6	61.0	60.5	
2	13.0	15.6	8.5	
3	4.9	9.4	10.1	
4	4.4	14.0	20.9	
Killip class ≥ 3 (%)	9.3	23.4	31.0	<0.001
Symptom-to-door time (minutes)*	150 (72-287)	170 (73-309)	112 (46-223)	0.102
Door-to-balloon time (minutes)*	85 (60-127)	91 (64-136)	110 (69-138)	0.038
Medical history (%)				
Hypertension	40.1	61.4	67.4	<0.001
Diabetes	20.3	32.7	42.1	<0.001
Hyperlipidemia [†]	18.6	16.6	16.9	0.373
Current smoking	53.5	30.2	32.6	<0.001
Family history of heart disease	7.8	4.0	0.8	<0.001
Previous MI	27.9	25.6	32.0	0.773
Previous CABG	3.1	4.0	4.0	0.883
Congestive heart failure	0.4	2.0	1.5	<0.001
Creatinine (mg/dL)	0.93 \pm 0.18	1.37 \pm 0.26	5.60 \pm 6.57	<0.001
GFR (mL/min/1.73 m ²)	87.9 \pm 41.3	49.6 \pm 7.9	17.5 \pm 9.1	<0.001
Peak CK-MB (IU/L)*	198 (73-300)	144 (33-273)	159 (51-251)	<0.001
hs-CRP (mg/L)*	0.53 (0.14-1.95)	0.50 (0.12-1.98)	1.23 (0.12-5.49)	<0.001
BNP (pg/mL)*	58 (18-204)	128 (30-494)	211 (51-797)	<0.001
LV ejection fraction (%)	51.2 \pm 11.3	48.7 \pm 12.6	48.4 \pm 12.9	<0.001
Heparin [‡]	58.5	14.1	2.3	0.042
GP IIb/IIIa inhibitor	21.6	5.8	0.8	0.745

*Data are presented as the median with 25-75 percentiles, [†]Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dL, [‡]Heparin means low-molecular weight heparin or unfractionated heparin. GFR: glomerular filtration rate, BMI: body mass index, SBP: systolic blood pressure, HR: heart rate, PCI: percutaneous coronary intervention, MI: myocardial infarction, CABG: coronary artery bypass graft surgery, CK-MB: creatine kinase MB fraction, BNP: B-type natriuretic peptide, hs-CRP: high sensitivity C-reactive protein, GP: glycoprotein

Results

Baseline clinical characteristics

A total 1,027 (22.6%) patients had at least moderate RD. Patients with RD were older, were more often females and had lower BMI values. Also, they were more likely to have lower systolic blood pressure, increased heart rate and higher Killip class at presentation. Pre-hospital delay time was similar in the RD group and the normal RF group, but door-to-balloon time was longer in the RD group as compared to the normal RF group. On medical history, they were more likely to have hypertension, diabetes and congestive heart failure. With respect to laboratory findings, high sensitivity C-reactive protein and B-type natriuretic peptide levels were higher in the RD group, but peak creatine kinase-MB level and left ventric-

ular ejection fraction were lower in the RD group as compared to the normal RF group. Use of both heparin and GP IIb/IIIa inhibitor was lower in the RD group as compared to the normal RF group (Table 1).

Angiographic and procedural characteristics

Patients with RD were more likely to have multivessel disease and left main coronary artery stenosis. The location of infarct-related artery was significantly different in the three groups, according to their RF. While involvement of the left anterior descending coronary artery was less frequent, involvement of the right coronary artery was more frequent in the severe RD group. Also, rate of successful PCI decreased significantly as RF declined; however, rate of stent insertion remained similar in all the three groups (Table 2).

Table 2. Angiographic and procedural characteristics

	Estimated GFR			p
	≥60 mL/min/1.73 m ² (n=3,515)	30-60 mL/min/1.73 m ² (n=894)	<30 mL/min/1.73 m ² (n=133)	
No. of diseased vessels (%)				<0.001
1	51.8	37.0	31.8	
2	30.0	34.8	35.6	
3	18.2	28.2	32.6	
Presence of LM stenosis (%)	1.4	3.3	4.5	<0.001
Location of infarct-related artery (%)				<0.001
LM	3.8	3.9	4.1	
LAD	17.3	16.5	12.3	
LCX	26.6	25.0	18.9	
RCA	52.2	54.6	64.8	
Type of lesion (%)				0.408
A/B1	16.4	4.0	0.5	
B2/C	61.1	15.7	2.4	
Rate of successful PCI (%)	93.1	87.7	87.2	<0.001
Rate of stent use (%)	94.3	93.0	93.0	0.315

LM: left main, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery

Table 3. Incidence of in-hospital complications

	Estimated GFR			p
	≥60 mL/min/1.73 m ² (n=3,515)	30-60 mL/min/1.73 m ² (n=894)	<30 mL/min/1.73 m ² (n=133)	
Complications (%)	14.1	31.8	45.5	<0.001
AV block	2.6	7.0	8.3	<0.001
VT/VF	3.4	5.8	6.0	0.002
Atrial fibrillation	1.1	2.1	4.5	0.001
Cardiogenic shock	4.3	14.1	19.5	<0.001
Ischemic event*	0.9	2.0	3.0	0.005
Acute renal failure [†]	0.1	1.8	6.0	<0.001
Major bleeding	0.3	1.9	4.8	<0.001

*Ischemic event includes recurrent ischemia, re-infarction and cerebrovascular event, [†]Acute renal failure requiring renal replacement therapy. AV block: atrioventricular block, VT: ventricular tachycardia, VF: ventricular fibrillation

Clinical outcomes

In-hospital complications, including arrhythmia, cardiogenic shock, ischemic events, acute renal failure and major bleeding, developed more frequently in patients with RD (Table 3). In-hospital mortality rates increased significantly as estimated GFR decreased ($p < 0.001$), and approximately one-fourth of the patients (25.6%) in the severe RD group died (Fig. 2). Although the main cause of in-hospital mortality was pump failure ($p < 0.001$), frequencies of the causes of mortality were not significantly different between the three groups ($p = 0.165$) (Table 4). On multivariate logistic regression analysis, age, diabetes, Killip class ≥ 3 , successful PCI and left ventricular ejection fraction were identified as independent predictors of in-hospital mortality. In addition, decreased estimated GFR was also identified as a powerful independent predictor of in-hospital mortality. When compared with the normal RF group, adjusted OR was 2.67 {95% confidence interval (CI): 1.44 to 4.93; $p = 0.002$ } in the moderate RD group and 4.09 (95% CI: 1.48 to 11.28; $p = 0.006$) in the severe RD group (Table 5).

Discussion

The main finding of the present study is that RD defined by estimated GFR at admission is an independent predictor of in-hospital mortality in patients with STEMI undergoing primary PCI; this increased mortality risk was observed not only

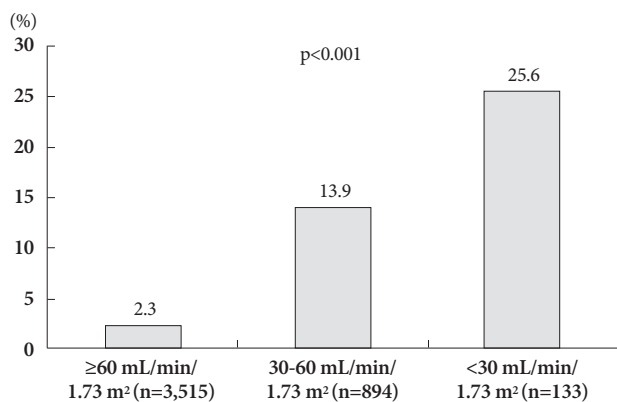


Fig. 2. Incidence of in-hospital mortality according to the levels of estimated glomerular filtration rate.

Table 4. Causes of in-hospital mortality

Cause of hospital mortality (%)	Estimated GFR			p
	≥60 mL/min/1.73 m ² (n=3,515)	30-60 mL/min/1.73 m ² (n=894)	<30 mL/min/1.73 m ² (n=133)	
Pump failure	52.4	71.3	67.6	0.165
Mechanical complications	7.3	4.1	8.8	
Arrhythmia	12.2	9.0	11.8	
Multi-organ failure	11.0	9.0	11.8	
Bleeding	1.8	1.6	2.4	

GFR: glomerular filtration rate

in the patients with severe RD but also in the patients with moderate RD.

In the present study, RD was defined by estimated GFR calculated using the MDRD equation, which is currently recommended in clinical practice,¹⁷ and patients were divided into three groups. Although RD, as defined by either serum creatinine level or estimated GFR, has been associated with increased mortality in patients with AMI,¹³⁻¹⁵⁾¹⁸⁾¹⁹⁾²¹ serum creatinine level is insensitive for an early detection of RD and could underestimate the incidence of moderate or severe RD concealed behind the near-normal creatinine levels,⁹⁾²²⁾²³ thereby underscoring the risk of RD in AMI patients. Furthermore, a graded risk of RD clearly exists, RF should be classified into at least 3 groups using estimated GFR for appropriate RD risk stratification in clinical practice. Our study on the basis of estimated GFR, showed that patients with moderate RD had a six-fold higher in-hospital mortality rate, while

Table 5. Multivariate logistic regression analysis of predictors of in-hospital mortality

	Adjusted OR	95% CI	p
Estimated GFR (mL/min/1.73 m ²)			
≥60	1.00		
30-60	2.67	1.44-4.93	0.002
<30	4.09	1.48-11.28	0.006
Age (per year)	1.06	1.03-1.09	<0.001
Killip class ≥ 3	2.85	1.58-5.14	<0.001
LV ejection fraction	0.91	0.89-0.93	<0.001
Successful PCI	0.39	0.19-0.81	0.011
Diabetes	2.08	1.15-3.74	0.015
Presence of left main artery stenosis	2.74	0.86-8.75	0.090
Stent use	0.60	0.22-1.61	0.310
Male gender	0.73	0.39-1.36	0.318
Hypertension	1.27	0.70-2.30	0.427
Multivessel disease	0.76	0.38-1.53	0.449
Body mass index	1.02	0.94-1.11	0.650

OR: odds ratio, CI: confidence interval, GFR: glomerular filtration rate, LV: left ventricle, PCI: percutaneous coronary intervention

patients with severe RD had a eleven-fold higher in-hospital mortality rate as compared to the patients with normal RF. In our study, patients with RD were older, and were more often women. Although RF decreases with age and women tend to be older than men at the time of AMI presentation,²⁴⁾ it may also be an inherent influence of the variables used in the MD-RD equation. In addition to older age and female gender, RD was more frequently associated with hypertension, diabetes, higher Killip class, multivessel disease and low left ventricular ejection fraction. These findings which have been described by other authors¹³⁾¹⁹⁾²¹⁾ predispose to worse clinical outcomes after AMI. However, after adjustment for baseline differences, increased in-hospital mortality persisted in the patients with RD, suggesting that an increased mortality in patients with RD was not fully explained by these associated conditions, and that RD is a strong independent predictor of in-hospital mortality.

The rate of in-hospital complications was higher in the patients with RD as compared to the patients with normal RF. Cardiogenic shock, the most common cause of death in this study regardless of RF, developed with a three-fold higher frequency. It may be possible that the high incidence of unsuccessful PCI, recurrent ischemia or re-infarction and bleeding may potentiate the already existing weakened ischemic resistance reflected by high prevalence of diabetes and multivessel disease in the RD group. Also, acute renal failure developed more frequently in the RD group. After AMI, acute renal failure more commonly developed among those patients with low left ventricular ejection fraction, higher Killip class, anterior wall infarction, a hematocrit <30%, congestive heart failure, cardiogenic shock or stroke during admission.²⁵⁾ The RD group in our study shared many of these features, and although this study did not assess contrast-induced nephropathy (CIN) it may also contribute to it. Usually, the clinical benefit of primary PCI is accompanied by an increased risk of bleeding in AMI patients with RD, and a previous study has reported that RD is independently associated with bleeding after primary PCI.¹⁹⁾ As expected, despite the less frequent use of heparin and glycoprotein IIb/IIIa inhibitors in the RD group as compared to the normal RF group, which have a proven efficacy in the setting of AMI, major bleeding increased significantly in the RD group as compared to the normal RF group.

Despite the fact that primary PCI is the most effective AMI treatment in terms of improvement in survival, this mortality benefit is attenuated in some patient subgroups, including the elderly, women, patients with renal insufficiency, heart failure, diabetes, anaemia, acute hyperglycemia, cardiogenic shock, and those developing CIN.¹⁵⁾ Because the patients with RD frequently have more than one of these conditions, they might be at a very high risk of mortality after AMI. Therefore, management of AMI in patients with RD is particularly problema-

tic. A recent study by Medi et al.²⁶⁾ which investigated the benefit of reperfusion strategies in STEMI patients in the presence of RD, reported that mortality rates remain high; they also found that primary PCI was associated with a lower adjusted in-hospital mortality than fibrinolytic therapy in the patients with normal RF and moderate RD. However, in the patients with severe RD, primary PCI was not associated with reduced mortality. In conclusion, we have limited knowledge on the optimal reperfusion strategy for the severe RD group.

To improve the survival in AMI patients with RD undergoing primary PCI, more aggressive treatment and meticulous care are needed. Firstly, the success of primary PCI has special importance because a successful PCI is an independent predictor of in-hospital mortality as shown in our study and RD was shown to be associated with the risk of unsuccessful PCI results. Secondly, medications such as aspirin, beta-blockers, and ACE inhibitors should be administered early after AMI, so that the patients with RD could gain a similar mortality benefit as their normal RF counterparts.²⁷⁾²⁸⁾ Thirdly, reducing bleeding complications²⁹⁾ by using the radial artery approach and direct thrombin inhibitor during PCI is needed.³⁰⁾ Fourthly, an effort should be made to prevent CIN, including adequate hydration, reducing contrast use, use of low-osmolality contrast and administration of N-acetylcysteine.¹⁹⁾²⁰⁾

Because KAMIR is a large multicenter population-based prospectively-designed study including unselected patients with AMI, it provides comprehensive information on treatments and outcomes among patients with AMI and RD in the contemporary PCI era. Because this study included STEMI patients only, the median pre-hospital delay time in the RD group was relatively short as compared to that in the previous studies¹³⁾¹⁹⁾; this feature could minimize the hemodynamic compromising effect of AMI on baseline serum creatinine level.

Limitations

The present study had several limitations. Firstly, we included only those individuals who underwent primary PCI. Similar to a previous study, because the patients with RD underwent PCI less often as compared to those with normal RF, there might be a selection bias and unidentified confounders, which might limit the generalizability of the data. Secondly, we did not collect information on medications relevant for prognostication, and therefore analyses in this study was not controlled for the impact of these drugs. Thirdly, there are inherent limitations of the estimated GFR calculation.¹⁷⁾

Conclusions

Decreased estimated GFR on admission is a strong risk factor for increased in-hospital complications and mortality in STEMI patients undergoing primary PCI. These risks increased

in a stepwise fashion according to the degree of decreased estimated GFR. Clinicians should be alert to the increased mortality in patients with RD and make all the attempts to reduce complications of primary PCI and stress intensive medical management of these high-risk patients.

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