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Concomitant Impact of High-Sensitivity C-Reactive Protein and Renal Dysfunction in Patients with Acute Myocardial Infarction

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Purpose: The present study aimed to investigate the impact of high-sensitivity C-reactive protein (hs-CRP) and renal dysfunction on clinical outcomes in acute myocardial infarction (AMI) patients. **Materials and Methods:** The study involved a retrospective cohort of 8332 patients admitted with AMI. The participants were divided into 4 groups according to the levels of estimated glomerular filtration rate (eGFR) and hs-CRP: group I, no renal dysfunction (eGFR ≥60 mL·min^{-1}·1.73 m^{-2}) with low hs-CRP (≤2.0 mg/dL); group II, no renal dysfunction with high hs-CRP; group III, renal dysfunction with low hs-CRP; and group IV, renal dysfunction with high hs-CRP. We compared major adverse cardiac events (MACE) over a 1-year follow-up period. **Results:** The 4 groups demonstrated a graded association with increased MACE rates (group I, 8.8%; group II, 13.8%; group III, 18.6%; group IV, 30.1%; p<0.001). In a Cox proportional hazards model, mortality at 12 months increased in groups II, III, and IV compared with group I [hazard ratio (HR) 2.038, 95% confidence interval (CI) 1.450-2.863, p<0.001; HR 3.003, 95% CI 2.269-3.974, p<0.001; HR 5.087, 95% CI 3.755-6.891, p<0.001]. **Conclusion:** High hs-CRP, especially in association with renal dysfunction, is related to the occurrence of composite MACE, and indicates poor prognosis in AMI patients.

Key Words: C-reactive protein, glomerular filtration rate, myocardial infarction

INTRODUCTION

Chronic kidney disease (CKD) is strongly related to high risk for cardiovascular disease (CVD) and all-cause mortality.[1] A recent meta-analysis demonstrated strong evidence that patients with CKD experience a 1.4- to 3.7-fold increased risk for CVD mortality compared with those without CKD.[2] A reduced estimated glomerular filtration rate (eGFR) was also independently associated with the risk of death, cardiovascular events, and hospitalization in a large, community-based population.[3] The unique pathophysiology of CKD leads to accelerated severe CVD.

CKD is primarily a state of accelerated atherosclerosis.[4,5] Atherosclerosis in turn is a well-known inflammatory process associated with elevated levels of C-reactive protein (CRP).[6] Thus, patients with CKD are known to demonstrate elevated CRP levels, which may be associated with high all-cause and cardiovascular mortality in CKD.[7-9]

Among the available inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) is one of the most accessibles for clinical practice. Several studies have demonstrated an association between elevated hs-CRP and cardiovascular events in healthy general populations.[10] Recently, CKD and elevated hs-CRP were found to be additively associated with a higher risk of CVD and also to be independent predictors of cardiovascular events after acute coronary syndrome.[11,12] Although strong evidence links high hs-CRP to poorer outcomes in patients with CKD, it is unclear whether the risk of CVD associated with decreased kidney function is at least partially mediated by inflammation, and whether the association between inflammation and CVD is influenced by the level of kidney function. Few studies have evaluated the relationship between hs-CRP and vascular events in patients with CKD.

The present study was undertaken to evaluate the impact of hs-CRP and renal dysfunction on clinical outcomes in patients with acute myocardial infarction (AMI).

MATERIALS AND METHODS

Korea Acute Myocardial Infarction Registry

The study subjects were enrolled from the Korea Acute Myocardial Infarction Registry (KAMIR). The KAMIR is a Korean prospective, open, observational, multi-center online registry and aimed to investigate the risk factors of mortality in patients with myocardial infarction (MI) since November 2005. The 52 hospitals with primary percutaneous coronary intervention (PCI) facilities entered and enrolled patients who agreed with participation in this registry. Data were collected by a well-trained study coordinator on the basis of a standardized case report form and protocol. The study protocol was approved by the ethics committee at each participating institution.

Study design and patient population

We assessed a retrospective cohort of 13901 consecutive patients who were admitted to the hospital between November 2005 and July 2008 and diagnosed as AMI. The following patients were excluded sequentially: patients who were not available for estimation of glomerular filtration rate; patients lacking information on levels of hs-CRP; patients with hs-CRP greater than 10 mg/dL and with active infections, tumors, or inflammatory disease; and patients who could not be followed over 1 year or whose data were uncertain. A final population of 8332 patients were analyzed in this study.

The patients were categorized into 4 groups on the basis of the presence of renal dysfunction (eGFR <60 mL·min^{-1}·1.73 m^{-2}) and hs-CRP greater than 2.0 mg/dL. This hs-CRP value was selected as the cut-off point because it was previously used to predict adverse outcomes in several trials.[13,14] Levels of hs-CRP were measured at the admission time of each patient and analyzed by immunoturbidimetric analysis (Tina-quant hs-CRP latex assay, Roche/Hitachi, Cobas, Mannheim, Germany). Group I (n=5166) had no renal dysfunction (eGFR ≥60 mL·min^{-1}·1.73 m^{-2}) and low hs-CRP (≤2.0 mg/dL); group II (n=1065), no renal dysfunction and high hs-CRP (>2.0 mg/dL); group III (n=1489), renal dysfunction (eGFR <60 mL·min^{-1}·1.73 m^{-2}) and low hs-CRP; group IV (n=612), renal dysfunction and high hs-CRP.

Assessment of renal function

Renal function was assessed based on eGFR. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR in mL·min^{-1}·1.73 m^{-2}.[15]

Definitions

Renal dysfunction was defined by eGFR (<60 mL·min^{-1}·1.73 m^{-2}).[16] AMI was determined by positive cardiac biomarkers (creatine kinase-MB, troponin-I, or troponin-T) or 12-lead electrocardiography. ST-segment elevation myocardial infarction (STEMI) definition was the presence of new ST-segment elevation of more than 1 mm (0.1 mV) in continuous leads or new left bundle-branch block on electrocardiography. Non ST-segment elevation myocardial infarction (NSTEMI) was defined as those who were not classified as STEMI and the presence of positive biomarkers. Left ventricular ejection fraction (LVEF) was assessed by 2-dimensional echocardiography. In-hospital outcome was death over the course of hospital treatment. The primary endpoints were major adverse cardiac events (MACE) including cardiogenic death, MI, and need for emergency or elective repeat PCI or coronary artery bypass graft (CABG) over a 1-y follow-up period.

Data collection

Baseline variables included age, gender, body mass index

(BMI), clinical symptoms at admission (chest pain or dyspnea), Killips class, and coronary risk factors, which included hypertension (defined as history of hypertension, admission blood pressure >140 mm Hg systolic or >90 mm Hg diastolic), current smoking, previous history of coronary artery disease (CAD), hyperlipidemia [defined as history of hyperlipidemia, total cholesterol (TC) level >240 mg/dL, or low density lipoprotein cholesterol (LDL-C) level >120 mg/dL], and diabetes mellitus (DM; defined as history of DM or fasting blood glucose level ≥126 mg/dL).

Use of certain medications was recorded on admission [aspirin, angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), statin, beta blocker or calcium channel blocker (CCB)]. Interventions (CABG, thrombolysis or PCI) were also recorded. Clinical follow-up was performed for 12 months. Patients were required to visit the outpatient clinic at the end of the first month, 6 months and 12 months after discharge, and also when angina-like symptoms occurred.

Statistical analysis

Continuous variables with normal distributions were expressed as means±SD for each group. They were compared using one-way ANOVA and unpaired Student's t-tests. Discrete variables were expressed as percentages and frequencies, and compared with the chi-squared test. Logistic regression was performed to identify the effect of renal dysfunction and hs-CRP of MACE at 1-year clinical follow-up. Cox proportional hazards modeling was used to examine the effect of the 4 groups on survival over the 12-month follow-up period. Analyses were adjusted for age, Killip class 4, gender, hypertension, DM, hyperlipidemia, previous CAD, smoking, PCI, medication (aspirin, beta-blocker, ACEi or ARB, and statin), and angiographic findings (left anterior descending artery, Thrombolysis in Myocardial Infarction (TIMI) flow 0-1 before PCI, and complex left main disease) in a 1-year follow-up period. A *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with the SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 8332 patients (age, 62±13 years; male, 71.2%) were included in the present study (STEMI, 60.5%; NSTEMI, 39.5%). The patients in groups I and II were younger than those in groups III and IV and demonstrated a higher proportion of males; lower rates of previous hypertension, DM, and CAD; lower frequency of Killip class 4 MI; and higher prevalence of STEMI. Groups I and II had higher BMI, rates of positive smoking history, and systolic blood pressure at admission (Table 1).

Biochemical parameters, LVEF, and hospital treatment on admission

eGFR levels did not differ between groups I and II, and the

Table 1. Baseline Characteristics

Baseline variables	Group I (n=5166)	Group II (n=1065)	Group III (n=1489)	Group IV (n=612)	*p* value
Age (yrs)	60.0±12.2	62.3±12.6	70.8±11.0	72.0±11.0	<0.001
Male (%)	3931 (76.1)	801 (75.2)	863 (58.0)	339 (55.4)	<0.001
Body mass index (kg/m^2)	24.2±3.1	23.9±3.4	23.7±3.2	23.1±3.5	<0.001
Risk factor (%)					
Hypertension	2174 (42.2)	486 (45.9)	973 (65.6)	416 (68.2)	<0.001
Diabetes mellitus	1167 (22.6)	281 (26.4)	579 (39.0)	266 (43.5)	<0.001
Smoking	2549 (49.6)	540 (50.8)	404 (27.4)	161 (26.5)	<0.001
Hyperlipidemia	521 (10.1)	88 (8.3)	152 (10.2)	54 (8.9)	0.231
Previous CAD	696 (13.5)	118 (11.1)	343 (23.1)	138 (22.7)	<0.001
At admission					
SBP (mm Hg)	132±27	126±26	127±33	124±35	<0.001
DBP (mm Hg)	80±16	78±16	76±19	74±20	<0.001
Killip class 4 (%)	101 (2.0)	56 (5.3)	112 (7.7)	67 (11.2)	<0.001
Diagnosis (%)					
STEMI	3188 (61.7)	670 (62.9)	861 (57.8)	319 (52.1)	<0.001
NSTEMI	1978 (38.3)	395 (37.1)	628 (42.2)	293 (47.9)	<0.001

CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment myocardial infarction.

eGFR of group IV was lower than that of group III. Creatine kinase-MB and high-density lipoprotein cholesterol did not differ among groups I, II, and III, and were lower in group IV. TC, LDL-C, and LVEF did not differ between groups II and III and were lowest in group IV and highest in group I. hs-CRP levels did not differ between groups I and III, while the hs-CRP level of group IV was higher than that of group II. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels increased stepwise from groups II to IV compared with group I. The use of aspirin, beta blocker, ACEi or ARB, and statins was lower with decreasing eGFR and increasing hs-CRP. However, CCB was used more in group III and IV (Table 2).

Coronary angiographic findings

The number of involved vessels, complex left main lesions, and type C lesion was higher with decreasing eGFR and increasing hs-CRP levels. By contrast, the prevalence of single vessel disease was higher with increasing eGFR and decreasing hs-CRP. The use of thrombolysis and PCI was lower with decreasing eGFR and increasing hs-CRP, but CABG was higher with decreasing eGFR and increasing hs-CRP (Table 3).

In-hospital and out-of-hospital outcomes among the 4 groups

A graded association was observed between each group, the risk of in-hospital death and the incidence of MACE during follow-up (Table 4).

Multivariate analysis of 1-year MACEs after AMI

MACEs at 12 months increased in groups II, III, and IV compared with group I [hazard ratio (HR) 1.478, 95% confidence interval (CI) 1.187-1.840, $p<0.001$; HR 1.513, 95% CI 1.234-1.855, $p<0.001$; HR 2.638, 95% CI 2.051-3.392, $p<0.001$] (Table 5). Other predictors of 1-year MACEs were older age (HR 1.011, 95% CI 1.004-1.019, $p=0.001$), previous CAD (HR 1.314, 95% CI 1.080-1.598, $p=0.006$), DM (HR 1.314, 95% CI 1.117-1.546, $p=0.001$), Killip class 4 MI (HR 2.355, 95% CI 1.774-3.128, $p<0.001$), TIMI flow 0-1 before PCI (HR 1.298, 95% CI 1.113-1.514, $p=0.001$), and complex left main disease (HR 3.058, 95% CI 2.177-4.296, $p<0.001$). However, the use of beta blocker (HR 0.780, 95% CI 0.653-0.932, $p=0.006$), ACEi or ARB (HR 0.691,

Table 2. Biochemical Parameters, LVEF, and Hospital Treatment at Admission among the 4 Groups

	Group I (n=5166)	Group II (n=1065)	Group III (n=1489)	Group IV (n=612)	*p* value
GFR (mL·min^{-1}·1.73 m^{-2})	85±15	84±14	43±15	40±16	<0.001
Creatinine (mg/dL)	0.9±0.2	0.9±0.2	2.0±2.8	2.1±2.1	<0.001
CK-MB (U/L)	151±291	160±327	137±243	103±137	<0.001
Troponin I (ng/mL)	46±88	48±75	47±104	47±83	0.892
TC (mg/dL)	187±43	177±41	180±46	169±48	<0.001
Triglyceride (mg/dL)	133±114	117±102	123±80	109±62	<0.001
HDL-C (mg/dL)	46±20	44±12	44±26	41±13	<0.001
LDL-C (mg/dL)	120±39	115±48	115±45	107±41	<0.001
hs-CRP (mg/dL)	0.45±0.47	4.62±2.26	0.53±0.53	5.04±2.28	<0.001
NT-proBNP (pg/mL)	828±1783	2320±3989	4549±8304	10325±12362	<0.001
LVEF (%)	54±11	49±12	50±13	45±14	<0.001
Intervention (%)					
Thrombolysis	412 (8.0)	75 (7.1)	81 (5.5)	20 (3.3)	<0.001
PCI	4851 (93.9)	994 (93.4)	1332 (89.5)	506 (82.8)	<0.001
CABG	103 (2.0)	51 (4.8)	50 (3.4)	24 (3.9)	<0.001
Hospital treatment at admission (%)					
Aspirin	5110 (98.9)	1051 (98.7)	1455 (97.7)	600 (98.0)	0.003
Beta blocker	4050 (78.4)	807 (75.8)	1056 (70.9)	416 (68.0)	<0.001
ACEi or ARB	4292 (83.1)	868 (81.5)	1142 (76.7)	459 (75.0)	<0.001
CCB	647 (12.5)	122 (11.5)	248 (16.7)	130 (21.2)	<0.001
Statin	3980 (77.0)	777 (73.0)	1021 (68.6)	397 (64.9)	<0.001

GFR, glomerular filtration rate; CK, creatine kinase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive C-reactive protein; NT-proBNP, N-terminal pro B type natriuretic peptide; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 3. Baseline Coronary Angiographic Findings

Variable	Group I (n=5166)	Group II (n=1065)	Group III (n=1489)	Group IV (n=612)	*p* value
Coronary angiography (%)	5041 (97.9)	1022 (96.4)	1362 (91.7)	515 (84.6)	<0.001
Infarct-related artery (%)					
Left anterior descending artery	2339 (48.7)	492 (50.0)	560 (42.6)	215 (43.3)	<0.001
Left circumflex artery	854 (17.8)	157 (16.0)	197 (15.0)	74 (14.9)	0.041
Right coronary artery	1537 (32.0)	314 (31.9)	522 (39.7)	188 (37.9)	<0.001
Left main stem	68 (1.4)	21 (2.1)	37 (2.8)	19 (3.8)	<0.001
Involved vessel number (%)					
1 vessel	2327 (48.5)	403 (40.9)	425 (32.2)	131 (26.1)	<0.001
2 vessels	1438 (30.0)	294 (29.8)	406 (30.8)	147 (29.3)	0.922
3 vessels	910 (19.0)	256 (26.0)	434 (32.9)	197 (39.2)	<0.001
Left main, isolated	18 (0.4)	3 (0.3)	9 (0.7)	2 (0.4)	0.439
Left main, complex	104 (2.2)	29 (2.9)	46 (3.5)	25 (5.0)	<0.001
ACC/AHA classification (%)					
A	227 (5.0)	28 (3.0)	50 (4.2)	19 (4.1)	0.043
B1	851 (18.9)	176 (19.0)	200 (16.7)	71 (15.3)	0.090
B2	1353 (30.1)	270 (29.1)	279 (23.2)	121 (26.0)	<0.001
C	2067 (46.0)	453 (48.9)	672 (56.0)	254 (54.6)	<0.001
TIMI flow (%)					
TIMI 0	1949 (42.0)	459 (48.5)	554 (44.2)	188 (39.4)	<0.001
TIMI 1	458 (9.9)	111 (11.7)	138 (11.0)	52 (10.9)	0.285
TIMI 2	727 (15.7)	138 (14.6)	211 (16.8)	105 (22.0)	0.002
TIMI 3	1502 (32.4)	238 (25.2)	350 (37.9)	132 (27.7)	<0.001

ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis in Myocardial Infarction.

Table 4. In-Hospital and Out-of-Hospital Outcomes among the 4 Groups

Outcomes	Group I (n=5166)	Group II (n=1065)	Group III (n=1489)	Group IV (n=612)	*p* value
In-hospital outcomes (%)					
In-hospital death	127 (2.5)	74 (6.9)	220 (14.8)	162 (26.5)	<0.001
Out-hospital outcomes (%)					
1 month MACEs	157 (3.0)	79 (7.4)	177 (11.9)	118 (19.3)	<0.001
Cardiac death	79 (1.5)	53 (5.0)	146 (9.8)	107 (17.5)	<0.001
Non-cardiac death	12 (0.2)	7 (0.7)	14 (0.9)	15 (2.5)	<0.001
Myocardial infarction	23 (0.4)	4 (0.4)	10 (0.7)	4 (0.7)	0.608
Repeat-PCI	45 (0.9)	14 (1.3)	17 (1.1)	6 (1.0)	0.522
CABG	10 (0.2)	8 (0.8)	4 (0.3)	1 (0.2)	0.016
12 month MACEs	454 (8.8)	147 (13.8)	277 (18.6)	184 (30.1)	<0.001
Cardiac death	100 (1.9)	59 (5.5)	185 (12.4)	136 (22.2)	<0.001
Non-cardiac death	27 (0.5)	15 (1.4)	35 (2.4)	27 (4.4)	<0.001
Myocardial infarction	38 (0.7)	8 (0.8)	17 (1.1)	9 (1.5)	0.148
Repeat-PCI	301 (5.8)	70 (6.6)	68 (4.6)	37 (6.0)	0.262
CABG	15 (0.3)	10 (0.9)	7 (0.5)	2 (0.3)	0.025

MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

95% CI 0.572-0.835, p<0.001), and statin (HR 0.676, 95% CI 0.574-0.797, p<0.001) was associated with reduced risk of MACEs.

Cox regression analysis for mortality during follow-up

Mortality at 12 months increased in groups II, III, and IV compared with group I (HR 2.038, 95% CI 1.450-2.863, p<0.001; HR 3.003, 95% CI 2.269-3.974, p<0.001; HR 5.087, 95% CI 3.755-6.891, p<0.001) (Table 6, Fig. 1).

DISCUSSION

The most common cause of death in patients with CKD is

Table 5. Multivariate Analysis of 1-Year MACEs after AMI

Analyses	Hazard ratio (95% confidence interval)				*p* value
	Group I	Group II	Group III	Group IV	
Unadjusted	1	1.662 (1.362-2.028)	2.372 (2.017-2.790)	4.462 (3.661-5.438)	<0.001
1) Adjusted for age, sex	1	1.603 (1.313-1.958)	2.000 (1.683-2.376)	3.704 (3.009-4.558)	<0.001
2) Model 1 plus comorbidity*	1	1.614 (1.320-1.974)	1.912 (1.601-2.283)	3.528 (2.851-4.366)	<0.001
3) Model 2 plus killip class 4	1	1.545 (1.261-1.894)	1.776 (1.482-2.128)	3.137 (2.521-3.902)	<0.001
4) Model 3 plus PCI	1	1.544 (1.251-1.893)	1.750 (1.459-2.099)	2.991 (2.400-3.729)	<0.001
5) Model 4 plus medication†	1	1.511 (1.230-1.856)	1.638 (1.363-1.969)	2.801 (2.242-3.500)	<0.001
6) Model 5 plus angiographic findings‡	1	1.478 (1.187-1.840)	1.513 (1.234-1.855)	2.638 (2.051-3.392)	<0.001

MACE, major adverse cardiac events; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
*Hypertension, diabetes mellitus, hyperlidemia, previous coronary artery disease, smoking.
†Aspirin, beta blocker, angiotensin converting enzyme inhibitir or angiotensin receptor blocker, statin.
‡Left anterior descending artery, TIMI flow 0-1 before PCI, complex left main disease.

CVD.[1] The high prevalence of CVD in CKD patients suggests the importance of traditional (hypertension, DM, smoking, and hyperlipidemia) as well as non-traditional [CRP, fibrinogen, interleukin-6, factor VIIIc, lipoprotein(a) and hemoglobin] CKD risk factors in the pathogenesis of CVD.[7,17] The present study compared clinical outcomes and investigated the association between CKD and hs-CRP in patients with AMI.

Our results revealed that the prevalence of hypertension, DM, and previous CAD were higher with decreasing eGFR and increasing hs-CRP levels. The prevalence of smoking was highest in group II and lower with decreasing eGFR and increasing hs-CRP in the other groups. These findings are consistent with the results of previous studies.[1,14] As eGFR decreased and hs-CRP increased, the frequency of high Killip class 4 and NT-proBNP levels were increased and LVEF decreased at admission. Based on the finding that increased NT-proBNP in patients with decreased eGFR was correlated with severity of heart failure, left ventricle dysfunction, volume overload, and ischemic heart disease, it was assumed that clinically severe manifestations such as cardiogenic shock and pulmonary edema are developed in patients with more decreased eGFR.[18] Conversely, BMI and LDL-C level were significantly lower with decreasing eGFR and increasing hs-CRP. Therefore, the age-related decline in eGFR and lower prevalence of hyperlipidemia may indicate increased malnutrition and inflammation in patients with severely decreased kidney function.[19]

Although absolute impacts or the relationship between CKD and mortality or morbidity after development of CVD are not clearly understood, previous studies indicated that more severely decreased indicators of kidney function are significant independent predictors of cardiovascular events.[2,4]

Table 6. Multiple Cox Proportional Hazards Regression Analysis for Mortality Over 1-Year Follow-Up

Categories	Hazard ratio (95% CI)	*p* value
Group I	1	
Group II	2.038 (1.450-2.863)	<0.001
Group III	3.003 (2.269-3.974)	<0.001
Group IV	5.097 (3.755-6.891)	<0.001

CI, confidence interval; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention.
Adjusted for factors included in age, sex, hypertension, diabetes mellitus, hyperlidemia, previous coronary artery disease, smoking, killip class 4, percutaneous coronary intervention, aspirin, beta blocker, angiotensin converting enzyme inhibitir or angiotensin receptor blocker, statin, left anterior descending artery, TIMI flow 0-1 before PCI, and complex left main disease.

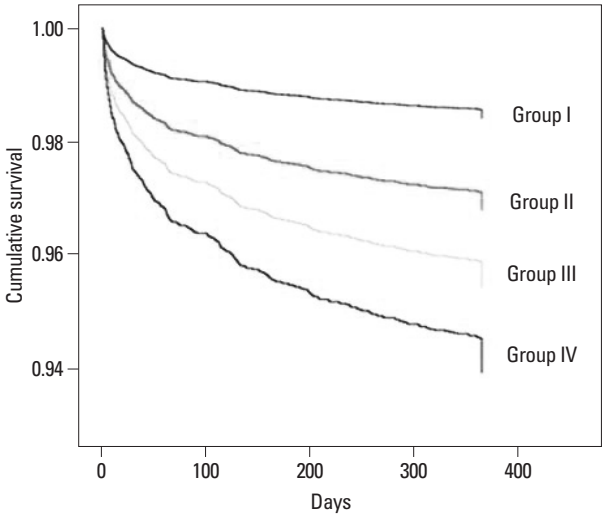

Fig. 1. Cox regression survival curve in patients with acute myocardial infarction over a 1-year follow-up according to each group.

Furthermore, recent studies clearly provided an independent, and inversely graded association between decreasing levels of renal function and increasing risk of death, and cardiovascular events as eGFR fell below 60 mL·min^{-1}·1.73

m^{-2} of body surface area.[3,20] In the present study, the prevalence of in-hospital death and short- and long-term MACE was higher in patients with renal dysfunction compared to those without renal dysfunction. Furthermore, mortality at 12 months increased in renal dysfunction patients compared with non-renal dysfunction patients (HR 2.991, 95% CI 2.454-3.645, p<0.001; data not shown).

Previous studies have shown that hs-CRP elevation is associated with CVD in the healthy general population.[21,22] Recently, CKD and high hs-CRP were found to be additively associated with a higher risk of CVD and found to be independent predictors of cardiovascular events after acute coronary syndrome.[11,12] Furthermore, CRP was independently associated with all-cause and cardiovascular mortality in dialysis patients.[23] The rationales that inflammatory biomarkers can selectively predict cardiovascular event risk in patients with renal dysfunction are unclear. But, several studies in literature proposes that renal dysfunction may result from and directly cause a chronic inflammatory state.[24] The pathophysiologic changes associated with renal dysfunction, such as endothelial dysfunction and increased hemodynamic stress, may produce more vulnerable development and rupture of coronary artery plaques in the setting of increased chronic inflammation.[25,26] We found that eGFR as determined by the CKD-EPI equation was correlated negatively with hs-CRP (r=-0.64, p<0.001; data not shown). LDL-C levels, LVEF, percentage of PCI and thrombolysis, and use of beta blocker, ACEi or ARB, and statin were lower in group IV compared with the other groups. The number of involved vessels and complex left main lesions in coronary angiographic findings were higher with more decreased eGFR and increased hs-CRP. These factors may affect the grave prognosis in group IV.

Additionally, the prevalence of in-hospital death and short- and long-term MACE was consistently higher with decreasing eGFR and increasing hs-CRP. Furthermore, Cox proportional hazards model indicated that, mortality at 12 months was increased in groups II, III, and IV compared with group I (HR 2.038, 95% CI 1.450-2.863, p<0.001; HR 3.003, 95% CI 2.269-3.974, p<0.001; HR 5.087, 95% CI 3.755-6.891, p<0.001) and singnificantly differ between groups II and III (HR 1.525, 95% CI 1.099-2.117, p=0.012; data not shown). Also, mortality in group IV was higher than that in group III (HR 1.735, 95% CI 1.342-2.242, p<0.001; data not shown). These findings suggested that high hs-CRP levels provided prognostic information in AMI patients with or without renal dysfunction. Concomitant high hs-CRP and renal dysfunction were a highly independent predictor of mortality.

The present study has several limitations. First, Increased hs-CRP levels after AMI can not differentiate the component related to baseline inflammation from that related to myocardial necrosis. Because the extent of myocardial necrosis is a known prognostic factor after AMI, this potentially confounds the association between hs-CRP and renal dysfunction. The second limitation is that patients with acute kidney injury might have been included, because assessment of kidney function was based on a single serum creatinine value obtained at the time of presentation to the hospital. Third, we could not assess the different predictive value of elevated inflammatory biomarkers between pre-dialysis and dialysis patients by the lack of data regarding renal replacement therapy. Forth, regarding the laboratory determination, specifically hs-CRP, these determinations were done in each hospital. Therefore, there can be an inter-laboratory variability. However, we emphasize that these potential limitations should be consistently attenuated by the very large sample size of our study.

In conclusion, the present findings confirmed that high hs-CRP levels were prognostic indicators in AMI patients independent of renal dysfunction, and highlighted concomitant high hs-CRP and renal dysfunction as a predictor of short- and long-term MACE. Therefore, randomized trials are needed to determine whether individuals with kidney dysfunction and elevated levels of these inflammatory biomarker may selectively benefit through preventative strategies to reduce inflammation, and consequently CVD.[27]

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