

Prognostic Impact of Baseline High-Sensitivity C-Reactive Protein in Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention Based on Body Mass Index

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Background and Objectives: Serum high sensitivity C-reactive protein (hs-CRP) is a marker of inflammation and may lead to the development of atherosclerosis, adversely affecting mortality. The aim of this study was to evaluate the relationship between baseline hs-CRP level and 12-month clinical outcomes in patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) according to their body mass index (BMI) status.

Subjects and Methods: Using data from the Korea Acute Myocardial Infarction Registry from November 2005 to September 2008, a total of 8174 consecutive AMI patients were studied. Cox proportional hazard model revealed that higher baseline levels of hs-CRP was associated with 12-month all-cause mortality ($p=0.045$). To further understand this association, patients were divided into 3 groups based on their body mass index: 1) overweight/obese, 2) normal weight, and 3) underweight patients. Then each group was stratified into quartiles based on their hs-CRP.

Results: In overweight/obese patients, Cox model showed significant association of hs-CRP with 12-month mortality when adjusted for age and gender ($p<0.001$), however, after adjustment with multiple covariates, mortality was highest in the 4th quartile {HR 2.382, (1.079-5.259), $p=0.032$ } though statistically insignificant ($p=0.172$). We observed no significant association of serum hs-CRP with 12-month mortality in normal weight ($p=0.681$) and underweight ($p=0.760$) patients.

Conclusion: Higher baseline hs-CRP level (≥ 4.08 mg/dL) in overweight/obese AMI patients showed significant association with 12-month all-cause mortality independent of other prognostic markers. (Korean Circ J 2012;42:164-172)

KEY WORDS: C-reactive protein; Overweight; Obesity; Body mass index; Myocardial infarction.

Introduction

There is increasing evidence that higher levels of high sensitivity C-reactive protein (hs-CRP) is a marker of inflammation and a po-

tential independent predictor of cardiovascular disease, as it may play a role in the development of atherosclerosis, adversely affecting mortality.¹⁾²⁾ Rate of obesity is increasing globally where studies have shown association of body weight as assessed by body

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mass index (BMI) with clinical outcomes after percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI) patients.³⁾ Previous reports have also indicated that hs-CRP level is correlated with BMI and fat distribution.⁴⁾⁵⁾ The mechanism for elevation of plasma hs-CRP in obese subjects could be through a high production of cytokines, e.g., interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), by excess adipose tissue which could induce high hs-CRP production in liver.⁴⁾

Currently there is no data available evaluating the relationship between higher baseline hs-CRP levels, body mass index (BMI) status, and adverse outcomes in patients with AMI undergoing PCI. Therefore, in the present study we attempted to assess the association between baseline hs-CRP level and 12-month clinical outcomes in patients with AMI.

Subjects and Methods

This retrospective study was carried out at The Heart Center of Chonnam National University Hospital, Korea. The permission to carry out the study had been sought from the hospital authorities (IRB No.05-49) and informed consent obtained from the patients. Patient medical documents were used to obtain the demographic data, clinical characteristics and relevant laboratory results. Patients were enrolled in the registry after admission to participating hospitals with a suspected diagnosis of AMI.

Korea Acute Myocardial Infarction Registry

The Korea Acute Myocardial Infarction Registry (KAMIR) is a prospective, multicenter, observational registry designed to examine current epidemiology in hospital management and outcome of patients with AMI in Korea. The registry included 52 community and university hospitals capable of primary PCI with one-year clinical follow up. Data was collected at each site by a well-trained study coordinator based on a standardized protocol.⁶⁻⁸⁾

Study population

A total of 10974 consecutive patients with AMI (both ST-segment elevation MI and non-ST-segment elevation MI) undergoing PCI from November 2005 to September 2008 were assessed in this study. Patients with unknown BMI (n=395) and missing hs-CRP (n=2405) data were excluded from this study; hence the total study population was 8174 patients. The aim was to evaluate the impact of baseline hs-CRP on 12-month clinical outcomes according to BMI status. Initially we studied this in terms of the total study population. Then, according to BMI categories suggested by the World Health Organization for Asian population, the total study population was divided into three groups that included 1) overweight/obese (BMI

≥ 23 kg/m², n=5647), 2) normal-weight (BMI 18.5 to 22.9 kg/m², n=2246) and 3) underweight (BMI <18.5 kg/m², n=281).⁹⁾ Each group was then stratified into quartiles based on their hs-CRP levels.

Definitions and clinical endpoints

A final diagnosis of AMI was made by the European Society of Cardiology/American College of Cardiology (ESC/ACC) diagnostic criteria for AMI.¹⁰⁾ BMI was calculated as weight (kg) divided by height squared (m²). Diabetes mellitus (DM) was defined as requiring the use of oral hypoglycaemic agent or insulin to lower blood glucose levels. Hypertension was defined as patient systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg at rest, over a series of repeated measurements, or after treatment with anti-hypertensive medications. For diabetics and patients with chronic renal disease, hypertension was defined as systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg. Hyperlipidemia was defined as patient total cholesterol level >200 mg/dL or treatment with a lipid-lowering agent. Coronary artery disease (CAD) was defined as patient having a history of myocardial infarction (MI) revascularization procedure, or obstructive CAD.

Peripheral blood samples were obtained on admission using direct venipuncture. Blood samples were centrifuged and serum was removed and stored at a temperature of -700°C until the assay for sugar and proteins was performed. Absolute creatine kinase-MB levels were determined by radioimmunoassay (Dade Behring, Inc., Miami, FL, USA). Cardiac specific troponin I levels were measured using a paramagnetic particle, chemiluminescent immunoenzymatic assay (Beckman, Coulter, Inc., Fullerton, CA, USA). Twelve-hour fasting serum levels of total cholesterol, triglyceride, and low and high density lipoprotein-cholesterol were measured by standard enzymatic methods. Blood sample for hs-CRP was obtained on admission and was analyzed turbidimetrically with sheep antibodies against human CRP; this has been validated against the Dade Behring method. Each group was divided into quartiles based on their hs-CRP levels. Overweight/obese quartiles were: first quartile <0.2 mg/dL, n=1370, second quartile ≥ 0.2 to <0.82 mg/dL, n=1451, third quartile ≥ 0.82 to <4.08 mg/dL, n=1413 and fourth quartile ≥ 4.08 mg/dL, n=1413. Normal-weight quartiles were: first quartile <0.2 mg/dL, n=548, second quartile ≥ 0.2 to <0.92 mg/dL, n=575, third quartile ≥ 0.92 to <5.23, n=563 mg/dL and fourth quartile ≥ 5.23 mg/dL, n=563. Underweight quartiles were: first quartile <0.31 mg/dL, n=70, second quartile ≥ 0.31 to <1.54 mg/dL, n=70, third quartile ≥ 1.54 to <8.76 mg/dL, n=71 and fourth quartile ≥ 8.76 mg/dL, n=70.

Two-dimensional echocardiography was performed in all patients and left ventricular ejection fraction (LVEF) was assessed using a modified Simpson's biplane method. The morphology in coronary angiography was classified by criteria from the American

College of Cardiology/American Heart Association (ACC/AHA).¹¹ The degree of coronary flow was classified by Thrombolysis in Myocardial Infarction (TIMI) score. The presence of left main coronary artery stenosis was defined as a luminal stenosis $\geq 50\%$. Multivessel disease was defined as the presence of a lesion with $>50\%$ diameter stenosis in a non-infarct related coronary artery. Successful PCI was defined as TIMI flow 3 with residual stenosis $\leq 50\%$ in the infarct related artery. In-hospital complications included atrio-ventricular block, bradycardia, ventricular tachycardia/ventricular fibrillation, atrial fibrillation, no reflow, dissection, cardiogenic shock, acute renal failure, metabolic acidosis/lactic acidosis.

Major adverse cardiac event (MACE) were defined as all-cause death, recurrent MI, or repeat revascularization.

The primary endpoint of this study was all-cause mortality at 12-month clinical follow up. All data were recorded on a standardized, electronic, web based registry at <http://www.kamir.or.kr>.

Statistical analysis

SPSS 17.0 for windows (SPSS, Inc., Chicago, IL, USA) was used for all analyses. Continuous variables were presented as the mean \pm SD; comparisons were conducted by one-way ANOVA test. Discrete variables were presented as percentages and frequencies; comparisons were conducted by chi-square statistics. A $p < 0.05$ was considered statistically significant. Cox regression analysis was performed to identify a model with independent predictive factors including determination of a hazard ratio and its 95% confidence interval (CI) for each variable in the model. Cox analysis was performed to identify variables that most affected the hazard ratio of hs-CRP, with a cut off at $p < 0.20$ for entry into the model.

Results

A total of 8,174 AMI patients, mean age = 62.7 ± 12.4 years and 76% male gender ($n = 6217$), were stratified into quartiles based on their hs-CRP level to study their 12-month clinical outcomes. Twelve-month all-cause death and 12-month composite of MACE increased as the value of hs-CRP increased from 1st to 4th quartile. Cox proportional hazard analysis showed 12-month mortality to be highest in patients of 4th quartile {HR = 2.80 (1.335-5.873), $p = 0.006$ } followed by 3rd quartile {HR = 2.495 (1.186-5.248), $p = 0.016$ }. It was statistically significant among hs-CRP quartiles ($p = 0.045$). Independent factors for 12-month mortality were age greater than 60 years, in-hospital complications, Killip class > 1 , use of statin, heart rate > 100 beats/min, N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 3000 pg/mL, left ventricular ejection fraction (LVEF) $< 55\%$ and creatinine clearance < 60 min/mL (data not provided).

As the 12-month mortality was statistically borderline significant

among hs-CRP quartiles in the total study population, we sought to further evaluate this finding by dividing the total study population into three groups based on their BMI. Overweight and obese patients were grouped together as there was no baseline significant difference in their 12-month all-cause mortality ($p = 0.076$, data not provided).

Overweight/Obese group

($n = 5647$, mean age = 60.4 ± 12.2 years, 75.2% male)

Baseline clinical characteristics and laboratory findings of this group are presented in Table 1 and 2 respectively. Overweight/obese patients with higher hs-CRP (i.e., 2nd, 3rd and 4th quartiles) were older, more often female, had higher Killip classes, heart rate and NT-proBNP; and had lower blood pressure, LVEF and creatinine clearance. They were associated with higher incidence of DM, hypertension, CAD, heart failure and cerebrovascular disease. Statin use was not significant among the quartiles ($p = 0.702$). As per past regular medication history, 7.15% of the patients at the time of admission were on statin ($n = 404$).

Coronary angiographic findings are presented in Table 3. Multivessel involvement, ACC/AHA lesion type C, and Pre-PCI TIMI flow grade 0 were observed to increase with an increase in hs-CRP. Post-PCI TIMI flow grade 3 was nearly similar among all quartiles. PCI success rate decreased and in-hospital complication rate increased with increasing hs-CRP.

Table 4 shows the clinical outcomes during the 12-month follow-up. In-hospital death, composite MACE at 1 month and 12 months, and mortality at 1 month and 12 months were more frequent with increasing hs-CRP levels. Twelve-month mortality increased as the value of hs-CRP increased; 2.0% ($n = 27$) in 1st, 2.5% ($n = 37$) in 2nd, 4.4% ($n = 62$) in 3rd and highest 6.6% ($n = 94$) in the 4th quartile.

Cox proportional hazard model was implemented to identify the independent predictors of mortality at the 12-month clinical follow-up. Serum hs-CRP quartiles showed significant association with 12-month mortality when adjusted for age and gender ($p < 0.001$). With quartile 1 as a reference, the risk of 12-month mortality was higher in the 3rd quartile {2.153 (1.369-3.384), $p = 0.001$ } and 4th quartile {3.268 (2.129-5.016), $p < 0.001$ }. After adjustment with multiple covariates, 12-month mortality was highest in patients within the 4th quartile compared to other patients {hazard ratio (HR) 2.382 (1.079-5.259), $p = 0.032$ } though statistical significance was not achieved ($p = 0.172$). Independent factors for 12-month mortality were old age (> 60 years), heart rate > 100 beats/min, LVEF $< 55\%$, creatinine clearance < 60 min/mL and in-hospital complications. The variables included in Cox model were age, male gender, heart rate, systolic blood pressure, smoking history, history of hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease and

Table 1. Baseline clinical characteristics of overweight/obese patients according to levels of high sensitivity C-reactive protein

Variables	Quartile 1 (<0.2 mg/dL) n=1370	Quartile 2 (≥0.2 - <0.82 mg/dL) n=1451	Quartile 3 (≥0.82 - <4.08 mg/dL) n=1413	Quartile 4 (≥4.08 mg/dL) n=1413	p
Age (years)	59.18±11.99	59.96±12.16	60.97±12.02	61.58±12.62	<0.001
Male gender, n (%)	1061 (77.5)	1113 (76.8)	1037 (73.4)	1032 (73.0)	0.010
Body mass index (kg/m ²)	25.72±2.61	25.60±2.52	25.66±2.55	25.77±3.23	0.367
Systolic BP (mm Hg)	132.69±27.41	133.41±27.63	129.78±29.05	125.42±27.26	<0.001
Heart rate (beats/min)	74.40±17.45	75.71±17.18	76.82±19.44	79.23±26.27	<0.001
LVEF (%)	54.95±10.92	53.45±11.12	52.38±11.54	49.17±11.95	<0.001
Killip >1, n (%)	270 (19.7)	247 (17.0)	301 (21.3)	368 (26.0)	<0.001
Past history, n (%)					
Smoking	888 (64.8)	931 (64.1)	887 (62.7)	803 (56.8)	<0.001
Diabetes mellitus	342 (24.9)	379 (26.1)	430 (30.4)	414 (29.3)	0.003
Hypertension	641 (46.8)	719 (49.5)	749 (53.0)	722 (51.1)	0.009
Hyperlipidemia	162 (11.8)	163 (11.2)	162 (11.5)	138 (9.8)	0.310
Coronary artery disease	243 (17.7)	177 (12.2)	196 (13.9)	203 (14.4)	<0.001
Heart failure	6 (0.4)	10 (0.7)	27 (1.9)	20 (1.4)	0.001
CVD	51 (3.7)	71 (4.9)	71 (5.0)	98 (6.9)	0.002
PVD	5 (0.4)	6 (0.4)	13 (0.9)	15 (1.1)	0.054
Family history of CAD, n (%)	109 (8.0)	130 (9.0)	99 (7.0)	117 (8.3)	0.270
Statin use	1040 (76)	1127 (77.7)	1085 (76.8)	1087 (76.9)	0.702
Clinical presentation, n (%)					
STEMI	886 (64.7)	963 (66.4)	898 (63.6)	917 (64.9)	0.470
Non-STEMI	484 (35.3)	488 (33.6)	515 (36.4)	496 (35.1)	0.470

Data are expressed as mean±SD or as number (percentage). BP: blood pressure, CAD: coronary artery disease, CVD: cerebrovascular disease, LVEF: left ventricular ejection fraction, PVD: peripheral vascular disease, STEMI: ST elevation myocardial infarction

heart failure, LVEF, Killip classes >1, glucose, total cholesterol, triglyceride, creatinine clearance, NT-proBNP, left main and multivessel involvement, pre-TIMI flow grade 0, post-TIMI flow grade 3, ACC/AHA lesion type C, PCI success rate, in-hospital complications and use of statin.

**Normal-weight group
(n=2246, mean age=66.5±11.6 years, 68.6% male)**

Patients were also stratified into quartiles based on hs-CRP level to evaluate their 12-month clinical outcomes. Patients with higher hs-CRP were found to be older (p<0.001), with increased heart rate (p=0.015) and higher Killip classes (p=0.002). They had more association with diabetes mellitus (p=0.019), hypertension (p=0.049), heart failure (p=0.001) and peripheral vascular disease (p=0.001). Creatinine clearance, LVEF and high-density lipoprotein cholesterol decreased with higher hs-CRP (p<0.001, p<0.001 and p=0.001 respectively). NTproBNP showed an increasing trend among quartiles (p<0.001). Total cholesterol, triglyceride and low density lipoprotein-cholesterol (LDL-C) were also significant among quartiles (p<0.001, p=0.001 and p=0.001 respectively). They were more associated

with ACC/AHA lesion type C, multivessel involvement, pre-TIMI flow grade 0 and in-hospital complications. Twelve-month composite of MACE (p=0.009) and all-cause death (p<0.001) increased as the value of hs-CRP increased from 1st to 4th quartile. Cox proportional hazard model showed 12-month mortality to be statistically insignificant among hs-CRP quartiles in this group (p=0.681). The variables included in the model were age, DM, hypertension, hyperlipidemia, heart failure, peripheral vascular disease, smoking history, clinical presentation ST-elevation MI, total cholesterol, triglyceride, creatinine clearance, NT-proBNP, systolic blood pressure, heart rate, in-hospital complications, Killip class >1, LVEF <55%, pre-procedure TIMI grade 0 flow, ACC/AHA lesion type C, multivessel involvement, and use of statin.

**Underweight group
(n=281, mean age=71.5±11.0 years, 64.4% male)**

Patients from this study were additionally divided into quartiles based on hs-CRP level to study their 12-month clinical outcomes. The variables included in the model were age, systolic blood pressure, LVEF <55%, glucose, total cholesterol, LDL-C, creatinine clearance,

Table 2. Laboratory characteristics of overweight/obese patients according to high sensitivity C-reactive protein levels

Variables	Quartile 1 (<0.2 mg/dL) n=1370	Quartile 2 (≥0.2 - <0.82 mg/dL) n=1451	Quartile 3 (≥0.82 - <4.08 mg/dL) n=1413	Quartile 4 (≥4.08 mg/dL) n=1413	p
CK-MB (U/L)	162.34±357.40	171.68±290.18	161.26±326.0	170.05±309.94	0.76
Troponin I (ng/mL)	46.54±86.23	53.59±96.32	46.33±94.11	52.91±94.15	0.11
NT-proBNP (pg/mL)	629.27±2398.85	1166.35±3779.03	1807.84±5119.69	2909.69±5828.27	<0.001
Creatinine (mg/dL)	1.14±1.38	1.08±0.81	1.18±1.26	1.23±1.15	0.005
Creatinine clearance (min/mL)	80.70±32.95	78.89±32.11	75.36±33.21	73.03±31.53	<0.001
Glucose (mg/dL)	163.26±68.10	168.71±72.44	170.71±75.55	175.15±86.02	0.001
Total cholesterol (mg/dL)	189.69±42.02	193.98±44.43	187.03±42.77	182.13±44.50	<0.001
Triglyceride (mg/dL)	139.95±101.10	148.41±134.20	132.45±95.69	133.84±114.36	0.001
LDL-C (mg/dL)	121.87±39.88	124.48±38.56	121.26±47.45	117.07±43.13	<0.001
HDL-C (mg/dL)	46.21±24.84	44.80±17.91	43.99±20.48	42.76±17.31	<0.001

Data are expressed as mean±SD or as number (percentage). CK-MB: creatinine kinase-MB, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, NT-pro BNP: N-terminal pro-brain natriuretic peptide

Table 3. Angiographic findings and procedural results of overweight/obese patients according to high sensitivity C-reactive protein levels

Variables	Quartile 1 (<0.2 mg/dL) n=1370	Quartile 2 (≥0.2 - <0.82 mg/dL) n=1451	Quartile 3 (≥0.82 - 4.08 mg/dL) n=1413	Quartile 4 (≥4.08 mg/dL) n=1413	p
Infarct-related artery, n (%)					
Left main stem	15 (1.1)	14 (1.0)	26 (1.8)	22 (1.6)	0.14
Left anterior descending artery	626 (45.7)	679 (46.8)	620 (43.9)	665 (47.1)	0.46
Left circumflex artery	250 (18.2)	238 (16.4)	247 (17.5)	229 (16.2)	0.42
Right coronary artery	461 (33.6)	496 (34.2)	478 (33.8)	472 (33.4)	0.94
ACC/AHA lesion type C, n (%)	556 (40.6)	584 (40.2)	629 (44.5)	686 (48.5)	<0.001
PCI with stent, n (%)	1268 (92.5)	1351 (93.1)	1301 (92.0)	1290 (91.3)	0.212
Multivessel involvement, n (%)	656 (47.9)	764 (52.6)	813 (57.5)	848 (60.0)	<0.001
Pre-PCI TIMI flow grade 0, n (%)	538 (39.3)	615 (42.4)	590 (41.7)	670 (47.4)	0.002
Post-PCI TIMI flow grade III, n (%)	1210 (88.4)	1281 (88.3)	1210 (85.6)	1252 (88.6)	0.004
PCI success rate, n (%)	1311 (95.7)	1361 (93.8)	1315 (93.1)	1321 (93.5)	0.004
In-hospital complications, n (%)	120 (8.8)	117 (8.1)	157 (11.1)	226 (16.0)	<0.001

*in-hospital complications include atrio-ventricular block, bradycardia, ventricular tachycardia/ventricular fibrillation, atrial fibrillation, cardiogenic shock, acute renal failure, metabolic acidosis/lactic acidosis, cerebrovascular event or infection/sepsis. ACC/AHA: American college of cardiology/American heart association, PCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction

NT-proBNP, smoking history, heart failure, post-procedure TIMI grade 3, PCI success rate, and in-hospital complications. Age, NT-proBNP, Killip class >1 and in-hospital complications increased with increasing levels of hs-CRP ($p=0.006$, $p<0.001$, $p=0.009$ and $p=0.032$ respectively), while creatinine clearance decreased with rising level of hs-CRP ($p=0.001$). Systolic blood pressure, LVEF, total cholesterol and post-TIMI flow grade III were statistically significant among the quartiles ($p=0.043$, $p=0.023$, $p=0.038$ and $p=0.002$ respectively). Twelve-month composite of MACE increased as the value of hs-CRP increased from 1st to 4th quartile, but it was statistically insignificant ($p=0.382$), and twelve-month all-cause death showed no association among quartiles ($p=0.079$). Cox proportional hazard

model showed 12-month mortality to be statistically insignificant among hs-CRP quartiles in this group as well ($p=0.760$).

Fig. 1 shows adjusted survival curves of 12-month mortality in hs-CRP quartiles in (A) total study population, (B) overweight/obese group, (C) normal-weight group and (D) underweight group.

Discussion

This study demonstrated that higher baseline hs-CRP level (≥ 4.08 mg/dL) in overweight/obese AMI patients showed significant association with 12-month all-cause mortality independent of other prognostic markers.

Over the past few years, it has become increasingly clear that inflammation plays a pivotal role in cardiovascular disease, and increased circulating inflammation markers may be predictive of cardiovascular events.¹²⁾¹³⁾ Among the inflammation markers available,

hs-CRP is one of the independent predictors of cardiovascular events.¹⁴⁾¹⁵⁾ Adiposity is an inflammatory condition and IL-6, TNF- α and hs-CRP levels are positively correlated with adipocyte size.⁴⁾¹⁵⁾¹⁶⁾ These cytokines induce insulin resistance in adipose cells by inhib-

Table 4. Clinical outcomes and major adverse cardiac events (MACEs) during follow-up and at 12 months in overweight/obese patients

Outcomes, n (%)	Quartile 1 (<0.2 mg/dL) n=1370	Quartile 2 (\geq 0.2 - <0.82 mg/dL) n=1451	Quartile 3 (\geq 0.82 - <4.08 mg/dL) n=1413	Quartile 4 (\geq 4.08 mg/dL) n=1413	p
In-hospital death	14 (1.0)	17 (1.2)	31 (2.2)	47 (3.3)	<0.001
The composite of MACE at 1 month	37 (2.7)	50 (3.4)	53 (3.7)	86 (6.0)	<0.001
All cause death rate at 1 month	22 (1.6)	26 (1.8)	43 (3.0)	67 (4.7)	<0.001
The composite of MACE at 12 months	121 (8.8)	136 (9.4)	149 (10.5)	197 (13.9)	<0.001
All cause death rate at 12 months	27 (2.0)	37 (2.5)	62 (4.4)	94 (6.6)	<0.001

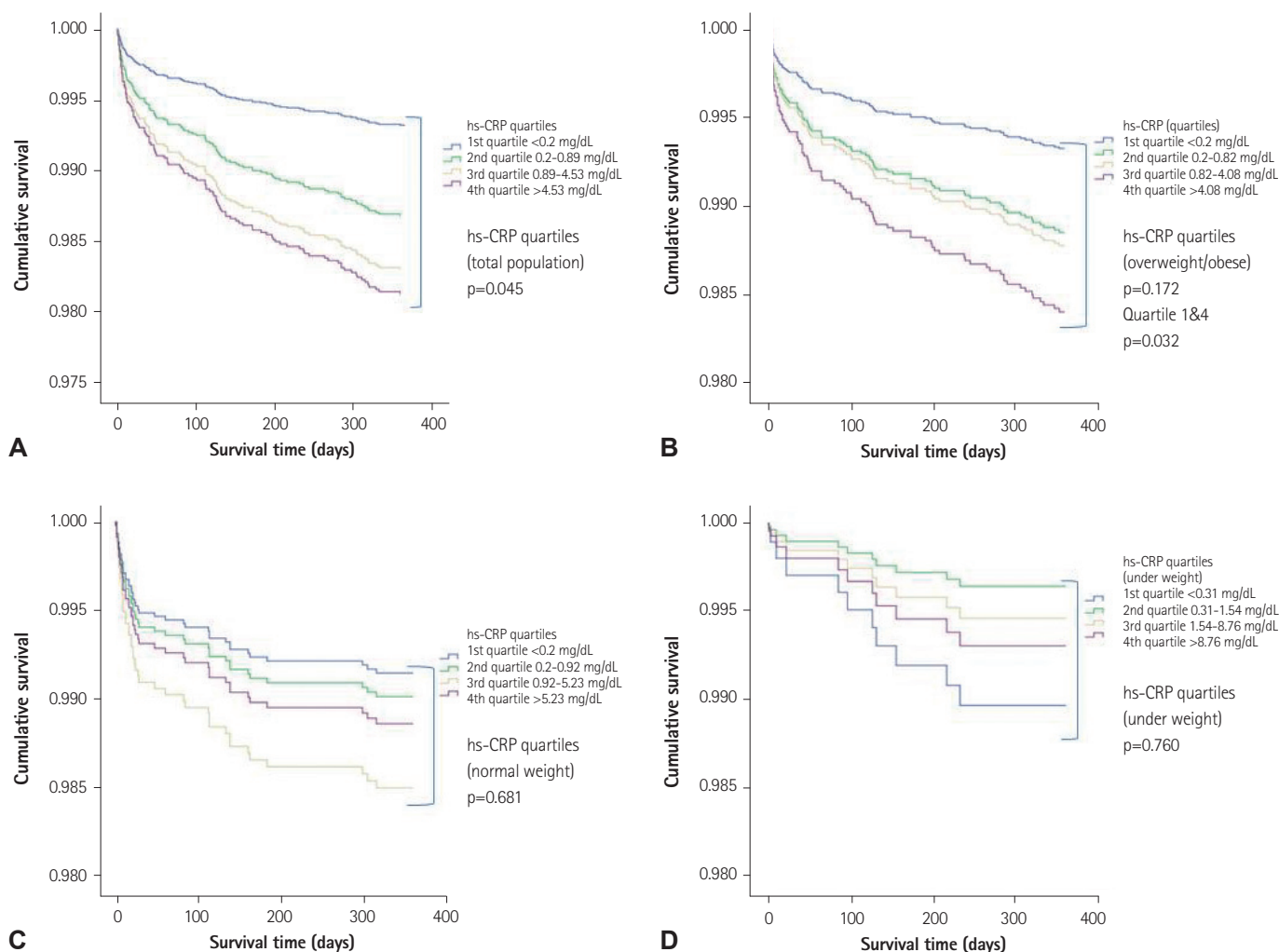


Fig. 1. Adjusted Cox proportional hazard survival curves for 12-month all-cause mortality and high sensitivity C-reactive protein (hs-CRP) quartiles in AMI patients undergoing PCI in (A) total study population, overall p=0.045, between 1st and 2nd quartile p=0.093, between 1st and 3rd quartile p=0.015 and between 1st and 4th quartile p=0.007; (B) overweight/obese group, overall p=0.172, between 1st and 2nd quartile p=0.213, between 1st and 3rd quartile p=0.150 and between 1st and 4th quartile p=0.032; (C) normal-weight group, overall p=0.681, between 1st and 2nd quartile p=0.824, between 1st and 3rd quartile p=0.337 and between 1st and 4th quartile p=0.623; and (D) underweight group, overall p=0.760, between 1st and 2nd quartile p=0.293, between 1st and 3rd quartile p=0.469 and between 1st and 4th quartile p=0.658. AMI: acute myocardial infarction, PCI: percutaneous coronary intervention.

iting insulin signaling.¹⁷⁾¹⁸⁾ CRP along with IL-6 and other cytokines/adipokines could be deleterious on the arterial wall since it has been found to directly promote endothelial cell inflammation and atherosclerotic processes.¹⁹⁾²⁰⁾ Thus, the link between adiposity, plaque accumulation/progression/rupture and atherothrombotic events, especially AMI, might be explained by higher levels of systemic inflammation and their chronic effect on coronary atherosclerosis over time.

Marsik et al.²⁾ report that patients with CRP concentrations >5 mg/L at the time of hospital admission had a 50% to 330% increase in risk of death from any cause. This increase in risk was present in both short-term and long-term follow-ups, and rose in magnitude as concentrations of CRP increased to >10 mg/L. Another study by Koenig et al.¹⁾ deals with the issue of hs-CRP as a predictor of death in the monitoring of trends and determinants in cardiovascular disease. Augsburg general population cohort in Southern Germany. In this prospective evaluation of 3620 initially healthy men followed over a 7.1-year period, 408 deaths occurred. After adjustment for age, smoking, hypertension, hyperlipidemia, diabetes, obesity and socioeconomic markers, those with baseline hs-CRP concentrations >3 mg/L had a 2-fold increase in risk of total mortality. Some studies have shown that higher BMI is associated with higher CRP concentrations even among young adults 17 to 39 years of age. These findings suggest a state of low-grade systemic inflammation in obese patients.²¹⁾

As previously reported by Sutter et al.²²⁾ it is known that increased levels of hs-CRP are greatly associated with extensive tissue destruction or infarct size. In such situations with more severe inflammation and extensive tissue damage, the relationship between adverse outcomes and CRP level might be considered independent from BMI status.

The present study shows that hs-CRP concentrations in the obese rise with increasing age, diabetes mellitus, hypertension, coronary artery disease, heart failure and cerebrovascular disease reaffirming data from earlier studies.²³⁻²⁵⁾ A prospective study by Brucci et al.²⁶⁾ on 329 patients with myocardial infarction at the time of admission showed CRP to be associated with a strong, positive graded increase in the risk of heart failure and death independently of known risk indicators. Ninety-four patients (29%) were in Killip class greater than 1 at presentation, and greater Killip class was associated with increased CRP. Interestingly, a study in Cairo by Fareed et al. noted that patients with hs-CRP >17 mg/L were prone to heart failure (at this value sensitivity=88%, specificity=51.2%). Our findings are in agreement with a recently published report that showed a trend to decreasing values of LVEF in relation to higher CRP levels.²⁷⁾ The significant relationship between CRP and LVEF suggests the implication of inflammatory mechanisms in left ventricular dysfunction and in

the pathogenesis of congestive heart failure, independently of the underlying atherosclerotic burden.

Angiographic findings of multivessel involvement, frequency of ACC/AHA lesion type C and subsequently higher pre-TIMI grade 0 flow, lower procedure success rate and higher complications support the previous study findings on acute coronary syndrome that demonstrated multiple complex stenoses with high plaque burden suggesting a pan-coronary involvement.²⁸⁾

This study showed a negative relation of smoking with hs-CRP in the overweight/obese subset. The mechanism whereby smoking is related to CRP concentration is unclear, but it may be multi-factorial, involving bronchial injury, endothelial activation and systemic inflammation.²⁹⁾ Use of a statin is a negative predictor of 12-month mortality in total study population. However, there was no significant association of statin use and hs-CRP levels in higher BMI patients though earlier studies have shown that statin reduces hs-CRP levels.³⁰⁾³¹⁾ This could be due to relatively small number of patients on a statin at the time of admission (7.15%) or unavailability of follow-up hs-CRP data in our registry. Moreover, in Anglo-Scandinavian Cardiac Outcomes Trial: Lipid Lowering Arm trial neither baseline nor on-treatment CRP provided useful information about the efficacy of statin treatment to reduce cardiovascular events beyond LDL-C reduction.³²⁾

Study limitations

This study should be interpreted in the light of the following limitations. This is not a randomized trial, but a retrospective evaluation on a large-scale multi-center registry. Blood samples for hs-CRP were obtained at the time of admission, hence higher levels of hs-CRP in our study may not be associated with myocardial necrosis.³³⁾ The time of onset and size of the myocardial infarction may also increase the hs-CRP levels. However, we did not determine the serial changes in hs-CRP concentration after AMI. Other inflammatory markers, such as IL-6, TNF- α or Lipoprotein-associated Phospholipase A2 (Lp-PLA2) that could have added more robust evidence of other inflammatory pathways associated with poor outcome were not a part of this study. Extreme variations in hs-CRP levels that could have made a difference in standard deviation in each group have not been excluded from this study.

Conclusions

Higher baseline hs-CRP level (≥ 4.08 mg/dL) in overweight/obese AMI patients showed significant association with 12-month all-cause mortality independent of other prognostic markers. We suggest further long term evaluation with serial changes in hs-CRP concentration after AMI and other inflammation markers to clearly elucidate its role in more diverse population.

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