

# Relationship between serum homocysteine levels and long-term outcomes in patients with ST-segment elevation myocardial infarction

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## Abstract

**Background:** The mortality of cardiovascular disease is constantly rising, and novel biomarkers help us predict residual risk. This study aimed to evaluate the predictive value of serum homocysteine (HCY) levels on prognosis in patients with ST-segment elevation myocardial infarction (STEMI).

**Methods:** The 419 consecutive patients with STEMI, treated at one medical center, from March 2010 to December 2015 were retrospectively investigated. Peripheral blood samples were obtained within 24 h of admission and HCY concentrations were measured using an enzymatic cycling assay. The patients were divided into high HCY level (H-HCY) and low HCY level (L-HCY) groups. Short- and long-term outcomes were compared, as were age-based subgroups (patients aged 60 years and younger *vs.* those older than 60 years). Statistical analyses were mainly conducted by Student *t*-test, Chi-squared test, logistic regression, and Cox proportional-hazards regression.

**Results:** The H-HCY group had more males (84.6% *vs.* 75.4%,  $P=0.018$ ), and a lower prevalence of diabetes (20.2% *vs.* 35.5%,  $P<0.001$ ), compared with the L-HCY group. During hospitalization, there were seven mortalities in the L-HCY group and 10 in the H-HCY group (3.3% *vs.* 4.8%,  $P=0.440$ ). During the median follow-up period of 35.8 (26.9–46.1) months, 33 (16.2%) patients in the L-HCY group and 48 (24.2%) in the H-HCY group experienced major adverse cardiovascular and cerebrovascular events (MACCE) ( $P=0.120$ ). History of hypertension (hazard ratio [HR]: 1.881, 95% confidence interval [CI]: 1.178–3.005,  $P=0.008$ ) and higher Killip class (HR: 1.923, 95% CI: 1.419–2.607,  $P<0.001$ ), but not HCY levels (HR: 1.007, 95% CI: 0.987–1.027,  $P=0.507$ ), were significantly associated with long-term outcomes. However, the subgroup analysis indicated that in older patients, HCY levels were significantly associated with long-term outcomes (HR: 1.036, 95% CI: 1.011–1.062,  $P=0.005$ ).

**Conclusion:** Serum HCY levels did not independently predict in-hospital or long-term outcomes in patients with STEMI; however, among elderly patients with STEMI, this study revealed a risk profile for late outcomes that incorporated HCY level.

**Keywords:** Homocysteine; Acute ST-segment elevation myocardial infarction; Percutaneous coronary intervention; Clinical outcome

## Introduction

Cardiovascular diseases are currently the major causes of mortality worldwide.<sup>[1,2]</sup> In China, the prevalence and mortality of cardiovascular diseases are constantly rising. While traditional risk factors are the main therapeutic targets for risk stratification, novel biomarkers may further

predict residual risk, and therefore improve the effectiveness of primary and secondary prevention.<sup>[3,4]</sup>

Homocysteine (HCY), a non-essential sulfur-containing amino acid, is an intermediate metabolite of methionine. Basic experiments indicated that HCY might be a risk factor for atherosclerosis.<sup>[5]</sup> Furthermore, there is clinical

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evidence that higher HCY levels may be associated with poor outcomes in patients with stable angina, stroke, and peripheral artery disease.<sup>[6,7]</sup> Nevertheless, the predictive value of serum HCY levels in patients with ST-segment elevation myocardial infarction (STEMI), which is caused by acute coronary occlusion, remains uncertain. This study was to compare HCY levels and short- and long-term outcomes in patients with STEMI.

## Methods

### Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University. Given the retrospective nature of this study, written informed consent was waived.

### Study population

The study cohort included 419 consecutive patients with STEMI who presented at Xuanwu Hospital, Capital Medical University from March 2010 to December 2015. STEMI was defined according to the presence of at least two of the following three criteria: (1) periods of prolonged chest pain ( $\geq 20$  min); (2) ST-segment elevation  $\geq 2$  mm in at least two contiguous precordial leads, or ST-segment elevation  $\geq 1$  mm in at least two inferior leads, or new left bundle branch block<sup>[8]</sup>; and (3) elevation of a myocardial biomarker (cardiac troponin [cTn] or creatine kinase MB/isoenzyme of creatine kinase [CK-MB])  $>99$ th percentile or two times the normal value. Patients were excluded if met the following criteria: (1) taking a folic acid supplement; (2) with a prior history of STEMI; (3) with a prior history of coronary revascularization; or (4) acute or chronic inflammatory disease.

Baseline information (clinical characteristics, laboratory results, and angiography) were collected by interviewing patients and medical record reviews. Patients were classified into two groups according to their serum HCY levels in relation to the median level (14.4  $\mu\text{mol/L}$ ). For the subgroup analysis, patients were divided into two subgroups according to age ( $\leq 60$  years and  $>60$  years).

### Coronary angiography

Diagnostic coronary angiography was performed using 5 to 6 French Judkins catheters (Cordis Corp., Miami Lakes, Florida, USA) and either a radial or femoral approach.<sup>[9]</sup> Performance of percutaneous coronary intervention (PCI) was determined by operators. All stenosis were evaluated visually and the Gensini score was determined.<sup>[10]</sup> Single vessel disease was defined as stenosis of at least 50% in one major epicardial coronary artery, while multi-vessel disease was defined as stenosis of at least 50% in  $\geq 2$  major epicardial coronary arteries.

### Biochemical measurements

Peripheral blood samples were obtained within 24 h of hospital admission. After coagulation at room temperature

for 30 min, the samples were centrifuged at  $3108 \times g$  for 5 min and the serum was aspirated. Serum HCY concentrations were measured by enzymatic cycling assay according to the kit instructions (Maccura Biotechnology Co., Ltd., Chengdu, China) with the Hitachi Automatic Analyzer 7600–210 (Hitachi, Tokyo, Japan). Serum concentrations of creatinine, uric acid, hemoglobin glycosylated hemoglobin (HbA1c), total cholesterol, high density lipoprotein (HDL)-cholesterol, and low density lipoprotein (LDL)-cholesterol were assessed using standard laboratory methods.

### In-hospital death and long-term outcomes

The in-hospital mortality, defined as all-cause death, was compared between groups. Patients were followed up via telephone calls at six and 12 months, and then annually. The primary endpoint was defined as major adverse cardiovascular and cerebrovascular events (MACCE), including all-cause death, nonfatal myocardial infarction (MI), stroke, heart failure, and revascularization.

### Statistical analysis

Continuous variables are shown as mean  $\pm$  standard deviation (SD) and compared using a two-tailed Student *t*-test, while medians (Q1, Q3) and Mann–Whitney *U* tests were used for non-normally distributed variables. Categorical variables are shown as frequency (group percentage) and between-group comparisons were made using the Pearson Chi-square or Fisher exact test. Serum HCY was first considered as a categorical variable divided into two groups (H-HCY and L-HCY), and later as a continuous value to examine the relationship with end points. Bivariate correlations were analyzed using the Pearson correlation model. Binary logistic regression was used for multivariate analyses to determine predictors of in-hospital events. Kaplan–Meier estimates were used to estimate survival curves, and the log-rank test to test between-group differences. Cox proportional-hazards regression models were used to examine the relationship between HCY levels and different end points, after adjustment for multiple clinical and angiographic covariates significantly associated with each end point during univariate analysis. Hazard ratios (HRs) were reported with corresponding 95% confidence intervals (CIs). The respective predictive cut-off values were constructed according to the receivers operating characteristic curve for HCY for discrimination between surviving and MACCE. The areas under the curve were compared using the Hanley and McNeil method. Statistical analyses were performed using the Statistical Package for Social Sciences software version 19.0 (SPSS Inc., Chicago, IL, USA). A two-sided  $P < 0.05$  was considered statistical significance.

## Results

### Baseline characteristics

A total of 419 consecutive patients were enrolled. The mean age was  $62.0 \pm 12.2$  years and 336 (80.2%) were males. The baseline clinical and angiographic characteristics of the two groups are presented in Table 1. The

**Table 1: Baseline characteristics of patients with ST-segment elevation myocardial infarction according to HCY levels.**

Characteristics	L-HCY group (n=211)	H-HCY group (n=208)	Statistical values	P
General conditions				
Age (years)	61.7±11.5	62.4±12.8	-0.602*	0.548
Male gender	159 (75.4)	176 (84.6)	5.603 <sup>†</sup>	0.018
Hypertension	117 (55.5)	105 (50.5)	1.038 <sup>†</sup>	0.308
Diabetes mellitus	75 (35.5)	42 (20.2)	12.267 <sup>†</sup>	<0.001
Hypercholesterolemia	85 (40.3)	96 (46.2)	1.471 <sup>†</sup>	0.225
Current smoking	126 (59.7)	141 (67.8)	3.735 <sup>†</sup>	0.154
Cerebrovascular disease	27 (12.8)	32 (15.4)	0.580 <sup>†</sup>	0.446
Peripheral vascular disease	2 (1.0)	7 (3.3)	2.913 <sup>†</sup>	0.088
Chest pain	174 (82.5)	168 (80.8)	2.097 <sup>†</sup>	0.552
Prior PCI	19 (9.0)	21 (10.1)	0.144 <sup>†</sup>	0.704
Emergency PCI	116 (55.0)	111 (53.4)	0.109 <sup>†</sup>	0.741
BMI (kg/m <sup>2</sup> )	25.25±3.28	25.37±3.41	-0.325*	0.745
HR (beat/min)	76.73±14.82	77.65±16.27	-0.605*	0.546
SBP (mmHg)	131.76±22.01	133.68±23.58	-0.862*	0.389
DBP (mmHg)	78.55±13.47	80.46±15.29	-1.352*	0.177
LVEF (%)	56.34±9.86	55.92±9.55	0.389*	0.697
Killip class			3.178 <sup>†</sup>	0.365
I	99 (46.9)	95 (45.7)		
II	95 (45.0)	94 (45.2)		
III	15 (7.1)	12 (5.8)		
IV	2 (0.9)	7 (3.4)		
GRACE score	152.01±29.77	153.51±35.64	-0.467*	0.641
Laboratory findings				
WBC (×10 <sup>9</sup> /L)	9.83±2.84	10.95±3.31	-3.721*	<0.001
Homocysteine (μmol/L)	11.8 (10.0, 12.9)	20.7 (16.6, 25.8)		
Creatinine (mg/L)	660 (570, 780)	730 (630, 860)	-4.280 <sup>‡</sup>	<0.001
Uric acid (μmol/L)	311.58±92.42	363.34±139.83	-3.654*	<0.001
HbA1c (%)	6.05 (5.60, 7.20)	5.90 (5.50, 6.80)	-1.671 <sup>‡</sup>	0.095
Total cholesterol (mg/L)	44.3±9.4	46.1±12.1	-1.612*	0.108
HDL cholesterol (mg/L)	13.2 (11.1, 14.9)	12.6 (10.0, 15.2)	-1.303 <sup>‡</sup>	0.193
LDL cholesterol (mg/L)	27.7±9.2	29.0±9.7	-1.345*	0.179
Preadmission therapy				
Aspirin	36 (17.1)	41 (19.7)	0.504 <sup>†</sup>	0.478
Statins	27 (12.8)	26 (12.5)	0.003 <sup>†</sup>	0.955
β-blockers	30 (14.2)	37 (17.8)	1.003 <sup>†</sup>	0.316
ACE inhibitors	27 (12.8)	19 (9.1)	1.439 <sup>†</sup>	0.230
Calcium channel blockers	59 (28.0)	35 (16.8)	7.974 <sup>†</sup>	0.005
Extent of vessels (mm)	2.08±0.83	1.92±0.88	1.713*	0.088
Lesion location				
LM	8 (4.5)	13 (7.7)	1.629 <sup>†</sup>	0.202
LAD	139 (77.7)	117 (69.6)	2.874 <sup>†</sup>	0.090
LCX	82 (45.8)	68 (40.5)	1.005 <sup>†</sup>	0.316
RCA	103 (57.5)	82 (48.8)	2.655 <sup>†</sup>	0.103
Multivessel lesion	146 (69.2)	123 (59.1)	3.292 <sup>†</sup>	0.070
IRA				
LAD	103 (48.8)	100 (48.1)		
LCX	33 (15.6)	34 (16.3)		
RCA	75 (35.5)	74 (35.6)		
Gensini score	48.0 (32.0, 80.0)	40.5 (22.3, 80.0)	-0.883 <sup>‡</sup>	0.377
Treatment strategy				
Primary PCI	116 (55.0)	111 (53.4)	0.109 <sup>†</sup>	0.741

Data are shown as mean ± SD, median (Q1, Q3), or n (%). \*t value †Chi-square value. ‡Z value. ACE: Angiotensin-converting enzyme; BMI: Body mass index; CABG: Coronary-artery bypass grafting; DBP: Diastolic blood pressure; HDL: High density lipoprotein; HR: Heart rate; IRA: Infarction related artery; LAD: Left anterior descending; LCX: Left circumflex; LDL: Low density lipoprotein; LM: Left main; LVEF: Left ventricle ejection fraction; PCI: Percutaneous coronary angiography; RCA: Right coronary artery; SBP: Systolic blood pressure; SD: Standard deviation; WBC: White blood cell.

H-HCY group had more male patients (84.6% *vs.* 75.4%,  $P=0.018$ ) and fewer patients with diabetes (20.2% *vs.* 35.5%,  $P<0.001$ ), compared with the L-HCY group. The levels of white blood cell (WBC), creatinine, and uric acid (UA) were higher in the H-HCY group, compared with the L-HCY group (all  $P<0.001$ ). There were no significant differences in prior medication use between L-HCY and H-HCY groups, with the exception of calcium channel blockers (28.0% *vs.* 16.8%,  $P=0.005$ ). The numbers of diseased vessels and Gensini scores were similar between the two groups.

### Correlation between serum HCY and biochemistry indicators

Serum HCY levels were positively correlated with WBC count ( $r=0.146$ ,  $P=0.003$ ), creatinine ( $r=0.254$ ,  $P<0.001$ ) and UA level ( $r=0.278$ ,  $P<0.001$ ).

### In-hospital outcomes

Seven patients died in the L-HCY group and 10 in the H-HCY group (3.3% *vs.* 4.8%,  $P=0.440$ ). After adjusting for general conditions and blood biochemistry indicators, serum HCY level (OR: 0.970, 95% CI: 0.905–1.039,  $P=0.387$ ) was not significantly associated with mortality. Age (OR: 1.114, 95% CI: 1.045–1.188,  $P=0.001$ ), Killip class (OR: 3.340, 95% CI: 1.693–6.591,  $P=0.001$ ), WBC counts (OR: 1.376, 95% CI: 1.130–1.675,  $P=0.001$ ) and creatinine levels (OR: 1.013, 95% CI: 1.000–1.026,  $P=0.044$ ) were independent predictors for in-hospital mortality [Table 2].

### Long-term outcomes

Follow-up information was available for 324 (80.6%) patients; 78 patients were lost to follow-up. Rates of lost follow-up were almost equal between L-HCY and H-HCY groups in overall population (21.6% *vs.* 17.2%,  $P=0.265$ ) as well as elder group (15.9% *vs.* 15.0%,  $P=0.852$ ). During the median follow-up period of 35.8 (26.9, 46.1) months,

81 (20.2%) patients experienced MACCE, including 33 in L-HCY group and 48 in H-HCY group. The unadjusted Kaplan–Meier estimates of MACCE at 7 years were comparable between the two groups ( $P=0.120$ ) [Figure 1].

### Cox multivariate models for long-term outcomes

The independent predictive value of HCY level on long-term mortality (HR: 1.022, 95% CI: 0.992–1.053,  $P=0.153$ ) and MACCE (HR: 1.007, 95% CI: 0.987–1.027,  $P=0.507$ ) was not statistically significant. Age (HR: 1.041, 95% CI: 1.005–1.079,  $P=0.025$ ), history of hypertension (HR: 2.879, 95% CI: 1.109–7.475,  $P=0.030$ ) and Killip class (HR: 2.365, 95% CI: 1.339–4.177,  $P=0.003$ ) retained statistical significance for long-term mortality [Table 2]. Meanwhile, hypertension (HR: 1.881, 95% CI: 1.178–3.005,  $P=0.008$ ) and Killip class (HR: 1.923, 95% CI: 1.419–2.607,  $P<0.001$ ) were independent predictors of long-term MACCE.

### Subgroup analysis

All subjects were classified according to age as either younger (age  $\leq 60$  years) or older (age  $>60$  years) groups and their clinical characteristics were compared [Table 3]. The younger group included more males (93.2% *vs.* 69.0%,  $P<0.001$ ) and smokers (78.9% *vs.* 51.1%,  $P<0.001$ ). In contrast, the older group had a worse average Killip classification (66.8 *vs.* 37.9%,  $P<0.001$ ), higher mean GRACE score (128.34  $\pm$  22.52 *vs.* 173.02  $\pm$  25.31,  $P<0.001$ ) and more multivessel disease (70.3% *vs.* 58.0%,  $P=0.027$ ). After following a similar treatment strategy, one patient died in the younger group while 16 patients died in older group during hospitalization (0.5% *vs.* 7.0%,  $P=0.001$ ). During follow-up, 31 patients in the younger group and 50 in the elder group suffered MACCE (16.4% *vs.* 24.5%,  $P=0.044$ ).

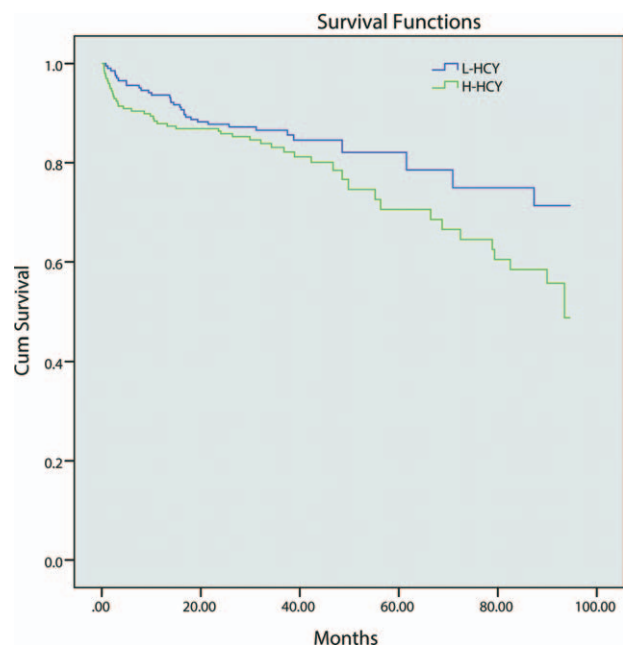
After adjustment for confounding factors in the multivariate Cox regression analysis, hypertension (HR: 2.424, 95% CI: 1.087–5.403,  $P=0.030$ ) and WBC count (HR: 1.135, 95% CI: 1.022–1.260,  $P=0.0181$ ) remained

**Table 2: Multivariate logistic and Cox regression analyses on in-hospital mortality and long-term outcomes.**

Variable	In-hospital outcome			Long-term outcomes					
	Mortality			Mortality			MACCE		
	OR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age (years)	1.114	1.045–1.188	0.001	1.041	1.005–1.079	0.025	1.021	0.998–1.044	0.080
Male gender	0.554	0.115–2.661	0.460	0.893	0.265–3.007	0.856	1.267	0.666–2.408	0.471
Hypertension	2.765	0.659–11.599	0.165	2.879	1.109–7.475	0.030	1.881	1.178–3.005	0.008
Diabetes mellitus	0.615	0.156–2.422	0.487	0.433	0.140–1.337	0.146	1.473	0.913–2.375	0.112
Smoking	0.576	0.162–2.052	0.395	2.003	0.855–4.690	0.110	1.492	0.931–2.389	0.096
Killip class	3.340	1.693–6.591	0.001	2.365	1.339–4.177	0.003	1.923	1.419–2.607	<0.001
WBC counts	1.376	1.130–1.675	0.001	1.057	0.905–1.234	0.484	1.056	0.976–1.142	0.173
Creatinine levels	0.874	0.430–1.780	0.711	1.005	0.989–1.021	0.568	1.014	0.787–1.307	0.913
LDL cholesterol levels	1.013	1.000–1.026	0.044	1.183	0.712–1.966	0.516	1.005	0.998–1.011	0.163
HCY levels	0.970	0.905–1.039	0.387	1.022	0.992–1.053	0.153	1.007	0.987–1.027	0.507

CI: Confidence interval; HCY: Homocysteine; HR: Hazard ratio; LDL: Low density lipoprotein; MACCE: Major adverse cardiovascular and cerebrovascular events; OR: Odds ratio; WBC: White blood cell.





**Figure 1:** Kaplan–Meier survival rate curve for MACCE. The unadjusted Kaplan–Meier estimates of MACCE at 7 years were comparable between two groups ( $P=0.120$ ). H-HCY: High homocysteine level; L-HCY: Low homocysteine level; MACCE: Major adverse cardiovascular and cerebrovascular events.

independent predictors for the younger group, while Killip class (HR: 2.186, 95% CI: 1.441–3.316,  $P < 0.001$ ), HCY level (HR: 1.036, 95% CI: 1.011–1.062,  $P=0.005$ ) and creatinine level (HR: 1.009, 95% CI: 1.002–1.016,  $P=0.009$ ) retained statistical significance for the older group [Table 4].

### Diagnostic power of HCY for long-term MACCE in the older group

The area under the receiver operating characteristics curve was 0.662 (0.579, 0.746,  $P < 0.001$ ) [Figure 2]. The predictive cut-off value of HCY for MACCE was 14.05  $\mu\text{mol/L}$  (sensitivity: 0.740; specificity: 0.564).

### Discussion

There were no statistically significant associations between serum HCY levels and short- and long-term outcomes among all patients; however, among older patients, HCY independently predicted prognosis. Traditional risk factors, such as age, hypertension, and Killip class, remain the predominant predictors for outcomes in patients with STEMI.

HCY is formed during metabolism of methionine, and its recycling is mediated by vitamin B<sub>6</sub>, B<sub>12</sub>, or folic acid. Dietary deficiency of the aforementioned vitamins, genetic abnormalities including CBS and MTHFR mutations, and kidney failure are the main causes of elevated serum HCY levels, termed homocysteinemia.

It is widely accepted that elevated plasma HCY levels are associated with increased adverse cardiovascular events, independent of other factors.<sup>[11,12]</sup> Evidence from

case-control and prospective studies suggested a graded and independent association between HCY levels and prognosis in patients with coronary artery disease (CAD). Nygard *et al*<sup>[13]</sup> reported that HCY levels were strong predictors of long-term mortality in 587 patients with angiographically confirmed CAD, after a median follow-up period of 4.6 years.

Besides its heavy burden to health, there is inadequate or conflicting evidence of the prognostic value of HCY in patients with acute coronary syndrome (ACS).<sup>[14,15]</sup> Omland *et al*<sup>[16]</sup> firstly investigated the possible prognostic value of HCY on survival in 579 patients with acute coronary syndrome after a median follow-up of 628 days. While Foussas *et al*<sup>[17]</sup> suggested HCY levels on admission were not an independent predictor of long-term mortality in patients with ACS.

Meanwhile, elevated serum HCY level was accompanied by the prevalence of clinical and subclinical cerebral injury, as well as long-term overall mortality and stroke recurrence.<sup>[18]</sup> However, the efficiency of HCY lowering therapy in stroke prevention warrant further investigation.<sup>[19]</sup>

Nevertheless, due to the lack of relevant research, the possibility for HCY level in predicting outcomes of STEMI remains unclear.

Above all, the pathophysiological mechanism of serum HCY-mediated vascular dysfunction and STEMI procedure triggering was not in full accord.

STEMI is characterized as rupture of an atherosclerotic plaque, alteration in coronary vasomotor tone, platelet aggregation, and an active thrombotic procedure, which lead to interruption of blood flow and MI.<sup>[20]</sup> Pathological studies and intracoronary imaging showed that the occurrence of STEMI procedure directly associated with vulnerable plaques<sup>[21,22]</sup> and systemic low-grade inflammation.<sup>[23]</sup>

The mechanisms that elevated HCY impairs vascular function are not definitely known. Several potential mechanisms consist of endothelial dysfunction,<sup>[24]</sup> oxidative stress,<sup>[25]</sup> activation of inflammation,<sup>[26]</sup> proliferation of smooth-muscle, increased adhesion of monocytes to endothelial cells<sup>[27]</sup> and platelet dysfunction.<sup>[28,29]</sup>

During hospitalization, the critical risk factor of mortality was the infarct location and proportion. STEMI triggers a systemic acute-phase response, in which neutrophils and monocytes/macrophages attacks the infarcted myocardial.<sup>[23]</sup> Besides, systemic inflammation that manifested as elevated WBC count, is associated with impaired microvascular reperfusion after PCI. Elder age and worse Killip classification also symbolize poorer cardiac function. HCY might affect the infarction indirectly by activation of inflammation, but the effectiveness of which was too limited to be revealed.

As for long-term management, secondary prevention of CAD serves as the pivotal role. Before discharge, all patients were advised for regular medication (antihypertensive, antiplatelet, and lipid-lowering therapy), smoking

**Table 3: Baseline characteristics of patients with ST-segment elevation myocardial infarction according to age.**

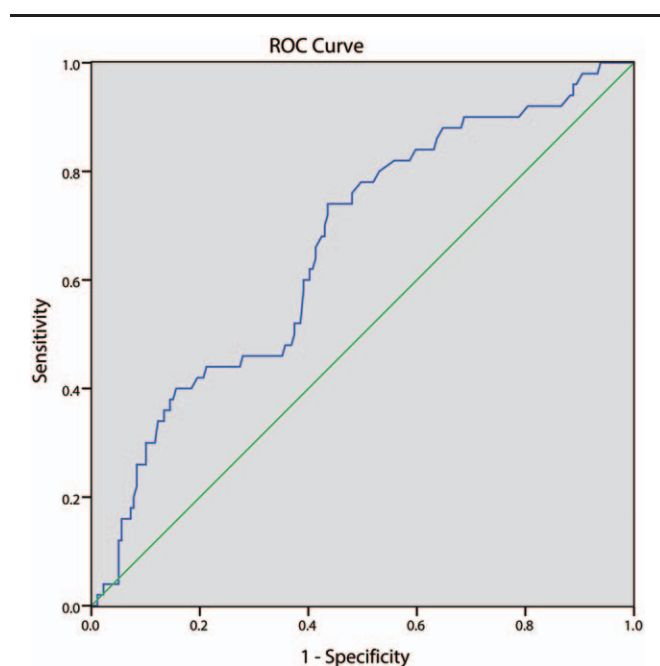
Characteristics	Age ≤ 60 years (n=190)	Age > 60 years (n=229)	Statistical values	P
<b>General conditions</b>				
Age (years)	51.4 ± 6.3	70.9 ± 8.1	-27.141*	<0.001
Male gender	177 (93.2)	158 (69.0)	37.823†	<0.001
Hypertension	90 (47.4)	132 (57.6)	4.400†	0.036
Diabetes mellitus	46 (24.2)	71 (31.0)	2.381†	0.123
Hypercholesterolemia	85 (44.7)	96 (41.9)	0.335†	0.562
Current smoking	150 (78.9)	117 (51.1)	35.137†	<0.001
CVD	11 (5.8)	48 (21.0)	19.756†	<0.001
PAD	6 (3.2)	3 (1.3)	1.687†	0.311
Chest pain	168 (88.4)	176 (76.9)	9.451†	0.002
Emergency PCI	110 (57.9)	117 (51.1)	1.936†	0.164
Killip class			37.176†	<0.001
I	118 (62.1)	76 (33.2)		
II	64 (33.7)	125 (54.6)		
III	7 (3.7)	20 (8.7)		
IV	1 (0.5)	8 (3.5)		
Killip class ≥II, n (%)	72 (37.9)	153 (66.8)	34.925†	<0.001
BMI (kg/m <sup>2</sup> )	25.82 ± 3.27	24.91 ± 3.35	2.568*	0.011
HR (beat/min)	76.46 ± 14.32	77.79 ± 16.49	-0.873*	0.383
SBP (mmHg)	133.41 ± 22.77	132.14 ± 22.85	0.568*	0.571
DBP (mmHg)	82.89 ± 15.39	76.68 ± 12.94	4.420*	<0.001
LVEF (%)	56.92 ± 9.57	55.38 ± 9.76	1.434*	0.152
GRACE score	128.34 ± 22.52	173.02 ± 25.31	-19.112*	<0.001
<b>Laboratory findings</b>				
WBC (×10 <sup>9</sup> /L)	10.93 ± 3.44	9.93 ± 2.78	3.245*	0.001
Homocysteine (μmol/L)	14.7 (12.2, 20.2)	14.1 (11.5, 20.5)	-1.426‡	0.154
Creatinine (mg/L)	665 (590, 770)	710 (620, 895)	-3.762‡	<0.001
Uric acid (μmol/L)	346.75 ± 136.14	329.41 ± 106.53	1.463*	0.144
HbA1c (%)	5.90 (5.40, 6.95)	6.00 (5.60, 7.08)	-2.008‡	0.045
Total cholesterol (mg/L)	46.4 ± 11.1	44.2 ± 10.4	1.958*	0.051
HDL cholesterol (mg/L)	11.7 (9.8, 14.3)	13.6 (11.7, 15.6)	-4.980‡	<0.001
LDL cholesterol (mg/L)	28.9 ± 10.0	28.0 ± 8.9	1.121*	0.263
<b>Preadmission therapy</b>				
Aspirin	23 (12.2)	52 (23.9)	9.194†	0.002
Statins	17 (9.0)	35 (16.1)	4.528†	0.033
β-blockers	25 (13.2)	42 (19.3)	2.684†	0.101
ACE inhibitors	18 (9.5)	28 (12.8)	1.113†	0.291
Calcium channel blockers	33 (17.6)	61 (27.9)	5.906†	0.015
<b>Lesion conditions</b>				
Multivessel lesion (%)	83 (58.0)	111 (70.3)	4.885†	0.027
IRA			0.162†	0.922
LAD	90 (47.4)	113 (49.3)		
LCX	31 (16.3)	36 (15.7)		
RCA	69 (36.3)	80 (34.9)		
Gensini score	40.00 (21.00, 80.00)	48.00 (32.00, 80.00)	-2.397‡	0.017
<b>Treatment strategy</b>				
Primary PCI	110 (57.9)	117 (51.1)	1.936†	0.164
<b>Prognosis</b>				
In-hospital mortality	1 (0.5)	16 (7.0)	11.135†	0.001
Long-term MACCE	31 (16.4)	50 (24.5)	4.078†	0.044

Data are shown as mean ± SD, median (Q1, Q3), or n (%). \* t value. † Chi-square value. ‡ Z value. ACE: Angiotensin-converting enzyme; BMI: Body mass index; CABG: Coronary-artery bypass grafting; DBP: Diastolic blood pressure; HDL: High density lipoprotein; HR: Heart rate; IRA: Infarction related artery; LAD: Left anterior descending; LCX: Left circumflex; LDL: Low density lipoprotein; LM: Left main; LVEF: Left ventricle ejection fraction; PCI: Percutaneous coronary angiography; RCA: Right coronary artery; SBP: Systolic blood pressure; WBC: White blood cell; SD: Standard deviation.

**Table 4: Multivariate Cox regression analysis on long-term MACCE.**

Variables	Age ≤60 years		Age >60 years	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.081 (0.999–1.168)	0.051	1.001 (0.959–1.044)	0.971
Male gender	0.359 (0.041–3.135)	0.354	1.806 (0.891–3.661)	0.101
Hypertension	2.424 (1.087–5.403)	0.030	1.229 (0.663–2.276)	0.513
Diabetes mellitus	1.657 (0.765–3.591)	0.201	1.441 (0.789–2.633)	0.234
Current smoking	1.241 (0.429–3.587)	0.690	1.379 (0.794–2.393)	0.254
Killip class	1.161 (0.659–2.046)	0.605	2.186 (1.441–3.316)	<0.001
WBC counts	1.135 (1.022–1.260)	0.018	1.020 (0.905–1.149)	0.748
HCY levels	0.972 (0.927–1.019)	0.233	1.036 (1.011–1.062)	0.005
LDL cholesterol levels	1.315 (0.868–1.990)	0.196	0.841 (0.611–1.158)	0.290
Creatinine levels	0.993 (0.978–1.009)	0.396	1.009 (1.002–1.016)	0.009

CI: Confidence interval; HR: Hazard ratio; LDL: Low density lipoprotein; HCY: Homocysteine; MACCE: Major adverse cardiovascular and cerebrovascular events; WBC: White blood cell.



**Figure 2:** The receiver operating characteristic curve for homocysteine in subgroup with age >60 years. Area under the receiver operating characteristic curve was 0.662 (0.579, 0.746;  $P < 0.001$ ). The predictive cut-off value of homocysteine level for MACCE was 14.05  $\mu\text{mol/L}$  (sensitivity: 0.740 and specificity: 0.564). MACCE: Major adverse cardiovascular and cerebrovascular events.

cessation, body weight control, adequate exercise, and regular visit. High HCY level only leads to mild elevation of cardiovascular risk, which turns even inadequate after active secondary prevention was carried out.

During subgroup analysis, we drew different risk profiles for younger and older patients. Both groups shared similar HCY levels, but compared with younger patients, older patients exhibited higher creatinine levels and worse Killip risk stratification. Besides following similar treatment strategies, older patients exhibited poorer prognosis during hospitalization and follow-up. HCY level was retained as an independent prognostic factor in older patients, in addition to high Killip class and creatinine level. Between-

group differences in clinical characteristics and pathophysiology led to risk stratification.

On the one hand, elevated HCY levels were previously related to congestive heart failure in patients with STEMI, which was defined as Killip II or higher.<sup>[30]</sup> The predictive significance of HCY on long-term mortality and MACCE emerged following addition of worse cardiac function as baseline in the older group. HCY is naturally broken down to be excreted in the urine. Thus, renal dysfunction might lead to elevation of serum HCY during long-term follow-up, by which elevated HCY revealed its prognostic value in patients with STEMI.

Current studies are testing the possible benefits of HCY-lowering therapy. Currently, there is insufficient evidence to recommend treatment of elevated HCY levels with folic acid or other vitamins to prevent cardiovascular diseases, which indirectly supports our results. The NORVIT trial indicated that, despite effectively reducing HCY levels, folic acid and vitamin B did not lower the risk of MACCE in patients with acute MI; notably, this study actually showed a trend toward increased cardiovascular risk.<sup>[31]</sup> Folic acid supplementation as a primary prevention for MI also failed in a Chinese population.<sup>[32]</sup> In our previous research, HCY did not serve as an independent prognostic factor in a patient population with STEMI, not to mention its utility as a therapeutic target.

In the current study, age, a history of hypertension, higher Killip class, higher creatinine level, and WBC count were independently related with worse prognosis in patients with STEMI. Thus, risk stratification should be carried out according to these characteristics. Additionally, more attention should be paid to patients in treatment during hospitalization and long-term management.

This study provided important, complementary information to previous studies of the prognostic value of HCY levels in patients with stable coronary artery disease or among those without cardiac diseases. The usefulness of HCY might be overrated, and large, randomized, controlled trials are necessary to determine the prognostic

value of serum HCY concentrations on risk profile modification for patients with STEMI.

Several limitations to the present study should be considered. This was a single-center, cohort study with unequal baseline characteristics, involving multiple operators. Meanwhile, secondary prevention medications, residual atherothrombotic burdens on non-culprit vessels, and cardiac rehabilitation are important determiners of long-term prognosis, and may emerge as confounders. Multivariate regression analysis might mitigate bias by adjusting confounding factors, but unmeasured indicators might leave room for residual bias. Secondly, our sample size and number of events was limited. Cohort studies with larger sample sizes and long-term follow-up will be much more valuable. Rate of lost follow-up in current study was relatively high, which might impact on reliability of results, to a certain extent. At the same time, a small sample size, low follow-up rate, and relatively small events might lead to over fitting. Moreover, serum HCY levels were measured once upon admission to the present study. Serum HCY concentrations were not obtained during follow-up; thus, we were not able to include this valuable information in our analysis. Finally, we did not include patients who took folic acid supplements, so the prognostic value of HCY level interventions remained unclear in the present study.

In conclusion, this study provided evidence that elevated HCY levels on admission did not indicate increased risk of hospital duration or long-term mortality and MACCE among all patients with STEMI we examined. For patients older than 60 years, HCY predicted long-term MACCE.

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### Conflicts of interest

None.

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