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Homocysteine as a potential predictive factor for high major adverse cardiovascular events risk in female patients with premature acute coronary syndrome

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Abstract

We aimed to investigate the correlation of homocysteine (Hcy) level with clinical characteristics, and explore its predictive value for major adverse cardiovascular events (MACE) risk in female patients with premature acute coronary syndrome (ACS).

The serum Hcy level was detected from 1299 female patients with premature ACS. According to the tertile of Hcy level, patients were divided into 3 groups: lowest tertile group (≤9.1 μmol/L), middle tertile group (9.2–11.6 μmol/L) and highest tertile group (>11.6 μmol/L). MACE incidence was recorded and MACE-free survival was caculated with the median follow-up duration of 28.3 months.

Increased Hcy correlated with older age ($P < .001$), higher creatinine level ($P < .001$), and enhanced uric acid level ($P = .001$), while reduced fasting glucose concentration ($P < .001$). MACE incidence was 10.7% and it was highest in highest tertile group (22.1%), followed by middle tertile group (7.7%) and lowest tertile group (2.4%) ($P < .001$). Receiver operating characteristic curve showed that Hcy distinguished MACE patients from non-MACE patients with the area under the curve of 0.789 (95% CI: 0.742–0.835). Kaplan–Meier curves revealed that MACE-free survival was shortest in Hcy highest tertile group, followed by middle tertile group and lowest tertile group ($P < .001$). Multivariate Cox analyses further showed that higher Hcy level was an independent predictive factor for poor MACE-free survival (middle tertile vs lowest tertile ($P = .001$, HR: 3.615, 95% CI: 1.661–7.864); highest tertile vs lowest tertile ($P < .001$, HR: 11.023, 95% CI: 5.356-22.684)).

Hcy serves as a potential predictive factor for increased MACE risk in female patients with premature ACS.

Abbreviations: ACS = acute coronary syndrome, AMI = acute myocardial infarction, AUC = area under the curve, CABG = coronary artery bypass grafting, CHD = coronary heart disease, Hcy = homocysteine, HDL = high density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile range, LDL = low density lipoprotein, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, NSTEMI = non-ST-segment elevation myocardial infarction, OMI = old myocardial infarction, PCI = percutaneous coronary intervention, ROC = receiver operating characteristic, SD = standard deviation, STEMI = ST-elevation myocardial infarction, VLDL = very low-density lipoprotein.

Keywords: acute coronary syndrome, female, Homocysteine, major adverse cardiovascular events, premature

1. Introduction

Coronary heart disease (CHD) is the leading cause of global mortality and morbidity in males as well as in females.[1] As one of the most common types of CHD, acute coronary syndrome (ACS) is a group of disease conditions including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina.[2] Although the rapid improvement has been achieved in ACS management with the use of adjunctive pharmacotherapy (specifically novel antiplatelets and anticoagulants), advanced percutaneous coronary intervention (PCI) procedures with drug-eluting stents, as well as coronary artery bypass grafting (CABG), differences in mortality between males and females still exists.[2,3] The possible causes for worse prognosis in females are multifactorial, which partly include higher baseline prevalence of risk factors for cardiovascular disease and insufficient awareness on ACS in females that results in a delayed treatment plan and poorer access to care.[3–5] Therefore, investigating additional and convincing biomarkers in female ACS patients, particularly in female patients with premature ACS, to monitor disease progression and predict prognosis is necessary.

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Homocysteine (Hcy) is a naturally occurring non-proteinogenic, sulfur-containing amino acid derived from methionine metabolism through methyl group metabolism.[6] It could not only influence endothelial function to cause a prothrombotic environment, platelet activation, and endothelial leukocyte interactions, but also increase inflammatory responses, which has been considered as a risk factor for the development of atherosclerosis and has a potential effect in the prediction of risk for developing CHD.[7,8] Furthermore, a previous study discloses that plasma Hcy is highly expressed in young patients with premature CHD compared to older patients, and it serves as an independent predictor for the age of onset of CHD.[9] Considering that the role of Hcy as a potential risk factor in CHD (including premature CHD), we hypostatized that Hcy plays an important role in female patients with premature ASC. However, information about it is still largely unknown. Therefore, we carried out this study with the purpose for investigating the correlation of Hcy level with clinical characteristics, and exploring its predictive value for major adverse cardiovascular events (MACE) risk in female patients with premature ACS.

2. Methods

2.1. Patients

A total of 1299 female patients with premature ACS in our hospital from March 1, 2014 to December 31, 2017 were screened. The screening criteria were as follows:

1. diagnosed as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA), according to the World Health Organization definition[10];
2. female with age at diagnosis < 55 years;
3. agreed to the study protocol and the schedule of clinical and angiographic follow-up.

The exclusion criteria included severe cardiomyopathy, severe valvular disease requiring surgical treatment, malignant neoplasms, systemic immune disease, severe liver, and kidney dysfunction. Finally, a total of 1102 female patients with premature ACS were eligible and analyzed in the present study. Written informed consent was obtained from each patient, and this research was approved by the Institutional Review Board of our hospital.

2.2. Data collection and sample detection

Clinical characteristics (such as age, smoking status, hypertension, diabetes, family history of coronary heart disease (CHD), history of stroke, CHD, old myocardial infarction (OMI), PCI, CABG, etc.) were recorded for each patient. Blood samples were collected from all patients on an empty stomach at the next morning after admission. Biochemical indicators (such as total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, apolipoprotein (a), apolipoprotein (b), lipoprotein (a), fibrinogen, high-sensitivity C-reactive protein (hs-CRP), fasting glucose, creatinine, uric acid, etc.) were measured as hospital usual practice and were documented. Meanwhile, left ventricular ejection fraction (LVEF) was measured by Ultrasound Cardiogram and was recorded as well. Most importantly, the serum was isolated from the blood sample by centrifugation, and the serum Hcy level was detected by a fully automated analyzer.

2.3. Coronary angiography and treatment

All patients underwent coronary angiography using standard Judkins technique after admission. And the coronary angiography findings, such as numbers of stenosis vessels, lesion location, etc., were also recorded. The appropriate treatments, such as pain relief, antiplatelet, anticoagulation, and reperfusion therapy (PCI, CABG or thrombolytic therapy), were administered to the patients according to the clinical status. And the reperfusion therapy type and drugs used after operation were documented as well.

2.4. Follow-up and assessment

After discharge from hospital, patients were followed up every 3–6 months (or as clinically indicated) by telephone and outpatient visits. The median follow-up duration was 28.3 moths (interquartile range: 20.0–38.8 months) with the deadline of 2018/12/31. During the follow-up, MACE occurred among patients were recorded, which was defined as a composite of cardiac death, acute myocardial infarction (AMI) and UA. The cardiac death was defined as sudden death with no other explanation available, death due to arrhythmia or after MI or heart failure, or death caused by heart surgery or endocarditis.[11] The AMI was defined in line with Third Universal Definition of Myocardial Infarction,[12] and the UA was defined according to the World Health Organization definition.[10] And the MACE-free survival was defined as the time interval from the date of initial therapy for ACS to the date of first MACE occurred. Patients who had not experienced MACE were censored on the last follow-up date.

2.5. Statistical analysis

In the analysis of this study, patients were categorized into three groups based on the tertile values of Hcy level as follows: lowest tertile: $\leq 9.1\,\mu$mol/L; middle tertile: 9.2–11.6 μmol/L; highest tertile: $>11.6\,\mu$mol/L. Continuous variables were determined by the Shapiro–Wilk test for normality. The normal-distributed continuous variable was displayed as mean $\pm$ standard deviation (SD), while the skewed-distributed continuous variable was displayed as median and interquartile range (IQR). The categorized variable was described as count (percentage). Comparison of continuous variable among tertile groups was determined by the one-way analysis of variance (ANOVA) (for normal-distributed variable) or by the Kruskal–Wallis H test (for skewed-distributed variable); comparison of skewed-distributed continuous variable between patients with MACE and patients without MACE was determined by the Wilcoxon rank sum test; comparison of categorized variable among tertile groups was determined by Chi-Squared test. The performance of the variable in predicting MACE risk was assessed by the receiver operating characteristic (ROC) curve and the derived area under the curve (AUC). The MACE-free survival was displayed by the Kaplan–Meier (K–M) curves and was determined by the log-rank test among tertile groups. The factors predicting the MACE-free survival were assessed by univariable and multivariable Cox proportional hazard regression model analyses. All tests were 2-sided, and P value $<.05$ was considered statistically significant. All statistical analyses were performed in SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA), and all figures were plotted by the GraphPad Prism software version 7.02 (GraphPad Software Inc., San Diego, CA, USA).

3. Results

3.1. Baseline characteristics

The mean age of 1102 female patients with premature ACS was 51.5 ± 3.7 years (Table 1). There were 916 (83.1%) patients diagnosed as UA, 137 (12.4%) patients diagnosed as NSTEMI as well as 49 (4.5%) patients diagnosed as STEMI. And the median value of LVEF was 62.00% (58.00%–65.00%). According to the coronary angiography findings, the number of patients with artery lesion in LM, LAD, LCX, and RCA was 40 (3.6%), 373 (33.8%), 141 (12.8%), and 176 (16.0%), respectively. As for treatment, there were 59 (5.4%) patients received CABG, 556 (50.4%) patients received PCI and 487 (44.2%) patients received thrombolytic therapy. Detailed information about other characteristics were shown in Table 1.

3.2. Association of Hcy with clinical characteristics

According to the tertile of Hcy level, we divided all patients into 3 groups, including lowest tertile group, middle tertile group, and highest tertile group. Increased Hcy level was correlated with older age ($P < 01$), higher creatinine level ($P < .001$), and enhanced uric acid level ($P = .001$), while reduced fasting glucose concentration ($P < .001$). However, there was no difference in other clinical characteristics among these three groups (All $P > .05$) (Table 2).

3.3. Association of Hcy with MACE incidence

In a total of 1102 female patients with premature ACS, there were 118 (10.7%) patients occurring MACE during follow-up, which included 100 (9.1%) patients with UA alone, 10 (0.9%) patients with AML alone, 6 (0.5%) patients with UA and AML, as well as 2 (0.2%) cardiac deaths (Table 3). Increased Hcy level was associated with higher MACE incidence ($P < .001$), as well as elevated UA incidence ($P < .001$), raised AML incidence ($P = .042$), as well as boosted UA, and AML incidence ($P = .029$). However, no correlation of Hcy level with cardiac death was discovered in these female patients with premature ACS ($P = .598$).

3.4. The predictive value of Hcy for MACE risk and its correlation with MACE-free survival

There were 118 MACE patients and 984 non-MACE patients, and Hcy level was higher in MACE patients (median value: 17.15 (10.80–21.43) μmol/L) compared to non-MACE patients (median value: 10.10 (8.20–12.10) μmol/L) ($P < .001$) (Fig. 1A). Further ROC curve showed that Hcy level could distinguish MACE patients from non-MACE patients with AUC of 0.789 (95% CI: 0.742–0.835). The sensitivity and specificity was 51.7% and 95.0% respectively at the best cut of point (Hcy level value: 16.85 μmol/L) (Fig. 1B). In order to explore the correlation of MACE-free survival with Hcy level in female patients with premature ACS, K–M curve was performed and revealed that MACE-free survival was shortest in Hcy highest tertile group, followed by middle tertile group and then lowest tertile group ($P < .001$) (Fig. 1C).

3.5. Potential factors affecting MACE-free survival

To investigate potential factors predicting MACE-free survival in female patients with premature ACS, univariate Cox proportional hazard regression model analyses was performed, which disclosed that higher level of Hcy was associated with worse MACE-free survival in female patients with premature ACS (middle tertile of Hcy level vs lowest tertile of Hcy level

Table 1

Baseline characteristics of female patients with premature ACS.

Items	Female patients with premature ACS (N = 1102)
Age (years), mean ± SD	51.5 ± 3.7
Diagnosis, No. (%)	
UA	916 (83.1)
NSTEMI	137 (12.4)
STEMI	49 (4.5)
Smoke status, No. (%)	225 (20.4)
Hypertension, No. (%)	725 (65.8)
Diabetes, No. (%)	350 (31.8)
Family history of CHD, No. (%)	219 (19.9)
History of stroke, No. (%)	83 (7.5)
History of OMI, No. (%)	44 (4.0)
History of PCI, No. (%)	95 (8.6)
History of CABG, No. (%)	6 (0.5)
LVEF (%), median (IQR)	62.00 (58.00–65.00)
Biochemical indexes, median (IQR)	
Total cholesterol (mmol/L)	4.71 (3.98–5.42)
HDL (mmol/L)	1.13 (0.96–1.32)
LDL (mmol/L)	3.09 (2.41–3.75)
VLDL (mmol/L)	0.41 (0.25–0.61)
Triglyceride (mmol/L)	1.57 (1.12–2.20)
Apolipoprotein (a) (g/L)	1.27 (1.14–1.41)
Apolipoprotein (b) (g/L)	1.02 (0.85–1.23)
Lipoprotein (a) (mg/dl)	26.45 (10.30–75.53)
Fibrinogen (mg/dl)	3.26 (2.89–3.70)
Hs-CRP (mg/L)	1.53 (0.63–3.95)
Fasting glucose (mmol/L)	5.47 (4.91–7.11)
Creatinine (μmol/L)	56.00 (50.00–63.00)
Uric acid (μmol/L)	269.00 (227.75–320.25)
Coronary angiography findings, No. (%)	
Number of disease vessel	
Normal	64 (5.8)
One-vessel disease	464 (42.1)
Two-vessel disease	265 (24.1)
Three-vessel disease	309 (28.0)
Location of artery lesion	
LM	40 (3.6)
LAD	373 (33.8)
LCX	141 (12.8)
RCA	176 (16.0)
Treatment, No. (%)	
CABG	59 (5.4)
PCI	556 (50.4)
Thrombolytic therapy	487 (44.2)
Drugs used after surgery, No. (%)	
Aspirin	1049 (95.2)
Clopidogrel	719 (65.2)
Statins	1007 (91.4)
Nitrate	468 (42.5)
ACEI	467 (42.4)
Beta blocker	727 (66.0)
Calcium antagonist	316 (28.7)

ACEI = angiotensin converting enzymes inhibitor, ACS = acute coronary syndromes, CABG = coronary artery bypass grafting, CHD = coronary heart disease, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile range, LAD = left anterior descending branch, LCX = left circumflex artery, LDL = low-density lipoprotein, LEVEF = left ventricular ejection fraction, LM = Left main, NSTEMI = non-ST-elevation myocardial infarction, OMI = old myocardial infarction, PCI = percutaneous transluminal coronary intervention, RCA = right coronary artery, SD = standard deviation, STEM = ST-elevation myocardial infarction, UA = unstable angina, VLDL = very low-density lipoprotein.

Table 2

Correlation of Hcy with clinical characteristics.

Items	Lowest tertile (≤9.1 μmol/L)	Middle tertile (9.2-11.6 μmol/L)	Highest tertile (>11.6 μmol/L)	*P* value
No.	374	362	366	
Age (years), mean ± SD	50.9 ± 4.2	51.9 ± 3.4	51.7 ± 3.3	**<.001**
Diagnosis, No. (%)				.672
UA	305 (81.6)	308 (85.1)	303 (82.8)	
NSTEMI	53 (14.2)	38 (10.5)	46 (12.6)	
STEMI	16 (4.3)	16 (4.4)	17 (4.6)	
Smoke status, No. (%)	64 (17.1)	75 (20.7)	86 (23.5)	.097
Hypertension, No. (%)	230 (61.5)	249 (68.8)	246 (67.2)	.089
Diabetes, No. (%)	134 (35.8)	110 (30.4)	106 (29.0)	.106
Family history of CHD, No. (%)	68 (18.2)	69 (19.1)	82 (22.4)	.317
History of stroke, No. (%)	23 (6.1)	34 (9.4)	26 (7.1)	.232
History of OMI, No. (%)	11 (2.9)	14 (3.9)	19 (5.2)	.292
History of PCI, No. (%)	33 (8.8)	28 (7.7)	34 (9.3)	.745
History of CABG, No. (%)	3 (0.8)	0 (0.0)	3 (0.8)	.229
LVEF (%), median (IQR)	62.0 (58.0–65.0)	62.0 (58.0–65.0)	61.0 (58.0–65.0)	.200
Biochemical indexes, median (IQR)				
Total cholesterol (mmol/L)	4.68 (3.97–5.40)	4.74 (4.02–5.45)	4.72 (3.96–5.40)	.874
HDL (mmol/L)	1.11 (0.95–1.33)	1.15 (0.99–1.32)	1.12 (0.94–1.30)	.314
LDL (mmol/L)	3.06 (2.37–3.76)	3.13 (2.46–3.84)	3.07 (2.42–3.64)	.744
VLDL (mmol/L)	0.39 (0.23–0.59)	0.40 (0.26–0.58)	0.43 (0.26–0.64)	.334
Triglyceride (mmol/L)	1.54 (1.11–2.31)	1.58 (1.10–2.17)	1.59 (1.14–2.15)	.889
Apolipoprotein (a) (g/L)	1.27 (1.15–1.41)	1.28 (1.15–1.42)	1.27 (1.11–1.41)	.283
Apolipoprotein (b) (g/L)	1.03 (0.84–1.24)	1.01 (0.85–1.24)	1.02 (0.86–1.21)	.936
Lipoprotein (a) (mg/dL)	29.85 (11.50–80.83)	24.85 (10.48–72.50)	23.00 (8.10—73.20)	.174
Fibrinogen (mg/dL)	3.26 (2.89–3.68)	3.25 (2.84–3.74)	3.28 (2.93–2.70)	.909
Hs-CRP (mg/L)	1.44 (0.61–3.83)	1.84 (0.72–4.22)	1.41 (0.59–4.12)	.509
Fasting glucose (mmol/L)	5.72 (5.11–7.86)	5.31 (4.82–6.85)	5.36 (4.88–6.63)	**<.001**
Creatinine (μmol/L)	53.00 (47.00–59.00)	57.00 (50.00–63.00)	59.00 (52.50–67.00)	**<.001**
Uric acid (μmol/L)	261.00 (220.00–316.00)	266.00 (228.00–318.00)	284.00 (236.5-334.00)	**.001**
Coronary angiography findings, No. (%)				
Number of disease vessel				.111
Normal	23 (6.1)	21 (5.8)	20 (5.5)	
One-vessel disease	159 (42.5)	147 (40.6)	158 (43.2)	
Two-vessel disease	93 (24.9)	102 (28.2)	70 (19.1)	
Three-vessel disease	99 (26.5)	92 (25.4)	118 (32.2)	
Location of artery lesion				
LM	19 (5.1)	7 (1.9)	14 (3.8)	.072
LAD	109 (29.1)	133 (36.7)	131 (25.8)	.059
LCX	52 (13.9)	48 (13.3)	41 (11.2)	.518
RCA	62 (16.6)	53 (14.6)	61 (16.7)	.701
Treatment, No. (%)				
CABG	17 (4.5)	14 (3.9)	28 (7.7)	.053
PCI	183 (48.9)	181 (50.0)	192 (52.5)	.617
Thrombolytic therapy	174 (46.5)	167 (46.1)	146 (39.9)	.127
Drugs used after surgery, No. (%)				
Aspirin	356 (95.2)	345 (95.3)	348 (95.1)	.990
Clopidogrel	245 (65.5)	236 (65.2)	238 (65.0)	.990
Statins	340 (90.9)	334 (92.3)	333 (91.5)	.803
Nitrate	154 (41.2)	146 (40.3)	168 (45.9)	.260
ACEI	164 (43.9)	150 (41.4)	153 (41.8)	.774
Beta blocker	261 (69.8)	235 (64.9)	231 (63.1)	.140
Calcium antagonist	93 (24.9)	116 (32.0)	107 (29.2)	.095

Comparison was determined by one-way analysis of variance (ANOVA), Chi-Squared test or Kruskal–Wallis H rank sum test.

ACEI = angiotensin converting enzymes inhibitor, CABG = coronary artery bypass grafting, CHD = coronary heart disease,Hcy = homocysteine, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile range, LAD = left anterior descending branch, LCX = left circumflex artery, LDL = low-density lipoprotein, LEVEF = left ventricular ejection fraction, LM = Left main, NSTEMI = non-ST-elevation myocardial infarction, OMI = old myocardial infarction, PCI = percutaneous transluminal coronary intervention, RCA = right coronary artery, SD = standard deviation, STEM = ST-elevation myocardial infarction, UA = unstable angina, VLDL = very low-density lipoprotein.

(*P* = .003, HR: 3.160, 95% CI: 1.491–6.698); highest tertile of Hcy level vs lowest tertile of Hcy level (*P* < .001, HR: 9.441, 95% CI: 4.739–18.807)). Meanwhile, diagnosis of NSTEMI (*P* = .008), smoke (*P* = .038), high creatinine level (*P* = .024), location of artery lesion at LAD (vs others) (*P* < .001), treatment of CABG (*P* = .013), treatment of PCI (*P* < .001), and clopidogrel use after surgery (*P* = .008) were also correlated with shorter MACE-free survival in female patients with premature ACS (Table 4). Further multivariate Cox proportional hazard regression model analyses showed that higher level of Hcy was

Table 3

MACE across tertiles according to Hcy level.

Items	Total patients	Lowest tertile (≤9.1 μmol/L)	Middle tertile (9.2-11.6 μmol/L)	Highest tertile (>11.6 μmol/L)	*P* value
No.	1102	374	362	366	
UA alone, No. (%)	100 (9.1)	8 (2.1)	24 (6.6)	68 (18.6)	**<.001**
AMI alone, No. (%)	10 (0.9)	1 (0.3)	2 (0.6)	7 (1.9)	**.042**
UA and AMI, No. (%)	6 (0.5)	0 (0.0)	1 (0.3)	5 (1.4)	**.029**
Cardiac death, No. (%)	2 (0.2)	0 (0.0)	1 (0.3)	1 (0.3)	.598
MACE incidence, No. (%)	118 (10.7)	9 (2.4)	28 (7.7)	81 (22.1)	**<.001**

Comparison was determined by Chi-Squared test.

AMI = acute myocardial infarction, Hcy = homocysteine, MACE = major adverse cardiovascular events, UA = unstable angina.

an independently predictive factor for poor MACE-free survival (middle tertile of Hcy level vs lowest tertile of Hcy level ($P = .001$, HR: 3.615, 95% CI: 1.661–7.864); highest tertile of Hcy level vs lowest tertile of Hcy level ($P < .001$, HR: 11.023, 95% CI: 5.356–22.684)). Meanwhile, diagnosis of NSTEMI ($P = .047$), high Hs-CRP ($P = .044$) as well as treatment of PCI ($P = .018$) also could independently predict poor MACE-free survival in female patients with premature ACS.

4. Discussion

The underlying pathophysiology of ACS is coronary atherosclerotic plaque ruptures or surface erosion to induce thrombosis or vasospasm, thereby decreasing blood flow to a part of heart musculature and causing a sudden decrease in myocardial oxygen supply.[2] Although ACS is a kind of commonly diagnosed disease and the leading cause of death globally in males as well as females, greater mortality rates after hospital discharge have been reported among female patients with premature ACS (aged 55 years or younger) compared with males of the same age.[5,13–15] For instance, a previous study enrolling over 91,088 ACS patients discloses that young females (<50 years old) present with a higher risk of in-hospital mortality compared to male patients with similar age.[13] Another study recruits 1163 patients with premature ACS and illustrates that female patients with premature ACS appear to have a higher incidence of rehospitalization compared to male patients with premature ACS.[5] Therefore, these previous studies indicate that female patients with premature ACS present with a worse prognosis than male patients with premature ACS. With regard to this, exploration of additional and convincing biomarkers for supervising diseases progression and predicting prognosis in female patients with ACS, particularly in female patients with premature ACS, is vital.

According to previous studies, Hcy could not only directly damage blood vessels, but also indirectly increase the affinity of lipoprotein (a) for fibrin, promote vascular smooth muscle cells, and inhibit endothelial cell growth to trigger and exacerbate atherosclerosis.[16–18] In addition, Hcy also contributes to the processes of inflammation. For instance, increased Hcy level plays a chemotactic role for leukocytes to leukocyte mobilization in ischemic conditions, and it also upregulates cathepsin to subsequent promote nuclear translocation of extracellular signal regulated kinase 1/2 (ERK1/2) and phosphorylation of signal transducer and activator of transcription 1 (STAT1), thereby medicating vascular endothelial inflammation that is an early and vital event in the development of vascular disease, including ACS.[19,20] Therefore, Hcy may be a potential role in the development and progression of ACS.

Although great attention has been paid in the underlying mechanism of Hcy in ACS, few studies are focusing on the correlation of Hcy level with clinical characteristics in ACS patients, particularly in female patients with premature ACS. Hence, we enrolled 1102 female patients with premature ACS and investigated the correlation of Hcy with clinical characteristics in these patients. The results showed that evaluated Hcy level was associated with older age, increased creatinine, and enhanced uric acid, but with decreased fasting

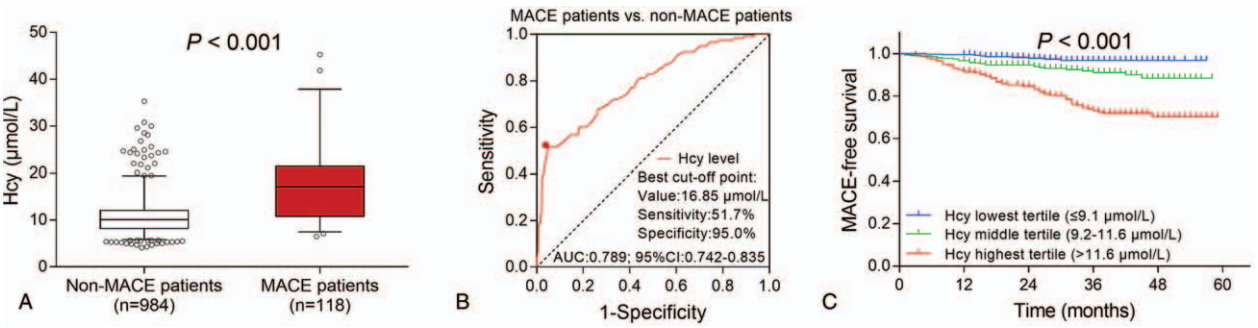

Figure 1. The effect of Hcy on MACE risk and MACE-free survival. A: The comparison of Hcy level between MACE patients and non-MACE patients. B: The predictive value of Hcy level for MACE risk. C: The correlation of Hcy level with MACE-free survival. Comparison of Hcy level between patients with MACE and patients without MACE was determined by the Wilcoxon rank sum test. The predictive value of Hcy level for MACE risk was assessed by the ROC curve and the derived AUC. The MACE-free survival was displayed by the Kaplan–Meier curves and was compared by the log-rank test among tertile groups. Hcy: homocysteine; MACE: major adverse cardiovascular events; ROC: receiver operating characteristic; AUC: area under the curve.

Table 4

Univariate and multivariate Cox proportional hazard regression model analyses of factors predicting MACE-free survival.

Items	Univariate Cox regression		Multivariate Cox regression	
	P value	HR (95%CI)	*P* value	HR (95%CI)
Hcy				
Lowest tertile	-	Reference	-	Reference
Middle tertile	**0.003**	3.160 (1.491–6.698)	**.001**	3.615 (1.661–7.864)
Highest tertile	<**0.001**	9.441 (4.739–18.807)	<**.001**	11.023 (5.356–22.684)
Age	0.857	1.005 (0.955–1.057)	.820	1.007 (0.950–1.068)
Diagnosis				
UA	-	Reference	-	Reference
NSTEMI	**0.008**	2.434 (1.266–4.680)	**.047**	2.115 (1.009–4.434)
STEMI	0.896	1.037 (0.601–1.790)	.884	0.948 (0.464–1.938)
Smoke	**0.038**	1.533 (1.025–2.294)	.188	1.338 (0.867–2.064)
Hypertension	0.959	0.990 (0.676–1.451)	.289	0.761 (0.460–1.261)
Diabetes	0.082	1.390 (0.959–2.015)	.055	1.646 (0.990–2.735)
Family history of CHD	0.813	1.054 (0.681–1.631)	.996	0.999 (0.632–1.578)
History of stroke	0.781	1.096 (0.573–2.097)	.829	0.924 (0.452–1.887)
History of OMI	0.209	1.631 (0.760–3.503)	.462	1.413 (0.563–3.545)
History of PCI	0.331	1.331 (0.748–2.369)	.516	1.248 (0.639–2.439)
History of CABG	0.778	1.327 (0.185–9.516)	.859	0.829 (0.106–6.500)
LVEF	0.415	0.990 (0.966–1.014)	.450	1.013 (0.980–1.047)
HDL	0.052	0.516 (0.265–1.007)	.052	0.200 (0.039–1.012)
LDL	0.383	0.919 (0.760–1.111)	.309	0.681 (0.326–1.426)
VLDL	0.667	1.093 (0.730–1.635)	.139	0.448 (0.155–1.298)
Triglyceride	0.520	1.046 (0.912–1.199)	.616	1.094 (0.770–1.556)
Apolipoprotein (a)	0.297	0.632 (0.266–1.498)	.195	3.521 (0.525–23.610)
Apolipoprotein (b)	0.679	0.875 (0.466–1.645)	.571	2.122 (0.157–28.675)
Lipoprotein (a)	0.777	1.000 (0.997–1.002)	.914	1.000 (0.997–1.002)
Fibrinogen	0.246	1.154 (0.906–1.469)	.755	0.957 (0.725–1.262)
Hs-CRP	0.136	1.005 (0.999–1.011)	**.044**	1.009 (1.000–1.019)
Fasting glucose	0.302	1.033 (0.971–1.098)	.948	0.997 (0.912–1.089)
Creatinine	**0.024**	1.014 (1.002–1.026)	.995	1.000 (0.984–1.016)
Uric acid	0.577	1.001 (0.998–1.003)	.576	0.999 (0.997–1.002)
Number of disease vessel				
Normal	-	Reference	-	Reference
One-vessel disease	0.923	1.043 (0.444–2.451)	.384	0.661 (0.260–1.678)
Two-vessel disease	0.663	1.217 (0.504–2.940)	.326	0.608 (0.225–1.643)
Three-vessel disease	0.324	1.540 (0.653–3.634)	.405	0.647 (0.232–1.803)
Location of artery lesion				
LM vs. others	0.122	1.828 (0.850–3.931)	.130	1.927 (0.825–4.503)
LAD vs. others	<**0.001**	1.975 (1.372–2.844)	.644	1.153 (0.629–2.115)
LCX vs. others	0.998	1.001 (0.589–1.699)	.428	0.767 (0.398–1.478)
RCA vs. others	0.151	1.398 (0.885–2.207)	.426	0.777 (0.417–1.447)
Treatment				
Thrombolytic therapy	-	Reference	-	Reference
CABG	**0.013**	2.583 (1.222–5.459)	.078	2.303 (0.910–5.830)
PCI	<**0.001**	2.639 (1.724–4.040)	**.018**	2.696 (1.184–6.139)
Drugs used after surgery				
Aspirin	0.703	1.261 (0.383–4.155)	.488	1.557 (0.445–5.441)
Clopidogrel	**0.008**	1.812 (1.171–2.804)	.986	1.006 (0.509–1.990)
Statins	0.605	1.234 (0.557–2.731)	.901	1.055 (0.452–2.461)
Nitrate	0.910	1.021 (0.707–1.475)	.518	0.873 (0.578–1.319)
ACEI	0.317	0.826 (0.568–1.201)	.545	0.871 (0.557–1.363)
Beta blocker	0.192	1.313 (0.872–1.976)	.154	1.363 (0.891–2.085)
Calcium antagonist	0.489	1.151 (0.772–1.715)	.197	1.363 (0.851–2.184)

ACEI = angiotensin converting enzymes inhibitor, CABG = coronary artery bypass grafting, CHD = coronary heart disease, CI = confidence, Hcy = homocysteine, HDL = high-density lipoprotein, HR = hazard ratio, hs-CRP = high-sensitivity C-reactive protein, LAD = left anterior descending branch, LCX = left circumflex artery, LDL = low-density lipoprotein, LEVEF = left ventricular ejection fraction, LM = Left main, MACE = major adverse cardiovascular events, NSTEMI = non-ST-elevation myocardial infarction, OMI = old myocardial infarction, PCI = percutaneous transluminal coronary intervention, RCA = right coronary artery, STEM = ST-elevation myocardial infarction, UA = unstable angina, VLDL = very low-density lipoprotein.

glucose in female patients with premature ACS. The possible reasons were that

1. For age: Hcy served as a risk factor for peripheral neuropathy through affecting nerve demyelination in the central and peripheral nervous systems.[21–23] Meanwhile, peripheral neuropathy itself had been disclosed to be related to gait speed decline in older adults.[23,24] Thus, increased Hcy level might be correlated with older age in female patients with premature ACS.

2. For creatinine and uric acid: Hcy was an independent risk factor for cardiovascular diseases.[25] Meanwhile, creatinine and uric acid were also important risk factors for cardiovascular diseases.[26] Hence, increased Hcy level might be indirectly associated with higher concentrations of creatinine and uric acid in female patients with premature ACS.
3. For fasting glucose: Hcy correlated with increased uric acid (that promoted emergence of free oxygen species and state of oxidative stress), which was closely related to high metabolism, thereby promoted glycometabolism and decreased fasting glucose in female patients with premature ACS.

Currently, concerns have been raised regarding an increased risk of MACE in ACS patients. Based on previous studies, the incidence of MACE is 9% and 8% in female ACS patients and male ACS patients after 12-month follow-up, respectively.[5] Whereas there is a total of 35% of the incidence of MACE in ACS patients after 24-month follow-up.[27] Although there were several studies focusing on the incidence of MACE in ACS patients, little was known about the occurrence of MACE in patients with premature ACS, particular in female patients with premature ACS. In this study, we discovered that the MACE incidence was 10.7% in female patients with premature ACS with a median follow-up duration of 28.3 months, which was lower compared to those previous study. The major explanation might that the MACE incidence has been reported to be increased in ASC patients with age of 65 years or older, while all patients enrolled in the present study were young with age <55 years who presented with better resilience and stronger immunity compared to older patients, thus the incidence of MAEC was relatively lower in female patients with premature ACS enrolled in this study compared to ASC patients in previous studies.[2]

Subsequently, we further explored the impact of Hcy on the MACE risk in female patient with premature ACS, and we found that higher Hcy level was correlated with increased MACE incidence, and it presented with a good predictive value for MACE risk with AUC of 0.789 (95% CI: 0.742–0.835). Meanwhile, K–M curve revealed that MACE-free survival was shortest in Hcy highest tertile group, followed by middle tertile group and then lowest tertile group. The possible explanations were as follows:

1. Hcy enhanced the affinity of lipoprotein (a) for fibrin, induced vascular smooth muscle cells, and reduced endothelial cell growth to accelerate thrombosis and vasospasm, thereby cause a high risk of MACE in female patients with premature ACS.
2. Hcy was involved in the vascular inflammation, which contributed to the decrease of blood flow and the reduction of myocardial oxygen supply, thereby increasing MACE occurrence in female patients with premature ACS.

Although there was no evidence about the influence of Hcy on MACE incidence in female patients with premature ACS, there are several previous studies focusing on the role of Hcy in premature ACS. Compared to these previous studies, the results in this study had the similar trend about the role of Hcy in ASC. For example, a Chinese prospective cohort study enrolls 2009 participants who are free from stroke, CHD and cancer (with the follow-up duration of 11.95 years), and reveals that the participants with Hcy >9.47 micromol/L present with a 2.3-fold risk for cardiovascular events, and participants with Hcy >11.84 micromol/L present with a 2.4-fold risk for death, suggesting that Hcy is associated with high risk of cardiovascular events and all-cause mortality in Asian populations.[28] In addition, another previous study discloses that Hcy level is higher in young patients (<56 years old) who have the combined event (including ACS, ischemic stroke and cardiac death) during follow-up compared to those free of the event, and high Hcy level at admission acts as a potential predictive factor for worse late cardiac events in patients with premature ACS.[29]

Interesting results were discovered in this study, while some limitations still existed. This study was a single-center study, and all patients enrolled were from our hospital, which might cause selection bias. Thus, further study with more patients from multicenter is needed. Furthermore, the underlying mechanism of Hcy on MACE in female premature ASC is still unclear. Furthermore, the follow-up duration with the median value of 28.3 months (interquartile range: 20.0–38.8 months) in this study was relatively short, the effect of Hcy on long-term MACE risk was not investigated. Thus, further study with longer follow-up period is necessary.

In conclusion, Hcy serves as a potential predictive factor for increased MACE risk in female patients with premature ACS.

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