Clinical implication of homocysteine in premature acute coronary syndrome female patients
Its distribution and association with clinical characteristics and major adverse cardiovascular events risk

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Abstract
Homocysteine (Hcy) is a risk factor for the presence of atherosclerotic vascular disease and hypercoagulability states, which is associated with increased risk of cardiovascular events in cardiovascular disease patients. Whereas the role of Hcy in premature acute coronary syndrome (ACS) female patients is still obscure. Hence, we aimed to explore the relationship of Hcy with clinical features, and more importantly, to probe its predictive value for major adverse cardiovascular events (MACE) risk in premature ACS female patients.

By retrospectively reviewing the medical charts of 1441 premature ACS female patients, we collected patients’ Hcy level (at diagnosis) and other clinical data. According to the follow-up records, the accumulating MACE occurrence was calculated. Hcy presented with a skewed distribution with median value 11.3 μmol/L (range: 4.4–64.0 μmol/L, inter quartile: 9.2–14.1 μmol/L). Hcy was associated with older age, heavy body mass index, dysregulated liver/renal/cardiac indexes, hypertension history, and old myocardial infarction history. The 1-year, 3-year, 5-year MACE incidence was 2.9%, 10.7%, and 12.6%, respectively. Interestingly, Hcy was increased in 1-year MACE patients compared with 1-year non-MACE patients, in 3-year MACE patients compared with 3-year non-MACE patients, in 5-year MACE patients compared with 5-year non-MACE patients, and it had a good value for predicting 1-year/3-year/5-year MACE risk. Furthermore, Hcy was also correlated with increased accumulating MACE occurrence. Hcy associates with increased age and body mass index, dysregulated liver, renal, and cardiac indexes; more interestingly, it predicts increased MACE risk in premature ACS female patients.

Abbreviations: ACS = acute coronary syndrome, BMI = body mass index, Hcy = homocysteine, MACE = major adverse cardiovascular events, NF-κB = nuclear factor kappa B, NSTEMI = non-ST elevation myocardial infarction, ROS = reactive oxygen species, STEMI = ST-elevation myocardial infarction, UA = unstable angina.

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

1. Introduction
Acute coronary syndrome (ACS) refers to a disease condition with rapid progression that unstable atherosclerotic plaque ruptures cause to fresh thrombus formation, followed by partially or completely blocking of the coronary arteries, eventually resulting in acute myocardial ischemia and infarction.[1,2] Ground on the clinical manifestations of this disease, ACS comprises 3 presentations: ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA).[3] From the existing data, ACS is one of the most common cardiovascular diseases with incidence between 1 in 80 and 1 in 170 each year, and it more frequently occurs in young people, especially in female patients.[4,5] According to clinical reports, there are several potential problems indirectly causing poor prognosis in ACS female patients, including little awareness about ACS occurrence caused by unobvious potential cardiovascular risk factors, and failure to receive early medical services and intervention immediately after diagnosis.[6–8] Therefore, it is significative to deeply probe potential biomarker for monitoring disease progression in ACS female patients, especially in premature ACS female patients (disease onset at ≤55 years old).[9]

Homocysteine (Hcy) is a sulphydryl-containing amino acid produced through the demethylation of dietary methionine, whose chemical properties present a similarity to cysteine, thereby named homocysteine.[10] From the early evidence, Hcy not only impacts endothelial function to result in a prothrombotic environment, but also initiates an inflammatory response to accelerate atherosclerosis in cardiovascular diseases through regulation multiple pathways (such as N-methyl-D-aspartate
receptor (NMDAr)-reactive oxygen species (ROS)-extracellular signal-regulated kinase (ERK)1/2/p38-nuclear factor kappa B (NF-κB) signal pathway [11]). Besides, Hcy is considered a risk factor for the presence of atherosclerotic vascular disease and hypercoagulability states, and it has been recognized to be closely associated with increased risk of cardiovascular events in patients with cardiovascular disease.[12,13] In regard of ACS patients, several information reveal that elevated Hcy relates to increased risk of cardiovascular events in patients associated with increased risk of cardiovascular events in patients with hypercoagulability states, and it has been recognized to be closely associated with increased risk of cardiovascular events in patients with cardiovascular disease.

2. Methods

2.1. Study population

This study retrospectively analyzed 1441 premature ACS female patients treated in our hospital from January 2015 to December 2019. By reviewing the medical charts, only patients who met all of following requirements were eligible to be included in the study analysis: patients had a diagnosis of STEMI, NSTEMI, or UA; female patients who had an onset age younger than 55 years; according to the disease status, patients were treated by standard procedure after admission, including coronary artery bypass grafting, percutaneous coronary intervention (PCI), or thrombolytic therapy; patients had records of Hcy tests after admission; clinical characteristics, examination information, treatment information, and follow-up data of patients were completed and accessible; patients without complication of systemic immune disease or infection at the diagnosis; patients had no history of malignant blood disease or solid tumors. This study was approved by the Institutional Review Board of our hospital, and the written informed consents or verbal agreements were collected from patients or their family members.

2.2. Variables collected for analysis

Patient’s Hcy level at diagnosis was collected from the medical charts, and the following clinical data of patients were also collected for study analysis: demographics: age and body mass index (BMI); diagnosis: UA, NSTEMI, and STEMI; risk factors of ACS: family history of Coronary Heart Disease, history of stroke, history of hypertension, history of diabetes; medical history of cardio-cerebrovascular diseases: history of stroke, history of old myocardial infarction (OMI), history of PCI, history of coronary artery bypass grafting; laboratory indexes at diagnosis: white blood cell, platelet, hemoglobin, fasting blood-glucose, glycosylated hemoglobin, alanine transaminase, aspartate aminotransferase, serum creatinine, serum uric acid, triglyceride, total cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, fibrinogen, N-terminal prohormone of brain natriuretic peptide, and high-sensitivity C-reactive protein; left ventricular ejection fraction at diagnosis; disease features: number of lesion vessel, and location of artery lesion; treatment information: reperfusion therapy method, and drugs used after reperfusion therapy.

2.3. MACE assessment

According to the follow-up records, the accumulating MACE occurrence rate was calculated. MACE 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 after MI or heart failure, or death caused by heart surgery or endocarditis.[14] The AMI was defined in line with Third Universal Definition of Myocardial Infarction,[15] and the UA was defined according to the World Health Organization definition.[16]

2.4. Statistical analysis

SPSS software 24.0 (IBM Corporation, Armonk, NY) was used for data analysis, and GraphPad Prism software 7.01 (GraphPad Software Inc, San Diego, CA) was applied to plot graphs. Kolmogorov–Smirnov (K) test was performed to check whether the continuous variables were normal distributed. The normally distributed continuous variables were expressed as mean with standard deviation, and the non-normally distributed continuous variables were described as median and interquartile range. The categorized variables were described as number with percentage (No. [%]). Correlation of Hcy with continuous variables was analyzed by Spearman’s rank correlation test. Comparison of Hcy level among patients with different clinical features was determined by Wilcoxon rank sum test or Kruskal–Wallis H rank sum test. Comparison of Hcy level between MACE patients and non-MACE patients was determined by Wilcoxon rank sum test. The receiver operating characteristic curve and the derived area under the curve (AUC) were used to assess the variable performance in predicting MACE risk. Accumulating MACE occurrence was displayed by Kaplan–Meier curve. Patients were categorized into 4 groups according to the Hcy level: quartile 1 (Q1): 4.4 to 9.2 μmol/L, quartile 2 (Q2): 9.2 to 11.3 μmol/L, quartile 3 (Q3): 11.3 to 14.1 μmol/L, and quartile 4 (Q4): 14.1 to 64.0 μmol/L.[17,18] Comparison of accumulating MACE occurrence among 4 groups (Q1/Q2/Q3/Q4) was determined by log-rank test. P value < .05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients

There were 1441 female patients with premature ACS with mean age of 51.1 ± 3.6 years (including 1202 (83.4%) patients diagnosed as UA, 171 (11.9%) patients diagnosed as STEMI, and 68 (4.7%) patients diagnosed as NSTEMI). In terms of risk factors of ACS, 277 (19.2%), 295 (20.5%), 955 (66.3%), and 470 (32.6%) patients had family history of CHD, history of smoking, history of hypertension, and history of diabetes, respectively. Besides, median value of left ventricular ejection fraction was 62.0 (57.0–66.0) %. There were 83 (5.8%), 603 (41.8%), 351 (24.3%), 403 (28.0%), and 1 (0.1%) patients with 0, 1, 2, 3, and 4 lesion vessels, respectively. The detailed information involving other characteristics was shown in Table 1.

3.2. Treatment information of patients

With respect to reperfusion therapy, 73 (5.1%) patients received CAGB, 737 (51.1%) patients received PCI, and 631 (43.8%) patients received thrombolytic therapy. As to drugs used after

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3.3. Hcy distribution

As Figure 1 showed, Hcy presented with a skewed distribution in premature ACS female patients. The median value of Hcy was 11.3 μmol/L, and its range was from 4.4 to 64.0 μmol/L. Besides, the interquartile range of Hcy was 9.2 to 14.1 μmol/L, and the Q1, Q2, Q3, and Q4 were 4.4 to 9.2 μmol/L, 9.2 to 11.3 μmol/L, 11.3 to 14.1 μmol/L, and 14.1 to 64.0 μmol/L respectively.

3.4. Relationship of Hcy with clinical characteristics

Hcy was positively associated with age (P = .026), BMI (P = .011), alanine transaminase (P = .015), serum creatinine (P < .001), serum uric acid (P < .001), very low-density lipoprotein-cholesterol (P = .018), N-terminal prohormone of brain natriuretic peptide (P = .014), and high-sensitivity C-reactive protein (P < .001, Table 3). Meanwhile, Hcy was also associated with history of hypertension (P = .025), history of OMI (P = .048), a greater number of lesion vessel (P = .027), and left anterior descending branch (LAD) of artery lesion (P = .029, Table 4), while Hcy was correlated with less history of diabetes (P = .005).

3.5. Accumulating MACE occurrence

Accumulating MACE occurrence data was shown in Figure 2A, in detail, the incidence of MACE at 1 year, 3 year, and 5 year was...
Correlation of Hcy with continuous variables of clinical characteristics.

| Items          | Hcy level | P value | Spearman r |
|----------------|-----------|---------|------------|
| Age            | .026      | .059    |            |
| BMI            | .011      | .067    |            |
| WBC            | .106      | .043    |            |
| Platelet       | .677      | .011    |            |
| Hb             | .103      | .043    |            |
| FBG            | .083      | .046    |            |
| Ghb            | .805      | .006    |            |
| ALT            | .015      | .064    |            |
| AST            | .493      | .018    |            |
| Scr            | <.001     | .215    |            |
| SUA            | <.001     | .103    |            |
| Triglyceride   | .389      | .023    |            |
| TC             | .703      | .010    |            |
| LDL-C          | .977      | .001    |            |
| VLDL-C         | .018      | .062    |            |
| HDL-C          | .140      | .039    |            |
| Fibrinogen     | .826      | .006    |            |
| NT-proBNP      | .014      | .080    |            |
| hs-CRP         | <.001     | .200    |            |
| LVEF           | .186      | .035    |            |

Boldface represented P value < .05. Correlation was determined by Spearman rank correlation test.

2.9%, 10.7%, and 12.6% respectively (Fig. 2B). Among 181 (12.6%) patients occurred MACE during the follow-up, there were 149 (10.3%) patients having UA, 17 (1.2%) patients having AMI, 4 (0.3%) patients having cardiac death, as well as 11 (0.8%) patients having UA accompanied with AMI (Fig. 2C).

3.6. The predictive value of Hcy for 1-year/3-year/5-year MACE risk

According to 1-year, 3-year, and 5-year MACE occurrence, all patients were divided into 1-year MACE patients and 1-year non-MACE patients, 3-year MACE patients and 3-year non-MACE patients, 5-year MACE patients, and 5-year non-MACE patients, respectively. Hcy was increased in 1-year MACE patients compared with 1-year non-MACE patients (P < .001, Fig. 3A), which had a good value for predicting 1-year MACE risk with AUC of 0.804 (95% CI: 0.735–0.874, Fig. 3B); Also, Hcy was higher in 3-year MACE patients compared with 3-year non-MACE patients (P < .001, Fig. 3C), which had an acceptable value for predicting 3-year MACE risk with AUC of 0.785 (95% CI: 0.744–0.826, Fig. 3D); Furthermore, Hcy was raised in 5-year MACE patients compared with 5-year non-MACE patients as well (P < .001, Fig. 3E), which had a certain value for predicting 5-year MACE risk with AUC of 0.775 (95% CI: 0.737–0.813, Fig. 3F).

3.7. Correlation of Hcy with accumulating MACE occurrence

Accumulating MACE occurrence was increased with Hcy quantile. The details were as followed: it was highest in Q4 group, followed by Q3 group, Q2 group, and the lowest in Q1 group (P < .001, Fig. 4).

4. Discussion

Hcy has been recognized as an important factor participating in the development processes of cardiovascular diseases. Recent study reveals that Hcy enhances the expression of chemokine and...
oxidized low-density lipoprotein\textsuperscript{19} to cause endothelial cell injury,\textsuperscript{20,21} subsequently converting a stable plaque into an unstable one. Apart from the impact of Hcy on plaque formation and vascular injury, Hcy also exerts effects on inflammation response in vascular disease. For example, Hcy has been discovered to increase the secretion of inflammatory cytokines (such as tumor necrosis factor-alpha, IL-1 beta, IL-6, IL-8) through activating monocytes in vascular diseases.\textsuperscript{22} In addition, Hcy regulates NMDAr-ROS-ERK1/2/p38-NF-\textsuperscript{k}B signal pathway to increase CRP production, thereby initiating inflammation response in vascular smooth muscle cells.\textsuperscript{11}

Recent years have shown a dramatic increase in research toward the role of Hcy in cardiovascular diseases patients: One interesting study displays a positive line of Hcy with platelet aggregation after stimulation with collagen, thrombin receptor peptide, and adenosine diphosphate in ACS patients.\textsuperscript{23} Another study illustrated a positive relationship between Hcy and the Global Registry of Acute Coronary Events scores in ACS patients.\textsuperscript{24} In brief, obvious association of Hcy with worse clinical features in ACS patients is discovered according to previous evidence. However, due to that females have been confirmed to present higher mortality compared with males among ACS patients, thus, more attention should be paid in this specific group. Even so, the character of Hcy in premature ACS female patients is still unclear. In the current study, we discovered that Hcy presented with a skewed distribution in premature ACS female patients with a median value of 11.3 m\text{mol/L}, besides, it was associated with older age, increased BMI, dysregulated liver/renal/cardiac indexes, history of hypertension, history of OMI, a greater number of lesion vessel, and LAD of artery lesion. There were several possible explanations: As to older age and BMI: Hcy had been reported to be associated with large artery stiffness and thickness in elderly population, also, it might be related to lipid metabolism through increased resistance to inhibitor of fatty acid synthase cerulenin.\textsuperscript{25} As for dysregulated liver/renal indexes: Hcy could participate in multiple mechanisms (including local oxidative stress, endoplasmic reticulum stress, inflammation, and hypomethylation) to cause liver dysfunction and renal dysfunction.\textsuperscript{26} As for dysregulated cardiac indexes, a greater number of lesion vessel and LAD of artery lesion: Hyc might exert some effects on the remodel of the arterial wall to vascular damage, thereby related to cardiac dysfunction.\textsuperscript{11–13} As to history of hypertension or OMI: Hcy had the potential to increase blood pressure via regulated vascular endothelial integrity,\textsuperscript{27} thereby related to history of hypertension, thereby related to history of diabetes; it might contribute to increased inflammation damaged to deposition of plasma lipids in plaques and fibrosis, thereby related to history of old myocardial infarction. In addition, we
also found the correlation of Hcy with less diabetes history, which might be caused by the relationship of Hcy with insulin resistance.\textsuperscript{[28]} Whereas the detailed mechanism of Hcy on diabetes in ACS is still unclear, further relevant study is needed (Supplemental Digital Content, original data.xlsx, http://links.lww.com/MD2/A107).

Clinical research displays that the incidence of MACE occurrence is 11.1\% during a median follow-up of 43.3 months in ACS patients.\textsuperscript{[24]} In this study, our results showed that the 1-year, 3-year, and 5-year MACE incidence was 2.9\%, 10.7\%, and 12.6\% respectively in premature ACS female patients. According to recent data, Hcy has been recognized as an independent risk factor for predicting cardiovascular events (such as myocardial infarction) in ACS patients.\textsuperscript{[11]} Meanwhile, Hcy also serves as an independent risk factor for recurrent cardiovascular events in ACS hospitalized patients.\textsuperscript{[29]} Furthermore, it could independently predict all-cause death and MACE in STEMI patients.\textsuperscript{[30]} Regarding the predictive value of Hcy for MACE risk in premature ACS female patients, little was known. In the current study, we discovered that Hcy had a great predictive value for 1-year/3-year/5-year MACE risk and accumulating MACE occurrence was increased with Hcy quantile in premature ACS female patients. Potential interpretations were: Hcy might participate in multiple mechanisms: such as promoting vascular smooth muscle cells proliferation, endothelial dysfunction, oxidative damage, enhancing collagen synthesis, and aggravating arterial wall elastic material, thereby caused vascular injuries, eventually increased MACE risk in premature ACS female patients.\textsuperscript{[12,13]} Hcy might promote inflammation response through mediated several pathways (including NMDAr-ROS-ERK1/2/p38-NF-\kappaB signal pathway) to result in increased permeability of arterial intima to plasma, plasma lipids deposition, plaques calcification, subsequently increased MACE risk in premature ACS female patients.\textsuperscript{[11,31]} Hcy might have potential to accelerate platelet adhesion to endothelial cells as well as activate prothrombotic factors (including \beta-thromboglobulin and tissue plasminogen activator), and then augmented thrombus formation, eventually increased MACE risk in premature ACS female patients.\textsuperscript{[32]}

Whilst this study had strengths including the extent and quality of data, while we still recognized the limitations of our research. One major limitation was this retrospective study with selected patients form a single center, which might cause several biases, hence, further prospective study enrolling more patients form multicenter is essential. Another limitation was the unclear pathophysiological mechanism of Hcy in premature ACS female patients. Further relevant experiments are important.

In conclusion, Hcy associates with increased age and BMI, dysregulated liver, renal and cardiac indexes; more interestingly, it predicts increased MACE risk in premature ACS female patients.

**Author contributions**

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