Observational Study

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# Blood homocysteine levels could predict major adverse cardiac events in patients with acute coronary syndrome

## A STROBE-compliant observational study

Jianlin Liu, MD[a], Jianjun Quan, MD[a,b], Yanzi Li, MD[c], Yue Wu, MD[d], Lin Yang, PhD, MD[a,*]

**Abstract**

The Global Registry of Acute Coronary Events (GRACE) risk score independently predicts major adverse cardiac events (MACEs) in patients with acute coronary syndrome (ACS). This study aims to evaluate whether the level of plasma homocysteine in addition to the GRACE score enhances the predictive value for MACEs in patients with acute coronary syndrome.

A total of 361 patients with ACS evaluated at our hospital were included in the study and tested for blood homocysteine levels. We recorded 40 (11.1%) instances of MACE during a median follow-up of 43.3 months (quartile 40.6–44.4 months), including 29 cases (8.0%) of all-cause death and 11 cases (3.1%) of nonfatal myocardial infarction.

The GRACE score was significantly associated with homocysteine levels, and multivariate Cox regression analysis showed that both the GRACE risk score and homocysteine content were independent predictors of MACEs (HR 2.63; 95% confidence interval (CI) 1.54 to 4.49; $P < .001$ and 2.27; 1.06 to 4.86; $P = .035$, respectively). Moreover, meta-analysis showed that as the homocysteine level increased, the incidence of MACEs also increased (log-rank 8.41; $P = .015$). GRACE scores adjusted by homocysteine level increased the area under the curve (AUC) from 0.78 to 0.83 ($P = 0.006$).

Blood homocysteine levels are significantly associated with the GRACE risk score, and using both parameters can further improve risk stratification in patients with acute coronary syndrome.

**Abbreviations:** ACS = acute coronary syndrome, BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, Glu = blood glucose, GRACE = global registry of acute coronary events, HCY = homocysteine, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MACEs = major adverse cardiac events, MI = myocardial infarction, NT-proBNP = N-terminal pronatriuretic *pep*tide, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

**Keywords:** acute coronary syndrome, coronary artery disease, homocysteine

## 1. Introduction

Patients with acute coronary syndrome (ACS) have diverse clinical manifestations and a high risk of death. Outcomes in high-risk cases can be improved by accurate clinical decisions made following a thorough patient assessment. To identify high-risk patients with acute coronary syndrome, current guidelines recommend using a standardized and useful grading system such as the Global Registry of Acute Coronary Events (GRACE) score.[1] Although the GRACE score has been clinically adopted, it does not include some important biomarkers.[2] Therefore, whether GRACE scores combined with other biomarkers provide a more accurate risk score for people with acute coronary syndrome remains to be explored.

Homocysteine (Hcy) is a detrimental intermediate of cellular metabolism in the human body. An increased level of Hcy in the blood is an indicator of a high risk of stroke. Even more dangerous is the increased risk of stroke compared with the normal population when both blood pressure and Hcy increase.[3,4] Clinical scholars consider "hypertension with elevated homocysteine levels" as "H-type hypertension."[5,6] Due to genetic background, the interaction of diet and other factors, the level of homocysteine in the Chinese population is elevated and the folic acid level is low, which in turn leads to a high incidence of stroke. A total of 300 million hypertensive patients have been identified in China, and roughly two-thirds have H-type hypertension.[7,8] It has been found that high levels of homocysteine increase the risk of cardiovascular events.[9–11] However, there are few reports in the literature detailing the relationship of homocysteine combined with GRACE scores in patients with ACS.

In the present study, we found that homocysteine levels and GRACE scores independently predicted MACE in patients with acute coronary syndrome, and considering homocysteine levels can potentially augment estimates based upon the GRACE score values alone. This relationship has rarely been reported in the literature.

## 2. Patients and methods

### 2.1. Patients

This was a single-center observational study that continuously collected data from patients diagnosed with acute coronary

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*[a] Department of Vascular Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, [b] Department of Interventional Cardiology, Hanzhong Central Hospital, Hanzhong, [c] Department of Operation, [d] Department of Cardiology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

*[*] Correspondence: Lin Yang, Department of Vascular Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China (e-mail: jdvascs@163.com).*



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syndrome from January 2013 to August 2014 in our hospital. Those with unstable angina pectoris, non-ST-segment elevation myocardial infarction, and ST-segment elevated myocardial infarction were included. Exclusion criteria included advanced liver disease, kidney failure, cancer, valvular heart disease, stroke, idiopathic dilated cardiomyopathy or hypertrophic cardiomyopathy, peripheral arterial disease, pregnancy, anti-inflammatory drug treatment, acute or chronic infection, autoimmune disease, and hematological or thyroid disease.

Clinical data were collected and analyzed from the patients' medical records, included demographic data, cardiovascular risk factors and cardiovascular-related medications used. Enrollment was conducted in accordance with the Declaration of Helsinki (2008) of the World Medical Association. This study was approved by the ethics committee and institutional review board of the First Hospital of Xi'an, Jiaotong University, and all patients provided written informed consent.

### 2.2. Blood tests

EDTA anticoagulated plasma samples were measured by ELISA. After patients had fasted for 12 hours, blood samples were drawn between 8:00 and 10:00 AM the next morning. Plasma and whole blood were immediately separated by centrifugation (1000×g/15 min, 4°C). Plasma aliquots were stored at −70°C and thawed before testing. Homocysteine concentration was measured with a commercially available ELISA kit (Ortho-Clinical Diagnostics, Inc., Rochester, New York) according to the manufacturer's instructions. Standard measurements of blood parameters and serum biochemistry were performed with a DIRUI CS 400 Analyzer (Dirui, Changchun, China). Venous plasma glucose, blood lipids, lipoproteins, serum creatinine, NT-proBNP, leukocytes, and platelet count were assessed.

### 2.3. GRACE score calculation

The GRACE score was derived from the values calculated for cardiovascular variables.[1,12] These variables included age, heart rate, systolic blood pressure, serum creatinine, congestive heart failure, PCI and coronary bypass surgery procedures, a history of myocardial infarction, the magnitude of ST-depression, and the elevation of myocardial enzymes. The GRACE risk score was originally used to predict lethality 6 months after discharge from the hospital and more than 4 years after myocardial ischemic events. According to ESC guidelines, patients can be divided into 3 categories based on GRACE scores: low risk (1–88), moderate risk (89–118), and high risk (>118).

### 2.4. Follow-up

MACEs were defined as all-cause death or nonfatal myocardial infarction. All patients were followed-up by telephone and at outpatient visits. The end event was defined as the first MACE occurrence.

### 2.5. Statistical analysis

All data were analyzed using SPSS version 11.0 (SPSS, 127 Chicago, IL). Continuity variables were expressed as the mean ± standard deviation, and categorical variables were expressed as frequency and percentage. The Kolmogorov–Smirnov test was used to describe the normal distribution of quantitative variables. An independent-samples *t*-test was used to compare the 2 groups and the Chi-square test was used to compare categorical variables. One-way ANOVA was used to compare the differences among multiple groups. Correlation analysis was performed using Spearman's correlation. Univariate and multivariate survival analysis included COX regression analysis. A Kaplan–Meier survival curve was used to assess the predictive value of homocysteine for risk of death in patients with acute coronary syndrome. The predictive value of homocysteine alone and the value combined with the GRACE score were expressed as the area under the ROC curve. $P < .05$ was defined as statistically significant.

## 3. Results

### 3.1. Baseline data

As shown in Table 1, of the 361 eligible patients enrolled in this study, 12 were lost to follow-up (3.4%) by study end at approximately 43.3 months. The remaining 347 patients were divided into 3 groups based on homocysteine values as follows: Group 1 <16 μmol / L, Group 2 = 16 to 30 μmol/L, and Group 3 > 30 μmol/L (Table 1). As the homocysteine value increased, the total cholesterol value also increased ($P < .05$). Platelet count, NT-proBNP level and ApoB in Group 3 were higher than in Groups 1 and 2 ($P < .05$, $P = 0.003$ and $P = 0.048$).

### 3.2. Clinical characteristics of patients with and without MACEs

Of all 347 patients enrolled, 40 (11.5%) suffered MACEs, including 29 all-cause deaths and 11 nonfatal MI. According to the GRACE score, the incidence of MACEs was greater in the high-risk group than in the low-risk and intermediate-risk groups. We performed a correlation analysis between GRACE score and Hcy level as a continuous variable which revealed a significant correlation between the 2 ($R = 0.172$, $P = .001$).

### 3.3. Hcy level was an independent predictor of MACE rates

As determined by univariate Cox regression analysis, the most significant predictors of MACE were age, body mass index (BMI), history of hypertension, history of myocardial infarction, leukocyte and platelet count, homocysteine levels, and GRACE scores (Table 2). In multivariate COX regression analysis, Hcy levels were an independent factor shown to be significantly predictive of MACEs (HR 2.270; 95% CI 1.061 to 4.856; $P < .05$), as well as GRACE scores (HR 2.634; 95% CI 1.544 to 4.493; $P < .001$) (Table 3).

### 3.4. The combination effect of Hcy and GRACE on the incidence of MACE

Since Hcy levels and GRACE scores are both independent risk factors for MACE, we evaluated the combination effect on the prediction of long-term MACE. The AUC for the GRACE score alone was 0.78 (95% CI 0.73–0.83), which increased to 0.83 (95% CI 0.80–0.88) with the addition of Hcy. The change in AUC was statistically significant ($P = 0.006$) when both measures were combined, suggesting that the combination of Hcy level with the GRACE score contributes to the estimation of MACE.

**Table 1**

**The demographic characteristics data in the study.**

| | Tertile 1 (n = 115) | Tertile 2 (n = 115) | Tertile 3 (n = 115) | *P* value |
|---|---|---|---|---|
| Age, years | 60.42 ± 14.24 | 60.48 ± 14.50 | 60.74 ± 10.98 | .98 |
| Gender (male) | 77 | 69 | 63 | .13 |
| BMI, kg/m$^2$ | 24.42 ± 2.67 | 24.16 ± 3.17 | 24.58 ± 2.57 | .51 |
| Smoking | 72 | 66 | 75 | .55 |
| Hypertension | 29 | 32 | 34 | .80 |
| Prior MI | 3 | 7 | 5 | .43 |
| DBP, mm Hg | 79.55 ± 13.31 | 77.62 ± 12.61 | 78.45 ± 13.44 | .54 |
| SBP, mm Hg | 129.11 ± 20.15 | 125.94 ± 18.63 | 124.97 ± 19.83 | .24 |
| Heart rate, bmp | 76.82 ± 13.59 | 76.28 ± 14.29 | 75.52 ± 11.93 | .76 |
| eGFR, mL min$^{-1}$ 1.73 m$^2$ | 77.79 ± 31.70 | 72.47 ± 21.65 | 70.45 ± 20.82 | .07 |
| GLU, mmol/L | 5.94 ± 1.37 | 6.09 ± 1.70 | 6.23 ± 1.99 | .43 |
| TC, mmol/L | 3.80 ± 0.87 | 3.89 ± 0.95 | 4.18 ± 1.53 | .035 |
| TG, mmol/L | 1.70 ± 0.74 | 1.64 ± 1.41 | 1.67 ± 0.99 | .90 |
| HDL, mmol/L | 0.98 ± 0.22 | 1.00 ± 0.24 | 1.01 ± 0.28 | 70 |
| LDL, mmol/L | 2.25 ± 0.71 | 2.31 ± 0.81 | 2.38 ± 0.83 | .43 |
| Apo AI, g/L | 1.11 ± 0.17 | 1.10 ± 0.16 | 1.11 ± 0.23 | .80 |
| Apo B, g/L | 0.76 ± 0.21 | 0.75 ± 0.22 | 0.82 ± 0.25 | .048 |
| NT-proBNP | 5.48 ± 1.40 | 5.01 ± 1.62 | 5.72 ± 1.74 | .003 |
| PLT, 10$^9$/L | 186.94 ± 69.03 | 184.98 ± 51.45 | 206.26 ± 84.50 | .038 |
| WBC, 10$^9$/L | 7.25 ± 2.52 | 7.39 ± 3.05 | 7.82 ± 3.16 | .30 |
| Discharge medication | | | | |
| Aspirin (n) | 103 | 101 | 107 | .66 |
| Statins | 83 | 79 | 75 | .42 |
| ACEI/ARB | 48 | 51 | 55 | .72 |
| β-blocker | 48 | 51 | 55 | .72 |

ACEI = angiotensin converting enzyme inhibitors, ARB = α receptor blockers, BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, Glu = blood glucose, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MI = myocardial infarction, NT-proBNP = N-terminal pronatriuretic *pep*tide, PLT = platelets, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WBC = white blood cell.

**Table 2**

**Univariate COX regression analysis of MACEs events.**

| | HR | 95% CI | *P* value |
|---|---|---|---|
| Age, per 1 year | 1.03 | 1.01–1.06 | <.01 |
| Male (vs female) | 0.91 | 0.18–1.73 | .77 |
| BMI, per 1 kg/m$^2$ | 1.18 | 1.07–1.30 | <.01 |
| Smoking | 1.73 | 0.87–3.47 | .12 |
| Hypertension | 6.33 | 3.27–12.27 | <.01 |
| Prior MI | 6.45 | 2.97–14.03 | <.01 |
| DBP, per 1 mm Hg | 1.01 | 0.98–1.03 | .69 |
| SBP, per 1 mm Hg | 1.01 | 0.99–1.02 | .49 |
| Heart rate, per 1 bmp | 1.02 | 0.99–1.04 | .07 |
| eGFR, per 1 ml min$^{-1}$ 1.73 m$^2$ | 0.99 | 0.98–1.01 | .56 |
| GLU, per 1 mmol/L | 1.04 | 0.88–1.24 | .62 |
| TC, per 1 mmol/L | 1.06 | 0.84–1.33 | .65 |
| TG, per 1 mmol/L | 0.98 | 0.72–133 | .89 |
| HDL, per 1 mmol/L | 0.79 | 0.22–2.86 | .72 |
| LDL, per 1 mmol/L | 1.16 | 0.80–1.68 | .44 |
| Apo AI, per 1 g/L | 0.53 | 0.09–2.93 | .47 |
| Apo B, per 1 g/L | 1.30 | 0.35–4.78 | .70 |
| LnNT-proBNP, per 1 ln unit | 0.95 | 0.78–1.15 | .58 |
| PLT, per 10$^9$/L | 1.004 | 1.001–1.01 | .02 |
| WBC, per 10$^9$/L | 1.13 | 1.04–1.23 | <.01 |
| Hcy level, per 1% | 2.89 | 1.41–5.95 | <.01 |
| GRACE score | 3.97 | 2.45–6.45 | <.01 |

BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, Glu = blood glucose, GRACE = global registry of acute coronary events, Hcy = homocysteine, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MACEs = major adverse cardiac events, MI = myocardial infarction, NT-proBNP = N-terminal pronatriuretic *pep*tide, PLT = platelets, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WBC = white blood cell.

## 4. Discussion

Homocysteine is a sulfur-containing amino acid formed after methionine demethylation, belonging to the intermediate product of the methionine cycle. The earliest reports of metabolic disorders originated from observations of homocystinuria in patients with congenital cystathionine synthase deficiency.[13] Since then, scientists have also found several other metabolic changes in HCY metabolism of enzymes or coenzymes caused by metabolic disorders. In recent years, with improvements in measurement techniques, HCY in various forms has been measured in normal human plasma and found to be a potential effective factor in the treatment of several ailments including cardiovascular, cerebrovascular and peripheral vascular diseases. HCY metabolic disorders have been found in patients suffering from chronic renal insufficiency, psoriasis and vitamin B12 deficiency as well.[12,14–18]

**Table 3**

**Multivariate cox regression analysis of MACEs events.**

| | HR | 95% CI | *P* value |
|---|---|---|---|
| Hcy, per 1% | 2.27 | 1.06–4.86 | .035 |
| HT (vs non-HT) | 3.29 | 1.64–6.72 | <.01 |
| GRACE score reclassified | 2.63 | 1.54–4.49 | <.01 |
| BMI, per 1 kg/m$^2$ | 1.14 | 1.02–1.28 | .02 |
| Prior MI | 3.69 | 1.65–8.24 | <.01 |
| WBC, per 10$^9$/L | 1.12 | 1.02–1.22 | .013 |

BMI = body mass index, GRACE = global registry of acute coronary events, Hcy = homocysteine, MACEs = major adverse cardiac events, MI = myocardial infarction, WBC = white blood cell.

Subsequent clinical and experimental studies have shown that high levels of HCY can cause vascular damage, and lead to lesions in the coronary arteries, peripheral vasculature, and cerebrovasculature.[19] Plasma HCY levels in patients with peripheral vascular disease and those with intermittent claudication confirmed by angiography were higher than those in normal subjects. Plasma homocysteine levels in patients with thickened carotid intima and myometrium confirmed by B ultrasound were also higher than those in normal subjects.[20] These clinical studies of plasma HCY in relation to various vascular diseases indicate that HCY may be an independent risk factor for the development of such lesions.

The clinical management of patients with acute coronary syndrome should be based on risk stratification. In this study, the GRACE score provided a valid independent predictor of MACE in ACS patients, consistent with previous findings. However, the AUC for the GRACE score alone was only 0.78, possibly because underlying risk factors were not included in the scoring system. Furthermore, different scoring systems combine other clinical parameters indicating different clinical predictive values for patients with ACS or myocardial infarction. A previous study revealed that 3-dimensional global peak longitudinal strain (GPLS) could be a reproducible and efficient method to evaluate complex coronary artery disease in patients with non-ST-segment elevation acute coronary syndrome, and the value of GPLS was significantly associated with the complexity of coronary artery lesions.[21] Other authors described 3-dimensional global longitudinal strain as an excellent predictor with the highest predictive value for future left ventricular remodeling after acute myocardial infarction,[22] and the waist circumference could be more accurate to assess the cardiac function through the changes of let ventricular structure on the cardiac rehabilitation program ater ACS patients.[23] Moreover, other authors considered that the combination of computer-tomography-based fractional flow reserve pullback curve and wall shear stress distributions can provide more accurate evaluation the clinical outcome of the patients suffer from coronary stenoses,[24] and the non-invasive fractional low reserve derived from coronary computed tomographic angiography may be an simplified method to assess the *hemodynamic* characteristics for coronary stenosis.[25] These reports demonstrate that many potential questions remain in relation to the selection of optimal prognostic predictive factors for ACS.

Epidemiological data demonstrate that Hcy level is a risk factors for independent cardiovascular events (including myocardial infarction) in both general and hypertensive populations.[2,9–11] However, previous studies did not include Hcy in the GRACE scoring system. In the present study, the value of the GRACE score increased with increasing Hcy levels, and both correlated with MACE. Furthermore, the combination of Hcy and GRACE enhanced the predictive value for MACE in patients with ACS and no DM comorbidity (AUC 0.78 for the GRACE score alone and 0.83 for Hcy and GRACE). In patients with ACS, whether or not Hcy levels are independent predictors of cardiovascular events is uncertain. In this study, Hcy levels were independently predictive of long-term MACE in patients with ACS and those with comorbidities.

A previous study found that the addition of C-reactive protein (CRP), NT-proBNP, fatty acids, growth-differentiation factor-15, cystatin C, Dickkopf protein, RDW/PDW, troponin, mean platelet volume (MPV), and other factors to the scoring system can increase the predictive value of major cardiac adverse events in patients with ACS.[26–33] Even the functional assessment and computational fluid dynamics of a hemodynamic significant stenosis base on blood pressure variation has been applied for the evaluation of the myocardial ischemic event,[34–36] and the alterations of these parameters under pathological conditions are important indicators for diagnosis of cardiovascular disease. However, the effect of Hcy combined with GRACE scores was unclear. Our results demonstrate that the GRACE score was significantly associated with baseline Hcy levels, and the combination effect between Hcy and GRACE scores could improve the predictive value. However, whether or not the combination effect could further improve the clinical prognosis of patients with ACS still needs further investigation in clinical practice.

In conclusion, Hcy levels predict the occurrence of MACE in patients with ACS, and Hcy levels correlate significantly with GRACE scores. Combining the predictive effect of the 2 could improve risk stratification of the ACS population. However, this study was a retrospective study at a single center conducted in a select patient population and thus may be subject to some bias, and the pathophysiological mechanism of this effect remains known. The results of the study therefore, should be confirmed via RCTs study in the future.

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## Author contributions

**Conceptualization:** Jianlin Liu, Jianjun Quan, Yanzi Li, Yue Wu, Lin Yang.
**Data curation:** Jianlin Liu, Jianjun Quan, Yanzi Li, Yue Wu, Lin Yang.
**Formal analysis:** Jianlin Liu, Jianjun Quan, Yanzi Li, Yue Wu, Lin Yang.
**Investigation:** Jianlin Liu, Jianjun Quan, Yanzi Li, Yue Wu, Lin Yang.
**Methodology:** Jianlin Liu, Jianjun Quan, Yanzi Li, Yue Wu, Lin Yang.
**Project administration:** Jianlin Liu, Yanzi Li, Yue Wu, Lin Yang.
**Resources:** Jianlin Liu, Yue Wu, Lin Yang.
**Software:** Yanzi Li, Yue Wu, Lin Yang.
**Supervision:** Jianlin Liu, Yue Wu, Lin Yang.
**Validation:** Yue Wu, Lin Yang.
**Visualization:** Lin Yang.
**Writing – original draft:** Lin Yang.
**Writing – review & editing:** Jianlin Liu, Yue Wu, Lin Yang.

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