Hyperhomocysteinemia and Acute Coronary Syndrome: A Hospital-Based Observational Study Among Very Young Adults ≤35 Years of Age

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Research Article

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Abstract

**Background:** The prevalence of acute coronary syndrome (ACS) continues to increase among young Chinese adults. Homocysteine (HCY) has been suggested as a crucial promoter of atherosclerosis leading to coronary artery disease (CAD). Yet, it remains uncertain whether HCY is associated with the ACS and the severity of coronary artery stenosis in very young adults.

**Methods:** Very young patients (18-35 years of age) diagnosed with ACS who underwent coronary angiography (CAG) at Anzhen Hospital between January 2013 and June 2019 were assigned to the ACS group. An equivalent age-matched population without CAD, as confirmed by CAG during the same period, was assigned to the non-CAD group. A serum HCY level > 15µmol/L was defined as hyperhomocysteinemia (HHCY). The Gensini score assessed the severity of coronary artery stenosis.

**Results:** A total of 1,103 participants, including 828 ACS patients and 275 non-CAD subjects, were included in this study. Very young ACS patients had higher level of serum HCY and greater prevalence of HHCY compared with non-CAD subjects [for HCY, 16.55 (11.93- 29.68) vs 12.50 (9.71- 17.42), P<0.001; for HHCY prevalence, 62.08% vs 26.18%, P<0.001]. Multivariate logistic regression analysis with the stepwise method indicated that HHCY was an independent predictor associated with the presence of ACS, after adjusting for traditional confounders (OR, 4.393; 95% CI, 3.171-6.087; P<0.001). Moreover, young ACS patients with HHCY had increased prevalence of ST-segment elevation myocardial infarction (STEMI) (P=0.041), multi-vessel disease (P=0.036), and decreased value of left ventricular ejection fraction (LVEF) (P=0.01). Also, the HCY level was significantly correlated with Gensini Score in ACS patients (r=0.142, P<0.001).

**Conclusion:** HHCY was significantly associated with the presence of ACS and the severity of coronary artery stenosis in very young patients ≤35 years of age.

Introduction

Acute coronary syndrome (ACS) has become a significant public health problem and the leading cause of morbidity and mortality in the entire world as well in China. Although ACS primarily occurs in older people, the incidence of ACS has been gradually increasing among younger Chinese individuals aged ≤45 years [1]. Several traditional risk factors for coronary artery disease (CAD), which include current smoking status, elevated body mass index (BMI), and a family history of premature acute myocardial infarction (AMI), have been associated with younger age [2]. In addition, non-traditional risk factors, such as hyperhomocysteinemia (HHCY), have also been considered as novel markers for CAD and are supposed to be added to Framingham Risk Factors (FRFs) to boost their predictive value [3, 4]. In an observational study conducted in elderly patients undergoing coronary angiography (CAG), the elevation of homocysteine (HCY) level was closely associated with severity of coronary artery stenosis [5]; still, the impact of HHCY on ACS in very young adults has not drawn much attention among research community due to the relatively low prevalence of ACS among young adults.
Since general HHCY prevalence has increased over the last two decades in China [6], as well as prevalence among young individuals, the aim of the current study was to analyze the association between HHCY and ACS, including the presence and the severity of coronary artery stenosis among young adults who are 35 years of age and younger.

**Methods**

**Study population**

In this single-center observational study, very young patients (18–35 years of age), diagnosed with ACS who underwent coronary angiography (CAG) at Anzhen Hospital between January 2013 and June 2019 were assigned to the ACS group. An equivalent age-matched population who underwent CAG for suspected CAD during the same time period at our center, but were finally confirmed as not having the coronary disease were assigned to the non-CAD group. Participants who met any of the exclusion criteria were excluded from the study: 1. missing homocysteine data; 2. repeated hospitalization; 3. renal impairment (an estimated glomerular filtration rate [eGFR] < 60 mL/minute per 1.73 m²), pernicious anaemia, hypothyroidism, various cancers, psoriasis; 4. myocarditis, cardiomyopathy, valvular heart disease, congenital heart disease, infective endocarditis, multiple arteritis, Kawasaki disease, rheumatic heart disease; 5. vitamin or folate supplementation within three months.

Our study was approved by the Institutional Ethics Committee at Beijing Anzhen Hospital. The data we used were retrospectively obtained from electronic medical records.

**Data Collection And Related Definitions**

Baseline fasting venous blood samples were taken from all participants and tested for the level of HCY and other laboratory indicators, such as triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid (UA) and high-sensitivity C-reactive protein (hs-CRP). HCY was measured by a Beckman Coulter AU5400 automatic biochemical analyzer using an HCY commercial kit (enzymatic cycling method). According to the testing results, TG ≥ 1.7 mmol/L was considered as hypertriglyceridemia, TC ≥ 5.2 mmol/L was considered as hypercholesterolemia, LDL-C ≥ 3.4 mmol/L was considered as a high LDL-C level, and HDL-C < 1.0 mmol/L was considered as a low HDL-C level [7]. In addition, HHHCY was defined as HCY level > 15umol/L [8], while hyperuricemia was defined as UA level ≥ 420 mmol/L in males and ≥ 357 mmol/L in females [9].

Participants’ demographic and clinical data were collected from electronic medical records. Hypertension was defined as a systolic pressure (SBP) ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg, or currently taking antihypertensive medications [10]. DM was defined as FBG ≥ 7.0 mmol/L and/or random glucose level ≥ 11.1 mmol/L or previously diagnosed DM treated with diet, oral agents, or insulin [11]. Familial hypercholesterolemia (FH) was defined by satisfying ≥ 2 of the following criteria: LDL-C ≥ 4.68 mmol/L,
tendon/skin xanthomas, and history of FH or premature CAD [12]. Smoking status was defined as occasional or regular smoking ≥ 1 cig/day, and former smokers with cessation period ≤ 1 year were also included [13]. Drinker was defined as someone with average alcohol intake ≥ 50 g/day.

All participants received coronary angiography via standard techniques. Major coronary vessels, including the left main, left anterior descending, left circumflex, right coronary artery, and main branches with a diameter of more than 2.0 mm, were evaluated. Major coronary arteries with luminal diameter stenosis ≥ 50% were considered as a lesion coronary artery. Left main stenosis ≥ 50% was considered as a double-vessel disease. Moreover, ACS diagnosis was determined by the European Society of Cardiology 2015 guidelines [14]. Young ACS patients were divided into AMI and unstable angina pectoris (UAP) groups according to the clinical diagnosis, single-vessel, and multi-vessel groups according to the number of lesion vessels, left ventricular ejection fraction (LVEF) ≥ 50% and LVEF < 50% groups according to the cardiac function. The severity of coronary artery stenosis was evaluated by the Gensini Score [15].

Statistical analysis

Statistical software SPSS 22.0 (IBM-SPSS Inc., Chicago, USA) was used to conduct all the analysis. The normality of data was evaluated by the Kolmogorov-Smirnov test. Accordingly, continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared between two groups using the independent samples t-test. Otherwise, data were expressed as the median and interquartile range (IQR) in case of skewed distribution, and differences between the two groups were determined by the Mann-Whitney U test. Categorical variables were presented as counts and percentages (%) and compared using the Chi-square test. The relationship between serum HCY level and Gensini Score was evaluated using Spearman analysis. Univariate logistic regression analysis was performed first, then variables with a P-value < 0.2 were selected and added into multivariate logistic regression model using the stepwise method (entry, 0.05; removal, 0.05) so as to determine their independent risk associated with ACS, which was calculated by odds ratio (OR) with 95% confidence intervals (95% CI). A value of P < 0.05 in a two-sided test was considered statistically significant.

Results

Baseline clinical characteristics

A total of 1103 participants, including 828 ACS patients and 275 non-CAD individuals, were enrolled in this study. The flowchart of the study is shown in Fig. 1. Clinical characteristics and biochemical findings of involved participants are listed in Table 1. The majority of young patients with ACS were male (96.01% vs. 89.09%, P < 0.001). The higher prevalence of current smoker status, hypertension, DM, family history of CAD, and familial hypercholesterolemia was found in the ACS group compared to the non-CAD group. ACS patients also had higher HR, BMI, and increased levels of FBG, HbA1c, TG, TC, LDL-C, UA as well as hs CRP. Moreover, there was a greater percentage of patients with HHCY in the ACS group compared to
the non-CAD group (62.08% vs. 26.18%, \( P < 0.001 \)). On the contrary, the HDL-C level and LVEF were significantly lower in ACS patients compared to non-CAD subjects.
Table 1
Baseline clinical characteristics of study participants

| Characteristics                           | ACS (n = 828)          | Non-CAD (n = 275) | P       |
|------------------------------------------|------------------------|-------------------|---------|
| Age (years)                              | 33 (30–34)             | 32 (30–34)        | 0.206   |
| Male, n (%)                              | 795 (96.01)            | 245 (89.09)       | <0.001  |
| SBP (mmHg)                               | 126.04 ± 16.01         | 125.69 ± 14.66    | 0.64    |
| DBP (mmHg)                               | 77.71 ± 13.26          | 76.95 ± 11.48     | 0.297   |
| HR (bpm)                                 | 75.73 ± 11.94          | 73.45 ± 12.09     | 0.004   |
| Drinker, n (%)                           | 148 (17.87)            | 56 (20.36)        | 0.361   |

Medical history and coronary risk factors

| Characteristic                          | ACS (n = 828)          | Non-CAD (n = 275) | P       |
|-----------------------------------------|------------------------|-------------------|---------|
| Smoker, n (%)                           | 572 (69.08)            | 139 (50.55)       | <0.001  |
| BMI (kg/m²)                             | 28.52 ± 4.64           | 26.80 ± 4.75      | <0.001  |
| Hypertension, n (%)                     | 402 (48.55)            | 92 (33.45)        | <0.001  |
| Diabetes mellitus, n (%)                | 162 (19.57)            | 21 (7.64)         | <0.001  |
| Hypertriglyceridemia, n (%)             | 468 (56.52)            | 89 (32.36)        | <0.001  |
| Hypercholesterolemia, n (%)             | 257 (31.04)            | 52 (18.91)        | <0.001  |
| High LDL-C, n (%)                       | 237 (28.62)            | 44 (16.00)        | <0.001  |
| Low HDL-C, n (%)                        | 580 (70.05)            | 138 (50.18)       | <0.001  |
| Family history of CAD, n (%)            | 116 (14.01)            | 24 (8.73)         | 0.023   |
| Familial hypercholesterolemia, n (%)    | 25 (3.02)              | 1 (0.36)          | 0.01    |
| Hyperuricemia, n (%)                    | 367 (44.32)            | 97 (35.27)        | 0.008   |
| Hyperhomocysteinemia, n (%)             | 514 (62.08)            | 72 (26.18)        | <0.001  |
| Prior stroke, n (%)                     | 4 (0.48)               | 0 (0.00)          | 0.577   |

Laboratory results

Data are expressed as mean ± standard deviation, medians with interquartile range or number (%)

CAD coronary artery disease, ACS acute coronary syndrome, SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, BMI body mass index, BUN blood urea nitrogen, CR creatinine, FBG fasting blood glucose, HbA1c glycosylated hemoglobin, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, UA uric acid, HCY homocysteine, hs CRP high-sensitivity C-reactive protein, LVEF left ventricular ejection fraction.

Bold values indicate statistical significance
## Characteristics

| Characteristics  | ACS (n = 828) | Non-CAD (n = 275) | P   |
|------------------|--------------|------------------|-----|
| BUN (mmol/L)     | 4.94 ± 1.39  | 4.79 ± 1.34      | 0.1 |
| CR (µmol/L)      | 74.68 ± 15.14| 74.69 ± 14.08    | 0.988 |
| FBG (mmol/L)     | 5.35 (4.91–6.43) | 5.04 (4.79–5.60) | < 0.001 |
| HbA1c (%)        | 5.6 (5.2–6.2) | 5.4 (5.1–5.7)    | < 0.001 |
| TG (mmol/L)      | 1.88 (1.31–2.89) | 1.45 (1.01–2.18) | < 0.001 |
| TC (mmol/L)      | 4.72 ± 1.78  | 4.34 ± 1.03      | < 0.001 |
| HDL-C (mmol/L)   | 0.91 ± 0.21  | 1.02 ± 0.22      | < 0.001 |
| LDL-C (mmol/L)   | 3.01 ± 1.61  | 2.65 ± 0.98      | < 0.001 |
| UA (µmol/L)      | 410.19 ± 96.67 | 385.83 ± 93.82   | < 0.001 |
| HCY (µmol/L)     | 16.55 (11.93–29.68) | 12.50 (9.71–17.42) | < 0.001 |
| hs CRP (mg/L)    | 3.11 (1.09–11.40) | 1.12 (0.49–2.80) | < 0.001 |

### Cardiac function

| LVEF             | 60 (54–65) | 66 (62–68) | < 0.001 |

Data are expressed as mean ± standard deviation, medians with interquartile range or number (%)

CAD coronary artery disease, ACS acute coronary syndrome, SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, BMI body mass index, BUN blood urea nitrogen, CR creatinine, FBG fasting blood glucose, HbA1c glycosylated hemoglobin, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, UA uric acid, HCY homocysteine, hs CRP high-sensitivity C-reactive protein, LVEF left ventricular ejection fraction.

Bold values indicate statistical significance

### Univariate Analysis Of Different Acs Risk Factors

As shown in Table 2, traditional ACS risk factors such as male gender, BMI, current smoker status, hypertension, DM, hypertriglyceridemia, hypercholesterolemia, High LDL-C, low HDL-C, family history of CAD, and familial hypercholesterolemia were obviously associated with the occurrence of ACS (P < 0.05).

On the contrary, age and drinker status showed no significant association with ACS. Moreover, non-traditional risk factors, such as hyperuricemia, especially HHCY, were also apparently related to the presence of ACS (for HHCY, OR, 4.615; 95% CI, 3.408–6.250; P < 0.001).
Table 2
Univariate logistic regression analysis of the association of ACS with variables

| Variables                  | OR   | 95% Cl          | P    |
|----------------------------|------|-----------------|------|
| Age                        | 0.970| 0.925–1.017     | 0.206|
| Male                       | 3.628| 2.199–5.985     | <0.001|
| BMI                        | 1.104| 1.067–1.142     | <0.001|
| Drinker                    | 0.851| 0.604–1.200     | 0.357|
| Smoker                     | 2.186| 1.655–2.188     | <0.001|
| Hypertension               | 1.712| 1.287–2.277     | <0.001|
| Diabetes mellitus          | 2.875| 1.783–4.634     | <0.001|
| Hypertriglyceridemia       | 2.717| 2.038–3.622     | <0.001|
| Hypercholesterolemia       | 1.930| 1.380–2.700     | <0.001|
| High LDL-C                 | 2.105| 1.475–3.005     | <0.001|
| Low HDL-C                  | 2.322| 1.756–3.070     | <0.001|
| Family history of CAD      | 1.704| 1.073–2.706     | 0.024|
| Familial hypercholesterolemia | 8.531| 1.15–63.252 | 0.036|
| Hyperuricemia              | 1.461| 1.101–1.938     | 0.009|
| Hyperhomocysteinemia       | 4.615| 3.408–6.250     | <0.001|

CAD coronary artery disease, ACS acute coronary syndrome, BMI body mass index, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, OR odds ratio, CI confidence interval

Bold values indicate statistical significance

Multivariate Logistic Regression Analysis Of Different Acs Risk Factors

Multivariate analysis with stepwise method further indicated that variables including male gender, BMI, current smoker status, DM, hypertriglyceridemia, high LDL-C, and low HDL-C were identified as the independent predictors associated with the occurrence of ACS among young adults, while hypercholesterolemia, hypertension, family history of CAD, familial hypercholesterolemia, and hyperuricemia were not. After adjusting for the traditional risk factors mentioned above, HHCY was also significantly related to the presence of ACS in young subjects (OR, 4.393; 95% CI, 3.171–6.087; P< 0.001) (Table 3).
Table 3
Multivariate logistic regression analysis of different ACS risk factors

| Variables              | OR   | 95% Cl       | P     |
|------------------------|------|--------------|-------|
| Male                   | 2.207| 1.166–4.177  | 0.015 |
| BMI                    | 1.097| 1.055–1.140  | <0.001|
| Smoker                 | 1.552| 1.115–2.161  | 0.009 |
| Diabetes mellitus      | 2.911| 1.734–4.886  | <0.001|
| Hypertriglyceridemia   | 1.953| 1.416–2.695  | <0.001|
| High LDL-C             | 1.560| 1.047–2.326  | 0.029 |
| Low HDL-C              | 1.823| 1.321–2.516  | <0.001|
| Hyperhomocysteinemia   | 4.393| 3.171–6.087  | <0.001|

ACS acute coronary syndrome, BMI body mass index, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, OR odds ratio, CI confidence interval.

Bold values indicate statistical significance.

Clinical characteristics of young ACS patients in normal homocysteine and hyperhomocysteinemia groups

Young ACS patients were divided into two groups based on HCY levels (≤15, >15 µmol/L). As shown in Table 4, young patients with HHCY were more likely to be male (97.28% vs. 93.95%, \(P = 0.026\)). The level of UA was elevated in the HHCY group, while the prevalence of DM was lower. Moreover, the HHCY group had an increased prevalence of ST-segment elevation myocardial infarction (STEMI) \(P = 0.041\), multi-vessel disease \(P = 0.036\), and decreased value of LVEF \(P = 0.01\). In addition, the Gensini Score was also obviously elevated in the HHCY group \(P = 0.043\).
Table 4  
Clinical characteristics of young ACS patients according to homocysteine levels

| Characteristics                  | HCY ≤ 15 µmol/L (n = 314) | HCY > 15 µmol/L (n = 514) | P     |
|----------------------------------|-----------------------------|---------------------------|-------|
| **Baseline characteristics**     |                             |                           |       |
| Age (years)                      | 33 (30–34)                  | 32 (30–34)                | 0.303 |
| Male, n (%)                      | 295 (93.95)                 | 500 (97.28)               | **0.026** |
| Drinker, n (%)                   | 64 (20.38)                  | 84 (16.34)                | 0.161 |
| **Traditional coronary risk factors** |                             |                           |       |
| BMI (kg/m$^2$)                   | 28.38 ± 4.09                | 28.60 ± 4.95              | 0.553 |
| Smoker, n (%)                    | 215 (68.47)                 | 357 (69.46)               | 0.816 |
| Hypertension, n (%)              | 154 (49.04)                 | 248 (48.25)               | 0.830 |
| Diabetes mellitus, n (%)         | 91 (28.98)                  | 71 (13.81)                | **< 0.001** |
| Family history of CAD, n (%)     | 41 (13.06)                  | 75 (14.59)                | 0.606 |
| **Laboratory results**           |                             |                           |       |
| TG (mmol/L)                      | 1.84 (1.26–3.06)            | 1.94 (1.36–2.84)          | 0.571 |
| TC (mmol/L)                      | 4.80 ± 1.56                 | 4.65 ± 1.69               | 0.213 |
| HDL-C (mmol/L)                   | 0.91 ± 0.22                 | 0.90 ± 0.20               | 0.729 |
| LDL-C (mmol/L)                   | 3.06 ± 1.55                 | 2.97 ± 1.52               | 0.386 |
| hs CRP (mg/L)                    | 3.10 (1.12–11.9)            | 2.97 (0.98–11.77)         | 0.818 |
| UA (µmol/L)                      | 397.56 ± 89.78              | 417.65 ± 99.77            | **0.004** |
| **Clinical type of ACS**         |                             |                           |       |
| STEMI, n (%)                     | 100 (31.85)                 | 201 (39.11)               | **0.041** |
| NSTEMI, n (%)                    | 73 (23.25)                  | 94 (18.29)                | 0.090 |

Data are expressed as mean ± standard deviation, medians with interquartile range or number (%)

CAD coronary artery disease, ACS acute coronary syndrome, BMI body mass index, HCY homocysteine, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, UA uric acid, STEMI ST-segment elevation myocardial infarction, NSTEMI non ST-segment elevation myocardial infarction, UAP Unstable Angina Pectoris, CAG coronary angiography, hs CRP high-sensitivity C-reactive protein, UA uric acid, LVEF left ventricular ejection fraction

Bold values indicate statistical significance
| Characteristics          | HCY ≤ 15 µmol/L (n = 314) | HCY > 15 µmol/L (n = 514) | P     |
|-------------------------|---------------------------|---------------------------|-------|
| UAP, n (%)              | 141 (44.90)               | 219 (42.61)               | 0.563 |
| CAG characters           |                           |                           |       |
| None                    | 25 (7.96)                 | 24 (4.67)                 | 0.068 |
| Single-vessel, n (%)     | 142 (45.22)               | 209 (40.66)               | 0.218 |
| Double-vessel, n (%)     | 71 (22.61)                | 132 (25.68)               | 0.360 |
| Triple-vessel, n (%)     | 76 (24.20)                | 149 (28.99)               | 0.147 |
| Multi-vessel, n (%)      | 147 (46.82)               | 281 (54.67)               | 0.036 |
| Gensini Score            | 30 (12–48)                | 32 (16–62)                | 0.043 |
| Cardiac function         |                           |                           |       |
| LVEF                    | 60 (56–65)                | 60 (52–65)                | 0.01  |

Data are expressed as mean ± standard deviation, medians with interquartile range or number (%)

CAD coronary artery disease, ACS acute coronary syndrome, BMI body mass index, HCY homocysteine, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, UA uric acid, STEMI ST-segment elevation myocardial infarction, NSTEMI non ST-segment elevation myocardial infarction, UAP Unstable Angina Pectoris, CAG coronary angiography, hs CRP high-sensitivity C-reactive protein, UA uric acid, LVEF left ventricular ejection fraction

Bold values indicate statistical significance

**Serum HCY level in different groups of young ACS patients**

As shown in Fig. 2A, the serum HCY was higher in patients with AMI (P = 0.046). Moreover, 49 ACS patients had no lesion coronary arteries (major coronary arteries with luminal diameter stenosis ≥ 50%) according to the results of coronary angiography. So, except for these patients, the others were classified into a single-vessel group (n = 351) and multi-vessel group (n = 428). Similarly, as shown in Fig. 2B, an increased HCY level was observed in the multi-vessel group (P = 0.012). Finally, since LVEF data were lost for 117 patients, ACS patients were divided into LVEF ≥ 50% group (n = 606) and LVEF < 50% group (n = 105). Figure 2C indicated that serum HCY was elevated in LVEF < 50% group.

**Correlation of serum HCY levels with Gensini Scores in young ACS patients**

Figure 3 showed that serum HCY levels were significantly correlated with Gensini Score in ACS patients (r = 0.142, P < 0.001).

**Discussion**
In this observational study that included young patients who were ≤ 35 years of age, we found that HHCY was significantly associated with the presence of ACS, which was independent of traditional risk factors. In addition, HHCY had a strong correlation with the severity of coronary artery stenosis.

Due to the changes in lifestyle, especially the increased obesity rates and reduced physical activity, the onset age for CAD has been gradually decreasing [16]. A previous study showed that nearly 4–10% of patients with AMI were younger than 45 years old [17]. In contrast, the prevalence of AMI among young patients (< 35 years old) in China has more than doubled over a decade [18], which caused serious consequences for families and society. Compared with older patients, younger ones may have different coronary risk factor profiles. Results from a review identified male gender, current smoking status, alcohol consumption, diabetes, hypertension, dyslipidemia, psychosocial factors, sedentary lifestyle, obesity, and family history of premature MI as the leading causes of ACS in most young patients [19]. In the current study, we narrowed the age range of young participants to 18–35 years to determine the association between HHHCY and ACS. Our results showed that very young ACS patients were more likely to have HHCY.

Studies performed over the last two decades identified HHHCY as a crucial promoter for atherosclerotic vascular disease. There is a great controversy on the association between HHHCY and the incidence of CAD, and whether it is casual, since lowering HCY levels in patients with CAD has not shown any benefit [3]. Nevertheless, many observational studies found that HHHCY, which acts as an essential marker, is strongly associated with CAD and major adverse cardiac events (MACE) (death, reinfarction, restenosis) after PCI [4]; however, most of these studies were conducted in older people. Despite the increasing population of young ACS and the growing proportion of sudden death among these patients, there is limited evidence on the effect of HHHCY on the risk of ACS in very young patients. Additionally, the results of few available researches were conflicting; a case-control study carried out among patients aged < 40 years showed a positive correlation between HHHCY and CAD occurrence [20], while another study showed no difference of serum HCY level between healthy controls and young AMI patients aged ≤ 35 years [21]. Thus, we conducted this large-scale observational study, which revealed that the very young patients with ACS had higher HCY level than non-CAD participants [16.55 (11.93–29.68) vs. 12.50 (9.71–17.42), \( P < 0.001 \)], and HHHCY was identified as an independent predictor associated with the presence of ACS (OR, 4.393; 95% CI, 3.171–6.087; \( P < 0.001 \)).

The relationship between HCY and the severity of coronary artery stenosis has been investigated by several studies before. Still, the current study is the only one conducted among the young ACS population. The results of this study showed a positive correlation between HHHCY and angiographic severity expressed by Gensini Score. Li et al [22] studied 667 middle-aged and elderly CAD patients who underwent drug-eluting stent implantation and reported that patients with HHHCY had a higher stenosis degree, as indicated by elevated SYNTAX scores. In their study, Shenoy et al [23] suggested that serum HCY level was significantly correlated with the Gensini Score of CAD patients (\( r = 0.443 \)), which was consistent with our data. However, the sample size in a study conducted by Shenoy et al [23] was smaller, and the participants of Li et al [22] and Shenoy et al [23] study were much older compared with ours. In addition, Li and colleagues [22] also showed that the number of coronary artery target vessels in the
HHCY group was obviously higher, and patients with high HCY levels had a higher proportion of coronary lesions. Another study involving HCY levels and premature CAD (56.1 ± 6.2 years of age) in 2019 [24] showed that the HCY levels were significantly higher in patients with multi-vessel disease. These findings were in agreement with the current study on the association between HHCY and the number of lesion vessels. Nonetheless, their participants were older than the participants in the present study. Moreover, we found young ACS patients with HHCY had decreased value of LVEF, which might be due to the relatively high prevalence of AMI in patients with higher HCY.

Many possible mechanisms have been reported as relevant for the association between HCY and CAD. A recent review [25] showed that HCY had a vast array of toxic effects on the vasculature, including impairing endothelial function by reducing the production of nitric oxide (NO), inducing vascular remodeling and vessel stiffening by increasing the synthesis of smooth muscle cells (SMC) as well as elevating adventitial inflammation, which might lead to the development of atherosclerosis. This review [25] also hypothesized that besides serum HCY, tissue-bound HCY and the incorporation of HCY into proteins could also stress the toxic effects of HCY on the vasculature. In their study, Yun et al. [26] indicated the enhancement of arterial stiffness in HHCY might be attributed to HCY-related LDL atherogenesis, such as small LDL particle size and its oxidative modification. Bianca et al [27] suggested that HCY exerted a prothrombotic effect by enhancing platelet aggregation. Also, several studies showed that HHCY might enhance the adverse effects of CAD risk factors such as essential hypertension, smoking, dyslipidemia, and diabetes mellitus [28–31]. These were probably related to the formation and progression of CAD in young adults.

Although traditional risk factors have a vital role in the development of cardiovascular disease, only 50% of these diseases could be explained by classical factors, which is why non-traditional risk factors have drawn more attention. The clinical significance of this article is to identify that HHCY played an important role in the occurrence and progression of ACS, which increased awareness of the importance of the HCY level among patients ≤ 35 years of age. Since excessive weight, current smoker status, alcohol and caffeine intake, and insufficient vitamin B and folic acid levels could increase HCY concentration, very young patients should adhere to a healthy lifestyle so as to maintain HCY levels within the normal range.

**Limitations**

Our study has a few limitations. First, this was a retrospective study. Although the serum HCY level was mainly determined by vitamin B and folic acid intake, the levels of vitamin B and folate were not measured in the study. Second, since all the medical history data of participants were obtained from electronic medical records, it was hard to ensure whether these data were accurate. Third, majority of patients with ACS who had high homocysteine levels were males, therefore results had limited value for young female population.

**Conclusion**
In this study, HHCY was shown to be significantly associated with the presence of ACS and the severity of coronary artery stenosis in very young patients $\leq$ 35 years of age.

**List Of Abbreviations**

acute coronary syndrome (ACS)

Homocysteine (HCY)

coronary artery disease (CAD)

coronary angiography (CAG)

hyperhomocysteinemia (HHCY)

ST-segment elevation myocardial infarction (STEMI)

left ventricular ejection fraction (LVEF)

body mass index (BMI)

acute myocardial infarction (AMI)

Framingham Risk Factors (FRFs)

triglycerides (TG)

total cholesterol (TC)

high-density lipoprotein cholesterol (HDL-C)

uric acid (UA)

systolic pressure (SBP)

Familial hypercholesterolemia (FH)

left ventricular ejection fraction (LVEF)

standard deviation (SD)

interquartile range (IQR)

major adverse cardiac events (MACE)

**Declarations**
Ethics approval and consent to participate

This study was complied with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Beijing Anzhen Hospital. Written informed consent was waived by the ethics committee because of the data retrospectively obtained from electronic medical records.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors’ contributions

Study conception and design: Wei Liu, Jiayin Sun. Literature search: Jiayin Sun. Data collection and analysis: Jiayin Sun, Wei Han, Sijing Wu, Shuo Jia, Zhenxian Yan, Yonghe Guo. Data interpretation: Wei Liu, Yujie Zhou, Yingxin Zhao, Jiayin Sun. Writing: Jiayin Sun. All authors read and approved the final manuscript.

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