

Original Research

Prognostic Significance of Homocysteine Levels in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Propensity Score Matching and Weighting Analysis

Qianfeng Xiong¹, Shaoyong Chen¹, Junke Luo², Pengfeng Xiong¹, Zhenyun Nie¹, Lei Huang¹, Yao Wang¹, Zhen Lei³, Lihui Zhang^{4,5,*}, Jing Wang^{6,*}

¹Department of Cardiology, Fengcheng People's Hospital, The Affiliated Fengcheng Hospital of Yichun University, 331100 Fengcheng, Jiangxi, China

²Department of Cardiac Intensive Care Unit, Fengcheng People's Hospital, The Affiliated Fengcheng Hospital of Yichun University, 331100 Fengcheng, Jiangxi, China

³Department of Thoracic Surgery, Fengcheng People's Hospital, The Affiliated Fengcheng Hospital of Yichun University, 331100 Fengcheng, Jiangxi, China

⁴Health Care Bureau, Health Commission of Shanxi Province, 030032 Taiyuan, Shanxi, China

⁵Department of Cardiology, The Third Clinical Medical College of Shanxi Medical University, 030032 Taiyuan, Shanxi, China

⁶Prevention & Healthcare Department, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, 030032 Taiyuan, Shanxi, China

*Correspondence: 13485385229@163.com (Lihui Zhang); 2285731411@qq.com (Jing Wang)

Academic Editor: Antonio Maria Leone

Submitted: 2 July 2024 Revised: 9 September 2024 Accepted: 26 September 2024 Published: 19 February 2025

Abstract

Background: Elevated homocysteine (Hcy) levels have been linked to poorer outcomes in acute coronary syndrome. This study aimed to assess the predictive value of elevated Hcy levels for major adverse cardiac events (MACE) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). **Methods:** This retrospective cohort study included 183 STEMI patients who underwent primary PCI at a tertiary university hospital in southern China from January 2020 to December 2021. Laboratory values, including Hcy levels, were obtained within 24 hours of admission. Patients were categorized into elevated and normal Hcy groups using a threshold of 12 $\mu\text{mol/L}$. The study outcome was the occurrence of 6-point MACE, defined as cardiac death, nonfatal myocardial infarction, stroke, ischemia-driven revascularization (PCI or coronary artery bypass grafting), heart failure and all-cause death. Survival analyses were conducted using Kaplan-Meier and Cox proportional hazard methods. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) approaches were employed to minimize bias. **Results:** The mean age of the patients was 64.8 years, with 76.0% being male. After adjusting with PSM or IPTW, covariate imbalances between the two groups were corrected. Over a median follow-up period of 25.8 months, 55 MACE events occurred, resulting in an event rate of 30.1%. Patients with elevated Hcy levels had a higher incidence of MACE in both unadjusted (hazard ratio [HR] = 2.778; 95% confidence interval [CI]: 1.591–4.850; $p < 0.001$) and adjusted analyses (PSM: HR = 2.995; 95% CI: 1.397–6.423, $p = 0.005$; IPTW: HR = 3.2; 95% CI: 1.631–6.280, $p < 0.001$). Multivariate Cox regression further confirmed that elevated Hcy levels were associated with a worse prognosis across the entire cohort (HR = 1.062, 95% CI: 1.029–1.097, $p < 0.001$), PSM cohort (HR = 1.089, 95% CI: 1.036–1.145, $p < 0.001$), and IPTW cohort (HR = 1.052, 95% CI: 1.020–1.086, $p = 0.001$). **Conclusions:** Elevated plasma levels of Hcy ($\geq 12 \mu\text{mol/L}$) are associated with worse outcomes in STEMI patients undergoing primary PCI, highlighting the potential role of Hcy as a prognostic marker in this population.

Keywords: homocysteine; ST-segment elevation myocardial infarction; primary percutaneous coronary intervention; major adverse cardiac events; propensity score

1. Introduction

Acute coronary syndrome (ACS), which affects millions of people annually, encompasses three types of coronary artery disease (CAD) and leads to approximately 7 million new diagnoses worldwide each year [1]. ST-segment elevation myocardial infarction (STEMI), the most critical type of ACS, constitutes about 36% of all ACS cases and results from the rupture of a vulnerable atherosclerotic

plaque in a coronary artery, leading to complete occlusion and blockage of blood flow [1]. Accordingly, timely coronary catheterization and percutaneous coronary intervention (PCI) are the most effective strategies to reduce mortality in STEMI patients. However, some patients will still experience certain adverse events, such as heart failure, stroke, recurrent myocardial infarction, and even death [2]. Although traditional risk factors are still the main focus for risk stratification, emerging biomarkers like homocysteine



(Hcy) hold promise for more accurately predicting residual risk and improving the efficacy of secondary prevention measures [3].

Discovered almost a century ago, Hcy is a sulfur-containing amino acid that undergoes metabolism via two main pathways: remethylation, which transform Hcy into methionine, and transsulfuration, which converts it into cysteine. Hcy levels can be significantly elevated due to deficiencies in dietary folate and B vitamins, as well as in individuals with the *MTHFR* 677 TT genotype. Conversely, B vitamin supplementation, including folic acid, B6, and B12, can lower Hcy levels. Several factors such as nutrition, age, gender, ethnicity, and genetics may also influence Hcy levels [4].

In the 1960s, pathologist Kilmer McCully made the seminal clinical observation that connected elevated plasma Hcy concentrations with vascular disease. This led him to propose the “homocysteine theory of atherosclerosis” [5], which spurred epidemiological studies revealing significant associations between even slight elevations in blood homocysteine and major vascular diseases including cardiovascular, cerebrovascular, and peripheral vascular diseases [4]; more recent studies, particularly those conducted in Chinese populations, have further corroborated these findings, demonstrating that hyperhomocysteinemia is an independent risk factor for CAD and highlighting its predictive value for obstructive CAD [6,7].

Nonetheless, the relationship between Hcy levels and adverse outcomes in ACS remains unclear. This study, therefore, sought to evaluate the prognostic significance of elevated Hcy levels in predicting major adverse cardiac events (MACE) among STEMI patients undergoing primary PCI.

2. Methods

2.1 Study Population

This single-center retrospective cohort study involved 183 consecutive STEMI patients who underwent primary PCI at The Affiliated Fengcheng Hospital of Yichun University, a tertiary care institution in southern China, from January 2020 to December 2021. The study protocol adhered to the 1975 Declaration of Helsinki and was approved by the Ethics Committee of The Affiliated Fengcheng Hospital of Yichun University (Approval No. 202256). A threshold of 12 $\mu\text{mol/L}$ was set to define hyperhomocysteinemia [8]. Based on this cutoff, patients were categorized into two groups: the normal Hcy group, with a median Hcy level of 8.7 $\mu\text{mol/L}$ (range: 6.9–10.0 $\mu\text{mol/L}$), and the elevated Hcy group, with a median Hcy level of 16.6 $\mu\text{mol/L}$ (range: 14.3–18.9 $\mu\text{mol/L}$). STEMI was defined by the presence of the following criteria: (1) prolonged chest pain (≥ 20 minutes); (2) based on the Fourth Universal Definition of Myocardial Infarction, acute STEMI on an electrocardiogram is characterized by new ST-segment elevation at the J-point in two adjacent leads. The required elevation is

generally ≥ 1 mm, except in leads V2–V3, where the thresholds are: ≥ 2 mm for men aged 40 and above, ≥ 2.5 mm for men under 40, and ≥ 1.5 mm for women, regardless of age [9]; (3) elevated cardiac biomarkers above the accepted threshold [1]. Patients were excluded if they met any of the following criteria: use of folic acid supplements, presence of cancer, acute or chronic inflammatory diseases, previous history of STEMI, or prior coronary revascularization. Primary PCI, defined as percutaneous coronary intervention to the culprit artery within 12 hours of symptom onset without preceding thrombolytic therapy, was performed by an experienced team within 120 minutes of first medical contact (FMC) [10].

2.2 Data Collection

Two authors independently reviewed hospital medical records and the China Chest Pain Center Data Reporting Platform to collect baseline data for each patient, including demographic characteristics, laboratory findings, medical history, and angiographic and procedural details. Demographic and clinical characteristics included age, sex, body mass index (BMI), heart rate, blood pressure, Killip classification, left ventricular ejection fraction (LVEF), and laboratory results. Laboratory results primarily included blood tests conducted within 24 hours of admission, with troponin representing the highest value within 72 hours of admission, and LVEF reflecting the lowest value during hospitalization. Collected medical history data consisted of current smoking status, alcohol consumption, diabetes, hypercholesterolemia, hypertension, and chronic obstructive pulmonary disease (COPD). The diagnostic criteria for baseline characteristics were defined as follows: Hypertension was defined as having a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the current use of antihypertensive drugs. Diabetes was identified by a fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL), the use of glucose-lowering agents, or a previous diagnosis by a healthcare professional. Hypercholesterolemia was considered present if the total cholesterol level was ≥ 5.2 mmol/L (200 mg/dL) or if lipid-lowering therapy was being used. COPD was defined by a post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of less than 0.70. Documented procedural characteristics included door-to-wire time, culprit vessel anatomy, and preoperative thrombolysis in myocardial infarction (TIMI) flow grading of the culprit lesion. Single-vessel disease was defined as having at least 50% stenosis in one major coronary artery, while multivessel disease was characterized by at least 50% stenosis in two or more major coronary arteries with a diameter of 2.5 mm or more.

2.3 Study Outcome

The primary endpoint was the incidence of MACE, which included cardiac death, nonfatal myocardial infarction, stroke, ischemia-driven revascularization (PCI or

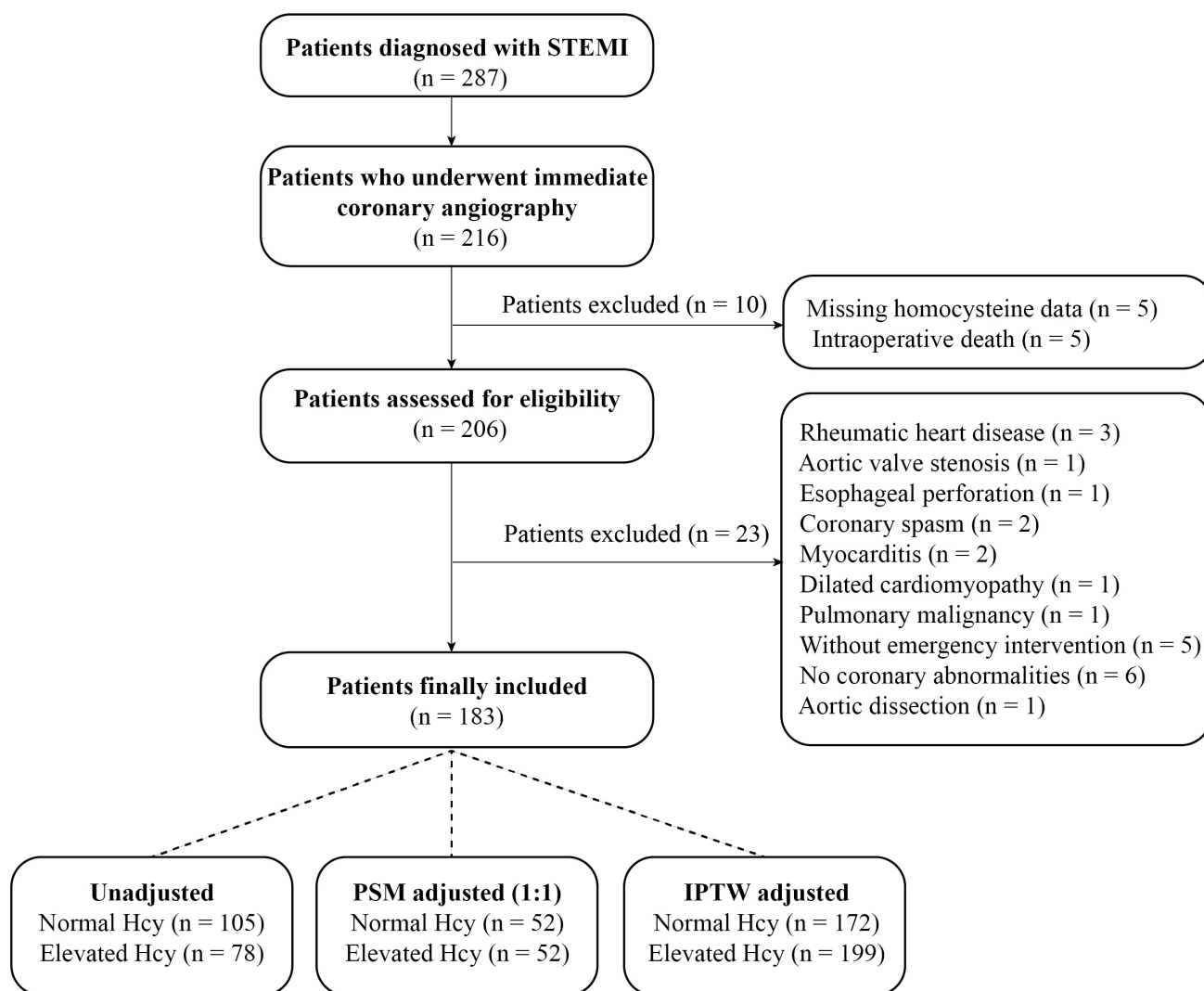


Fig. 1. Study flow diagram. Abbreviations: STEMI, ST-segment elevation myocardial infarction; Hcy, homocysteine; PSM, propensity score matching; IPTW, inverse probability of treatment weighting.

coronary artery bypass grafting [CABG]), heart failure and all-cause death. Stroke was defined as a sudden onset of neurological deficit caused by ischemia or hemorrhage within the brain, confirmed by clinical presentation and imaging studies. Heart failure is defined as a clinical syndrome characterized by symptoms and/or signs resulting from functional or structural cardiac abnormalities, typically confirmed by echocardiographic findings, evidence of pulmonary or systemic congestion, and/or elevated serum biomarkers such as proB-type natriuretic peptide (proBNP) [11]. Ischemia-driven revascularization was defined as revascularization procedures, such as PCI or CABG, prompted by symptoms or objective evidence of myocardial ischemia, which includes significant stenosis ($\geq 70\%$) in a major coronary artery or $\geq 50\%$ in the left main coronary artery as determined by coronary angiography, or a fractional flow reserve (FFR) ≤ 0.80 [12]. Follow-up assessments were conducted at 1, 3, and 6 months, followed by annual evaluations, with the final check-up scheduled

for April 2024. These follow-ups were performed via telephone or scheduled outpatient visits to monitor disease progression and the incidence of MACE.

2.4 Statistical Analysis

All statistical analyses were performed using R software (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria) and SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was employed to evaluate the normality of continuous variables. Variables following a normal distribution were summarized as mean (standard deviation) and compared between groups using an independent *t*-test. Those that did not follow a normal distribution were presented as median (Q1–Q3) and analyzed with the Mann-Whitney U test. Categorical variables were described as frequencies (percentages) and assessed using the chi-square test. Variables with less than 10% missing data in both groups were imputed using multiple imputation.

Table 1. Baseline clinical characteristics according to homocysteine level.

	Overall (n = 183)	Normal Hcy (n = 105)	Elevated Hcy (n = 78)	<i>p</i> -value
Demographics				
Age, year	64.8 (12.4)	63.6 (12.8)	66.4 (11.7)	0.128
Male, n (%)	139 (76.0%)	75 (71.4%)	64 (82.1%)	0.688
BMI, kg·m ⁻²	23.8 (3.2)	23.8 (3.2)	23.6 (3.0)	0.634
HR, bpm	73 (63, 86)	74.0 (63, 86)	73.0 (65, 87)	0.766
SBP, mmHg	131 (113, 147)	131 (113, 150)	131 (110, 145)	0.459
DBP, mmHg	81 (70, 94)	81 (73, 94)	80 (68, 91)	0.176
Troponin, ng/mL	28.8 (10.7, 50.0)	28.4 (13.0, 50.0)	31.6 (8.7, 50.0)	0.402
NT-proBNP, pg/mL	1314.0 (323.0, 2852.1)	1085.1 (306.2, 3208.0)	1368.2 (349.4, 2642.8)	0.548
TC, mmol/L	4.6 (1.1)	4.8 (1.1)	4.4 (1.0)	0.022
TG, mmol/L	1.1 (0.7, 1.5)	1.1 (0.8, 1.6)	1.0 (0.7, 1.4)	0.056
HDL-C, mmol/L	1.1 (1.0, 1.4)	1.2 (1.0, 1.4)	1.1 (1.0, 1.3)	0.280
LDL-C, mmol/L	2.9 (0.8)	3.0 (0.8)	2.8 (0.9)	0.046
WBC, 10 ⁹ /L	10.4 (8.4, 12.9)	11.3 (8.7, 13.3)	10.0 (7.9, 12.1)	0.062
RBC, 10 ¹² /L	4.2 (0.6)	4.2 (0.6)	4.1 (0.6)	0.216
PLT, 10 ⁹ /L	203.0 (173.5, 249.0)	206.0 (182.0, 250.0)	197.0 (170.3, 243.3)	0.223
HB, g/L	132.0 (116.0, 144.0)	132.0 (119.0, 145.0)	130.0 (113.3, 142.8)	0.259
HCT, %	38.3 (32.5, 41.9)	38.8 (33.3, 42.1)	36.7 (31.2, 40.9)	0.194
D-dimer, mg/L	0.4 (0.3, 0.6)	0.4 (0.2, 0.6)	0.4 (0.3, 0.7)	0.378
Serum creatinine, µmol/L	70.0 (60.0, 87.0)	66.1 (57.2, 76.9)	76.7 (65.9, 102.0)	<0.001
Na ⁺ , mmol/L	139.0 (136.8, 141.0)	138.6 (136.8, 140.3)	139.7 (137.0, 141.5)	0.122
K ⁺ , mmol/L	3.9 (3.7, 4.2)	3.9 (3.7, 4.2)	4.0 (3.7, 4.3)	0.311
Uric acid, µmol/L	363.0 (125.4)	350.5 (114.5)	379.8 (137.7)	0.119
LVEF ≥45%, n (%)	170 (92.9)	96 (91.4)	74 (94.9)	0.545
Killip classification ≥2, n (%)	39 (21.3)	24 (22.9)	15 (19.2)	0.682
Medical history				
Smoking, n (%)	101 (55.2)	50 (47.6)	51 (65.4)	0.025
Alcohol, n (%)	32 (17.5)	17 (16.2)	15 (19.2)	0.735
Hypertension, n (%)	108 (59.0)	55 (52.4)	53 (68.0)	0.049
Diabetes, n (%)	47 (25.7)	27 (25.7)	20 (25.6)	1
Hyperlipidemia, n (%)	28 (15.3)	18 (17.1)	10 (12.8)	0.551
COPD, n (%)	20 (10.9)	8 (7.6)	12 (15.4)	0.154
Angiographic characteristics				
D2W, mins	80 (62, 105)	83 (62, 106)	79 (63, 100)	0.715
Culprit lesion				0.640
RCA, n (%)	72 (39.3)	40 (38.1)	32 (41.0)	
LAD, n (%)	91 (49.7)	55 (52.4)	36 (46.2)	
LCX, n (%)	20 (10.9)	10 (9.5)	10 (12.8)	
Multivessel disease, n (%)	116 (63.4)	70 (66.7)	46 (59.0)	0.361
Preprocedural TIMI flow ≥2, n (%)	51 (27.9)	27 (25.7)	24 (30.8)	0.557
Number of stents ≥2, n (%)	82 (44.8)	51 (48.6)	31 (39.7)	0.300

Notes: Data are presented as mean (standard deviation), median (inter-quartile range), or n (%).

Abbreviations: BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal proB-type natriuretic peptide; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; HB, hemoglobin; HCT, hematocrit; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; D2W, door-to-wire time; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex artery; TIMI, thrombolysis in myocardial infarction; Hcy, homocysteine.

Table 2. Demographic, medical history, and angiographic characteristics in PSM and IPTW adjusted analysis.

	PSM adjusted		<i>p</i> -value	IPTW adjusted		<i>p</i> -value
	Normal Hcy (n = 52)	Elevated Hcy (n = 52)		Normal Hcy (n = 172)	Elevated Hcy (n = 199)	
Demographics						
Age, year	64.6 (13.0)	65.7 (12.2)	0.659	64.9 (12.7)	68.6 (15.1)	0.376
Male, n (%)	42 (80.8)	40 (76.9)	0.810	125.1 (72.8)	134.9 (68.0)	0.663
BMI, kg·m ^{−2}	23.4 (3.1)	23.7 (2.9)	0.542	23.5 (3.2)	23.4 (2.9)	0.828
HR, bpm	77 (63, 85)	73 (65, 86)	0.782	74 (62, 88)	75 (66, 88)	0.717
SBP, mmHg	130 (118, 149)	134 (112, 14)	0.656	130 (113, 145)	131 (106, 152)	0.868
DBP, mmHg	80 (72, 94)	84 (74, 91)	0.940	80 (72, 92)	82 (69, 94)	0.798
Troponin, ng/mL	28.0 (11.6, 50.0)	32.4 (9.9, 50.0)	0.675	26.7 (9.3, 50.0)	44.7 (11.1, 50.0)	0.293
NT-proBNP, pg/mL	1010.2 (314.6, 2285.8)	1386.3 (315.4, 2761.3)	0.656	1071.1 (254.5, 3420.8)	1599.7 (459.1, 4699.5)	0.250
TC, mmol/L	4.6 (1.0)	4.52 (1.1)	0.879	4.6 (1.1)	4.7 (1.1)	0.675
TG, mmol/L	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)	0.861	1.0 (0.7, 1.5)	1.0 (0.7, 1.4)	0.829
HDL-C, mmol/L	1.1 (1.0, 1.4)	1.2 (1.1, 1.4)	0.580	1.1 (1.0, 1.4)	1.1 (0.9, 1.3)	0.369
LDL-C, mmol/L	2.9 (0.8)	2.9 (0.9)	0.984	2.9 (0.9)	3.0 (1.0)	0.748
WBC, 10 ⁹ /L	10.5 (8.4, 13.2)	10.2 (8.3, 12.4)	0.772	11.2 (8.6, 13.1)	10.6 (9.0, 15.0)	0.649
RBC, 10 ¹² /L	4.2 (0.7)	4.1 (0.5)	0.564	4.1 (0.7)	4.1 (0.6)	0.951
PLT, 10 ⁹ /L	207.5 (176.0, 240.0)	200.5 (173.8, 241.8)	0.974	205.0 (173.7, 249.5)	194.5 (176.3, 241.6)	0.615
HB, g/L	133.0 (118.3, 145.0)	130.5 (115.5, 142.3)	0.491	132.0 (117.0, 144.4)	126.9 (112.0, 140.0)	0.283
HCT, %	38.6 (32.0, 42.0)	36.7 (32.4, 39.6)	0.246	38.5 (30.0, 41.8)	37.0 (32.8, 39.3)	0.475
D-dimer, mg/L	0.4 (0.3, 0.5)	0.4 (0.3, 0.6)	0.644	0.4 (0.3, 0.6)	0.4 (0.3, 0.9)	0.286
Serum creatinine, μmol/L	72.2 (62.9, 86.1)	70.5 (60.7, 86.9)	0.984	69.9 (59.0, 83.0)	70.0 (65.0, 80.9)	0.421
Na ⁺ , mmol/L	138.2 (136.7, 140.4)	139.1 (137.2, 141.1)	0.235	138.5 (136.7, 140.3)	138.9 (137.2, 141.2)	0.609
K ⁺ , mmol/L	3.9 (3.7, 4.3)	4.0 (3.7, 4.2)	0.718	3.9 (3.6, 4.2)	3.9 (3.8, 4.1)	0.873
Uric acid, μmol/L	364.7 (110.1)	364.6 (137.4)	0.997	355.5 (279.8, 437.8)	382.63 (286.9, 423.7)	0.393
LVEF ≥45%, n (%)	49 (94.2)	48 (92.3)	1	158.54 (92.3)	162.9 (82.0)	0.229
Killip classification ≥2, n (%)	10 (19.2)	11 (21.2)	1	36.84 (21.4)	48.72 (24.5)	0.713
Medical history						
Smoking, n (%)	33 (63.5)	32 (61.5)	1	91.1 (53.0)	107.3 (54.1)	0.923
Alcohol, n (%)	11 (21.2)	9 (17.3)	0.804	28.3 (16.5)	31.7 (16.0)	0.939
Hypertension, n (%)	30 (57.7)	32 (61.5)	0.842	93.0 (54.1)	101.6 (51.2)	0.778
Diabetes, n (%)	12 (23.1)	10 (19.2)	0.81	38.0 (22.1)	37.9 (19.1)	0.651
Hyperlipidemia, n (%)	8 (15.4)	7 (13.5)	1	25.0 (14.6)	27.3 (13.8)	0.898
COPD, n (%)	6 (11.5)	5 (9.6)	1	13.7 (8.0)	18.0 (9.1)	0.790

Table 2. Continued.

	PSM adjusted		<i>p</i> -value	IPTW adjusted		<i>p</i> -value
	Normal Hcy (n = 52)	Elevated Hcy (n = 52)		Normal Hcy (n = 172)	Elevated Hcy (n = 199)	
Angiographic characteristics						
D2W, mins	84 (62, 102)	78 (64, 98)	0.770	78.0 (57.6, 98.0)	80.0 (66.0, 97.1)	0.677
Culprit lesion			0.815			0.947
RCA, n (%)	20 (38.5)	20 (38.5)		63.3 (36.8)	71.0 (35.8)	
LAD, n (%)	25 (48.1)	27 (51.9)		91.4 (53.2)	103.8 (52.3)	
LCX, n (%)	7 (13.5)	5 (9.6)		17.2 (10.0)	23.7 (12.0)	
Multivessel disease, n (%)	34 (65.4)	31 (59.6)	0.685	115.7 (67.4)	141.94 (71.5)	0.607
Preprocedural TIMI flow ≥ 2 , n (%)	17 (32.7)	17 (32.7)	1	47.1 (27.4)	64.44 (32.5)	0.634
Number of stents ≥ 2 , n (%)	28 (53.9)	23 (44.2)	0.433	79.8 (46.5)	105.47 (53.1)	0.511

Notes: Data are presented as mean (standard deviation), median (inter-quartile range), or n (%).

Abbreviations: PSM, propensity score matching; IPTW, inverse probability of treatment weighting; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal proB-type natriuretic peptide; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; HB, hemoglobin; HCT, hematocrit; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; D2W, door-to-wire time; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex artery; TIMI, thrombolysis in myocardial infarction; Hcy, homocysteine.

To adjust for between-group differences, propensity score-based methods were utilized, including propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) [13]. For PSM, a greedy nearest-neighbor matching algorithm with a caliper width of 0.2 was applied for 1:1 matching. All covariates were initially considered for matching in PSM. To further validate our findings, we conducted sensitivity analyses using different sets of covariates, as detailed in **Supplementary Table 1**. For IPTW, the inverse propensity score was used as the weight for patients with elevated Hcy levels, and 1 minus the inverse propensity score was used as the weight for patients with normal Hcy levels. We also conducted a sensitivity analysis with E-values to evaluate the robustness of our results against potential unmeasured confounders [14]. The E-value quantifies the minimum association strength that an unmeasured confounder would require with both the exposure (elevated Hcy levels) and the outcome (MACE) to completely account for the observed relationship.

Survival analysis was conducted using Kaplan-Meier curves and Cox proportional hazards models to evaluate the association between elevated Hcy levels and MACE in STEMI patients undergoing primary PCI. Kaplan-Meier survival estimates were compared using the log-rank test. Univariate Cox regression analysis was initially conducted, and variables with a p -value < 0.05 were included in the multivariate Cox regression analysis to identify independent risk factors for MACE. Subgroup analysis was performed to evaluate the association between elevated Hcy levels and MACE across different subgroups, defined by baseline characteristics such as sex, age, BMI, smoking status, alcohol consumption, hypertension, diabetes, and LVEF (LVEF $\geq 45\%$ or $< 45\%$). Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) within each subgroup, and interaction terms were included to assess potential effect modification, with p -values reported for interaction tests. A two-tailed p -value < 0.05 was considered statistically significant.

3. Results

A total of 183 STEMI patients who underwent primary PCI were included in the final analysis of this study (Fig. 1). Among these patients, 76.0% were male, and the mean age was 64.8 ± 12.4 years. 105 patients were in the normal Hcy level group and the remaining 78 patients were in the elevated Hcy group. The overall Hcy level was $11.0 \mu\text{mol/L}$ (8.4, 15.2), with a median level of $8.7 \mu\text{mol/L}$ (6.9, 10.0) in the normal Hcy group and $16.6 \mu\text{mol/L}$ (14.3, 18.9) in the elevated Hcy group, respectively. The two groups had similar baseline clinical characteristics, medical histories and angiographic findings (Table 1). However, there were significant differences in several clinical characteristics, such as laboratory findings and medical history, between the two groups. Patients in the elevated Hcy group

had higher serum creatinine levels and a greater prevalence of hypertension and smoking, whereas those in the normal Hcy group exhibited higher levels of total cholesterol and low-density lipoprotein cholesterol.

After adjustment with the PSM or IPTW method, baseline covariates were balanced between the groups (Table 2). The propensity score jitter plot demonstrates that the distribution of propensity scores is well balanced following PSM adjustment (Fig. 2).

3.1 Follow-up Outcomes

Over a median follow-up period of 25.8 (10.1, 35.9) months, 55 patients (30.1%) experienced MACE, with 19 cases in the normal Hcy group and 36 in the elevated Hcy group. The incidence rates of different events are detailed in **Supplementary Table 2**. The Kaplan-Meier survival plot (Fig. 3) demonstrated a significantly higher incidence of MACE in the elevated Hcy group according to the Cox proportional hazard model (HR = 2.778, 95% CI: 1.591–4.850, $p < 0.001$). This increased incidence remained significant in the elevated Hcy group even after adjustments using PSM (HR = 2.995, 95% CI: 1.397–6.423, $p = 0.005$) and IPTW (HR = 3.2, 95% CI: 1.631–6.280, $p < 0.001$).

3.2 Sensitivity Analysis

The E-values for the unadjusted, PSM, and IPTW analyses were 5.000, 5.439, and 5.853, respectively, suggesting that an unmeasured confounder would require a strong association with both Hcy levels and MACE to fully explain away these findings (**Supplementary Table 3**). These findings support the robustness of the observed association between elevated Hcy levels and an increased risk of MACE, even in the presence of potential unmeasured confounders.

3.3 Subgroup Analysis

Subgroup analysis revealed varying associations between elevated homocysteine levels and MACE across different subgroups (**Supplementary Fig. 1**). The P-interaction values indicated no significant interaction effects among subgroups (all $p > 0.05$), demonstrating that our main findings were consistent across subgroups defined by age (< 60 or ≥ 60), sex, BMI (< 25 or ≥ 25), smoking status, alcohol consumption, hypertension, and diabetes.

3.4 Cox Multivariate Analysis

In the multivariate Cox proportional hazards analysis, age (HR = 1.052, 95% CI: 1.023–1.081, $p < 0.001$), Hcy (HR = 1.062, 95% CI: 1.029–1.097, $p < 0.001$), and LVEF $\geq 45\%$ (HR = 0.251, 95% CI: 0.116–0.543, $p < 0.001$) were identified as independent predictors of MACE (Table 3). Even after adjustments with PSM or IPTW, Hcy remained a significant risk factor in STEMI patients undergoing primary PCI (PSM adjusted: HR = 1.089, 95% CI: 1.036–1.145, $p < 0.001$; IPTW adjusted: HR = 1.052, 95% CI:

Distribution of Propensity Scores

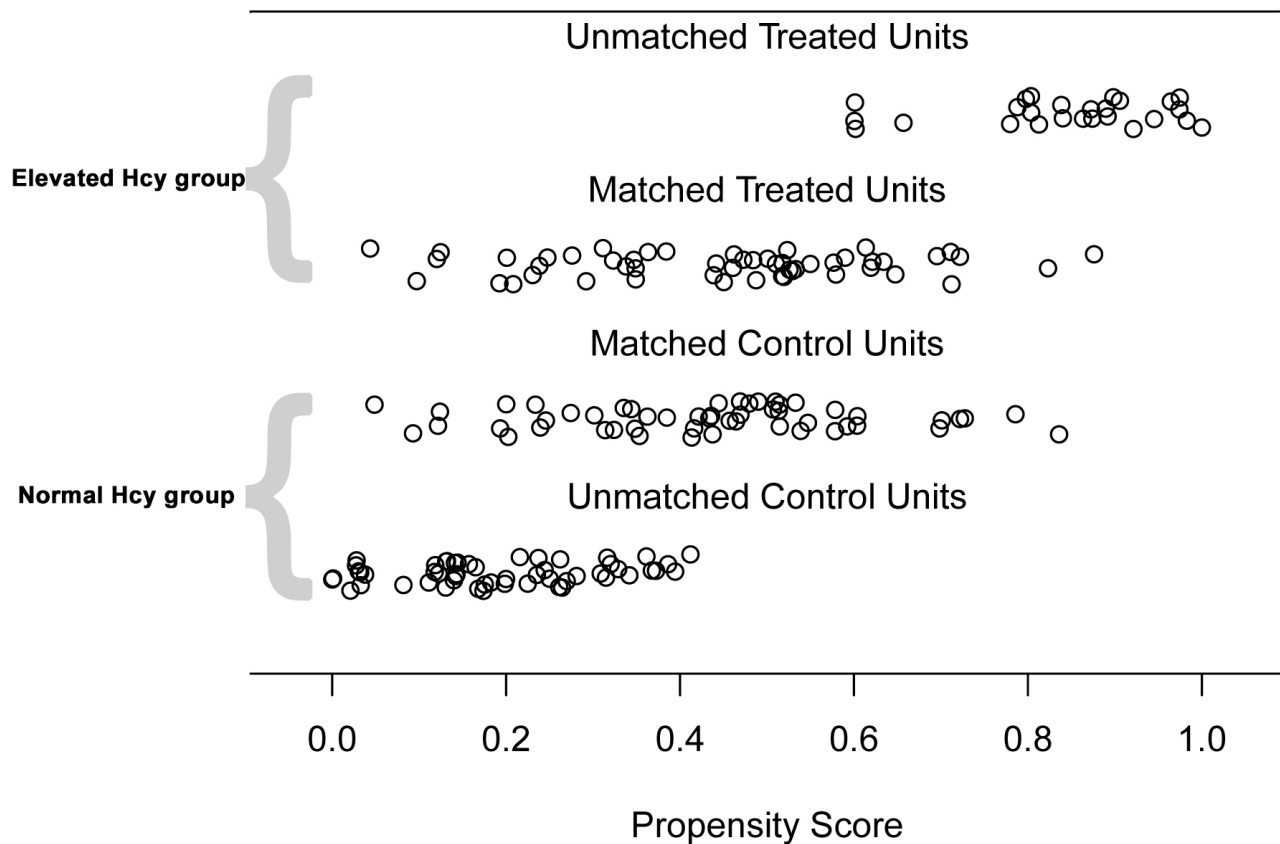


Fig. 2. Jitter plot of propensity score matching (PSM). This figure illustrates the distribution of propensity scores before and after matching between the elevated Hcy group (treated units) and the normal Hcy group (control units). “Unmatched Treated Units” and “Unmatched Control Units” represent the propensity scores of patients before matching, while “Matched Treated Units” and “Matched Control Units” indicate the scores after PSM. Hcy, homocysteine.

1.020–1.086, $p = 0.001$). Furthermore, both age (PSM adjusted: HR = 1.045, 95% CI: 1.012–1.079, $p = 0.008$; IPTW adjusted: HR = 1.051, 95% CI: 1.019–1.084, $p = 0.002$), and low-density lipoprotein cholesterol (LDL-C) (PSM adjusted: HR = 1.866, 95% CI: 1.162–2.996, $p = 0.010$; IPTW adjusted: HR = 2.765, 95% CI: 1.692–4.520, $p < 0.001$) were also independently associated with a worse prognosis (Table 4).

4. Discussion

In this cohort of 183 STEMI patients undergoing primary PCI, we observed that those with hyperhomocysteinemia ($\geq 12 \mu\text{mol/L}$) experienced a higher rate of long-term MACE. After two statistical adjustment approaches for differences between two groups, the association between elevated Hcy and MACE remained evident.

Hcy, an intermediate metabolite of methionine, contributes to endothelial dysfunction and inflammation, smooth muscle cell proliferation, platelet activation, and

increased risk of thrombosis [5,15]. With the advent of high-performance liquid chromatography methods for the rapid measurement of Hcy concentrations, epidemiological studies have uncovered significant links between modest increases in blood Hcy levels and cardiovascular, cerebrovascular, and peripheral vascular diseases [16,17]. Several *in vitro* and *in vivo* studies using pathogenic concentrations of Hcy and hyperhomocysteinemia animal models have demonstrated that Hcy induces harmful effects on both vascular resident cells and circulating leukocytes [18]. As an amino acid containing a reactive sulfhydryl group, Hcy is thought to contribute to vascular inflammation and injury by promoting oxidative stress through the accumulation of reactive oxygen species [19]. This oxidative stress can lead to endothelial dysfunction, smooth muscle cell proliferation, and vascular calcification, thereby increasing the risk of cardiac and vascular diseases [18]. Supporting this hypothesis, hyperhomocysteinemia has consistently been linked to a heightened risk of various cardiovascular conditions, including atherosclerosis, coronary heart disease,

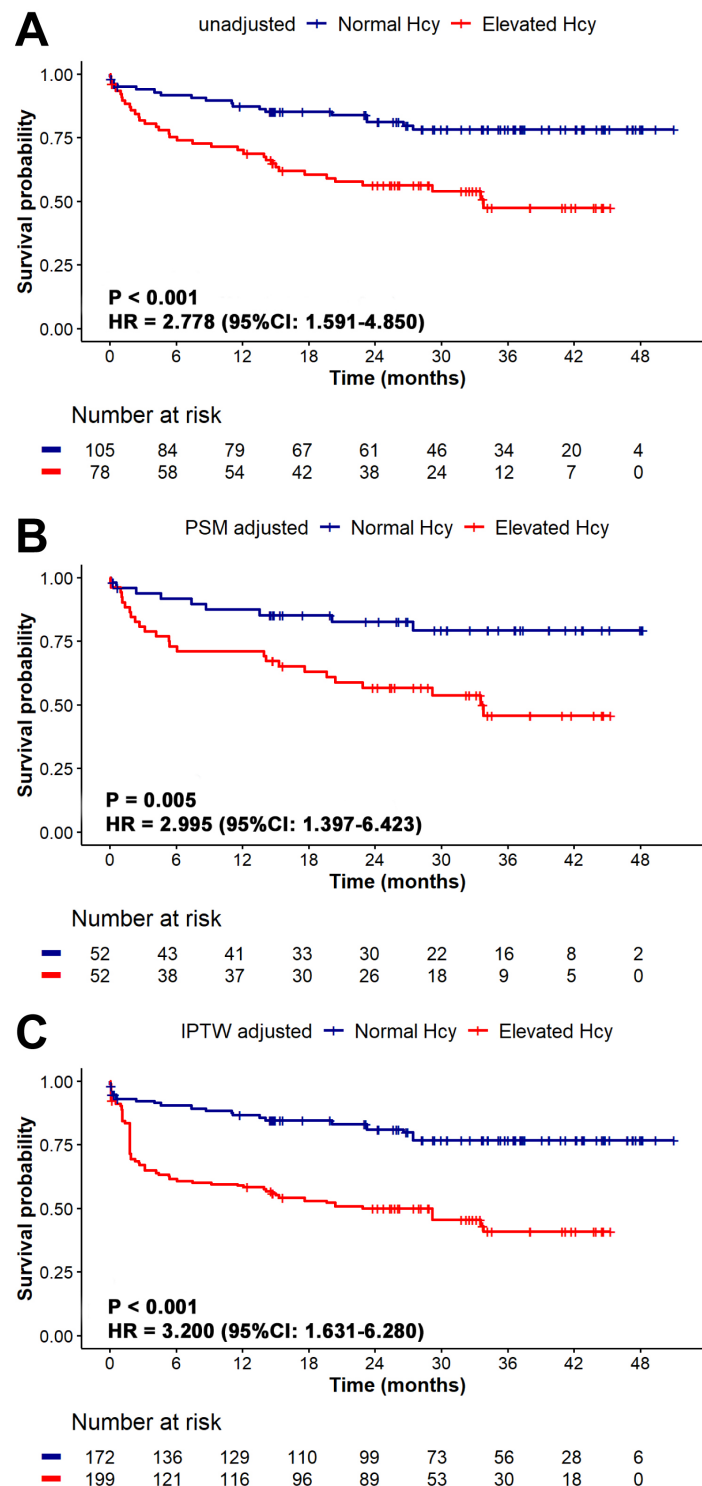


Fig. 3. Kaplan-Meier survival analysis for MACE according to Hcy levels: (A) unadjusted analysis, (B) PSM adjusted, (C) IPTW adjusted. The survival analysis is performed with the use of the Cox proportional-hazard model. The Kaplan-Meier survival analysis shows that the elevated Hcy group has a lower survival probability compared to the normal Hcy group, with unadjusted, PSM-adjusted, and IPTW-adjusted analyses all confirming an increased risk of MACE associated with higher Hcy levels and demonstrating the robustness of this association after adjusting for confounding factors. Hcy, homocysteine; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiac events.

Table 3. Univariate and multivariate Cox regression analysis for predicting MACE in total cohort.

	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age	1.072 (1.044–1.102)	<0.001	1.052 (1.023–1.081)	<0.001
Male	0.699 (0.391–1.251)	0.228		
BMI	0.978 (0.896–1.066)	0.609		
Heart rate	1.009 (0.996–1.022)	0.196		
SBP	1.008 (0.999–1.016)	0.098		
DBP	0.998 (0.984–1.012)	0.771		
Troponin	1.004 (0.999–1.009)	0.149		
NT-proBNP	1.001 (0.999–1.001)	0.241		
TC	1.008 (0.785–1.294)	0.952		
TG	0.781 (0.519–1.177)	0.238		
HDL-C	0.946 (0.474–1.888)	0.874		
LDL-C	1.267 (0.907–1.77)	0.166		
WBC	0.983 (0.922–1.048)	0.605		
RBC	0.474 (0.299–0.751)	0.001	1.32 (0.549–3.171)	0.535
PLT	1.003 (1–1.006)	0.068		
HB	0.974 (0.96–0.988)	<0.001	0.984 (0.954–1.014)	0.299
HCT	0.982 (0.968–0.997)	0.019	0.99 (0.972–1.008)	0.260
D-dimer	1.72 (1.227–2.413)	0.002	1.444 (0.881–2.367)	0.145
Serum creatinine	1.005 (1.001–1.009)	0.013	0.997 (0.991–1.003)	0.270
Na ⁺	0.997 (0.984–1.01)	0.615		
K ⁺	0.978 (0.878–1.089)	0.682		
Uric acid	1.001 (0.999–1.003)	0.357		
Hcy	1.035 (1.011–1.059)	0.004	1.062 (1.029–1.097)	<0.001
LVEF ≥45%	0.187 (0.094–0.375)	<0.001	0.251 (0.116–0.543)	<0.001
Killip classification ≥2	1.166 (0.614–2.211)	0.639		
Smoking	0.829 (0.488–1.407)	0.487		
Alcohol	1.029 (0.518–2.042)	0.935		
Hypertension	1.297 (0.744–2.262)	0.359		
Diabetes	1.106 (0.611–2.003)	0.739		
Hyperlipidemia	1.228 (0.619–2.438)	0.556		
COPD	1.711 (0.836–3.504)	0.142		
D2W	1.002 (0.997–1.008)	0.402		
Culprit lesion				
RCA	1 (reference)			
LAD	0.932 (0.528–1.645)	0.808		
LCX	1.262 (0.539–2.955)	0.592		
Multivessel disease	1.047 (0.604–1.814)	0.870		
Preprocedural TIMI flow ≥2	0.736 (0.395–1.371)	0.334		
Number of stents ≥2	0.966 (0.567–1.647)	0.900		

Notes: Variables with a *p*-value < 0.05 in univariate analysis were included in the multivariate analysis.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal proB-type natriuretic peptide; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; HB, hemoglobin; HCT, hematocrit; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; D2W, door-to-wire time; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex artery; TIMI, thrombolysis in myocardial infarction; Hcy, homocysteine; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac events.

Table 4. Univariate and multivariate Cox regression analysis for predicting MACE in PSM or IPTW adjusted cohort.

	PSM adjusted				IPTW adjusted			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age	1.062 (1.029–1.097)	<0.001	1.045 (1.012–1.079)	0.008	1.065 (1.041–1.089)	<0.001	1.051 (1.019–1.084)	0.002
Male	0.727 (0.329–1.607)	0.431			0.432 (0.2–0.934)	0.033	1.383 (0.708–2.702)	0.343
BMI	0.954 (0.855–1.064)	0.395			0.952 (0.861–1.053)	0.341		
Heart rate	1.022 (1.001–1.043)	0.037	0.998 (0.97–1.027)	0.895	1.016 (0.998–1.033)	0.075		
SBP	1.010 (0.998–1.021)	0.090			1.008 (0.994–1.022)	0.271		
DBP	1.002 (0.984–1.021)	0.812			1 (0.982–1.018)	0.959		
Troponin	1.004 (0.998–1.009)	0.186			1.003 (1.001–1.007)	0.062		
NT-proBNP	1.001 (0.999–1.001)	0.649			1.001 (0.999–1.001)	0.844		
TC	1.166 (0.827–1.643)	0.381			1.27 (0.939–1.718)	0.121		
TG	0.653 (0.333–1.278)	0.214			0.777 (0.49–1.232)	0.284		
HDL-C	0.914 (0.395–2.117)	0.834			0.482 (0.177–1.313)	0.154		
LDL-C	1.663 (1.077–2.567)	0.022	1.866 (1.162–2.996)	0.010	1.729 (1.083–2.761)	0.022	2.765 (1.692–4.520)	<0.001
WBC	0.989 (0.897–1.09)	0.825			1.048 (0.99–1.11)	0.107		
RBC	0.557 (0.303–1.025)	0.060			0.586 (0.363–0.947)	0.029	1.192 (0.396–3.588)	0.754
PLT	1.003 (0.998–1.008)	0.250			1.002 (0.998–1.006)	0.263		
HB	0.982 (0.963–1.001)	0.061			0.98 (0.962–0.999)	0.035	0.968 (0.927–1.011)	0.145
HCT	0.982 (0.964–0.999)	0.048	0.988 (0.968–1.008)	0.235	0.985 (0.97–1)	0.054		
D-dimer	4.856 (2.655–8.881)	<0.001	5.306 (2.354–11.955)	<0.001	2.067 (1.36–3.142)	0.001	1.566 (0.991–2.473)	0.054
Serum creatinine	1.005 (0.998–1.011)	0.139			1.001 (0.995–1.007)	0.739		
Na ⁺	1.036 (0.935–1.148)	0.499			0.998 (0.995–1.001)	0.177		
K ⁺	1.361 (0.604–3.065)	0.457			0.983 (0.955–1.011)	0.228		
Uric acid	1.001 (0.998–1.004)	0.412			1 (0.997–1.003)	0.828		
Hcy	1.072 (1.027–1.118)	0.001	1.089 (1.036–1.145)	<0.001	1.047 (1.016–1.079)	0.003	1.052 (1.020–1.086)	0.001
LVEF $\geq$ 45%	0.137 (0.055–0.344)	<0.001	0.339 (0.075–1.529)	0.159	0.138 (0.07–0.274)	<0.001	0.259 (0.111–0.605)	0.002
Killip Classification $\geq$ 2	1.495 (0.677–3.304)	0.320			1.276 (0.503–3.234)	0.608		
Smoking	0.639 (0.325–1.258)	0.195			0.562 (0.275–1.149)	0.114		
Alcohol	1.709 (0.796–3.667)	0.169			1.433 (0.614–3.344)	0.406		
Hypertension	1.391 (0.678–2.855)	0.368			0.711 (0.339–1.49)	0.366		
Diabetes	1.290 (0.584–2.851)	0.529			0.84 (0.406–1.736)	0.638		
Hyperlipidemia	1.357 (0.562–3.279)	0.498			0.808 (0.349–1.875)	0.620		
COPD	1.988 (0.82–4.819)	0.128			1.297 (0.599–2.807)	0.509		
D2W, mins	1.004 (0.998–1.011)	0.165			1.004 (0.999–1.008)	0.135		

Table 4. Continued.

	PSM adjusted				IPTW adjusted			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Culprit lesion								
RCA	1 (reference)				1 (reference)			
LAD	1.177 (0.571–2.425)	0.659			1.084 (0.479–2.454)	0.846		
LCX	0.722 (0.203–2.562)	0.614			1.274 (0.387–4.193)	0.691		
Multivessel disease	1.280 (0.624–2.628)	0.500			1.676 (0.872–3.221)	0.121		
Preprocedural TIMI flow ≥ 2	0.612 (0.277–1.353)	0.225			0.971 (0.362–2.603)	0.954		
Number of stents ≥ 2	1.056 (0.539–2.069)	0.874			1.403 (0.68–2.892)	0.359		

Notes: Variables with a *p*-value < 0.05 in univariate analysis were included in the multivariate analysis.

Abbreviations: MACE, major adverse cardiac events; PSM, propensity score matching; IPTW, inverse probability of treatment weighting; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal proB-type natriuretic peptide; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; HB, hemoglobin; HCT, hematocrit; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; D2W, door-to-wire time; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex artery; TIMI, thrombolysis in myocardial infarction; Hcy, homocysteine; HR, hazard ratio; CI, confidence interval.

heart failure, and atrial fibrillation. Moreover, it is strongly correlated with a higher incidence of stroke and greater overall mortality [20].

Despite the strong associations mentioned above, early large-scale trials of Hcy lowering with vitamins therapy, such as the Vitamin Intervention for Stroke Prevention (VISP) [21] and the Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial [22], did not demonstrate a reduction in stroke incidence. However, in 2015, the China Stroke Primary Prevention Trial (CSPPT), which included over 20,000 participants and had a five-year follow-up period, demonstrated that folic acid supplementation significantly reduced the incidence of stroke [23]. The underlying causes of these contradictory findings remain uncertain and may be linked to variations in ethnicity, genetics factors, or dietary habits. Notably, the traditional Chinese diet typically involves lower meat consumption, higher vegetable intake, and lacks folic acid fortification [24]. A meta-analysis has demonstrated a weaker association between Hcy levels and coronary heart disease compared to stroke, potentially due to differences in the pathogenesis of cardiovascular and cerebrovascular diseases [25].

Another interesting point of view is that prospective studies exhibited significantly weaker associations between homocysteine levels and the risks of ischemic heart disease compared to retrospective studies [25]. Both retrospective and prospective cohort data were included in this meta-analysis, and the target populations, follow-up times, and Hcy cut-off values varied. This discrepancy may arise from biases inherent in retrospective studies, including difficulties in selecting appropriate controls and the impact of changes in treatment and other factors following disease onset. Several studies have concluded that high Hcy levels adversely affect the prognosis of patients with ACS, increasing the risk of MACE [26–31] and all-cause mortality [31–33], with a targeted meta-analysis [34] indicating that the risk can more than double. Conversely, other studies have concluded that homocysteine acts as a bystander rather than a causative factor and does not independently predict cardiovascular mortality in STEMI patients [35,36]. Therefore, the heterogeneity among studies complicates the interpretation of the true effect of Hcy. Differences in race, geographic region, socioeconomic status, and dietary habits may contribute to the observed discrepancies. However, recent advancements in primary PCI, new-generation drug-eluting stents, and novel P2Y₁₂ inhibitors are more likely to have diminished the prognostic significance of Hcy in cardiovascular outcomes. To date, it remains unknown whether Hcy level has a prognostic impact on STEMI patients undergoing primary PCI. In this study, Kaplan-Meier survival analysis demonstrated a higher incidence of MACE in the elevated Hcy group compared to the normal Hcy group, and these results remain robust after adjusting for confounders using PSM and IPTW. Subgroup analysis further confirmed the consistency of this associ-

ation across various patient subgroups. The calculated E-value supported the robustness of the observed association between elevated Hcy levels and increased MACE risk, indicating that the findings are unlikely to be explained by unmeasured confounding alone. Cox regression analysis identified several factors significantly associated with prognosis, including Hcy, age, and LDL-C, indicating that these factors should be considered critical in assessing patient risk profiles.

This study has several strengths and limitations. One of the main strengths is the use of propensity score adjustments to account for various potential confounding factors, such as medical history and laboratory results. By employing two propensity score-based adjustment methods, we achieved a balanced distribution of baseline covariates between the elevated and the normal Hcy group, allowing for a more comprehensive evaluation of the results. To our knowledge, this is the first study to establish an association between Hcy levels and the risk of MACE in STEMI patients undergoing primary PCI in Southern China, a region without folic acid fortification. However, several limitations should be considered. The retrospective observational design, single-center setting, and relatively small sample size may affect the generalizability of our findings. Additionally, the absence of Hcy level monitoring during the follow-up period may have influenced the results. Although PSM and IPTW were employed to minimize selection bias, potential limitations inherent to a non-randomized study design may still be present.

5. Conclusions

In conclusion, elevated Hcy levels were a significant predictor of MACE in STEMI patients undergoing primary PCI. While these findings are encouraging, the current data highlight the need for future well-designed randomized controlled trials to investigate the long-term benefits of regulating Hcy levels in patients with coronary artery disease. The prevailing view is that lowering Hcy levels with folic acid and vitamin therapies does not change the prognosis for coronary artery disease [37,38]. Several factors may contribute to this phenomenon. Firstly, since Hcy is linked to coronary restenosis [39] and slow blood flow [15], the potential benefits of Hcy-lowering therapies may have been obscured by the widespread use of antiplatelet agents and intensive lipid modulation, especially with the availability of newer-generation drug-eluting stents. Additionally, dietary variations across different regions lead to varying folate levels, which might influence the effectiveness of such therapies. Finally, the benefits of these therapies might only become apparent over longer treatment durations and extended follow-up periods. Folic acid and vitamin B are inexpensive and readily accessible, and their potential to lower Hcy levels and reduce cardiovascular risk warrants further exploration from a health economics standpoint. Given the low commercial incentives to test these

affordable and non-patentable drugs, it is incumbent upon health authorities to take special responsibility in promoting and supporting such trials.

Availability of Data and Materials

The datasets are available from the corresponding author on reasonable request.

Author Contributions

QX contributed to the conception and design of the study, played a key role in the analysis and interpretation of data, and was responsible for preparing the manuscript and tables. SC and JL were involved in data acquisition, contributed significantly to data analysis and interpretation, and provided critical revisions to the manuscript for important intellectual content. YW, LH, PX, ZN, and ZL were responsible for patient follow-up and actively participated in the analysis and interpretation of the data. They also critically reviewed the manuscript and provided feedback for intellectual improvements. LZ and JW designed the manuscript outline, critically revised the manuscript for important intellectual content, and supervised the study. All authors reviewed and approved all versions of the article prior to submission, and agreed to be accountable for all aspects of the work to ensure accuracy and integrity.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of The Affiliated Fengcheng Hospital of Yichun University (Protocol No. 202256). In accordance with the guidelines of the Institutional Review Board, informed consent was waived due to the retrospective nature of the study and the use of de-identified data.

Acknowledgment

Not applicable.

Funding

This study was supported by the Science and Technology Plan Project of Jiangxi Provincial Health Commission (No. 202312257).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/RCM25518>.

References

- [1] Bhatt DL, Lopes RD, Harrington RA. Diagnosis and Treatment of Acute Coronary Syndromes: A Review. *JAMA*. 2022; 327: 662–675.
- [2] Bergmark BA, Mathenge N, Merlini PA, Lawrence-Wright MB, Giugliano RP. Acute coronary syndromes. *Lancet* (London, England). 2022; 399: 1347–1358.
- [3] Yayan J. Emerging families of biomarkers for coronary artery disease: inflammatory mediators. *Vascular Health and Risk Management*. 2013; 9: 435–456.
- [4] Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. *Lancet* (London, England). 1999; 354: 407–413.
- [5] Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *The New England Journal of Medicine*. 1998; 338: 1042–1050.
- [6] Wu HY, Gao TJ, Cao YW, Diao JY, You PH, Yao XW. Analysis of the association and predictive value of hyperhomocysteinemia for obstructive coronary artery disease. *The Journal of International Medical Research*. 2021; 49: 3000605211033495.
- [7] Wu Y, Huang Y, Hu Y, Zhong J, He Z, Li W, *et al*. Hyperhomocysteinemia is an independent risk factor in young patients with coronary artery disease in southern China. *Herz*. 2013; 38: 779–784.
- [8] Ubbink JB, Delpont R. Reference ranges for homocysteine concentrations. *Homocysteine and Vascular Disease* (pp. 41–57). Springer: Netherlands. 2000.
- [9] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al*. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*. 2018; 138: e618–e651.
- [10] Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, *et al*. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *European Heart Journal*. 2008; 29: 2909–2945.
- [11] Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, *et al*. Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure. *Journal of Cardiac Failure*. 2021. (online ahead of print)
- [12] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al*. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal*. 2019; 40: 87–165.
- [13] Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ (Clinical Research Ed.)*. 2019; 367: 15657.
- [14] VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Annals of Internal Medicine*. 2017; 167: 268–274.
- [15] Tanriverdi H, Evrengul H, Enli Y, Kuru O, Selegi D, Tanriverdi S, *et al*. Effect of homocysteine-induced oxidative stress on endothelial function in coronary slow-flow. *Cardiology*. 2007; 107: 313–320.
- [16] Refsum H, Smith AD, Ueland PM, Nexø E, Clarke R, McPartlin J, *et al*. Facts and recommendations about total homocysteine determinations: an expert opinion. *Clinical Chemistry*. 2004; 50: 3–32.
- [17] Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA*. 1995; 274: 1049–1057.
- [18] Fu Y, Wang X, Kong W. Hyperhomocysteinemia and vascular injury: advances in mechanisms and drug targets. *British Journal of Pharmacology*. 2018; 175: 1173–1189.
- [19] Tyagi N, Sedoris KC, Steed M, Ovechkin AV, Moshal KS, Tyagi SC. Mechanisms of homocysteine-induced oxidative stress.

American Journal of Physiology. Heart and Circulatory Physiology. 2005; 289: H2649–H2656.

- [20] Karger AB, Steffen BT, Nomura SO, Guan W, Garg PK, Szklo M, *et al.* Association Between Homocysteine and Vascular Calcification Incidence, Prevalence, and Progression in the MESA Cohort. *Journal of the American Heart Association.* 2020; 9: e013934.
- [21] Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, *et al.* Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA.* 2004; 291: 565–575.
- [22] Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E, Heart Outcomes Prevention Evaluation 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. *Stroke.* 2009; 40: 1365–1372.
- [23] Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, *et al.* Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA.* 2015; 313: 1325–1335.
- [24] Hu FB, Liu Y, Willett WC. Preventing chronic diseases by promoting healthy diet and lifestyle: public policy implications for China. *Obesity Reviews: an Official Journal of the International Association for the Study of Obesity.* 2011; 12: 552–559.
- [25] Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA.* 2002; 288: 2015–2022.
- [26] García-Pinilla JM, Espinosa-Caliani S, Gómez-Doblas JJ, Jiménez-Navarro M, Gaitán MJ, Muñoz-Morán E, *et al.* Influence of high homocysteine and low folate plasmatic levels in medium-term prognosis after acute coronary syndromes. *International Journal of Cardiology.* 2007; 118: 220–226.
- [27] Matetzky S, Freimark D, Ben-Ami S, Goldenberg I, Leor J, Doolman R, *et al.* Association of elevated homocysteine levels with a higher risk of recurrent coronary events and mortality in patients with acute myocardial infarction. *Archives of Internal Medicine.* 2003; 163: 1933–1937.
- [28] Martín-Herrero F, Martín-Moreiras J, Pabón P, Sánchez PL, Morínigo-Muñoz JL, Jiménez-Candil J, *et al.* Homocysteine and outcome in young patients with acute coronary syndromes. *International Journal of Cardiology.* 2007; 118: 183–188.
- [29] van Oijen MGH, Claessen BEPM, Clappers N, van Schaik A, Laheij RJF, Jansen JBMJ, *et al.* Prognostic value of free plasma homocysteine levels in patients hospitalized with acute coronary syndrome. *The American Journal of Cardiology.* 2008; 102: 135–139.
- [30] Pineda J, Marín F, Marco P, Roldán V, Valencia J, Ruiz-Nodar JM, *et al.* The prognostic value of biomarkers after a premature myocardial infarction. *International Journal of Cardiology.* 2010; 143: 249–254.
- [31] Fu Z, Qian G, Xue H, Guo J, Chen L, Yang X, *et al.* Hyperhomocysteinemia is an independent predictor of long-term clinical outcomes in Chinese octogenarians with acute coronary syndrome. *Clinical Interventions in Aging.* 2015; 10: 1467–1474.
- [32] Omland T, Samuelsson A, Hartford M, Herlitz J, Karlsson T, Christensen B, *et al.* Serum homocysteine concentration as an indicator of survival in patients with acute coronary syndromes. *Archives of Internal Medicine.* 2000; 160: 1834–1840.
- [33] Fácila L, Nuñez JE, G VB, Sanchis J, Bodi V, Chorro FJ, *et al.* Early determination of homocysteine levels in acute coronary syndromes, is it an independent prognostic factor? *International Journal of Cardiology.* 2005; 100: 275–279.
- [34] Zhu M, Mao M, Lou X. Elevated homocysteine level and prognosis in patients with acute coronary syndrome: a meta-analysis. *Biomarkers: Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals.* 2019; 24: 309–316.
- [35] Chen CYJ, Yang TC, Chang C, Lu SC, Chang PY. Homocysteine is a bystander for ST-segment elevation myocardial infarction: a case-control study. *BMC Cardiovascular Disorders.* 2018; 18: 33.
- [36] Foussas SG, Zairis MN, Makrygiannis SS, Manousakis SJ, Patourakos NG, Adamopoulou EN, *et al.* The impact of circulating total homocysteine levels on long-term cardiovascular mortality in patients with acute coronary syndromes. *International Journal of Cardiology.* 2008; 124: 312–318.
- [37] Smith AD, Refsum H. Homocysteine - from disease biomarker to disease prevention. *Journal of Internal Medicine.* 2021; 290: 826–854.
- [38] Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, Manson JE, *et al.* Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. *Archives of Internal Medicine.* 2010; 170: 1622–1631.
- [39] Schnyder G, Roffi M, Flammar Y, Pin R, Hess OM. Association of plasma homocysteine with restenosis after percutaneous coronary angioplasty. *European Heart Journal.* 2002; 23: 726–733.