ORIGINAL ARTICLE

Correlation Between Elevated Homocysteine Level and ST-Elevation Myocardial Infarction in Young Patients: A Cross-Sectional Study at a Tertiary Cardiac Center in Rawalpindi

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ABSTRACT

Objective: To determine the correlation between plasma homocysteine levels and coronary artery disease severity among young patients with ST-elevation myocardial infarction (STEMI).

Study Design: Analytical, cross-sectional study.

Place and Duration of Study: The study was conducted at the Department of Cardiology, Armed Forces Institute of Cardiology & National Institute of Heart Diseases (AFIC-NIHD), Rawalpindi, Pakistan, from 20th January 2026 to 30th June 2026.

Methods: 71 patients aged 18-45 years who had ST-elevation myocardial infarction (STEMI) and were admitted for coronary angiography were enrolled consecutively. Blood was drawn via venipuncture and plasma homocysteine concentrations were determined within 24 hours of presentation. Homocysteine levels >15 µmol/L were considered to be elevated. Coronary artery disease severity was assessed using the Gensini score, and demographic, clinical, and cardiovascular risk-factor data were obtained using a structured data form. Data were analyzed using SPSS 23.0 software, and appropriate parametric and non-parametric tests were performed. A *P*-value of <0.05 was considered statistically significant.

Results: Among 71 patients, 20 had normal homocysteine levels, and 51 had elevated homocysteine levels. Overall, 61 (85.9%) patients were male, and 54 (76.0%) were aged >35 years. Significant differences between the groups were observed in gender, family history of coronary artery disease, severity of the stenosis, peak troponin levels, left ventricular ejection fraction, and the Gensini score (*P*=0.012). Homocysteine levels were strongly positively correlated with peak troponin (r=0.682, *P*<0.001) and weakly positively correlated with the Gensini score (r=0.350*, P*=0.003). Multivariable analysis showed gender (*P*<0.001) and peak troponin levels *(P*<0.001) as independent predictors of elevated homocysteine levels.

Conclusion: Increased homocysteine levels were correlated with more myocardial injury and severity of coronary artery disease in ST-elevation myocardial infarction, which indicates that it could be used as a cardiovascular risk marker.

Keywords: *Acute Coronary Syndrome, Coronary Angiography, Homocysteine, ST Elevation Myocardial Infarction.*

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Introduction

Acute Coronary Syndrome (ACS) represents a major global public health challenge and continues to be one of the leading contributors to worldwide morbidity and mortality.[1] The ACS spectrum includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction

(NSTEMI), and unstable angina (UA).[1] Traditionally regarded as a disease of older adults, recent evidence indicates a rising incidence of ACS, including STEMI, among younger individuals, particularly those aged 45 years and below.[2,3] This increasing trend highlights a shifting epidemiological pattern and shows the need for greater attention toward early-onset coronary events and their underlying risk factors.

Several risk factors that contribute to coronary artery disease(CAD) include age, sex, genetic predisposition, smoking, physical inactivity, obesity, hypertension, diabetes, dyslipidemia, and unhealthy diet.[4] Emerging risk factors include increased fibrinogen, high-sensitivity C-reactive Protein, chronic inflammation, vitamin D deficiency, and lipoprotein(a), which may also be responsible for the development of atherosclerosis and premature coronary events.[5-7] Out of these, elevated homocysteine has emerged as a potential contributor to atherosclerosis causing STEMI. Observational studies have shown a relationship between elevated homocysteine levels and cardiovascular events.[8,9] Homocysteine is a sulfur-containing amino acid that serves a central role in methionine metabolism and may be elevated due to genetic, nutritional, or metabolic abnormalities. Possible mechanisms include oxidative stress, endothelial dysfunction, reduced nitric oxide production, vascular smooth muscle growth, and increased platelet aggregation leading to vascular damage and atherosclerosis.[10]

High levels of homocysteine have been linked with the severity of coronary artery disease and with poor outcomes in several studies. Ullah H et al. observed a positive correlation with coronary stenosis (r = 0.40) and an increase in in-hospital mortality by 10.5% for every 1 µmol/L increase in homocysteine.[11] Sun J et al. reported a significant relationship between homocysteine and the Gensini score (r = 0.142, $P < 0.001$).[1] Al-Obaidi MK et al. found that every 5 µmol/L rise in homocysteine level was related to an increased mortality from coronary heart disease (relative risk = 1.52), cardiovascular death (relative risk = 1.32), and death from any cause (relative risk = 1.27).[12] These results indicate that homocysteine could be a potential biomarker of the severity of coronary disease and cardiovascular prognosis.

Although elevated homocysteine levels have been widely linked to CAD, most studies have focused on older populations, leaving limited data on younger patients with ACS. Premature ACS is an emerging concern, particularly as many young individuals present without traditional cardiovascular risk factors. This highlights that non-conventional biomarkers, such as homocysteine, may play a crucial role in its pathogenesis. Hence, there was a clear need to explore the relationship between elevated homocysteine levels and STEMI in young adults. Exploring this association could aid in early risk identification, prevention, and management of premature coronary artery disease. In this context, this study provides context-specific evidence on the relationship between serum homocysteine levels and CAD severity in young Pakistani patients with STEMI, rather than introducing homocysteine as a new biomarker. Therefore, the current study aimed to assess the correlation between serum homocysteine levels and CAD severity, as measured by the Gensini score, among young patients presented with STEMI.

Methods

This analytical cross-sectional study was performed at the Department of Cardiology, Armed Forces Institute of Cardiology & National Institute of Heat Diseases (AFIC-NHID), Rawalpindi, Pakistan, from 20th January 2026 to 30th June 2026, after taking approval by the Institutional Ethical Review Board of the institute, vide letter no: 9/2/R&D/2025/397, dated: 18th December 2025. Participants were selected using a non-probability consecutive sampling approach.

The required sample size was determined using the WHO sample size calculator with an expected correlation coefficient of 0.4 between plasma homocysteine and STEMI 11, 90% power, and a 5% margin of error. The minimum sample size was calculated to be 62. However, 71 patients were recruited to increase the study power.

Inclusion Criteria: Individuals aged 18–45 years, male or female, with STEMI who underwent coronary angiography were eligible for the study.

Exclusion Criteria: Patients with renal impairment defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², pernicious anemia,

hypothyroidism, inflammatory and systemic diseases (cancer, psoriasis, multiple arteritis, Kawasaki disease), and structural heart diseases (valvular heart disease, congenital heart disease, infective endocarditis, or rheumatic heart disease) were excluded. Patients receiving vitamin B12 or folate supplementation within the preceding 3 months were also excluded.

Informed written consent was obtained from all eligible participants. Study identification numbers were used to maintain confidentiality, and each enrolled participant was given a unique study identification number. Data were collected using a structured data form which included demographic variables, clinical history, and cardiovascular risk factors. Within 24 hours of presentation, blood samples were drawn via venipuncture for plasma homocysteine levels. Samples were collected in EDTA-containing tubes, immediately sent to the laboratory, and centrifuged to obtain plasma. The separated plasma samples were frozen at −80°C until analyzed. All participants underwent clinically indicated coronary angiography. Angiographic information, such as vessel involvement, severity of stenosis, and lesion location, was recorded in a standardized manner. Other investigations were also noted, such as echocardiogram findings and cardiac troponin levels.

The diagnosis of ST-elevation myocardial infarction (STEMI) was based on the 2025 American Heart Association/ American college of Cardiology (AHA/ACC) guidelines which includes new or presumed new ST-elevation of ≥1 mm in ≥2 anatomically contiguous leads (measured at the J-point) in all leads other than V2-V3 and ≥2 mm in men ≥40 y, ≥2.5 mm in men <40 y, and ≥1.5 mm in women regardless of age in leads V2-V3.[13,14] CAD severity was graded using Gensini score, which reflects the coronary angiographic findings based on the standard scoring system, irrespective of the age of the patient.[11] The severity score of each coronary lesion was calculated according to the lumen stenosis percentage, which was then multiplied by a location-specific weighting (weight), and the sum of the weighted scores for all coronary segments was obtained as the total Gensini score. Gensini score was used for analysis and classified as no CAD = Gensini score: 0; mild CAD = Gensini score: 1–20; moderate CAD = Gensini score: 21–60; severe CAD = Gensini score: >60. The Gensini score was determined using the Gensini score calculator found online (Gensini Score Calculator – Appcardio). On coronary angiography, a lesion-positive vessel was defined as any major coronary artery with > 50% luminal diameter stenosis. More than 50% left main stem artery stenosis was considered hemodynamically significant, which was suggestive of double-vessel disease. EDTA blood samples were collected after an overnight fast and centrifuged at 3000 rpm for 10 min within 30 min of collection. Plasma was aliquoted and stored at −80°C until assayed. Homocysteine concentration was measured by Enzyme-linked immunosorbent assay (ELISA). Plasma homocysteine levels above 15 μmol/L were deemed to be elevated based on previous reference values.[11]

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 23.0. Categorical variables were expressed as frequencies and percentages, and continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate, based on the distribution of the data. Shapiro-Wilk test evaluated the normality of the data. The independent-samples t-test or Mann–Whitney U test was applied to compare continuous variables based on the normality between normal and elevated homocysteine levels. Categorical variables were assessed using Chi-Square/Fischer's exact test. Correlation between plasma homocysteine levels and age and Gensini score was determined by Pearson, while Spearman's rank correlation was applied to evaluate the correlation between plasma homocysteine and troponin levels. Independent risk factors for elevated homocysteine levels were determined using binary logistic regression. A two-sided P value < 0.05 was considered statistically significant.

Results

Of the 71 enrolled patients, 20 (28.2%) had normal homocysteine levels, and 51 (71.8%) had elevated homocysteine levels. Significant differences were observed in gender (χ^2=10.066, df=1, P=0.002) and family history of CAD (χ^2=7.988, df=1, P=0.005) between the groups. The proportion of male patients was higher in the elevated homocysteine

group than in the normal group (94.1% vs. 65.0%). Similarly, CAD severity differed significantly between the groups (χ^2=31.967, df=2, *P*<0.001), being more prevalent in patients with elevated homocysteine levels (52.9% vs. 5.0%). No notable associations were found in the other variables (*P*>0.05) (Table 1).

Table 1: Characteristics according to homocysteine status (n=71)

Variable	Category	Normal ≤15 µmol/L (n=20) n (%)	Elevated >15 µmol/L (n=51) n(%)	*Chi-Square* test value	*P*-value
Gender	Male	13 (65.0%)	48 (94.1%)	10.066	0.002
	Female	7 (35.0%)	3 (5.9%)		
Age	<35 years	7 (35.0%)	10 (19.6%)	1.869	0.172
	≥35 years	13 (65.0%)	41 (80.4%)		
Diabetes mellitus	No	15 (75.0%)	34 (66.7%)	0.467	0.495
	Yes	5 (25.0%)	17 (33.3%)		
Hypertension	No	17 (85.0%)	46 (90.2%)	0.388	0.533
	Yes	3 (15.0%)	5 (9.8%)		
Family history of CAD	No	17 (85.0%)	51 (100.0%)	7.988	0.005
	Yes	3 (15.0%)	0 (0.0%)		
Atrial fibrillation	No	20 (100.0%)	47 (92.2%)	1.662	0.197
	Yes	0 (0.0%)	4 (7.8%)		
Number of diseased vessels	Single vessel	16 (80.0%)	29 (56.9%)	3.320	0.190
	Double vessel	3 (15.0%)	17 (33.3%)		
	Triple vessel	1 (5.0%)	5 (9.8%)		
Severity of CAD	1-20	10 (50.0%)	0 (0.0%)	31.967	<0.001
	21-60	9 (45.0%)	16 (31.4%)		
	>60	1 (5.0%)	27 (52.9%)		
Left main stenosis ≥50%	No	20 (100.0%)	8 (14.7%)	2.570	0.025
	Yes	0 (0.0%)	6 (11.8%)		
Major coronary artery stenosis ≥50%	No	2 (10.0%)	6 (11.8%)	0.045	0.832
	Yes	18 (90.0%)	45 (88.2%)		
LAD lesion	No	9 (45.0%)	12 (23.5%)	3.179	0.075
	Yes	11 (55.0%)	39 (76.5%)		
RCA lesion	No	15 (75.0%)	39 (76.5%)	0.017	0.896
	Yes	5 (25.0%)	12 (23.5%)		
LCx lesion	No	12 (60.0%)	34 (66.7%)	0.280	0.597
	Yes	8 (40.0%)	17 (33.3%)		
Left main coronary artery lesion	No	20 (100.0%)	47 (92.2%)	1.662	0.197
	Yes	0 (0.0%)	4 (7.8%)		

BMI=Body Mass Index; CAD = coronary artery disease; LAD = left anterior descending; RCA = right coronary artery; LCx = left circumflex

Peak troponin (median 1,178.50 vs. 27,000.00 ng/mL, t = 5.492, *P*<0.001), LVEF (50.25% vs. 41.02%, t = 3.689, *P*=0.001), and Gensini Score (24.13 vs. 38.08, t = 2.642, *P*=0.012) were found to be markedly different across the study groups. No noticeable difference was seen between the groups in terms of blood pressure, heart rate, fasting blood glucose, serum lipid profile, or serum creatinine (*P*>0.05) (Table 2).

As shown in Figure 1, serum Homocysteine level showed a significant correlation with Gensini Score (r=0.350, *P*=0.003) in STEMI patients.

A highly positive association was found between homocysteine and peak troponin levels (r=0.682, *P*<0.001) and a low positive correlation with Gensini Score (r=0.350, *P*=0.003). No significant association

Table 2: Clinical and biochemical parameters by homocysteine status (n=71)

Variable	Normal ≤15 µmol/L (n=20) Mean± SD	Elevated >15 µmol/L (n=51) Mean± SD	*t*-test value	*P*-value
Systolic blood pressure (mmHg)	131.95 ± 17.35	131.75 ± 20.32	0.042	0.968
Diastolic blood pressure (mmHg)	81.35 ± 6.68	83.31 ± 8.87	1.009	0.318
Heart rate (bpm)	82.00 ± 14.20	80.35 ± 11.95	0.460	0.650
Left ventricular ejection fraction (%)	50.25 ± 9.80	41.02 ± 8.62	3.689	0.001
Gensini Score	24.13 ± 19.21	38.08 ± 21.92	2.642	0.012
Fasting blood glucose (mg/dL)	91.90 ± 13.27	91.35 ± 15.24	0.150	0.888
Total cholesterol (mg/dL)	154.70 ± 29.12	160.20 ± 36.90	0.662	0.553
HDL cholesterol (mg/dL)	36.05 ± 4.21	34.28 ± 4.55	1.557	0.136
Triglycerides (mg/dL)	186.85 ± 42.95	171.00 ± 42.62	1.402	0.164
Serum creatinine (mg/dL)	1.90 ± 2.44	1.24 ± 0.34	1.205	0.246
Peak troponin (ng/mL)[Median(IQR)]	1,178 (97.50–5,926)	27,000 (24,769–30,000)	5.492	<0.001

HDL=High density lipoprotein

Table 3: Correlation of homocysteine level with age, peak troponin, and Gensini score (n = 71)

Parameter	Correlation coefficient (r)	*P*-value
Age (years)	0.073	0.544
Peak Troponin (ng/mL)	0.682	<0.001
Gensini Score	0.350	0.003

Table 4: Predictors of elevated homocysteine levels in ST-segment elevation myocardial infarction patients (n=71)

Variable	Unadjusted OR	95% CI	*P*-value	Adjusted OR (aOR)	95% CI	*P*-value
Gender	8.615	1.952–38.031	0.004	0.024	0.001–0.500	0.016
LVEF (%)	0.894	0.837–0.955	0.001	0.972	0.849–1.114	0.685
Peak troponin level (ng/mL)	1.000	1.000–1.000	<0.001	1.000	1.000–1.300	<0.001
Gensini score	1.040	1.005–1.075	0.023	1.003	0.959–1.050	0.891

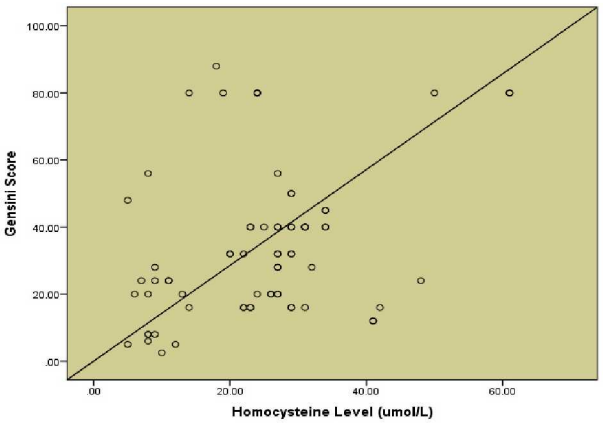

Fig.1: Relationship of serum homocysteine levels and Gensini scores (n=71)

was observed between homocysteine and age (r=0.073, *P*=0.544) (Table 3).

Male sex, low LVEF, high peak troponin, and high Gensini score were all associated with high homocysteine in unadjusted analysis. Multivariable analysis revealed that male sex (aOR 0.024, 95% CI 0.001–0.500; p=0.016) and peak troponin (aOR 1.000, 95% CI 1.00–1.300; *P*<0.001) were the only independent predictors, while LVEF and Gensini score were no longer significant (Table 4).

Discussion

The current study showed that high homocysteine levels correlate with increased myocardial injury and severity of CAD in young patients with STEMI. The

positive correlation between homocysteine and peak troponin levels indicates that homocysteine may be associated with myocardial injury to a greater extent during acute coronary syndrome. The biological plausibility for this finding is that homocysteine has been closely linked with endothelial dysfunction, oxidative stress, vascular wall inflammation, and prothrombotic processes, which may contribute to plaque destabilization and inadequate coronary perfusion.[9] Similarly, homocysteine was also positively associated with the Gensini Score, suggesting that the homocysteine level may also be linked with the anatomical extent of coronary atherosclerosis.[1] These findings indicate that elevated homocysteine levels could be considered a possible biomarker for increased coronary atherosclerotic burden in young STEMI patients.

Our analysis is in line with earlier literature by Ullah H et al., which has shown that high homocysteine levels are associated with CAD.[11,15] Our finding of high homocysteine levels in the STEMI patients has been confirmed by the study done by Nedelcu C et al., which showed a strong association between elevated homocysteine levels and first myocardial infarction in young patients.[16] Another study of 503 patients with ACS done by Shenoy V et al. also showed that higher homocysteine levels at admission directly correlated with advanced CAD as quantified by the SYNTAX score.[17] Similarly, a study by Karadeniz M et al. reported the same trend relevant to the association of elevated homocysteine with CAD severity.[18] A systematic review of 59 observational cohorts also confirmed significantly higher homocysteine among patients with CAD compared with controls, and a significant positive association between homocysteine and CAD severity (pooled association stronger in Asian populations).[19]

One of the most relevant results in our study was the significant positive linear relationship between homocysteine levels and the Gensini score (r=0.571, *P*<0.001). This result is similar to those of previous studies by Shenoy V et al showing that homocysteine is correlated with the severity of CAD as seen on angiography.[17] The association between homocysteine and peak troponin observed in our study is similar to the findings of Al-Obaidi MK et al., whose study reported an association between increasing homocysteine concentrations and greater ischemic myocardial injury among individuals diagnosed with acute coronary syndromes.[12] In their study, higher homocysteine concentrations were associated with greater myocardial injury, supporting a definitive link between homocysteine and the extent of myocardial injury.[12]

Furthermore, the association of elevated homocysteine with multivessel coronary artery disease and its significant association with the Gensini score in our study are consistent with the broader evidence linking higher homocysteine concentrations with CAD. A 2024 meta-analysis by Unadkat SV et al. demonstrated significantly higher homocysteine levels among patients with CAD compared with controls, further supporting an association between elevated homocysteine and coronary atherosclerotic disease.[19]

Homocysteine has also been shown to be closely related to the severity of CAD in previous studies. The study by Yeh JK et al. has found hyperhomocysteinemia (Homocysteine ≥12 μmol/L) to be a standalone marker of long-term cardiovascular outcomes after coronary stenting, indicating a potential role of homocysteine as a prognostic indicator in patients with CAD.[20] The higher Gensini score and more frequent presence of major stenosis and multivessel disease in patients with elevated homocysteine levels reinforce evidence that homocysteine is related to coronary atherosclerotic burden. These results are similar to previous literature showing that elevated homocysteine is associated with a greater coronary atherosclerotic burden.[21-23]

A strength of the present study was its inclusion of relatively young adults (aged 18-45 years) who reported STEMI and underwent coronary angiographic assessment, which enabled the examination of the relationship between homocysteine and coronary artery disease in younger age groups. Objective clinical, biochemical, echocardiographic, and angiographic parameters included in the study were peak troponin levels, LVEF, and the Gensini score, rather than clinical symptoms or self-reported information. Coronary angiography was used to assess coronary artery stenosis severity, and a standardized Gensini scoring system was used to provide an objective measure of

the angiographic burden of disease. Important conditions and factors (renal impairment, hypothyroidism, pernicious anemia, malignancy, or recent vitamin B12 or folate supplementation) that could affect homocysteine levels were excluded to reduce confounding.

Despite these strengths, this study has certain limitations. First, the limited sample size and single-institution setting may limit applicability to other populations or healthcare settings. Second, the cross-sectional observational design prevents inference about temporal or causal relationships between high homocysteine levels and myocardial injury or CAD severity. Third, homocysteine level was measured only once; it is thus not possible to evaluate changes of homocysteine concentrations over time. Lastly, the study enrolled young patients presenting with STEMI; thus, the results may not be applicable to patients with NSTEMI, UA, or those without ACS. larger multicenter prospective trials with various acute coronary syndrome presentations are warranted to confirm these associations and further assess the clinical impact of elevated homocysteine.

Conclusion

In conclusion, increased levels of homocysteine were correlated with myocardial injury and coronary artery disease in young patients with ST-elevation myocardial infarction. Its association with peak troponin and angiographic disease severity suggests it may serve as an additional marker of disease burden in this cohort. These results indicate that measuring homocysteine levels may be clinically useful for identifying young patients with higher coronary atherosclerosis burden.

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Ethical Approval and Consent: Institutional Review Board letter, reference no: 9/2/R&D/2025/397, and informed written consent were obtained from all the participants

Availability of Data: The data supporting the findings of this study are available from the corresponding author upon reasonable request

Conflict of Interest: The authors declare no conflict of interest

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Author Contributions

MN: Conception, design of the work, and approval for final submission, Data acquisition, curation, and statistical analysis

MNK: Manuscript writing for methodology design, investigation, and approval for final submission

QZBK: Writing the original draft, proofreading, and approval for final submission

SAA: Data acquisition, curation, statistical analysis, and approval for final submission

HM: Revising, editing, supervising for intellectual content, and approval for final submission

NA: Validation of data, interpretation, write-up of results, and approval for final submission

MN is the nominated guarantor and takes full responsibility for the overall content and integrity of the work

Note: All authors have accessed/verified the data reported in this manuscript, and all authors accept responsibility for this submission

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