

Correlation of Serum Homocysteine Levels With Various Types of Coronary Syndromes (CS) and In-Hospital Mortality – A Multicenter Study

Himayat Ullah¹, Sarwat Huma^{2,3}, Lubna Naeem⁴, Ghulam Yasin¹, Muhammad Ashraf¹, Nafisa Tahir⁵, Mohammed Yunus⁶, Hossam Shabana^{1,7}, Abdulrahman H Shalaby⁷, Ahmed Ali Hassan Ali⁷, Mohamed Elwan Mohamed Mahmoud⁷, Elsayed Mohamed Elsayed Tayee⁸, Ahmed Farag Abd Elkader Elbwab⁷, Ahmed Mohamed Ewis Alhawry⁷, Ahmed Ahmed Mohamed Abotaha⁷, Mahmoud Ezzat Abdelraouf⁷, Mohammed S Imam⁷, Hossam Aladi Aladi Aladi⁷, Taiseer Ahmed Shawky⁷, Ashraf Mohammed Said⁷, Mahmoud Saeed Mahmoud⁹, Kazem Mohamed Tayee⁷, Reda Fakhry Mohamed⁷, Ali Hosni Farahat⁷, Mohammad Mossaad Abd Allah Alsayyad⁹, Hesham El Sayed Lashin⁷, Hani Ismail Hamed⁷, Hazem Sayed Ahmed Sayed Ayoub⁷, Ayman Mohamed Salem Ahmed Nafie⁷

¹Department of Medicine, Shaqra College of Medicine, Shaqra University, Shaqra, Saudi Arabia; ²Department of Health Professions Education, Health Services Academy, Islamabad, Pakistan; ³Department of Cardiology, Hayatabad Medical Complex, Peshawar, Pakistan; ⁴Department of Oral Biology, Riphah International University, Islamabad, Pakistan; ⁵Department of Medicine, NSHS, National University of Science and Technology, Islamabad, Pakistan; ⁶Department of Pathology, Maiwand Teaching Hospital, Kabul University of Medical Sciences (KUMS), Kabul, Afghanistan; ⁷Internal Medicine Department, Al-Azhar University, Cairo, Egypt; ⁸Faculty of Medicine, Helwan University, Cairo, Egypt; ⁹Faculty of Medicine for Boys, Al-Azhar University, New Damietta, Egypt

Correspondence: Mohammed Yunus, Department of Pathology, Maiwand Teaching Hospital, Kabul University of Medical Sciences (KUMS), Kabul, Afghanistan, Email m_yunus6061@yahoo.com

Purpose: Coronary artery disease (CAD), clinically manifested as coronary syndrome (CS), is the leading cause of death and a significant contributor to morbidity worldwide. Elevated serum homocysteine levels have been associated with an increased risk of cardiovascular diseases, including CAD. Despite extensive research, the relationship between serum homocysteine and coronary syndromes with related short-term mortality is still under-studied. The main objective of this study is to evaluate the correlation between serum homocysteine levels and various types of CS, as well as in-hospital mortality in these patients.

Patients and Methods: This multicenter study included 381 CS patients from Afghanistan, Egypt, and Pakistan tertiary care hospitals. The relation of serum homocysteine levels with different types of CS as well as with in-hospital mortality was measured and analyzed using inferential statistics (ANOVA, Kruskal–Wallis test, Tukey’s post-hoc, Pearson correlation, etc.) and regression analysis (Binary regression).

Results: Among 381 patients from both genders, 160 were from Pakistan, 130 from Egypt, and 91 from Afghanistan. There was no significant difference in baseline characteristics, like age, gender, homocysteine level, CS type, and mortality, among the three countries ($p > 0.05$). The one-way ANOVA, the Kruskal Wallis Test, and Tukey’s post hoc test showed a significant difference among different CS groups based on serum homocysteine levels, and Pearson correlation showed a strong correlation between serum homocysteine and CS ($r = 0.4$). Binary regression analysis showed a 10.5% increase in in-hospital mortality for each 1 $\mu\text{mol/L}$ increase in homocysteine levels.

Conclusion: Serum homocysteine could serve as a valuable biomarker and mortality predictor in CS patients.

Keywords: serum homocysteine, coronary artery disease (CAD), coronary syndromes (CS), cardiac biomarkers, risk factors of CAD

Introduction

Coronary artery disease (CAD), also known as ischemic heart disease (IHD) or atherosclerotic heart disease, is one of the most prevalent global health issues leading to significant mortality and morbidity worldwide. It is the leading cause of non-traumatic death among all-cause deaths. The global burden of coronary artery disease is approximately 1.72% of the

total world population.¹ According to the World Health Organization's (WHO) latest figures, coronary artery disease accounts for 13% of all-cause mortality throughout the world with up to 18 million deaths every year.²

Coronary artery disease usually results from narrowing, partial, or complete blockage of the coronary arteries leading to myocardial ischemia, which can progress to infarction if left untreated.³ Clinically, it can be stratified as stable coronary artery disease termed as chronic coronary syndrome (CCS) including stable angina, and acute coronary syndrome (ACS) including unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) as follows,⁴

1. Stable Angina: exertional chest pain, or previous history of coronary artery disease, or positive exercise tolerance test, confirmed by coronary angiography with significant narrowing of more than 50%.
2. Unstable Angina: New-onset or worsening chest pain that occurs at rest or with minimal exertion, with no elevation in cardiac biomarkers but indicative of ischemia, confirmed by coronary angiography.
3. NSTEMI: Acute myocardial infarction characterized by chest pain with elevated cardiac biomarkers (troponin) but without ST-segment elevation on electrocardiogram (ECG).
4. STEMI: Acute myocardial infarction characterized by chest pain, elevated cardiac biomarkers, and persistent ST-segment elevation on ECG.

Several risk factors have been linked to the development of coronary artery disease, grossly divided into modifiable and non-modifiable risk factors. These include progressing age, male gender, genetics, and ethnicity as non-modifiable risks, while smoking, sedentary lifestyle, dietary habits, obesity, hypertension, diabetes mellitus, stress, dyslipidemia, etc., as modifiable ones.⁵ Modern research in the field of cardiology has identified certain non-conventional factors linked to the development of coronary artery disease. These include high serum fibrinogen, high c-reactive protein (CRP), chronic inflammatory conditions like inflammatory bowel disease, low vitamin D levels, high lipoprotein A levels, and many more.⁶⁻⁸

Homocysteine levels have been shown to be associated with an increased risk of atherosclerosis and thus coronary artery disease in several studies and meta-analyses.⁹ Homocysteine is a sulfur-containing amino acid, whose impaired metabolism due to genetic mutations, vitamin deficiencies, or any other reason, can lead to coronary artery disease. The exact mechanism of how high blood homocysteine levels lead to atherosclerosis and ischemic heart disease is unknown; however, several mechanisms have been proposed as possible answers to the question. Among these mechanisms, production of free radicals, smooth muscle hyper-proliferation, impairment in nitrous oxide production and thus vasodilation and platelet aggregation, are the leading mechanisms.^{10,11}

Several studies have been conducted on the potential role of homocysteine as a biomarker for coronary artery disease and stroke. One of the meta-analyses regarding the relation of homocysteine levels and ischemic heart disease involving more than 23 thousand subjects showed a significant relation between homocysteine levels and the occurrence of ischemic heart disease and related mortality.¹²

Although serum homocysteine level has been widely studied as a risk factor for coronary artery disease, its causal effect on coronary artery disease is still a point of debate. One of the trials on the effects of lowering homocysteine levels on coronary artery disease has demonstrated no significant effect of lowering serum homocysteine levels on decreasing the risk of coronary artery disease risk.¹³ This finding suggests that homocysteine levels may act as just a biomarker for coronary artery disease with no significant causal relation.

Though the published literature has well-documented evidence regarding the association of homocysteine levels with coronary artery disease risk, its relation with various types of coronary syndromes, ie; stable angina, unstable angina, NSTEMI, and STEMI has not been documented till now. Furthermore, the relation of homocysteine levels with in-hospital mortality due to coronary syndromes still needs further evidence, since none of the studies quantified the mortality risk with the rise in homocysteine levels.

The rationale behind this study is to fill these gaps in this important area of research, through a multicentric approach involving different demographic areas of the world. This will provide a more valid and comprehensive insight into the effects of homocysteine levels on the type of coronary syndrome and the short-term fatality, which may help in identifying high-risk groups.

The main objective of this study is to analyze the relation of serum homocysteine levels with different types of coronary syndromes including stable angina, unstable angina, NSTEMI, and STEMI. This study also aimed to evaluate and quantify the relationship between serum homocysteine and in-hospital mortality due to coronary syndromes.

Materials and Methods

Study Design

This multicentric study was conducted in tertiary care hospitals in three different countries, Pakistan (Hayatabad Medical Complex, Peshawar), Egypt (Al-Azhar University Hospital, Cairo), and Afghanistan (Maiwand Teaching Hospital, Kabul). The observational analytical study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The minimum sample size calculated by a standardized sample size calculator, using 13% all-cause mortality due to coronary artery disease as a variable for calculation, and keeping the confidence interval of 95% and margin of error as 5%, came out to be 173 patients. After obtaining ethical approval from the Institutional Research and Ethical Board (IREB), Hayatabad Medical Complex, Peshawar, and endorsed by Al-Azhar University Hospital, Cairo, and Maiwand Teaching Hospital, Kabul (reference number 599/HEC/B&PSE/2021 dated 15 February 2022), 381 coronary syndrome (CS) were recruited for this study between March 2022 and December 2023 (22 Months). Written informed consent was obtained from all patients before participation, and confidentiality of patient data was strictly maintained, with anonymization of the data. The sampling technique used was non-probability consecutive sampling.

The inclusion criteria were all types of coronary artery disease patients including stable angina, unstable angina, NSTEMI, and STEMI patients aged from 25 to 80 years, admitted to the respective hospitals. Patients with conditions that may affect the serum homocysteine levels, including grade 4 chronic kidney disease patients, chronic liver disease patients, pregnant and lactating females, patients on vitamin supplements and medications like anticonvulsants or immunomodulators, patients with active malignancy or chemotherapy, and patients with genetic homocysteine abnormalities were excluded from the study. Coronary syndromes were diagnosed and stratified by clinical features, ECG findings, cardiac enzymes (troponins and CK-MB) and angiographic findings of the coronary arteries as described in the introduction section. The in-hospital mortality was defined as the patient's stay in the hospital before discharge on home treatment or death, which ranged from 4 days to 9 days.

Data Collection

All the patients were subjected to detailed history and thorough physical examination, followed by investigations. The investigations include Serum homocysteine levels, fasting lipid profile (total cholesterol, LDL, HDL, triglycerides), blood glucose levels, hemoglobin A1c (in case of diabetes mellitus), and kidney function tests (serum creatinine, GFR).

Blood for measuring serum homocysteine levels (Normal value 5–15 $\mu\text{mol/L}$) was taken after overnight fasting and it was made sure that the same immune-electrochemical assay was used throughout all the centers to limit bias. Coronary artery disease was classified into different types ie; stable angina, unstable angina, NSTEMI, and STEMI based on clinical features and diagnostic investigations, as described in the introduction section above.

Statistical Analysis

The collected data were analyzed by MS Excel (Microsoft Corporation, Washington, USA) and Statistical Package for Social Sciences version 26 (IBM Corporation; Armonk, NY, USA). Continuous variables were expressed as means, median and standard deviation (SD), while categorical variables were presented as frequencies and percentages. Analysis of variance (ANOVA) was performed, followed by the Kruskal Wallis test as the data was not normally distributed, to show overall differences among different population groups. Tukey's post hoc test was used to assess the difference in the homocysteine values, by comparing each patient's group with the other based on three different countries. Pearson's correlation coefficient was used to examine the strength of the relationship between serum homocysteine levels and the type of coronary artery disease and Mann Whitney U rank test for homocysteine levels with in-hospital mortality. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of the correlation between homocysteine level and in-hospital mortality by using Binary regression analysis.

Results

Baseline Characteristics of the CS Patients

A total of 381 patients from both genders were included in this study, from different centers in three different countries. The biggest share was from Pakistan, followed by Egypt and Afghanistan, with 160, 130, and 91 CS patients respectively. The baseline characteristics, including age, gender, and serum homocysteine levels for all three countries are shown in [Table 1](#).

One-way ANOVA showed no significant difference between the three nations based on the above parameters ($p > 0.05$ for all).

These 381 CS patients were stratified according to the types of CS, with the biggest strata belonging to the patients with NSTEMI type followed by the STEMI type. These statistics are tabulated in [Table 2](#).

Serum Homocysteine Levels and Types of CS

[Table 3](#) shows the distribution of patients according to different CS types and serum homocysteine levels of each group. The STEMI group has the highest mean serum homocysteine level, followed by the NSTEMI group (p value 0.001).

The one-way ANOVA followed by the Kruskal Wallis Test showed a significant difference among different CS groups based on serum homocysteine levels ($F = 35.9$, $X^2 = 73.7$, p value 0.001). On further analysis, Tukey's post hoc showed a significant difference between angina vs NSTEMI groups, angina vs STEMI groups, Unstable angina vs NSTEMI group, unstable angina vs STEMI groups, and NSTEMI vs STEMI groups based on serum homocysteine levels ($p < 0.05$ for all). However, no significant difference was found between stable angina vs unstable angina groups in this regard ($p = 0.174$), as shown in [Figure 1](#).

The strength of the correlation between the homocysteine levels and the severity of CS was also calculated using the Pearson correlation coefficient, with stable angina on one extreme (mildest) and STEMI on the other extreme (most severe), with an r -value of 0.40 ($p = 0.001$).

Table 1 Baseline Characteristics of Study Participants (n=381)

Characteristic	Afghanistan	Egypt	Pakistan	Total	F. value	p. value
No. of Patients (%)	91 (24%)	130 (34%)	160 (42%)	381 (100%)		
Gender						
Male (%)	49 (53.8%)	82 (63.1%)	102 (63.7%)	233 (61.1%)	1.35	0.261
Female (%)	42 (46.2%)	48 (36.9%)	58 (36.3%)	148 (39.9%)		
Age (years), mean $\pm$ SD	56.8 $\pm$ 12.4	56.7 $\pm$ 14.0	57.8 $\pm$ 13.6	57.2 $\pm$ 13.5	0.263	0.769
Homocysteine (μ mol/L), mean $\pm$ SD	21.0 $\pm$ 7.7	21.5 $\pm$ 7.8	21.6 $\pm$ 7.3	21.4 $\pm$ 7.6	0.231	0.794

Table 2 Distribution of Patients According to Type of CAD

Nationality	Type of Coronary Artery Disease				
	Stable Angina n (%)	Unstable Angina n (%)	NSTEMI n (%)	STEMI n (%)	Total n (%)
Afghanistan	10 (10.9%)	6 (6.5%)	57 (62.6%)	18 (19.8%)	91 (100%)
Egypt	7 (5.4%)	10 (7.7%)	66 (50.7%)	47 (36.2%)	130 (100%)
Pakistan	16 (10%)	13 (8.1%)	75 (46.9%)	56 (35%)	160 (100%)
Total	33 (8.7%)	29 (7.6%)	198 (51.9%)	121 (31.8%)	381 (100%)

Table 3 Statistics of Serum Homocysteine Levels Across Various CAD Types

Type of CAD	Patients		Homocysteine Level ($\mu\text{mol/L}$)		Kruskal Wallis Test	
	No.	Percentage	Mean	S.D	Mean Rank	p value
Stable Angina	33	8.7	15.4	7.3	106.97	0.001
Unstable Angina	29	7.6	11.9	5.6	62.21	
NSTEMI	198	51.9	22.1	6.6	201.96	
STEMI	121	31.8	24.2	6.9	226.86	
Total	381	100	21.0	7.7		

Abbreviations: CAD, Coronary Artery Disease; NSTEMI, Non ST-segment Myocardial Infarction; STEMI, ST-segment Myocardial Infarction.

Serum Homocysteine and In-Hospital Mortality

Among 381 patients, 32 patients (8.4%) died during their stay in the hospital. Table 4 shows the statistics of these patients.

Mann–Whitney *U*-test showed significantly higher serum homocysteine levels in the non-survivors as compared to the survivors among CS patients ($p = 0.002$).

The Chi-Square test showed no significant difference among the outcomes of the CS patients of the three different countries ($p = 0.28$).

A binary logistic regression was performed to assess the impact of serum homocysteine levels on in-hospital mortality among CS patients. The model was statistically significant, ($\chi^2(1) = 15.49$, $p < 0.001$), indicating that serum homocysteine is a significant predictor of in-hospital mortality in these patients. The model explained 9.1% (Nagelkerke R^2) of

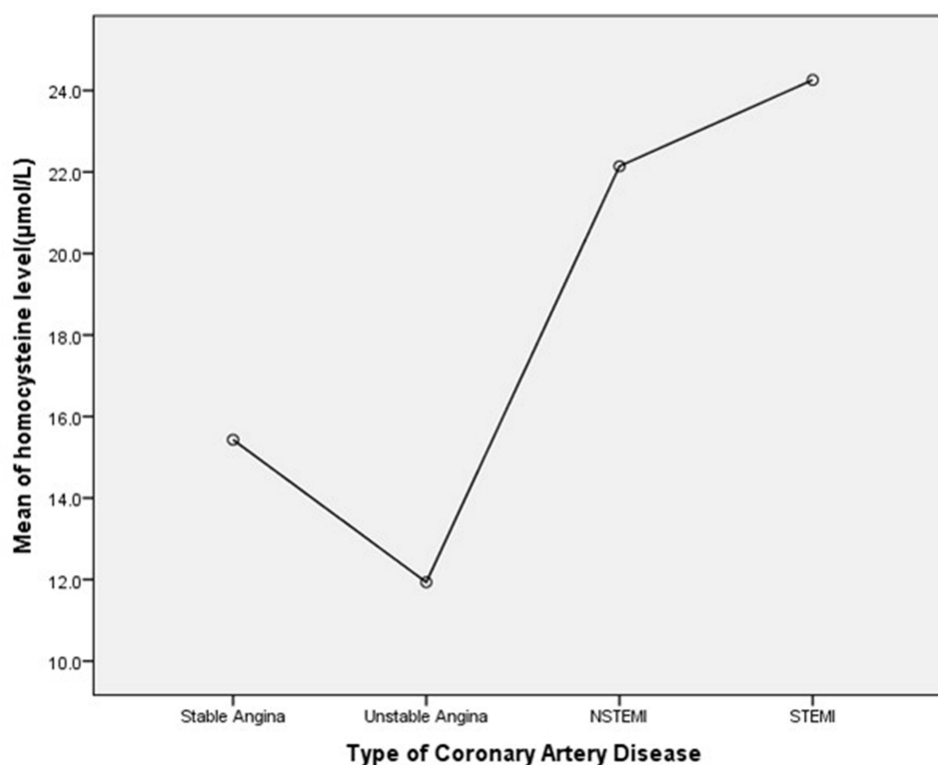


Figure 1 Mean serum homocysteine variations among different CAD types.

Table 4 Homocysteine Levels Between Survivors and Non-Survivors

Outcome	Patients		Homocysteine Level (μmol/L)		Mann–Whitney U-Test	
	Number	% of Total N	Mean	SD	Mean Rank	p. value
Survivors	349	91.6%	20.998	7.2980	185.75	0.002
Non-survivors	32	8.4%	26.453	8.9547	248.30	
Total	381	100.0%	21.456	7.5903	–	

the variance in in-hospital mortality and correctly classified 91.6% of cases. The odds of in-hospital mortality increase by 10.5% for each 1 μmol/L increase in homocysteine levels (Exp(B) = 1.105, 95% CI = 1.02–1.06, $p < 0.001$).

Discussion

In this multicenter study, we explored the relation of serum homocysteine levels with the type of coronary syndrome (CS) and in-hospital mortality in these patients. In our study, we found significantly higher levels of serum homocysteine in patients with more severe forms of CS ie; ST-segment myocardial infarction (STEMI), and non-ST segment myocardial infarction (NSTEMI), although there was no significant difference between the serum homocysteine levels of stable and unstable angina. Serum homocysteine has long been associated with atherosclerosis and vascular diseases including cardiovascular diseases.^{7,14} Kazemi et al and Unadkat et al in their study and meta-analysis of a large cohort of patients concluded a strong association between serum homocysteine and coronary syndrome.^{15,16} A similar conclusion was drawn by Schaffer and his et.al who stated that serum homocysteine level is associated with the severity of ischemia in coronary artery disease with higher serum homocysteine levels above 14.3 nmol/mL are associated with more severe stenosis of 77.6% compared to 71.8% in patients with serum homocysteine level below 14.3 nmol/mL.¹⁷ This finding is somewhat consistent with our findings showing higher mean serum homocysteine levels in patients with STEMI (24.2 μmol/L) and NSTEMI (22.1 μmol/L) as compared to that of patients with stable angina (15.4 μmol/L) and unstable angina (11.9 μmol/L). This finding might also be suggestive of the postulation that serum homocysteine level might be related to myocardial damage in coronary artery disease as both STEMI and NSTEMI are associated with myocardial damage with rising cardiac enzymes. N. Alam and et al deducted a similar conclusion from their study stating that patients with serum homocysteine levels of 15 μmol/L and above have 7 times more likelihood of raised cardiac troponins than those having serum homocysteine levels below 15 μmol/L.¹⁸ Similar findings have been reported by Niazi et al and Ye et al in their studies.^{19,20}

From this discussion, we can deduce the potential role of serum homocysteine level as a biomarker of myocardial damage and not just a risk factor for coronary artery disease. Moreover, the Kruskal–Wallis test demonstrated significant differences in homocysteine levels across CS types, with the STEMI and NSTEMI groups having higher levels compared to unstable angina and stable angina ($p < 0.001$). This aligns with studies that suggest hyperhomocysteinemia contributes to plaque instability, making it a critical factor in predicting the likelihood of more severe coronary events.²¹

In this study, we also found that rising serum homocysteine level is strongly associated with in-hospital mortality with non-survivors having significantly high mean homocysteine levels (26.45 μmol/L) as compared to survivors (20.99 μmol/L, $p = 0.002$). Several studies have discussed the fact that apart from the atherogenic effect of homocysteine, it is also involved in platelet activation and coagulation, thus enhancing thrombosis.²² This is of particular importance as this mechanism leads to STEMI which is the most severe form of CS and this might be the reason for adverse outcomes in these patients. Other mechanism behind this high mortality might be the higher endothelial dysfunction, systemic inflammation, arterial stiffness, oxidative damage, and microvascular ischemia, which is more prevalent in patients with higher homocysteine levels leading to more severe forms of coronary syndrome. In one of the meta-analyses regarding homocysteine levels and all-cause mortality, Peng and et al concluded that comparing the mortality among the lowest serum homocysteine group and the highest serum homocysteine group, the CS mortality is increased by 66%, cardiovascular mortality by 68%, and all-cause mortality by 93% in the highest serum homocysteine group.¹² However, they did not study the relationship of serum homocysteine levels with short-term (in-hospital) mortality.

One of the other notable points of our study is the odds of in-hospital mortality in CS patients, showing a 10.5% increase in mortality with each 1 $\mu\text{mol/L}$ rise in serum homocysteine level. In one of the meta-analyses of prospective studies, Fan et al have calculated the dose-response of serum homocysteine and all-cause mortality, showing a 33.6% increase in mortality for each 5 $\mu\text{mol/L}$ increase in serum homocysteine level.²³ This mortality is significantly lower than our calculations. The reason behind this high value might be the variation in the sampling as we selected a sample with already established CAD with the majority of the patients with acute coronary syndrome.

One of the aims of this study was to know the regional variations in the CS type and mortality among these patients. Interestingly there were no significant variations in CS type ($p = 0.09$) and in-hospital mortality ($p = 0.28$) among the patients of the three countries, Pakistan, Egypt, and Afghanistan. However, the sample collected during the stipulated time was significantly smaller in size from Afghanistan than the other two countries, showing the differences in healthcare of the three countries and the importance of socioeconomic status and accessibility to healthcare facilities.²⁴

Clinical Implication

Practically this study suggests that serum homocysteine levels should be routinely measured in patients with coronary syndrome generally and acute coronary syndrome specifically. In this way, clinicians can stratify the patients based on the level of risk and can guide monitoring, interventions, and follow-up. Since previous studies have variable evidence of the protective role of homocysteine-lowering therapies, this study can open the way for further research in generating evidence of homocysteine-lowering therapies in lowering the risk of severe cardiac events and mortality.^{25,26}

Strengths and Limitations

One of the key strengths of this study is its design involving a multicenter approach with patients from different regions. This makes the study findings generalized and applicable to a vast population of coronary syndrome patients throughout the globe. Another strength of this study is its robust methodology and statistical approach, establishing the strength of correlations and also quantifying the mortality risk with rising serum homocysteine levels.

The main limitation of the study is that although the strength of correlation is very strong, the other possible contributing factors are not studied in detail.

Conclusion

Serum homocysteine levels demonstrate a significant correlation with the severity of coronary syndrome as well as in-hospital mortality in these patients. Patients with higher homocysteine levels are more likely to present with severe forms of CS, such as STEMI and NSTEMI, and have a significantly higher risk of in-hospital death. Our findings suggest that homocysteine could serve as a valuable biomarker for risk stratification in CS patients and may help guide clinical management decisions. Further research is needed to explore the potential benefits of homocysteine-lowering therapies in high-risk populations and to assess the long-term prognostic value of homocysteine-lowering in CS patients.

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Disclosure

The authors report no conflicts of interest in this work.

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