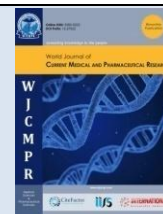




World Journal of Current Medical and Pharmaceutical Research

Content available at www.saap.org.in

ISSN: 2582-0222



SERUM HOMOCYSTEINE AND HIGH-SENSITIVITY C-REACTIVE PROTEIN AS PREDICTORS OF SEVERITY IN ACUTE CORONARY SYNDROME: A PROSPECTIVE OBSERVATIONAL STUDY

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ARTICLE HISTORY	ABSTRACT
Received on: 19-08-2026 Revised on: 22-09-2026 Accepted on: 13-10-2026	Background: Homocysteine and high-sensitivity C-reactive protein (hs-CRP) may reflect complementary pathways involved in coronary atherosclerosis. This study evaluated their relationship with angiographic severity in acute coronary syndrome (ACS). Methods: In this prospective observational study, 180 patients with ACS underwent serum homocysteine and hs-CRP measurement and coronary angiography. Disease burden was assessed using the Gensini score, with high severity defined as ≥ 40 . Results: Median homocysteine was 14.45 $\mu\text{mol/L}$ and hs-CRP 6.35 mg/L . Both biomarkers correlated with Gensini score (homocysteine $p=0.339$; hs-CRP $p=0.391$; both $p<0.001$) and were higher in patients with severe angiographic disease. After adjustment, hs-CRP remained independently associated with high Gensini severity (OR 2.52 per doubling; $p<0.001$), while homocysteine showed a borderline association (OR 1.38 per 5 $\mu\text{mol/L}$; $p=0.050$). Addition of both biomarkers increased AUC from 0.695 to 0.765. Conclusion: hs-CRP was a stronger predictor of angiographic severity, while homocysteine provided complementary prognostic information.
Keywords: Acute coronary syndrome; Homocysteine; hs-CRP; Gensini score; Coronary artery disease.	
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INTRODUCTION

Acute coronary syndrome (ACS) is the result of the interplay of atherosclerotic plaque burden, plaque instability, thrombosis and systemic inflammatory activity. Endothelial dysfunction, atherosclerotic lesion progression, plaque disruption and thrombotic complications are all associated with inflammation and are responsible for acute coronary events [1]. High-sensitivity C-reactive protein (hs-CRP) has been the focus of special interest because it is able to measure relatively small increases in systemic inflammatory activity and has been shown to be prognostic in patients with ACS. Patients with ACS demonstrated a progressive association between early CRP levels and cardiovascular events and mortality in a meta-analysis [2]. In addition to prognosis, hs-CRP could also be an indicator of the anatomical extent of coronary atherosclerosis. In patients with a recent acute coronary event, Monteiro et al. observed that hs-CRP was an independent predictor of the severity of coronary angiographic disease, even when other cardiovascular risk factors were taken into account [3]. This relationship is clinically important as it can either reflect underlying plaque biology or the inflammatory

response to myocardial injury in ACS. Thus, assessment of hs-CRP in combination with objective angiographic data might help to give further information about the severity of the disease.

Homocysteine is a different, but possibly complementary, pathway of vascular injury. High serum homocysteine levels have been linked to atherosclerotic vascular disease, perhaps by endothelial dysfunction, oxidative stress and prothrombotic effects [4]. Higher homocysteine levels have also been linked to increasingly higher risks of death in those with known coronary artery disease [5]. This relationship has also been confirmed by studies looking at anatomical coronary disease. Shenoy et al. showed a significant relationship between serum homocysteine and Gensini-defined coronary disease severity [6] and Karadeniz et al. found a positive correlation between homocysteine and angiographic complexity in 503 patients with ACS, with higher homocysteine levels in the higher SYNTAX-score categories [7].

Angiographic scoring systems offer a more quantitative evaluation of coronary disease than just the number of diseased vessels. The Gensini score takes into account the severity of coronary stenosis and the anatomical significance of the involved coronary segment, thus enabling

a continuous assessment of coronary atherosclerotic burden [8]. The relationship between hs-CRP and homocysteine to coronary disease has been established for each individually, but the association of each with the angiographic severity of ACS is less well defined. In the present study, therefore, serum levels of homocysteine and hs-CRP were evaluated in patients with ACS and their associations with Gensini score, extent of vessel disease, clinical severity indices, and in-hospital outcomes were examined. It also evaluated the ability of these biomarkers to predict high angiographic severity independently, and the ability of these biomarkers to enhance discrimination over traditional clinical risk factors.

METHODS

Study design and setting

This is a prospective observational study that was carried out over a period of 6 months in the second half of 2026 at JIMSH. Consecutive adult patients were screened for eligibility if they were admitted to the hospital with acute coronary syndrome (ACS) and underwent coronary angiography (CA) during the index hospitalization. The aim of the study was to assess the relationship between serum levels of homocysteine and high-sensitivity C-reactive protein (hs-CRP) and the clinical and angiographic severity of ACS.

Study population

Eligible patients were ≥ 18 years of age with a confirmed diagnosis of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina. Patients were eligible for inclusion if they underwent coronary angiography during the index admission and had all the required clinical, biochemical and angiographic data. Before coronary intervention, whenever possible, biomarker sampling was done.

Exclusion criteria included active infection or febrile illness, chronic inflammatory or autoimmune disease, active malignancy, recent major surgery or trauma, severe hepatic dysfunction, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², dialysis dependence, known active folate or vitamin B12 deficiency under treatment, pharmacological folate/vitamin B6/vitamin B12 therapy for hyperhomocysteinaemia, chronic corticosteroid or immunosuppressive therapy, and inadequate angiographic data.

One hundred eighty consecutive eligible patients were analyzed.

Clinical assessment

A standard study proforma was used to record baseline demographic parameters, cardiovascular risk factors, prior cardiovascular history, presenting symptoms and admission haemodynamic parameters. Known coronary artery disease, previous myocardial infarction, previous percutaneous coronary intervention, family history of premature coronary artery disease, smoking status, dyslipidaemia, type 2 diabetes mellitus, and hypertension were recorded risk factors.

Based on clinical presentation, electrocardiographic findings and cardiac biomarker profile, ACS was classified as STEMI, NSTEMI or unstable angina. The severity of the clinical presentation was also evaluated by Killip class and Global Registry of Acute Coronary Events (GRACE) score. Left ventricular ejection fraction (LVEF) and regional wall-

motion abnormalities were recorded at the time of the index hospitalization.

Laboratory assessment

Haemoglobin, total leukocyte count, platelet count, fasting glucose, glycated haemoglobin, serum creatinine, lipid profile and serum albumin were measured in the routine laboratory tests. eGFR was used as a measure of renal function.

The main biomarkers of interest were serum homocysteine and hs-CRP. Homocysteine was analysed as a continuous variable, and hyperhomocysteinaemia was defined as a serum concentration > 15 μ mol/L. hs-CRP was analysed as a continuous variable for the main analyses, as acute coronary syndromes may themselves be accompanied by significant increases in inflammatory markers.

Other data collected included admission and peak cardiac troponin levels.

Coronary angiography and evaluation of disease severity

Coronary angiography was performed during the index hospitalization in all participants. Luminal stenosis was recorded as a percentage in the left anterior descending, left circumflex, right coronary and left-main coronary arteries.

Significant coronary artery disease was defined as $\geq 70\%$ luminal stenosis in a major epicardial coronary artery or $\geq 50\%$ stenosis of the left-main coronary artery. Patients were categorized into no significant-vessel disease, single-vessel disease, double-vessel disease and triple-vessel disease depending on the number of major epicardial vessels significantly involved. Multivessel disease was considered to be when at least two major epicardial vessels were significantly involved. The preintervention Thrombolysis in Myocardial Infarction (TIMI) flow grade and culprit vessel were also noted.

Angiographic disease burden was expressed as the Gensini score, which is based on the severity of luminal narrowing and the anatomical importance of the involved coronary segment. The total Gensini score was used as a continuous variable representing the coronary atherosclerotic burden. Categorical analysis was performed using a Gensini score ≥ 40 as a cut-off for high angiographic severity.

In-hospital management and outcomes

Use of aspirin, P2Y12 inhibitors, statins, anticoagulation, thrombolysis, percutaneous coronary intervention, recommendation for coronary artery bypass grafting, and medical management were recorded.

Patients were followed throughout the index hospitalization for heart failure, cardiogenic shock, significant arrhythmia, ventricular tachycardia or ventricular fibrillation, acute kidney injury, recurrent ischaemia, reinfarction, and in-hospital mortality.

In-hospital major adverse cardiovascular events (MACE) were defined as the occurrence of at least one of the following: cardiovascular death, recurrent myocardial infarction, cardiogenic shock, malignant ventricular arrhythmia, or urgent repeat revascularization.

Study outcomes

The principal study outcomes were the relationships of serum homocysteine and hs-CRP with angiographic coronary artery disease severity, primarily assessed using the Gensini score.

Secondary analyses evaluated biomarker concentrations according to ACS subtype and extent of vessel disease,

correlations with GRACE score, LVEF and cardiac troponin, independent associations with high Gensini severity after adjustment for conventional cardiovascular risk factors, and the incremental discriminatory performance obtained by adding the biomarkers to a clinical risk model. Associations with in-hospital MACE and mortality were considered secondary exploratory outcomes.

Statistical analysis

Continuous variables were summarized as mean $\pm$ SD or median [IQR], as appropriate, and categorical variables as n (%). Biomarker levels across ACS and angiographic severity groups were compared using the Mann–Whitney U test or Kruskal–Wallis test, with Holm-adjusted post-hoc comparisons where required. Associations between homocysteine, hs-CRP, and continuous severity measures were assessed using Spearman correlation.

High angiographic severity was defined as a Gensini score ≥ 40 . Univariable and multivariable logistic regression were used to identify predictors of high Gensini severity, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). The multivariable model included homocysteine, hs-CRP, age, sex, diabetes, hypertension, smoking, dyslipidaemia, eGFR, and BMI. hs-CRP was log-transformed because of skewness. Continuous Gensini score was additionally analysed using multivariable regression after log transformation.

Receiver-operating-characteristic (ROC) analysis was used to compare the discriminatory performance of biomarker and clinical prediction models, with area under the curve (AUC) reported with 95% CIs. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee of JIMSH, and written informed consent was obtained from all participants before enrolment.

RESULTS

Study population

A total of 180 patients with acute coronary syndrome (ACS) were included. The mean age was 60.3 ± 10.1 years, and 132 (73.3%) were men. NSTEMI was the most frequent presentation, occurring in 77 (42.8%) patients, followed by STEMI in 71 (39.4%) and unstable angina in 32 (17.8%). Other baseline demographic and clinical characteristics are summarized in Table 01.

Table 01: Baseline demographic and clinical characteristics of the study population

Characteristic	Overall (N=180)
Age, years	60.3 ± 10.1
Male sex	132 (73.3%)
BMI, kg/m ²	25.5 ± 3.2
Hypertension	89 (49.4%)
Type 2 diabetes mellitus	79 (43.9%)
Dyslipidemia	87 (48.3%)
Smoking status	
Never	116 (64.4%)
Former	30 (16.7%)
Current	34 (18.9%)

left-main disease, whereas hs-CRP did not differ significantly according to left-main involvement.

eGFR, mL/min/1.73 m ²	78.4 ± 16.6
LVEF, %	50.1 ± 5.9
GRACE score	115.1 ± 15.4
ACS type	
STEMI	71 (39.4%)
NSTEMI	77 (42.8%)
Unstable angina	32 (17.8%)
Killip class	
I	124 (68.9%)
II	38 (21.1%)
III	15 (8.3%)
IV	3 (1.7%)

Data are presented as mean $\pm$ SD or n (%). BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.

Biomarker levels according to ACS subtype

The overall median serum homocysteine concentration was $14.45 \mu\text{mol/L}$ [IQR 11.18–18.90], and hyperhomocysteinemia ($>15 \mu\text{mol/L}$) was present in 85 (47.2%) patients. Median hs-CRP was 6.35 mg/L [IQR 4.33–8.81].

Homocysteine concentrations did not differ significantly among the three ACS subtypes (Kruskal–Wallis $H=1.39$, $p=0.499$). In contrast, hs-CRP differed significantly across ACS presentations ($H=21.00$, $p<0.001$), with lower concentrations among patients with unstable angina (Table 2).

Table 02: Homocysteine and hs-CRP levels according to ACS subtype

Biomarker	Overall (N=180)	STEMI (n=71)	NSTEMI (n=77)	Unstable angina (n=32)	Kruskal–Wallis H	p value
Homocysteine, $\mu\text{mol/L}$	14.45 [11.18–18.90]	14.70 [11.30–18.70]	13.50 [11.20–18.00]	16.65 [9.30–21.45]	1.39	0.499
hs-CRP, mg/L	6.35 [4.33–8.81]	7.45 [5.06–9.41]	6.57 [4.62–9.21]	4.15 [3.18–5.61]	21.00	<0.001

Data are median [IQR]. For hs-CRP, Holm-adjusted post-hoc comparisons showed higher levels in STEMI than unstable angina (Mann–Whitney $U=1754.5$, adjusted $p<0.001$) and in NSTEMI than unstable angina ($U=1790.5$, adjusted $p<0.001$); STEMI and NSTEMI did not differ significantly ($U=3080.5$, adjusted $p=0.184$).

Biomarkers and angiographic severity

The median Gensini score was 34.6 [IQR 14.4–55.4], and 75 (41.7%) patients had high angiographic severity, defined as a Gensini score ≥ 40 . Significant three-vessel disease was present in 30 (16.7%) patients and left-main disease in 11 (6.1%). Both homocysteine and hs-CRP showed significant differences across the number of diseased coronary vessels and were higher among patients with high Gensini severity (Table 03). Homocysteine was also higher in patients with

Table 03: Relationship of homocysteine and hs-CRP with angiographic coronary disease severity

Angiographic category	n (%)	Homocysteine, $\mu\text{mol/L}$	Test statistic; p value	hs-CRP, mg/L	Test statistic; p value
Number of significant vessels			H=20.12; p<0.001		H=27.14; p<0.001
0 vessels	69 (38.3%)	11.70 [9.00–16.20]		5.17 [3.52–7.24]	
1 vessel	45 (25.0%)	14.70 [11.50–18.70]		6.12 [4.38–8.08]	
2 vessels	36 (20.0%)	15.05 [12.68–18.95]		8.20 [6.44–10.12]	
3 vessels	30 (16.7%)	18.05 [13.80–23.43]		7.71 [5.35–10.23]	
High Gensini severity					
No	105 (58.3%)	12.60 [9.60–17.10]	U=2570.0; p<0.001	5.52 [3.88–7.80]	U=2537.0; p<0.001
Yes	75 (41.7%)	17.10 [12.80–20.65]		7.80 [5.33–9.60]	
Left-main disease					
No	169 (93.9%)	14.00 [11.00–18.70]	U=577.5; p=0.036	6.24 [4.33–8.77]	U=905.0; p=0.886
Yes	11 (6.1%)	18.10 [15.50–24.65]		7.47 [4.37–8.77]	

Data are median [IQR] or n (%). H, Kruskal–Wallis statistic; U, Mann–Whitney statistic. High Gensini severity was defined as Gensini score ≥ 40 .

Correlation with clinical and angiographic severity

Both biomarkers were positively correlated with Gensini score, with the association being somewhat stronger for hs-CRP (Spearman $\rho=0.391$, $p<0.001$) than for homocysteine ($\rho=0.339$, $p<0.001$) (Table 4). The relationship between hs-CRP and Gensini score is illustrated in Figure 1.

Higher hs-CRP was additionally associated with higher GRACE score, lower LVEF, and greater admission and peak troponin concentrations. Homocysteine showed an inverse association with LVEF but was not significantly related to GRACE score or troponin. Homocysteine and hs-CRP were only weakly correlated with each other ($\rho=0.079$, $p=0.293$).

Table 04: Correlation of homocysteine and hs-CRP with clinical and angiographic severity indices

Severity measure	Homocysteine, Spearman ρ	p value	hs-CRP, Spearman ρ	p value
Gensini score	0.339	<0.001	0.391	<0.001
GRACE score	0.082	0.272	0.264	<0.001
LVEF	–0.203	0.006	–0.219	0.003
Admission troponin	–0.048	0.519	0.213	0.004
Peak troponin	–0.051	0.492	0.189	0.011

All correlations are based on $n=180$ observations. LVEF, left ventricular ejection fraction.

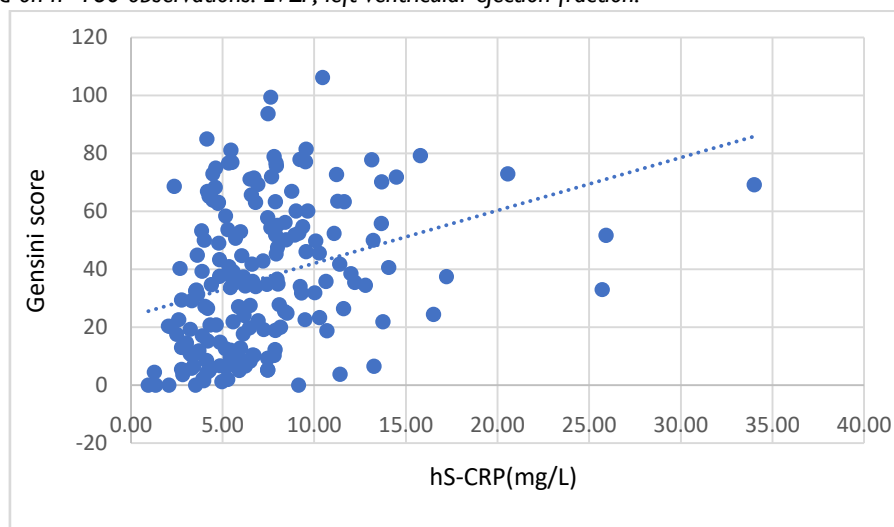


Figure 01: Association between hs-CRP and Gensini score

Scatter plot showing the relationship between hs-CRP and angiographic coronary disease burden. The fitted line is displayed for visual interpretation. Spearman $\rho=0.391$; $p<0.001$.

Univariable predictors of high angiographic severity

On univariable logistic regression, higher homocysteine, higher hs-CRP, older age, diabetes, and lower eGFR were associated with high Gensini severity (**Table 05**). The strongest biomarker association was observed for hs-CRP, with each doubling associated with an approximately 2.4-fold increase in the odds of high angiographic severity.

Table 05: Univariable predictors of high Gensini severity

Predictor	Crude OR (95% CI)	Wald z	p value
Homocysteine, per 5 $\mu\text{mol/L}$	1.62 (1.23–2.14)	3.41	<0.001
hs-CRP, per doubling	2.43 (1.55–3.82)	3.86	<0.001
Age, per 10 years	1.58 (1.15–2.16)	2.85	0.004
Male sex	1.12 (0.57–2.21)	0.34	0.733
Diabetes mellitus	1.93 (1.06–3.53)	2.15	0.032
Hypertension	1.19 (0.66–2.16)	0.58	0.562
Ever smoking	1.03 (0.56–1.92)	0.11	0.916
Dyslipidemia	1.07 (0.59–1.94)	0.23	0.821
eGFR, per 10 mL/min/1.73 m^2	0.70 (0.57–0.85)	-3.53	<0.001
BMI, per 5 kg/m^2	1.06 (0.67–1.68)	0.25	0.803

OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Independent predictors of angiographic severity

In the multivariable logistic regression model, hs-CRP remained independently associated with high Gensini severity. Each doubling of hs-CRP was associated with approximately 2.5-fold greater adjusted odds of high angiographic burden. Homocysteine showed a borderline independent association, whereas higher eGFR was independently associated with lower odds of high Gensini severity (Table 06).

When Gensini score was analysed as a continuous outcome after log transformation, both homocysteine and hs-CRP remained independently associated with greater angiographic disease burden.

Table 06: Multivariable associations with angiographic severity Panel A. Logistic regression for high Gensini severity

Predictor	Adjusted OR (95% CI)	Wald z	p value	VIF
Homocysteine, per 5 $\mu\text{mol/L}$	1.38 (1.00–1.89)	1.96	0.050	1.32
hs-CRP, per doubling	2.52 (1.55–4.09)	3.72	<0.001	1.04
Age, per 10 years	1.33 (0.91–1.94)	1.46	0.143	1.28
Male sex	1.12 (0.52–2.43)	0.29	0.768	1.07
Diabetes mellitus	1.57 (0.79–3.14)	1.28	0.200	1.09
Hypertension	0.84 (0.42–1.68)	-0.49	0.626	1.08
Ever smoking	0.84 (0.40–1.73)	-0.48	0.630	1.12
Dyslipidemia	0.95 (0.48–1.87)	-0.15	0.883	1.03
eGFR, per 10 mL/min/1.73 m^2	0.78 (0.62–0.99)	-2.08	0.037	1.24
BMI, per 5 kg/m^2	0.98 (0.56–1.72)	-0.06	0.950	1.11

Overall model: likelihood-ratio $\chi^2(10)=40.95$, $p<0.001$; McFadden pseudo- $R^2=0.167$.

Panel B. Adjusted analysis of continuous Gensini score

Biomarker	Adjusted β (95% CI)*	z statistic	p value
Homocysteine, per 5 $\mu\text{mol/L}$	0.129 (0.003–0.254)	2.01	0.044
hs-CRP, per doubling	0.528 (0.286–0.769)	4.29	<0.001

*Outcome modelled as $\log(1 + \text{Gensini score})$, with adjustment for age, sex, diabetes mellitus, hypertension, smoking, dyslipidemia, eGFR, and BMI. Model $R^2=0.288$.

Incremental predictive performance

The clinical risk-factor model yielded an AUC of 0.695. Addition of homocysteine alone produced only a modest increase in discrimination, whereas addition of hs-CRP produced a larger increase. The model incorporating both biomarkers together with conventional clinical risk factors achieved the highest AUC at 0.765 (95% CI 0.698–0.830) (Table 7;).

Adding both biomarkers significantly improved overall model fit compared with the clinical model alone (likelihood-ratio $\chi^2=19.83$, $\text{df}=2$, $p<0.001$).

Table 07: ROC performance for prediction of high Gensini severity

Prediction model	AUC (95% CI)	Exploratory Youden threshold	Sensitivity	Specificity	LR χ^2 vs clinical model	p value
Homocysteine alone	0.674 (0.593–0.749)	12.5 $\mu\text{mol/L}$	81.3%	49.5%	—	—

hs-CRP alone	0.678 (0.596–0.752)	6.5 mg/L	66.7%	63.8%	—	—
Homocysteine + hs-CRP	0.725 (0.649–0.797)	Probability 0.365	80.0%	56.2%	—	—
Clinical model	0.695 (0.617–0.771)	Probability 0.500	48.0%	82.9%	Reference	—
Clinical + homocysteine	0.709 (0.633–0.781)	Probability 0.392	74.7%	60.0%	3.58 (df=1)	0.059
Clinical + hs-CRP	0.750 (0.681–0.817)	Probability 0.397	73.3%	66.7%	15.94 (df=1)	<0.001
Clinical + both biomarkers	0.765 (0.698–0.830)	Probability 0.317	88.0%	53.3%	19.83 (df=2)	<0.001

Clinical model included age, sex, diabetes mellitus, hypertension, ever smoking, dyslipidemia, eGFR, and BMI. AUC confidence intervals were obtained by bootstrap resampling. Thresholds were selected using the Youden index and are exploratory.

In-hospital outcomes

In-hospital major adverse cardiovascular events occurred in 25 (13.9%) patients, and 7 (3.9%) patients died during hospitalization. hs-CRP was higher among patients who developed MACE than among those who did not (7.91 [5.51–10.69] vs 6.12 [4.26–8.26] mg/L; Mann–Whitney $U=1391.0$, $p=0.024$), whereas homocysteine did not differ significantly ($U=1773.5$, $p=0.499$). Neither homocysteine nor hs-CRP differed significantly according to in-hospital mortality ($U=461.0$, $p=0.287$ and $U=514.5$, $p=0.503$, respectively).

DISCUSSION

In the present study of 180 patients with acute coronary syndrome, both homocysteine and hs-CRP levels were correlated with the angiographic burden of coronary disease, with the latter showing the more consistent correlation. The patients with a Gensini score ≥ 40 had higher levels of both biomarkers, and there were significant correlations between the Gensini score and homocysteine ($p=0.339$) and hs-CRP ($p=0.391$). The odds of high angiographic severity were about 2.5-fold higher with each doubling of hs-CRP, while homocysteine showed a borderline association per 5 $\mu\text{mol/L}$ increase after multivariable adjustment. Both, however, were independently associated with continuous Gensini score.

The association between hs-CRP and angiographic disease burden is similar to that of several previous studies. Habib and Al Masri assessed 87 patients with angiographically proven CAD and 29 controls, and found that the concentration of hs-CRP was significantly higher in CAD patients, and positively associated with Gensini score ($r=0.423$); and the concentration of hs-CRP was higher in patients with triple-vessel disease than in those with less extensive involvement [9]. Dursunoğlu et al. also compared 100 patients with angiographic CAD with 45 controls, and found that the CRP levels were about three times higher in the CAD group (2.8 ± 1.5 mg/dL vs 0.9 ± 0.4 mg/dL), and that CRP was still correlated with the severity of lesions as measured by Gensini score [10]. This observation corroborates our observation that the burden of coronary atherosclerosis is associated with an increase in inflammatory activity.

In ACS, Ren et al. investigated 135 patients and found a strong positive correlation between the Gensini score and hs-CRP ($r=0.915$, $p<0.01$), and that hs-CRP was also associated with angiographic severity [11]. The present analysis included a wider range of traditional cardiovascular

risk factors and hs-CRP remained an independent predictor, although the magnitude of the correlation was less ($p=0.391$) in our cohort. The smaller correlation observed here may therefore be more representative of the diverse role of inflammation, chronic plaque burden, and acute myocardial injury in an unselected population of ACS.

Not all studies have demonstrated such a relationship. Bouzidi et al. analysed 310 patients undergoing coronary angiography and identified no significant relationship between hs-CRP and the severity of stenosis or the number of diseased vessels (71.7% had severe stenosis and 56.7% had multivessel disease, but these were not significantly different among the categories of hs-CRP). However, hs-CRP had good discrimination for myocardial injury in STEMI patients (AUC 0.905), but was not as good as cardiac troponin [12]. This difference is important for our results: hs-CRP was elevated in STEMI and NSTEMI compared to unstable angina and was associated with GRACE score, troponin levels and decreased LVEF. Therefore, levels of circulating hs-CRP in ACS can potentially be a marker of both the underlying atherosclerotic burden and the inflammatory response to acute myocardial injury.

Homocysteine was different. Concentrations were not significantly different among STEMI, NSTEMI, and unstable angina and were not associated with troponin or GRACE score, but were higher with greater vessel involvement, high Gensini severity, and left-main disease. This implies that there is a more intimate relationship with the chronic anatomical substrate than with the acute severity of myocardial injury. Recently, Jin et al. analyzed 617 patients with ACS and found that patients with a SYNTAX score >22 had elevated homocysteine levels. Hyperhomocysteinaemia was found to be associated with a 2.67-fold increase in the likelihood of severe lesions, and patients in the highest tertile of homocysteine had an OR of 3.51 compared to those in the lowest tertile [13]. They also found evidence of interaction between homocysteine and PCSK9 in their mediation analysis, which explained about 34% of the link between homocysteine and severe coronary lesions. The present results thus corroborate the role of homocysteine as a marker of the burden of coronary disease and suggest that its independent effect may be less than that of hs-CRP when conventional risk factors and renal function are taken into account.

The association of homocysteine with prognosis is stronger in studies with longer follow-up periods than in our in-hospital analysis. Fan et al. performed a prospective study

of 1,143 patients with STEMI over a median period of 36.7 months with 271 (23.7%) patients developing clinical endpoints. Homocysteine was an independent predictor of all-cause mortality and MACE, and the addition of homocysteine to the GRACE score raised the AUC for all-cause mortality from 0.786 to 0.884 and for MACE from 0.678 to 0.759 [14]. Likewise, Liu et al. studied 361 ACS patients over a median period of 43.3 months with 40 MACE events recorded. Elevated homocysteine was an independent predictor of MACE (HR 2.27; 95% CI 1.06–4.86) and the addition of homocysteine to GRACE improved the AUC from 0.78 to 0.83 [15].

A similar gradient was reported by Wei et al. in women with premature ACS. Overall incidence of MACE was 10.7% in the 1,102 eligible patients after about 28 months of follow-up, rising from 2.4% in the lowest homocysteine tertile to 7.7% in the middle and 22.1% in the highest tertile. Homocysteine discriminated subsequent MACE with an AUC of 0.789 [16]. Conversely, homocysteine was not linked to in-hospital MACE in our study. This difference may be partly due to the significantly shorter observation period and the relatively small number of events: 25 patients experienced in-hospital MACE and seven patients died. Homocysteine may thus be more useful as a marker of underlying vascular risk and longer-term prognosis than as a marker of immediate complications.

The complementary nature of the two biomarkers was an important finding of the present study. There was a weak correlation between homocysteine and hs-CRP ($p=0.079$), although both were related to angiographic severity. The addition of homocysteine alone to the conventional clinical model produced a modest improvement in AUC from 0.695 to 0.709, whereas the addition of hs-CRP to the conventional clinical model resulted in an improvement in AUC to 0.750. The model with both biomarkers had the highest AUC (0.765) and significantly enhanced the overall model fit. Such a pattern implies that inflammatory activity and vascular injury related to homocysteine levels may be partly independent biological pathways rather than redundant indices of the same pathway. The increased contribution of hs-CRP is also in line with its overall association with ACS phenotype, GRACE score, troponin, LVEF, and in-hospital MACE in our cohort.

This study compared both biomarkers with angiographic severity, as defined by Gensini score, and adjusted for major cardiovascular and renal confounders in a prospective study. The main limitations of the study were the single-centre design, modest sample size, measurement of biomarkers at a single time point, residual influences on both hs-CRP and homocysteine, and limited power for mortality analysis. The Gensini ≥ 40 threshold was also an operational categorization, and the borderline adjusted association for homocysteine highlights the information that may be lost when a continuous angiographic score is dichotomized.

CONCLUSION

Serum hs-CRP and homocysteine were associated with greater angiographic coronary disease burden in ACS. hs-CRP showed the stronger and more consistent independent relationship with severity, while homocysteine demonstrated a weaker but complementary association. Combining both biomarkers with conventional clinical

variables modestly improved prediction of high Gensini severity.

FUNDING

Nil

ACKNOWLEDGEMENT

Not Declared

AUTHOR CONTRIBUTION

All Authors are Contributed Equally.

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