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ORIGINAL ARTICLE

Association of High-Sensitivity C-Reactive Protein and Serum Malondialdehyde with Coronary Artery Disease Severity: A Cross-Sectional Study

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ABSTRACT

Background: Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide. Inflammatory and oxidative stress biomarkers have emerged as potential indicators of atherosclerotic burden. High-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, and malondialdehyde (MDA), a byproduct of lipid peroxidation, may provide valuable insights into the severity of CAD.

Aims and Objectives: The aims and objectives of present study was to evaluate the association of serum hs-CRP and MDA levels with the angiographic severity of CAD in patients undergoing coronary. angiography.

Methodology:
In this hospital-based cross-sectional study, 100 patients diagnosed with CAD at a tertiary cardiac center in Pakistan between May 2022 and May 2023 were enrolled. Serum levels of hs-CRP and MDA were measured using ELISA and spectrophotometric methods, respectively. Coronary angiography was performed, and disease severity was quantified using the Gensini scoring system. Patients were categorized into mild, moderate, and severe CAD groups. Correlations between biomarker levels and disease severity were analyzed using Spearman's rank correlation and multivariate regression analysis to adjust for confounders.

Results: Both hs-CRP and MDA levels were significantly elevated in patients with moderate and severe CAD compared to those with mild disease ($p < 0.001$). A strong positive correlation was observed between hs-CRP and Gensini score ($r = 0.64$, $p < 0.001$) as well as MDA and Gensini score ($r = 0.58$, $p < 0.001$). Multivariate analysis confirmed that elevated hs-CRP and MDA independently predicted higher CAD severity.

Conclusion: Elevated hs-CRP and MDA levels are significantly associated with increased severity of coronary artery disease, underscoring their potential role as non-invasive biomarkers for risk stratification in clinical settings.

Keywords: Coronary artery disease, hs-CRP, malondialdehyde, oxidative stress, inflammation, atherosclerosis, Gensini score.

INTRODUCTION

Coronary artery disease (CAD) continues to be the leading cause of cardiovascular morbidity and mortality globally, particularly in low- and middle-income countries such as Pakistan. It is primarily caused by the progressive narrowing and hardening of the coronary arteries due to atherosclerosis, which ultimately impairs myocardial perfusion. Despite substantial advancements in diagnostic and therapeutic interventions, early detection and stratification of disease severity remain a clinical challenge [1]. Traditional risk factors such as hypertension, diabetes mellitus, smoking, and dyslipidemia are well-established; however, they do not fully explain the variation in disease severity or progression among individuals. This has prompted a growing interest in the role of novel biochemical markers that reflect underlying pathophysiological processes, such as inflammation and oxidative stress [2].

Inflammation plays a crucial role in all stages of atherosclerosis, from endothelial dysfunction to plaque rupture. High-sensitivity C-reactive protein (hs-CRP), an acute-phase reactant synthesized by the liver in response to interleukin-6 and other cytokines, has emerged as a sensitive marker of systemic inflammation [3]. Elevated levels of hs-CRP have been consistently linked to the presence and severity of atherosclerotic lesions, and have also been shown to predict future cardiovascular events in both healthy individuals and those with established CAD. Owing to its sensitivity and predictive value, hs-CRP is increasingly being considered for risk assessment in cardiovascular clinical practice [4].

In parallel, oxidative stress is another major contributor to atherogenesis. It results from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense mechanisms. Malondialdehyde (MDA) is a key end-product of lipid peroxidation and serves as a reliable biomarker for oxidative stress [5]. Elevated serum MDA levels are indicative of increased free radical activity, which can damage endothelial cells, oxidize low-density lipoprotein (LDL), and promote foam cell formation processes that are central to the development and progression of atherosclerosis [6].

Although several studies have independently explored the roles of hs-CRP and MDA in CAD, there is a lack of integrated research examining their combined association with angiographically determined disease severity, particularly in South Asian populations where genetic predisposition, environmental factors, and lifestyle patterns significantly influence cardiovascular risk [7]. Furthermore, most existing literature focuses on either advanced diagnostic imaging or invasive procedures, which may not be feasible in resource-limited settings. Therefore, there is a pressing need to investigate cost-effective, easily measurable serum biomarkers that can aid in the early detection and risk stratification of CAD [8].

The study aims were to assess the association of hs-CRP and MDA with the angiographic severity of coronary artery disease in a cohort of Pakistani patients. By establishing a correlation between these biomarkers and disease severity scores, the findings of this study may contribute to the development of non-invasive, adjunct diagnostic tools that support clinical decision-making in cardiovascular care.

MATERIALS AND METHODS

Study Design: This hospital-based cross-sectional study was conducted in the Department of Cardiology at Lady Reading Hospital MTI, Peshawar Sandeman Provincial Hospital, Queeta Pakistan between january 2022 and january 2023. The study protocol was reviewed and approved by the Institutional Review

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Board, and written informed consent was obtained from all participants prior to enrollment.

Study Population: A total of 100 patients aged between 40 and 75 years, who were admitted with a clinical diagnosis of coronary artery disease and scheduled for elective coronary angiography, were recruited. CAD was defined based on the presence of ≥50% luminal narrowing in at least one major epicardial coronary artery.

Inclusion Criteria:

- Adult patients aged 40–75 years
- Diagnosed with CAD based on clinical findings and ECG/Echo/biomarker criteria
- Undergoing coronary angiography for diagnostic or pre-intervention purposes
- Willing to provide informed consent

Exclusion Criteria:

- History of acute or chronic inflammatory or autoimmune disorders
- Recent myocardial infarction (within 2 weeks)
- Chronic liver or kidney disease
- Malignancy or ongoing chemotherapy
- Patients on antioxidant or anti-inflammatory supplementation in the past 3 months

Data Collection: Detailed demographic and clinical information was collected through patient interviews and medical records, including age, sex, smoking status, blood pressure, body mass index (BMI), history of diabetes mellitus, hypertension, and lipid profiles.

Laboratory Analysis: Venous blood samples (5 mL) were drawn from fasting patients before coronary angiography. Samples were centrifuged, and serum was separated and stored at −80°C until analysis.

- High-sensitivity C-reactive protein (hs-CRP) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits with sensitivity up to 0.1 mg/L.
- Malondialdehyde (MDA) concentrations were determined by the thiobarbituric acid reactive substances (TBARS) method using spectrophotometry at 532 nm.

Angiographic Assessment: All patients underwent standard coronary angiography using the Judkins technique. Two experienced interventional cardiologists independently reviewed the angiograms without knowledge of the patients' biomarker levels. The severity of CAD was quantified using the Gensini scoring system, which assigns a weighted score to the degree and location of coronary stenosis. Based on the cumulative Gensini scores, patients were categorized into three groups:

- Mild CAD (Gensini score ≤20)
- Moderate CAD (Gensini score 21–40)
- Severe CAD (Gensini score >40)

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 25.0. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages.

- Comparisons between groups were made using one-way ANOVA or Kruskal–Wallis test for continuous variables and Chi-square test for categorical variables.
- Correlations between hs-CRP, MDA, and Gensini scores were evaluated using Spearman's rank correlation coefficient.
- Multivariate linear regression analysis was performed to adjust for potential confounding variables such as age, gender, BMI, diabetes, hypertension, and lipid levels.

Whereas p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 100 patients were enrolled in the study, with a mean age of 58.4 ± 9.7 years. Among them, 68% were male and 32% female. Diabetes mellitus was present in 52% of patients, hypertension in 60%, and 40% were current or former smokers. The mean BMI of the study population was 27.1 ± 3.4 kg/m². Based on coronary angiography and Gensini scoring, 24 patients had mild CAD, 36 had moderate CAD, and 40 had severe CAD. There was a progressive and statistically significant increase in serum hs-CRP and MDA levels with increasing CAD severity. The mean hs-CRP level in the mild group was 1.95 ± 0.61 mg/L, in the moderate group 3.64 ± 0.72 mg/L, and in the severe group 5.72 ± 1.15 mg/L ($p < 0.001$). The mean MDA level in the mild group was 2.91 ± 0.48 µmol/L, in the moderate group 4.19 ± 0.69 µmol/L, and in the severe group 5.53 ± 0.82 µmol/L ($p < 0.001$).

The baseline characteristics of the study participants stratified by the severity of coronary artery disease (CAD), as assessed by Gensini scores, revealed notable clinical and biochemical trends. The mean age of patients increased progressively across the groups, from 56.2 ± 8.7 years in the mild CAD group to 57.9 ± 9.4 years in the moderate group, and 60.5 ± 10.2 years in the severe group; however, this trend did not reach statistical significance ($p = 0.18$). Similarly, the proportion of male patients was higher in the severe CAD group (72.5%) compared to the moderate (66.7%) and mild (62.5%) groups, though the difference was not statistically significant ($p = 0.56$).

Regarding comorbidities, the prevalence of diabetes mellitus showed a statistically significant increase with disease severity. Diabetes was present in 37.5% of patients with mild CAD, 50.0% in those with moderate CAD, and 65.0% in the severe group ($p = 0.04$), indicating a strong association between glycemic dysregulation and advanced atherosclerosis. The prevalence of hypertension also rose from 50.0% in the mild group to 67.5% in the severe group, although the difference was not statistically significant ($p = 0.21$). Body mass index (BMI) values were relatively similar across groups, with mean values of 26.4 ± 3.1 kg/m², 27.3 ± 3.5 kg/m², and 27.6 ± 3.6 kg/m² in the mild, moderate, and severe groups, respectively, and no significant differences observed ($p = 0.32$) as shown in table 1.

Table 1: Baseline Characteristics of Study Participants by CAD Severity

Variable	Mild (n=24)	Moderate (n=36)	Severe (n=40)	p-value
Age (years)	56.2 ± 8.7	57.9 ± 9.4	60.5 ± 10.2	0.18
Male (%)	62.5	66.7	72.5	0.56
Diabetes (%)	37.5	50.0	65.0	0.04
Hypertension (%)	50.0	58.3	67.5	0.21
BMI (kg/m²)	26.4 ± 3.1	27.3 ± 3.5	27.6 ± 3.6	0.32
LDL-C (mg/dL)	116.5 ± 28.2	130.7 ± 31.5	139.2 ± 33.1	0.03
hs-CRP (mg/L)	1.95 ± 0.61	3.64 ± 0.72	5.72 ± 1.15	<0.001
MDA (µmol/L)	2.91 ± 0.48	4.19 ± 0.69	5.53 ± 0.82	<0.001

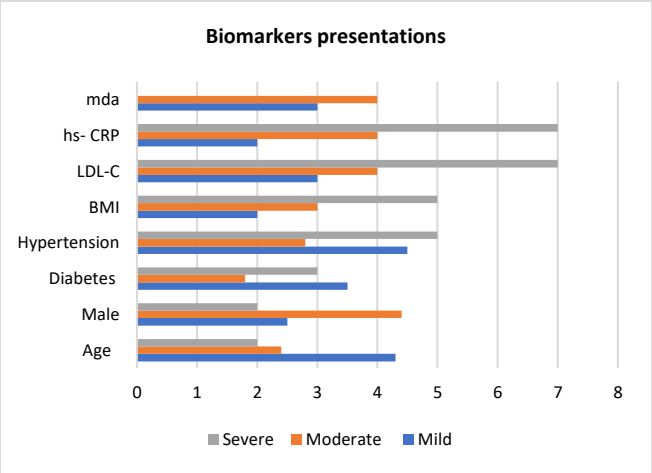

Fig-1: Baseline Characteristics of Study Participants by CAD Severity

In contrast, serum low-density lipoprotein cholesterol (LDL-C) levels increased significantly across the spectrum of CAD

severity. Patients with severe CAD had a mean LDL-C level of 139.2 ± 33.1 mg/dL, compared to 130.7 ± 31.5 mg/dL in the moderate group and 116.5 ± 28.2 mg/dL in the mild group ($p = 0.03$). This trend reinforces the role of dyslipidemia in the pathogenesis and progression of atherosclerosis. Biochemically, the study revealed highly significant increases in inflammatory and oxidative stress markers with advancing CAD severity. High-sensitivity C-reactive protein (hs-CRP) levels showed a marked and statistically significant elevation from 1.95 ± 0.61 mg/L in the mild group to 3.64 ± 0.72 mg/L in the moderate group, and 5.72 ± 1.15 mg/L in the severe group ($p < 0.001$) as shown in fig 1.

Similarly, serum malondialdehyde (MDA) levels, a marker of lipid peroxidation and oxidative stress, increased from 2.91 ± 0.48 µmol/L in the mild group to 4.19 ± 0.69 µmol/L in the moderate group and 5.53 ± 0.82 µmol/L in the severe group, also with a highly significant p-value of <0.001. These findings strongly support the hypothesis that systemic inflammation and oxidative stress are significantly associated with the severity of coronary artery disease and may serve as useful biomarkers for risk stratification.

DISCUSSION

This cross-sectional study was evaluated the association between serum high-sensitivity C-reactive protein (hs-CRP) and malondialdehyde (MDA) levels with the angiographic severity of coronary artery disease (CAD) in a Pakistani population [9]. The findings reveal a clear and statistically significant elevation in both inflammatory (hs-CRP) and oxidative stress (MDA) markers with increasing CAD severity, as assessed by the Gensini scoring system. These results underscore the pivotal role of systemic inflammation and oxidative stress in the pathogenesis and progression of atherosclerosis, aligning with global evidence and reinforcing their clinical relevance in cardiovascular risk stratification [10].

The progressive rise in hs-CRP levels across mild, moderate, and severe CAD groups highlights the pro-inflammatory milieu characteristic of advanced atherosclerotic disease. hs-CRP, as an acute-phase reactant, is not only a marker of inflammation but is increasingly being recognized as a mediator of endothelial dysfunction, plaque instability, and thrombosis. The strong positive correlation observed between hs-CRP levels and Gensini scores in our study suprts its potential utility as a surrogate marker for assessing CAD severity [11]. This is consistent with prior studies that have demonstrated elevated hs-CRP levels in patients with multi-vessel or complex coronary lesions and have linked elevated hs-CRP to adverse cardiovascular outcomes [12].

Similarly, the significant elevation in serum MDA levels with increasing CAD severity reflects enhanced lipid peroxidation and oxidative stress in patients with advanced disease [20]. MDA is a well-established end-product of polyunsaturated fatty acid peroxidation and serves as a reliable index of oxidative damage to cell membranes [13]. Its independent association with Gensini scores, even after adjustment for confounders such as LDL-C and diabetes, suggests that oxidative stress is not merely a bystander effect but a contributing factor in atherosclerosis. The role of oxidized LDL and free radicals in promoting endothelial dysfunction, smooth muscle proliferation, and foam cell formation is well documented, and our findings further support the mechanistic link between oxidative imbalance and CAD burden [14].

Notably, traditional risk factors such as diabetes and LDL-C were also more prevalent in patients with severe CAD, reaffirming their synergistic contribution to disease progression [19]. However, the independent predictive value of hs-CRP and MDA even after adjusting for these factors underscores their importance as non-traditional yet robust biomarkers [15]. These findings are particularly relevant for South Asian populations, which have a high burden of premature CAD and often present with more diffuse and aggressive disease phenotypes. The study was also added valuable local data from Pakistan, where limited resources and high cardiovascular disease burden demand cost-effective, accessible biomarkers for early detection and management [18]. hs-CRP and MDA assays are relatively inexpensive and feasible in most hospital laboratories, making them suitable adjuncts in routine clinical evaluation of CAD patients in resource-constrained settings [16].

However, this study is not without limitations. Being a single-center, cross-sectional design, it does not establish causality, and longitudinal data are needed to determine the prognostic implications of these biomarkers. Additionally, inflammatory and oxidative markers may be influenced by subclinical infections or other comorbidities not fully accounted for in this study [17]. Future multicenter, prospective studies with larger sample sizes and inclusion of other biomarkers (e.g., interleukins, oxidized LDL) could further refine risk stratification models.

CONCLUSION

In conclusion, this study demonstrates that elevated levels of hs-CRP and MDA are significantly associated with the severity of coronary artery disease. These biomarkers may serve as valuable, non-invasive tools in evaluating the inflammatory and oxidative burden in CAD patients and can aid in guiding clinical decision-making, especially in high-risk and resource-limited populations.

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Authors contribution: All authors contributed equally to the current study.

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