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ORIGINAL ARTICLE

Serum Inflammatory and Oxidative Biomarkers as Predictors of Severity and Clinical Outcomes in Ischemic Heart Disease. A Cross-Sectional Clinical Study

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ABSTRACT

Background: ischemic heart disease (IHD) remains a leading cause of morbidity and mortality worldwide. Inflammation and oxidative stress are central mechanisms in the development and progression of atherosclerosis. However, their role as clinical predictors of disease severity and outcomes remains underexplored, particularly in South Asian populations.

Objective: This study aimed to evaluate the association of serum inflammatory (high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6]) and oxidative stress biomarkers (malondialdehyde [MDA], superoxide dismutase) with angiographic severity and short-term clinical outcomes in patients with IHD.

Methods: A cross-sectional study was conducted at the Punjab Institute of Cardiology, Lahore, between March 2022 and June 2023, including 100 patients with confirmed IHD. Clinical data, echocardiographic findings, and coronary angiographic Gensini scores were recorded. Fasting serum samples were analyzed for hs-CRP, IL-6, MDA, and SOD. Patients were followed for three months for major adverse cardiovascular events (MACE).

Results: Higher hs-CRP, IL-6, and MDA levels, and lower SOD activity, were significantly associated with increasing disease severity ($p < 0.001$). Strong correlations were observed between the Gensini score and hs-CRP ($r = 0.69$), IL-6 ($r = 0.73$), MDA ($r = 0.66$), and inverse correlation with SOD ($r = –0.61$; all $p < 0.001$). Patients who experienced MACE (18%) had significantly higher inflammatory and oxidative biomarkers and lower SOD levels compared to those without events.

Conclusion: Serum inflammatory and oxidative biomarkers are robust predictors of angiographic severity and short-term outcomes in IHD. Incorporating these biomarkers into routine risk assessment may improve patient stratification and guide therapeutic strategies.

Keywords: ischemic heart disease, hs-CRP, interleukin-6, malondialdehyde, superoxide dismutase, biomarkers, coronary artery disease

INTRODUCTION

Ischemic heart disease (IHD), also known as coronary artery disease, is one of the leading causes of morbidity and mortality worldwide, accounting for nearly one-third of all deaths in individuals over the age of 35 [1]. Plaque development in the coronary arteries due to atherosclerosis leads to narrowing and blockage, and thus limits blood supply to the myocardium. Although major achievements have been made in diagnostic devices, medical treatments, and interventional procedures, the consistent determination of disease severity and the identification of patients who are at risk for an unfavorable course of clinical events remain major clinical challenges [2].

The mechanisms underlying IHD go beyond the lipid deposition in arterial walls and are believed to be of essentially inflammatory origin. From the initial stages of endothelial dysfunction to the final stages of plaque rupture and thrombosis, the development of atherosclerosis is essentially a consequence of inflammatory reactions [3]. When several inflammatory markers are considered, both high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) are considered especially important. Written by the liver in response to IL-6, hs-CRP acts as an acute-phase protein and is frequently studied for its ability to serve as a prognostic indicator for cardiovascular disorders. Patients with increased hs-CRP and IL-6 are at increased risk of myocardial infarction, stroke, and cardiovascular disease death [4].

Aside from inflammation, oxidative stress is known to be one of the key events in the onset and progression of atherosclerosis. Oxidative stress occurs when the body produces more production of reactive oxygen species (ROS) than the antioxidant defense system can manage [5]. The body's oxidative balance can be assessed using surrogate indicators such as malondialdehyde (MDA) from lipid peroxidation and superoxide dismutase (SOD), an antioxidant enzyme. If the oxidative stress increases, it results in endothelial dysfunction, promotes smooth muscle cell growth, and increases plaque instability, which affects the beginning of IHD [6].

Although hypertension, diabetes, hyperlipidemia, and smoking are widely recognized as risk factors for IHD, they are inadequate to fully explain differences in the level of disease severity and outcomes among individuals [7]. Therefore, there is continued research interest in finding new biomarkers that would help to refine our stratification and treatment of risk for IHD. There is increasing evidence that the inclusion of inflammatory and oxidative markers and clinical and imaging data can be used to optimize standards of severity assessment and the design of personalized treatment plans [8].

Despite extensive exploration of these biomarkers in Western populations, evidence from South Asian countries including Pakistan have been sparse. Considering the high prevalence of cardiovascular diseases in Pakistan and unique genetic and environmental risk factors, researching the use of these biomarkers for the prediction of severity and outcome of IHD is now more relevant than ever [9].

The purpose of this study was to assess how serum inflammatory and oxidative biomarkers, including hs-CRP, IL-6, MDA, and SOD, foretell disease severity and immediate clinical results in persons with IHD. The purpose of this study is to identify useful relations between these biomarkers and clinical events, so that the risk assessment and management procedures could be refined for the Pakistani population [10].

MATERIALS AND METHODS

This fifteen-month cross-sectional clinical study was carried out from March 2022 to June 2023 in the Punjab Institute of Cardiology, Lahore, Pakistan. Before enrolment, the study was

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approved by the institutional ethical review board, and all participants provided written informed consent according to the Declaration of Helsinki protocol.

The study recruited 100 adult subjects (aged 30-75) diagnosed with ischemic heart disease (IHD) by clinical diagnosis, electrocardiography, echocardiography, and coronary angiography. The study participants were sequentially recruited from the outpatient and inpatient cardiology departments. The eligible patients were those who had a documented diagnosis of IHD, characterized by stable angina, unstable angina, or previously experienced myocardial infarction, and who were willing to take part in a 3-month follow-up study. Patients with current or pre-existing acute or chronic inflammatory illnesses, autoimmune diseases, active infections, malignancies, chronic kidney disease, or significant hepatic illness; recent major surgical intervention; or long-term corticosteroids, immunosuppressants or antioxidants were excluded from the study because these conditions/therapies might interfere with the reading of serum biomarkers and distort the results.

Demographic and clinical data, including age, sex, body mass index, smoking history, hypertension, diabetes, dyslipidemia, and history of coronary artery disease in the family, were systematically obtained from patients. All patients underwent a clinical examination with blood pressure, heart rate, and functional classification based on the New York Heart Association (NYHA) criteria. Both electrocardiography and echocardiography were used to evaluate if there could be ischemia, determine the left ventricular ejection fraction, check the regional wall motion, and calculate diastolic function. All participants underwent evaluation by coronary angiography using the conventional femoral or radial approaches and the injection of contrast. Experienced cardiologists, ignorant of the biomarker outcomes, reviewed the angiographic data and identified the degree of coronary artery disease using the Gensini scoring system, which assigns scores based on luminal obstruction and the criticality of involved coronary segments.

Fasting venous blood samples (10 mL) were collected in the early morning hours after an overnight fast of 10 to 12 hours. Blood samples were centrifuged at 3000 rpm for ten minutes to separate the serum, which was then stored at –80°C until laboratory analysis. Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured using a high-sensitivity nephelometric assay, and interleukin-6 (IL-6) levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit. Malondialdehyde (MDA), which serves as a marker of lipid peroxidation and oxidative stress, was measured using the thiobarbituric acid reactive substances (TBARS) assay by spectrophotometry, while superoxide dismutase (SOD) activity, an indicator of antioxidant defense, was measured using a colorimetric method. All laboratory tests were performed in the institutional biochemistry laboratory by trained personnel who were blinded to the clinical and angiographic data.

Patients were followed for three months through scheduled outpatient visits and regular telephone follow-up. The primary outcome was to evaluate the correlation between serum biomarker levels (hs-CRP, IL-6, MDA, SOD) and angiographic disease severity as determined by the Gensini score. The secondary outcome was to assess the occurrence of major adverse cardiovascular events (MACE), which included nonfatal myocardial infarction, hospitalization for unstable angina, heart failure exacerbation, or cardiovascular death during the follow-up period.

The sample size was calculated as 100 patients, based on previous literature showing moderate-to-strong correlations between inflammatory and oxidative biomarkers and coronary artery disease severity, with an expected power of 80% and a significance level of 0.05, accounting for a possible 10% dropout or loss to follow-up. Statistical analyses were conducted using SPSS software version 26. Continuous variables were reported as mean ± standard deviation or median with interquartile range, while categorical variables were expressed as frequencies and percentages. Group comparisons were performed using the independent samples t-test or one-way ANOVA for continuous variables and the chi-square or Fisher's exact test for categorical variables. Correlations between biomarker levels and Gensini scores were assessed using Pearson's correlation coefficient. Multivariate logistic regression analysis was used to identify independent predictors of major adverse cardiovascular events, adjusting for conventional cardiovascular risk factors. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study enrolled 100 patients diagnosed with ischemic heart disease (IHD) at the Punjab Institute of Cardiology, Lahore, between March 2022 and June 2023. The mean age of the patients was 58.3 ± 9.6 years, with a predominance of male patients (64%) compared to female patients (36%). Hypertension was observed in 66% of the cohort, diabetes mellitus in 48%, and 32% were current smokers. The average body mass index (BMI) was 27.1 ± 3.4 kg/m², while the mean left ventricular ejection fraction (LVEF) was 49.2 ± 7.8%, indicating mildly impaired systolic function in a substantial portion of patients. The mean Gensini score across the cohort was 48.5 ± 18.7, reflecting a broad spectrum of coronary artery disease severity (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Value (n = 100)
Age (years)	58.3 ± 9.6
Male (%)	64%
Female (%)	36%
Hypertension (%)	66%
Diabetes mellitus (%)	48%
Smoking (%)	32%
BMI (kg/m²)	27.1 ± 3.4
LVEF (%)	49.2 ± 7.8
Mean Gensini score	48.5 ± 18.7

Analysis of the serum biomarkers revealed striking differences across the groups stratified by disease severity. Patients were divided into mild, moderate, and severe IHD groups based on the Gensini score. As shown in Table 2, hs-CRP, IL-6, and MDA levels increased progressively across the severity groups, while SOD levels showed a significant decline. Specifically, patients with mild IHD had mean hs-CRP levels of 2.5 ± 1.1 mg/L, which rose to 5.6 ± 1.8 mg/L in the moderate group and peaked at 10.2 ± 2.6 mg/L in the severe group. Similarly, IL-6 levels climbed from 5.1 ± 1.4 pg/mL in mild cases to 16.1 ± 3.8 pg/mL in severe cases. MDA levels, indicating lipid peroxidation, followed a parallel trend, increasing from 1.6 ± 0.5 nmol/mL in mild cases to 5.0 ± 0.9 nmol/mL in severe cases. In contrast, SOD activity, which reflects the body's antioxidant defense, showed a marked decline from 182 ± 26 U/mL in mild disease to 88 ± 18 U/mL in severe disease, suggesting significant depletion of antioxidant capacity in advanced disease. All these trends were statistically significant ($p < 0.001$).

Table 2: Serum Biomarker Levels by Disease Severity

Severity Group	hs-CRP (mg/L)	IL-6 (pg/mL)	MDA (nmol/mL)	SOD (U/mL)
Mild IHD (n=30)	2.5 ± 1.1	5.1 ± 1.4	1.6 ± 0.5	182 ± 26
Moderate IHD (n=35)	5.6 ± 1.8	9.6 ± 2.2	3.0 ± 0.6	136 ± 21
Severe IHD (n=35)	10.2 ± 2.6	16.1 ± 3.8	5.0 ± 0.9	88 ± 18
p-value	<0.001	<0.001	<0.001	<0.001

Correlation analysis, summarized in Table 3, showed strong positive relationships between the Gensini score and hs-CRP ($r = 0.69$, $p < 0.001$), IL-6 ($r = 0.73$, $p < 0.001$), and MDA ($r = 0.66$, $p < 0.001$), indicating that higher levels of inflammation and oxidative stress were closely linked to greater coronary artery involvement.

Interestingly, SOD showed a significant negative correlation with the Gensini score (r = –0.61, p <0.001), highlighting the depletion of antioxidant reserves as the disease burden worsened. These correlations provide robust evidence that these biomarkers reflect underlying disease severity.

Table 3: Correlation of Biomarkers with Gensini Score

Biomarker	Correlation coefficient (r)	p-value
hs-CRP	0.69	<0.001
IL-6	0.73	<0.001
MDA	0.66	<0.001
SOD	–0.61	<0.001

During the three-month follow-up period, 18 out of 100 patients (18%) developed major adverse cardiovascular events (MACE), which included 10 nonfatal myocardial infarctions, 5 cases of unstable angina requiring hospitalization, 2 heart failure admissions, and 1 cardiovascular death. As shown in Table 4, patients who experienced MACE had significantly higher baseline levels of hs-CRP (9.8 ± 2.4 mg/L), IL-6 (15.2 ± 3.4 pg/mL), and MDA (4.6 ± 0.7 nmol/mL), and notably lower SOD activity (93 ± 17 U/mL) compared to patients without MACE, whose mean levels were 5.4 ± 1.7 mg/L, 9.1 ± 2.0 pg/mL, 2.8 ± 0.6 nmol/mL, and 139 ± 22 U/mL respectively (all p-values <0.001). These biomarker differences were not only statistically significant but also clinically meaningful, underscoring their predictive value for adverse cardiovascular outcomes.

Table 4: Biomarker Levels in Patients With and Without MACE

Group	hs-CRP (mg/L)	IL-6 (pg/mL)	MDA (nmol/mL)	SOD (U/mL)
MACE (n=18)	9.8 ± 2.4	15.2 ± 3.4	4.6 ± 0.7	93 ± 17
No MACE (n=82)	5.4 ± 1.7	9.1 ± 2.0	2.8 ± 0.6	139 ± 22
p-value	<0.001	<0.001	<0.001	<0.001

Multivariate logistic regression analysis, adjusted for age, gender, hypertension, diabetes, and smoking, identified hs-CRP and IL-6 as independent predictors of MACE, with odds ratios of 2.6 (95% CI: 1.8–3.9) and 2.4 (95% CI: 1.6–3.6), respectively. This indicates that for every unit increase in hs-CRP or IL-6, the risk of adverse cardiovascular events nearly doubled, independent of other risk factors.

Altogether, these findings reflect the strong link between serum inflammatory and oxidative stress markers and the severity of coronary artery disease and their predictability of short-term clinical complications. The values in Tables 2, 3, and 4 confirm that those with elevated biomarker levels presented with more severe disease and inferior short-term clinical outcomes. This indicates that the assessment of these biomarkers may significantly improve risk stratification, as well as treatment advice, in IHD patients.

DISCUSSION

The study aimed at identifying the contribution of serum inflammatory and oxidative stress markers (hs-CRP, IL-6, MDA and SOD) in Pakistani IHD patients to assessing disease severity and predicting acute clinical outcomes [11]. Our study showed that increased inflammatory and oxidative biomarkers were associated with greater angiographic severity of coronary artery disease and greater risk of major adverse cardiovascular events within the subsequent three months [12].

The stepwise increase in hs-CRP and IL-6 across mild, moderate, and severe IHD groups observed in this study mirrors findings from prior landmark studies. Ridker et al. (1997) first demonstrated that elevated hs-CRP predicts future myocardial infarction and stroke among apparently healthy individuals, while the JUPITER trial extended this observation by showing that statin therapy reduced both hs-CRP levels and cardiovascular events in individuals with elevated hs-CRP but normal LDL cholesterol. Similarly, Libby et al. (2002) emphasized the critical role of IL-6 as an upstream mediator of CRP production, amplifying the vascular inflammatory cascade and promoting plaque vulnerability. Our results, consistent with these studies, suggest that heightened inflammatory burden reflects not only the presence of atherosclerotic disease but also the likelihood of future clinical instability [13, 14].

The oxidative stress biomarker malondialdehyde (MDA) also exhibited a significant upward trend with increasing disease severity. Elevated MDA levels are consistent with prior reports indicating increased lipid peroxidation and oxidative tissue injury in IHD patients (Madamanchi et al., 2005; Dhalla et al., 2000). Oxidative stress plays a dual role: it enhances low-density lipoprotein (LDL) oxidation, contributing to foam cell formation and plaque development, and impairs nitric oxide bioavailability, leading to endothelial dysfunction and impaired vasodilation. Our finding of significantly elevated MDA and depleted SOD activity in severe IHD patients supports this mechanistic framework, indicating that an imbalance between pro-oxidants and antioxidant defenses underpins the progression of coronary atherosclerosis [15].

Importantly, we found that patients who developed MACE during follow-up exhibited markedly higher baseline levels of hs-CRP, IL-6, and MDA, alongside significantly lower SOD levels, compared to those without events. These results align with the CANTOS trial (Ridker et al., 2017), which provided the first definitive evidence that selective targeting of inflammation with canakinumab (an IL-1β inhibitor) reduces cardiovascular event rates independent of lipid lowering, highlighting the centrality of inflammation in residual cardiovascular risk [16]. Furthermore, our findings support earlier observations by Kontush and Chapman (2006), who demonstrated that reduced antioxidant defense, including decreased SOD activity, predicts poor cardiovascular outcomes, suggesting that oxidative stress not only reflects disease severity but may actively drive plaque progression and rupture [17].

A key strength of our study is its combined evaluation of inflammatory and oxidative markers, providing an integrated picture of two critical pathological axes in IHD. While most previous studies focused on either inflammation or oxidative stress, our results suggest that simultaneous assessment of both pathways offers superior prognostic value [18]. Moreover, by focusing on a South Asian population, known to have a disproportionately high burden of premature IHD, our study adds important regional data to the global evidence base, which has largely been derived from Western populations [19].

Nevertheless, several limitations must be acknowledged. The cross-sectional design limits causal inference, and the relatively short three-month follow-up may underestimate the long-term prognostic value of these biomarkers [20]. The sample size, although adequate for primary analysis, may limit the detection of smaller effect sizes, and the single-center setting may affect generalizability. Furthermore, we did not evaluate newer biomarkers such as oxidized LDL, lipoprotein-associated phospholipase A2 (Lp-PLA2), or myeloperoxidase, which could provide additional mechanistic insights [21].

CONCLUSION

In conclusion, our study demonstrates that serum hs-CRP, IL-6, MDA, and SOD levels are significantly associated with angiographic severity and short-term clinical outcomes in patients with ischemic heart disease. These biomarkers serve as independent predictors of major adverse cardiovascular events, underscoring the intertwined roles of inflammation and oxidative stress in atherosclerosis. Incorporating these biomarkers into clinical risk assessment may improve the identification of high-risk patients who could benefit from intensive preventive strategies, including anti-inflammatory and antioxidant therapies. Future large-scale, multicenter, longitudinal studies are warranted to validate these findings and to evaluate the potential of biomarker-guided interventions to improve cardiovascular outcomes.

Conflict of Interest Statement: The authors declare no conflict of interest related to this study.
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