



DIAGNOSTIC AND CLINICAL SIGNIFICANCE OF HSCRP, H-FABP, MMP-9, AND PAPP-A IN PATIENTS WITH ACUTE CORONARY SYNDROME: A CASE–CONTROL STUDY

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ABSTRACT

Background:

Acute coronary syndrome (ACS) remains a leading cause of morbidity and mortality worldwide. Early diagnosis of myocardial injury and plaque instability is critical for improving patient outcomes. Novel biomarkers such as high-sensitivity C-reactive protein (HsCRP), heart-type fatty acid-binding protein (H-FABP), matrix metalloproteinase-9 (MMP-9), and pregnancy-associated plasma protein-A (PAPP-A) have been proposed as useful indicators of inflammation and plaque instability.

Methods:

A case–control study was conducted, including **110 patients with ACS** and **110 age-matched healthy controls**. Serum levels of HsCRP, H-FABP, MMP-9, and PAPP-A were measured along with conventional cardiac biomarkers, including CK-MB, Troponin-I, and IMA. Statistical comparisons between groups were performed using appropriate parametric and non-parametric tests.

Results:

All evaluated biomarkers were significantly elevated among ACS patients compared to controls ($p < 0.001$). Mean HsCRP levels were 4.8 ± 1.59 in ACS patients compared to 0.47 ± 0.25 in controls. H-FABP levels were 36.79 ± 4.26 in ACS patients versus 0.54 ± 0.26 in controls. Median MMP-9 levels were **4000 pg/mL** in ACS patients compared to **87 pg/mL** in controls. PAPP-A levels were significantly higher in ACS patients (65.37 ± 1.05 ng/mL) than in controls (10.86 ± 1.04 ng/mL).

Conclusion:

HsCRP, H-FABP, MMP-9, and PAPP-A demonstrate strong diagnostic significance in ACS patients and may enhance early detection when used alongside conventional cardiac biomarkers.

Keywords: Acute Coronary Syndrome, HsCRP, H-FABP, MMP-9, PAPP-A, Cardiac Biomarkers

INTRODUCTION

Acute coronary syndrome (ACS) comprises a spectrum of clinical conditions resulting from acute myocardial ischemia due to a sudden reduction in coronary blood flow, most commonly precipitated by rupture or erosion of vulnerable atherosclerotic plaques followed by thrombus formation [1]. ACS includes unstable angina, non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation

myocardial infarction (STEMI), and continues to represent a major public health concern worldwide. Despite substantial advances in pharmacological therapy, interventional cardiology, and preventive strategies, ACS remains one of the leading causes of morbidity and mortality globally [2].

Cardiac troponins are widely regarded as the gold standard biomarkers for the diagnosis of myocardial injury owing to their high sensitivity and specificity. However, a significant limitation of cardiac troponins is their delayed elevation following myocardial ischemia, which may restrict their diagnostic utility during the early hours after symptom onset [1]. Consequently, there has been increasing interest in identifying additional biomarkers that reflect various pathophysiological processes involved in ACS, including inflammation, myocardial necrosis, and plaque instability.

High-sensitivity C-reactive protein (HsCRP) is a well-established inflammatory biomarker that has been strongly associated with endothelial dysfunction, plaque instability, and increased risk of adverse cardiovascular events [3]. Elevated levels of HsCRP reflect systemic inflammatory activity, which plays a pivotal role in the initiation and progression of atherosclerosis. Heart-type fatty acid-binding protein (H-FABP), a low-molecular-weight cytoplasmic protein abundantly present in cardiomyocytes, is rapidly released into the circulation following myocardial injury and has been recognized as a sensitive early marker of myocardial ischemia [4].

Matrix metalloproteinase-9 (MMP-9), a member of the zinc-dependent endopeptidase family, plays a critical role in extracellular matrix remodeling and degradation. Increased expression of MMP-9 has been implicated in weakening of the fibrous cap and subsequent plaque rupture, thereby contributing to the pathogenesis of acute coronary events [5]. Similarly, pregnancy-associated plasma protein-A (PAPP-A), a metalloproteinase produced by activated macrophages within atherosclerotic plaques, has been identified as a biomarker associated with plaque instability and increased risk of acute coronary syndromes [6].

In view of the multifactorial pathophysiology of ACS, the identification of biomarkers that reflect different mechanisms of disease progression is of considerable clinical importance. Therefore, the present study was undertaken to evaluate the diagnostic significance of selected biomarkers—HsCRP, H-FABP, MMP-9, and PAPP-A—in patients with acute coronary syndrome and to assess their potential role in improving early detection and clinical assessment of myocardial injury.

MATERIALS AND METHODS

Study Design and Population: A hospital-based case–control study was conducted, including 220 participants, comprising 110 patients with acute coronary syndrome (ACS) and 110 healthy controls. ACS cases were diagnosed based on clinical presentation supported by electrocardiographic (ECG) findings and established biochemical cardiac markers.

Biomarker Estimation: Serum levels of high-sensitivity C-reactive protein (hsCRP), heart-type fatty acid-binding protein (H-FABP), matrix metalloproteinase-9 (MMP-9), pregnancy-associated plasma protein-A (PAPP-A), creatine kinase-MB (CK-MB), Troponin-I, and ischemia-modified albumin (IMA) were measured using standard laboratory methods.

Statistical Analysis: Data were expressed as mean $\pm$ standard deviation (SD). Comparisons between cases and controls were performed using the Mann–Whitney U test. A p-value < 0.05 was considered statistically significant.

RESULTS

In this present study, most participants in both groups were aged **>50 years** (34.5% cases; 35.5% controls), followed by **45–50 years** (18.2% vs. 20.0%) and **40–45 years** (15.5% vs. 18.2%). The mean age was **43.41 $\pm$ 8.61 years** in cases and **43.89 $\pm$ 8.32 years** in controls. No statistically significant difference was observed between groups ($\chi^2 = 1.00$, $p = 0.67$), indicating comparable age distribution. (Table 1)

In our study, we examined the distribution of physical activity patterns among the ACS and control groups. A higher proportion of sedentary individuals was observed in the ACS group (30.0%) compared to controls (10.0%), whereas moderate physical activities were more common among controls. The difference in physical activity patterns between groups was statistically significant ($\chi^2 = 13.02$, $df = 4$, $p = 0.011$), suggesting a significant association between sedentary lifestyle and ACS occurrence. (Table 2)

Table 2: Physical activity of study subjects			
Physical activity	ACS group (n=110)	Control group (n=110)	p-value=0.011 chi-square (χ^2) =13.02
Yoga	23(20.9%)	27	
walking	18(16.4%)	30	
Running	20(18.2%)	25	
Lightweight Exercise	16(14.5%)	22	
Sedentary	33(30%)	11	

The distribution of cardiac and inflammatory biomarker levels among ACS and control groups. Significantly higher levels of **hsCRP**, **H-FABP**, **PAPP-A**, **MMP-9**, **IMA**, **CK-MB**, and **Troponin I** were observed in the ACS group compared to controls. Median **MMP-9** levels were markedly elevated in ACS patients [4000 (IQR: 800–6000) p./mL] compared to controls [87 (IQR: 10–110) p./mL]. All biomarkers showed statistically significant differences between groups ($p < 0.001$), indicating strong associations with ACS. (Table 3)

Table 1: Distribution of Participants According to Age Groups Among Cases and Controls			
Table 1: Distribution of Participants According to Age Groups Among Cases and Controls			
Age groups	Case (n=110)	Control (n=110)	p-value=0.67 chi-square (χ^2) =1.00
25-30	7	5	
30-35	13	11	
35-40	15	13	
40-45	17	20	
45-50	20	22	
>50	38	39	
Mean±SD	43.41 ± 8.61	43.89 ± 8.32	

Table 3: Distribution of Cardiac and Inflammatory Biomarker Levels Among Study Groups			
Lab parameters	ACS groups (n=110)	Control groups (n=110)	P-value
hsCRP			<0.001
H-FABP	36.79±4.26	0.54±0.26	<0.001
PAPP-A(ng/ml))	65.37±1.05	10.86±1.04	<0.001 (Mann-Whitney)
MMP-9, median (IQR), p./mL	4000 (800-600)	87 (10-110)	<0.001
IMA(U/ml)	125.58±9.84	70.78±25.53	<0.001
Ck-MB(IU/L)	63.32±38.75	14.31±13.5	<0.001
Troponin I (ng/ml)	18.41±17.59	0.01±0.007	<0.001

DISCUSSION

The present study demonstrated significantly elevated levels of inflammatory, plaque instability, and myocardial injury biomarkers among patients with acute coronary syndrome (ACS) compared to

healthy controls. These findings reinforce the multifactorial nature of ACS, involving inflammation, endothelial dysfunction, plaque rupture, and myocardial necrosis. Similar pathophysiological mechanisms underlying ACS have been extensively described by **Thygesen et al. [1]**, **Libby [17]**, **Hansson [18]**, and **Ross [25]**, who highlighted the inflammatory basis of atherosclerosis and its role in plaque rupture.

In the present study, age distribution between cases and controls showed no statistically significant difference, indicating appropriate comparability between study groups. Most participants were aged above 50 years, which is consistent with epidemiological findings reported by **Benjamin et al. [2]** and **Wilson et al. [16]**, who demonstrated that increasing age is a major risk factor for coronary artery disease. Age-related vascular changes, including endothelial dysfunction and arterial stiffening, have been shown to contribute significantly to the development of ACS, as described by **Anderson and Morrow [24]**.

Physical activity analysis in the present study revealed a significantly higher proportion of sedentary individuals among ACS patients compared to controls. This observation supports the findings of **Wilson et al. [16]**, who emphasized the role of lifestyle-related risk factors in coronary heart disease prediction. Furthermore, **Libby [17]** and **Hansson [18]** highlighted that sedentary behavior contributes to increased inflammatory activity and endothelial dysfunction, thereby promoting atherosclerosis and increasing the risk of ACS.

Inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hsCRP), were significantly elevated among ACS patients in the present study. These findings are consistent with those reported by **Ridker et al. [3]**, who demonstrated that elevated CRP levels independently predict cardiovascular events. Similarly, **Liuzzo et al. [4]** reported that increased CRP concentrations were associated with poor prognosis in patients with unstable angina. The observed elevation of hsCRP supports the concept proposed by **Libby [17]** and **Hansson [18]** that inflammation plays a central role in plaque destabilization and subsequent coronary events.

Heart-type fatty acid-binding protein (H-FABP) levels were significantly elevated among ACS patients in the present study, indicating its potential role as an early biomarker of myocardial injury. These findings are consistent with observations reported by **Glatz and van der Vusse [5]**, who described the rapid release of H-FABP into circulation following myocardial injury due to its small molecular size and cytoplasmic location. Furthermore, **Ishii et al. [6]** demonstrated elevated serum H-FABP concentrations among patients with ACS, highlighting its usefulness in early diagnosis prior to troponin elevation.

Matrix metalloproteinase-9 (MMP-9) levels were markedly elevated among ACS patients in the present study, suggesting increased extracellular matrix degradation and plaque instability. This finding aligns with observations reported by **Kai et al. [7]**, who demonstrated significantly elevated circulating MMP-9 levels in patients with ACS. Additionally, **Blankenberg et al. [8]** reported that increased MMP-9 levels were associated with poor cardiovascular prognosis. Similar findings were reported by **Fukuda et al. [9]**, who observed significantly higher MMP-9 levels in patients with acute myocardial infarction compared to stable angina, reinforcing its role in plaque rupture and vascular remodeling.

Pregnancy-associated plasma protein-A (PAPP-A) levels were significantly elevated among ACS patients in the present study. These findings correspond with those reported by **Bayes-Genis et al. [10]**, who demonstrated that PAPP-A is released from unstable atherosclerotic plaques and is associated with acute coronary events. Furthermore, **Nilsson et al. [11]** reported that elevated PAPP-A levels are associated with increased long-term cardiovascular mortality, indicating its prognostic significance.

Ischemia-modified albumin (IMA) levels were significantly increased among ACS patients in the present study, suggesting the presence of early myocardial ischemia. Similar findings were reported by **Bar-Or et al. [12]**, who developed the cobalt-albumin binding assay and demonstrated its potential use as an early marker of myocardial ischemia. The early elevation of IMA before irreversible myocardial injury highlights its clinical relevance in ACS diagnosis.

Conventional cardiac biomarkers, including CK-MB and Troponin I, were significantly elevated among ACS patients in the present study, confirming myocardial injury. These findings are consistent with clinical guidelines proposed by **Apple et al. [13]** and **Newby et al. [21]**, which recognize cardiac troponins as the gold standard biomarkers for myocardial infarction diagnosis. Additionally, **Morrow et al. [14]** and **Hamm et al. [15]** emphasized the diagnostic reliability of troponin elevation in patients with acute coronary syndromes. The integration of conventional and novel biomarkers into clinical practice has been recommended by **Morrow and Braunwald [22]** and **Vasan [23]**, who highlighted the advantages of multimarker strategies in improving diagnostic accuracy and prognostic evaluation. Overall, the simultaneous elevation of inflammatory markers, plaque instability markers, and myocardial injury biomarkers observed in the present study supports the current understanding that ACS is driven by complex biological mechanisms involving inflammatory activation, endothelial dysfunction, and thrombus formation, as described by **Braunwald [19]** and **Tziakas et al. [20]**. The use of multiple biomarkers reflecting different stages of disease progression may significantly enhance early detection, risk stratification, and clinical management of patients with suspected ACS.

CONCLUSION

The present study demonstrated significantly elevated levels of inflammatory, plaque instability, and myocardial injury biomarkers, including **hsCRP, H-FABP, MMP-9, PAPP-A, IMA, CK-MB, and Troponin I**, among patients with acute coronary syndrome (ACS) compared to healthy controls. These findings highlight the critical role of inflammation, extracellular matrix degradation, and myocardial ischemia in the pathogenesis of ACS. The observed elevation of hsCRP supports the inflammatory basis of atherosclerosis, while increased levels of MMP-9 and PAPP-A reflect plaque instability and rupture. Similarly, elevated concentrations of H-FABP, CK-MB, Troponin I, and IMA confirm myocardial injury and ischemic changes associated with acute coronary events.

The combined assessment of novel biomarkers along with conventional cardiac markers demonstrated strong diagnostic significance and may enhance early detection and clinical evaluation of ACS. A multimarker approach provides improved sensitivity in identifying different stages of disease progression, thereby supporting more accurate diagnosis and risk stratification.

Overall, the findings of the present study suggest that simultaneous evaluation of inflammatory and cardiac biomarkers may serve as a valuable tool in the early diagnosis and management of ACS patients. Further large-scale prospective studies are recommended to validate the clinical utility of these biomarkers and to establish standardized diagnostic protocols for their routine use in cardiovascular risk assessment.

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