ORIGINAL ARTICLE

THE ROLE OF HIGH-SENSITIVE C-REACTIVE PROTEIN IN PREDICTING SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITH ACUTE CORONARY SYNDROMES

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Objectives: We investigated the correlation between baseline C-reactive protein (Hs-CRP) levels and severity of coronary artery disease (CAD), measured in terms of Syntax Score (SScore), among patients presenting with acute coronary syndromes (ACS).

Methodology: This cross-sectional study was conducted at the Armed Forces Institute of Cardiology (AFIC), Rawalpindi, from April 2022 to October 2022. Baseline Hs-CRP levels were obtained for all the patients. Patients were divided into three groups as per the SScore as low (≤ 22), intermediate (≥ 23), and high (≥ 33) burden of CAD.

Results: Out of the 200 patients studied, 82.5% (165) were males, and mean age was 60.16±10.66 years. Diabetics were 50% (100) of the sample, 48.5% (97) were hypertensive, and smokers were 17.5% (35). Median Hs-CRP was 4.0 mg/L [2.0-12.5 mg/L], and median left ventricular ejection fraction (LVEF) was 45% [40-55%]. Median SScore was 23.5 [14.5-30.0], with 44.5% (89) categorized as low, 36.5% (73) as intermediate, and 19% (38) as high burden of CAD. The correlation between Hs-CRP and SScore was 0.236 (p=0.001) and -0.229 (p=0.001) with LVEF. A significant increase in Hs-CRP was observed in relation to the burden of CAD (p<0.001) with median of 2.0 mg/L [1.0-4.2 mg/L], 6.0 mg/L [3.1-15.7 mg/L], and 12.5 mg/L [5.8-20.7 mg/L] for low, intermediate, high burden of CAD, respectively.

Conclusion: Admission Hs-CRP was found to be positively correlated with the burden of CAD and negatively correlated with LVEF in patients with ACS.

Keywords: acute coronary syndrome (ACS), high sensitive CRP (Hs-CRP), syntax score (SScore)

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death globally. Inflammation plays a central role in coronary atherosclerosis and is also responsible for the instability of atherosclerotic plaque and plaque rupture causing acute coronary syndrome (ACS).[1,2] High-sensitivity C-reactive protein (Hs-CRP), an inflammatory marker and an acute phase protein, is also considered among the risk factors for atherosclerotic coronary artery disease (CAD).[3,4] It has been found to be a predictor of cardiovascular outcomes in patients with myocardial infarction and in patients undergoing primary percutaneous coronary intervention (PCI).[5,6]

Syntax score is a well-known tool to define the severity and complexity of CAD on coronary angiogram,[7] and is widely used to decide revascularization strategy in patients having multi-vessel or left main stem (LMS) disease. It also helps in the prediction of short and long-term morbidity and mortality in patients with ACS.[8] Yue liu et al.[9] concluded that in patients having CAD undergoing PCI, Hs-CRP could be useful for predicting severity of CAD and in risk stratification. In a study conducted by Abdel Rezk, et al.[10] raised admission Hs-CRP levels in patients presenting with ACS were associated with more complex CAD as defined by syntax score.

There is little contemporary data available on the risk stratification of ACS patients as per Hs-CRP levels in our local population. The study aims to identify the high-risk subset of patients with raised Hs-CRP who are going to need aggressive medical treatment in addition to revascularization. This will also help in predicting the future outcomes of such patients. The purpose of this study is to determine association of Hs-CRP levels with the severity of CAD as determined by SYNTAX score in patients presenting with ACS.

METHODOLOGY

This prospective, cross-sectional study was conducted at the Armed Forces Institute of Cardiology & National Institute of Heart Diseases (AFIC-NIHD), Rawalpindi, from April 2022 to October 2022. Non-probability consecutive sampling was done to study 201 patients aged 18 years or above, regardless of gender, who presented to the emergency department with ACS and underwent coronary angiogram. One patient died during the angiogram, which was complicated by acute heart failure and was excluded from further analysis.

The ACS spectrum included patients presenting with ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina pectoris (USAP), which were diagnosed using history and examination, electrocardiography (ECG) changes and/or increase in cardiac biomarkers.

Exclusion criteria included patients with a history of previous coronary artery bypass graft surgery (CABG), advanced valvular heart disease, advanced hepatic or renal disease, cardiopulmonary resuscitation (CPR) before admission, sepsis and history of congestive cardiac failure, with or without acute decompensation (Killip class III or more) on admission.

Patients having typical ischemic chest pain at rest for more than 20 minutes and ST-segment elevation in ≥ 2 consecutive leads (> 0.2 mV in leads V1, V2, or V3, and > 0.1 mV in the rest of the leads) were classified as having STEMI and, those who did not have persistent ST elevation were classified as having NSTE-ACS, this included those having transient ST-elevation, those having ST–segment depression and/or T-wave inversion. The patients were classified as having NSTEMI if they had raised troponins in addition to the above-mentioned findings and USAP or unstable angina if serial troponins were normal, but they had persistent (> 20 minutes) angina pain at rest; new onset (de novo) angina (Class II or III of the Classification of the Canadian Cardiovascular Society), post-MI angina, or crescendo angina.

Blood samples for Hs-CRP levels, in addition to other baseline investigations, including Troponin I, baseline hematology, biochemistry, and renal and hepatic function tests, were obtained on admission. A coronary angiogram was done as per standard protocol. The complexity and severity of CAD were measured in a number of ways. First of all, a simple scoring was done depending on the number of major coronary vessels involved. The number of diseased vessels with ≥ 50% luminal stenosis in major coronary arteries were labeled as single vessel CAD (SCVAD), double vessel CAD (DVCAD), triple vessel CAD (TVCAD) if 1, 2, or 3 vessels were involved (respectively). The involvement of the left main stem (LMS) was documented separately. Secondly, Syntax scoring system was applied. All coronary vessels having a diameter ≥ 1.5 mm having lesion(s) causing ≥ 50% stenosis in any segment were included in the SScore calculation. An online syntax score calculator was used for calculation (http://www.syntaxscore.com). Two Interventional Cardiologists reviewed the calculated SScore. If the results were not comparable, the review of a senior Interventional Cardiologist was sought and a consensus opinion was formed. The patients were categorized into groups according to the SScore: low SScore (≤ 22), intermediate SScore (≥ 23) and high SScore (≥ 33) and further as having Complex CAD if syntax score was 23 or above (intermediate- high) and non-complex CAD if syntax was below 23 (low syntax tertile). 2D-Echo was done for all patients within 24 hours after admission and Left ventricular ejection fraction (LVEF) was documented.

The study protocol was approved by IERB (ethical board) and informed consent was taken from the participants in written form.

Statistical analysis was done using SPSS-22. Mean and standard deviation/median [interquartile range (IQR)] were calculated for quantitative variables like age, Syntax score, LVEF, and Hs-CRP. Frequency and percentage were calculated for qualitative variables like gender, hypertension, diabetes mellitus, smoking status, number of coronaries involved (SVCAD, DVCAD, TVCAD), grade of syntax score (low, intermediate, or high), the complexity of CAD, that is complex versus non-complex CAD and diagnosis at presentation, that is, STEMI, NSTEMI, USAP (unstable angina). The Chi-square test was used for the comparison between two qualitative variables. A p-value equals to, or less than 0.05 was considered statistically significant. The normality of data was checked and Kruskal Wallis test was applied to find variation in Hs-CRP level among syntax score grades and the number of coronary vessels involved (described as SVCAD, DVCAD, and TVCAD). Rank correlation was applied to determine the relationship between LVEF, syntax score, and Hs-CRP level. P-value equals to and less than 0.05 ($p \leq 0.05$) was considered statistically significant.

RESULTS

Out of the 200 patients studied, 82.5% (165) were males, while females were 17.8% (35). Mean age was 60.16±10.66 years. Diabetics were 50% (100) of the

sample, 48.5% (97) were hypertensive, and smokers were 17.5% (35). Mean serum creatinine was 1.05±0.47. Out of the study population, 50% (100) were diagnosed as having STEMI, 35.5% (71) with NSTEMI and 14.5% (29) as having USAP. On the angiogram, the largest proportion had TVCAD; 57% (114), 27.5% (55) had DVCAD, and 15.5% (31) had SVCAD and LMS disease was observed in 14% (28).

Table 1: Association between Hs-CRP and burden of coronary artery diseases

	Total (N)	Hs-CRP Median [IQR]	P-value
Number of vessels involved			
Single vessel	31	1.5 [1-4.2]	<0.001
Double vessel	55	3 [2-8.6]	
Triple vessel	114	6.5 [3-17]	
Severity of coronary artery disease			
Low	89	2 [1-4.2]	<0.001
Intermediate	73	6 [3.1-15.7]	
High	38	12.5 [5.8-20.7]	
Complexity of coronary artery disease			
Complex	111	7 [3.1-17.2]	<0.001
Non-Complex	89	2 [1-4.5]	

Median Hs-CRP was 4.0 mg/L [2.0-12.5 mg/L], and median left ventricular ejection fraction (LVEF) was 45% [40-55%]. Median SScore was 23.5 [14.5-30.0], with 44.5% (89) categorized as low, 36.5% (73) as intermediate, and 19% (38) as high burden of CAD. Overall, 44.5% (89) had non-complex CAD, and 55.5% (111) had complex CAD as per SScore.

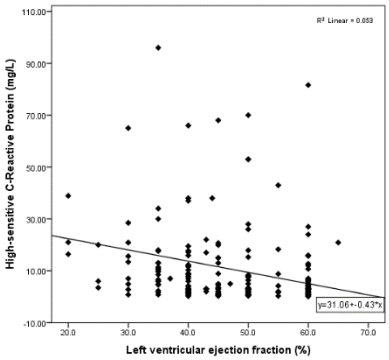

Figure 1: Correlation between left ventricle ejection fraction and HsCRP

A significant increase in Hs-CRP was observed in relation to the burden of CAD (p<0.001) with median of 2.0 mg/L [1.0-4.2 mg/L], 6.0 mg/L [3.1-15.7 mg/L], and 12.5 mg/L [5.8-20.7 mg/L] for low, intermediate, high burden of CAD, respectively (Table 1).

The correlation between Hs-CRP and SScore was 0.236 (p=0.001) and -0.229 (p=0.001) with LVEF. Scatter plot is also presenting the relationship of LVEF and SScore with Hs-CRP as shown in Figure 1 and 2.

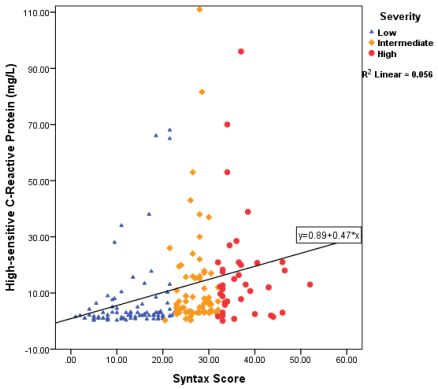

Figure 2: Correlation between Syntax Score and HsCRP

DISCUSSION

The importance of Hs-CRP in CAD development, prognosis, and its importance as a secondary prevention marker has been highlighted in various studies. The relationship between Hs-CRP and SScore has also been investigated. Yue liu et al.[9] concluded that Hs-CRP levels >10mg/L were an independent predictor of intermediate to high SScore. The results were similar in ACS population as well. Abdel Rezk, et al.[10] reported similar results who concluded that there was significant association between Hs-CRP levels on admission and intermediate to high SScore, indicating the complexity of CAD, in ACS population. They also reported that Hs-CRP level of ≥ 2.5mg/L was strongly associated with high SScore. These results are in line with our study, which proved that higher Hs-CRP levels are associated with more complex CAD in terms of raised SScore and multi-vessel involvement. Nadia Bouzidi et al.[11] concluded that Hs-CRP levels were greater in the STEMI population as compared to other acute coronary syndromes and correlated with myocardial necrosis and infarct size. This is also in line with our study, which showed that raised Hs-CRP levels are inversely related to LVEF; thus higher levels predict a greater degree of LV dysfunction, translating into greater infarct size.

In a recent study done by Preethi Mani et al.[12], initial and subsequent increases in Hs-CRP levels during 16 weeks after Acute coronary syndrome was associated with an elevated risk of MACE, cardiovascular death, and all-cause death. In addition, raised Hs-CRP levels on follow-up of patients who previously had PCI for CAD were significantly related to worse long-term outcomes,[13] thus further emphasizing the importance

of Hs-CRP in predicting the prognosis of CAD population.

In the recent CANTOS trial, treatment with canakinumab, with its anti-inflammatory properties, reduced Hs-CRP levels and interleukin-6, without lowering LDL-C and decreased the risk of recurrent cardiovascular events in patients with previous myocardial infarction and Hs-CRP level >2 mg/L.[14] Our study further emphasizes the fact that admission levels of Hs-CRP can aid in the risk stratification of patients with ACS and help identify those who need aggressive treatment. It can also help in predicting the degree of LV dysfunction.

The limitation of this study is being a single centered; a multi-centered study will better define the cutoff level of Hs-CRP associated with severe CAD in our local population. The sample size calculated was based on the prevalence of ACS in patients presenting to the emergency department with chest pain[15] as data based on the correlation of Hs-CRP with Syntax Score was scarce. Hs-CRP levels were not normally distributed, and there were few outliers.

Future directions include finding the correlation of other acute phase proteins, serum amyloid A and serum amyloid P, with coronary artery disease severity and outcomes in the ACS population. In addition, the relationship of Hs-CRP with the severity of CAD in patients with chronic coronary syndromes (CCS) can be explored in our local Asian population.

CONCLUSION

Hs-CRP is a sensitive marker of ACS, and the levels of admission in the ACS population are positively correlated with the severity of coronary atherosclerosis. Higher Hs-CRP levels are correlated with higher Syntax score and multi-vessel involvement. In addition, higher levels are directly related to the degree of LV dysfunction, thus indicating worse outcomes. Hence, on-admission levels of CRP are helpful in the risk stratification of ACS patients and help identify those who are at higher risk and thus need aggressive treatment.

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Conflict of interest: Authors declared no conflict of interest.

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