ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.ijcdw.org

Indian Journal of Cardiovascular Disease in Women

Cardiovascular *Original Article*

Association of Hs-CRP Levels in Patients with Acute Coronary Syndromes and it's Correlation with Angiographic Severity of Coronary Artery Stenosis

Aditya Sharma[1]

[1]Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.

***Corresponding author:**
Aditya Sharma,
Department of Cardiology,
Nizam's Institute of Medical Sciences, Hyderabad,
Telangana, India.

draditysharma0310@gmail.com

Received: 06 January 2023
Accepted: 16 January 2023
EPub Ahead of Print: 22 February 2023
Published: 01 March 2023

DOI
10.25259/IJCDW_9_2023

Quick Response Code:

Audio summary available at
https://doi.org/10.25259/IJCDW_9_2023

ABSTRACT

Objectives: Significant advances have been made toward the development of biomarkers for prognostication of patients with atherosclerotic cardiovascular disease. One such marker is high-sensitivity C-reactive protein (hs-CRP). It is a marker of inflammation mainly used to predict the risk of adverse cardiovascular (CV) events. Recent research also supports its role in atherogenesis. It is involved throughout the process of atheromatous plaque development. However, limited information is available about the relationship between levels of hs-CRP levels in patients presenting with acute coronary syndromes (ACS) and its association with outcomes. We conducted this study to assess the correlation between the levels of hs-CRP and the coronary angiographic findings in patients presenting with ACS and its correlation with outcomes.

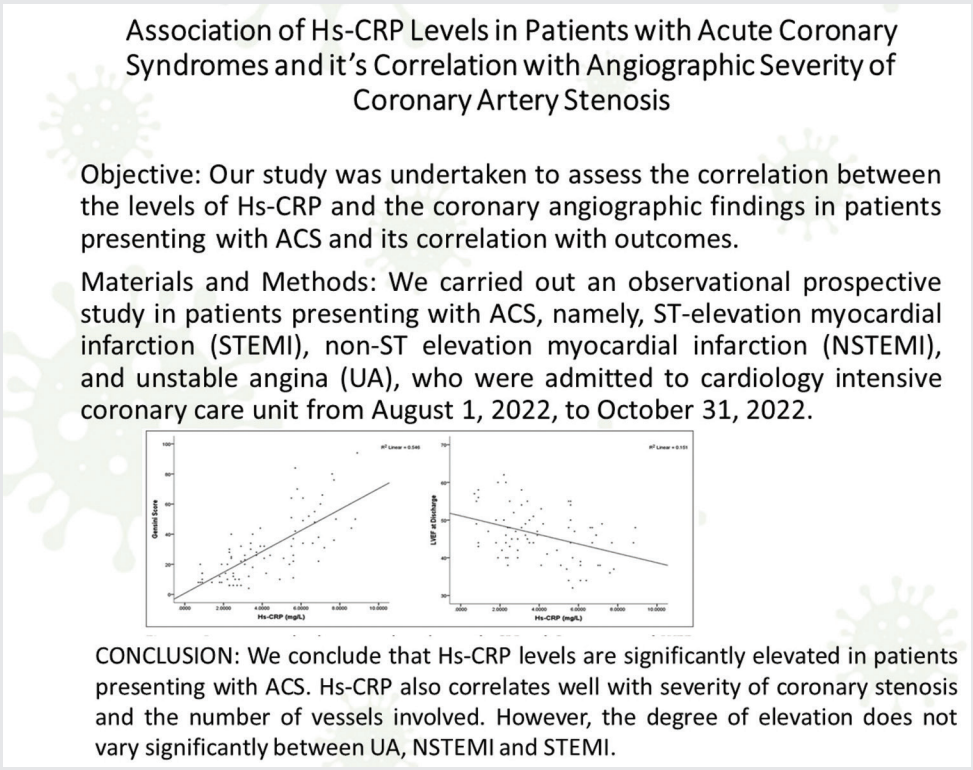
Materials and Methods: we carried an observational prospective study in patients presenting with ACS admitted to cardiology intensive coronary care unit in a tertiary care hospital. Patients underwent invasive coronary angiogram and serum Hs-CRP levels testing apart from other routine investigations. Correlation between severity of coronary stenosis, Hs-CRP levels and left ventricular ejection fraction (LVEF) at discharge was then assessed using statistical analysis.

Results: Positive correlation was found between Hs-CRP levels and severity of coronary stenosis. Negative correlation was found between Hs-CRP levels and LVEF at discharge.

Conclusion: We found that hs-CRP levels correlate well with angiographic severity. It was also observed that higher the hs-CRP levels more the number of vessels involved with patients with the left main + triple vessel disease (TVD) and TVD having maximum scores.

Keywords: Hs-CRP, Acute coronary syndromes, Angiographic severity

ABSTRACT IMAGE



INTRODUCTION

A tremendous amount of research has been done in developing biomarkers for the diagnosis and prognostication of atherosclerotic cardiovascular disease (ASCVD) including coronary artery disease (CAD), which is a major contributor to mortality and morbidity worldwide.

Numerous modifiable and non-modifiable risk factors are implicated in contributing to CVD. However, these traditional risk factors may not reliably predict coronary events all the time. Notably, a significant amount of acute coronary syndrome is being seen in patients with normal or borderline lipid profiles. This calls for looking into other markers for risk assessment of ASCVD to identify at-risk populations. As atherosclerosis is an inflammatory process, various markers of inflammation have been proposed for this purpose.[1] Among them, high-sensitivity C-reactive protein (Hs-CRP) has been the highlight. Hs-CRP may be involved in increasing thrombogenicity and vascular vulnerability through different mechanisms such as increased expression of cell adhesion molecules, endothelial plasminogen activator inhibitor 1, downregulation of endothelial nitric oxide, and altered LDL uptake by macrophages.[2] This makes Hs-CRP an attractive marker to be assessed in patients presenting with acute coronary events. Although Hs-CRP is being used for risk assessment and primary prevention for ASCVD, information regarding the relationship between levels of Hs-CRP levels in patients presenting with acute coronary syndromes (ACS) and its association with outcomes is scarce. Therefore, our study was undertaken to assess the correlation between the levels of Hs-CRP and the coronary angiographic findings in patients presenting with ACS and its correlation with outcomes.

MATERIALS AND METHODS

We carried out an observational prospective study in patients presenting with ACS, namely, ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA), who were admitted to cardiology intensive coronary care unit from August 1, 2022, to October 31, 2022. We included all patients who were aged 18 years or older, had confirmed diagnoses of acute coronary syndrome, and gave valid consent. We excluded patients with any overt infection or sepsis, acute or chronic renal failure, acute or chronic liver disease, known collagen vascular disease, febrile disorder (body temperature >37.5°C), or who were unwilling to give consent. Patients who were admitted and were a part of the study were managed by the

treating consultant and not the investigator as per standard guidelines. The investigator had no role in deciding the timing and manner of revascularization.

Patients were evaluated and investigated as per standard protocols which included electrocardiogram, chest radiogram, and transthoracic echocardiogram. Echocardiogram was performed using a Phillips iE33 machine. Blood was drawn for parameters such as complete blood count, renal parameters, serum electrolytes, lipid profile, and Hs-Trop I. Apart from these, estimation of serum Hs-CRP was also done at admission. Hs-CRP was quantified by immunoturbidimetric assay measured on Beckman Coulter AU5800.

Values of <1 mg/L were considered normal and values of 1–10 mg/L as elevated. Values >10 mg/L were rejected given the possibility of added sources of inflammation or sepsis. Patients, thereafter, underwent coronary angiogram after consent and were labeled as having single-vessel disease (SVD), double-vessel disease (DVD), triple-vessel disease (TVD), and left main + triple-vessel disease (LM+TVD) based on an angiographic cutoff of ≥50% stenosis. The extent and severity of CAD were assessed using the Gensini score. Echocardiogram was also done before discharge to assess the left ventricular ejection fraction (LVEF). We aimed to take 100 cases; however, valid measurements of Hs-CRP could be made for 80 cases.

Statistical analysis

All the qualitative factors such as sex, diagnosis, hypertension, and presence of risk factors were represented with frequencies and percentages. All the quantitative parameters such as age, body mass index, Hs-CRP, Hs-Trop I, Gensini score, and LVEF at discharge were represented with mean and standard deviation. To compare the mean difference between the two groups, we used *t*-test for independent samples. To compare the mean difference in Hs-CRP between the vessels involved, we used analysis of variance with *post hoc* test. To find the correlation between Hs-CRP, Gensini score, and LVEF at discharge, we used the Pearson correlation coefficient. All data were entered in Microsoft Excel and analyzed using SPSS19.0v. $P < 0.05$ was considered significant.

RESULTS

A total of 80 patients were enrolled in the study as per inclusion and exclusion criteria among which 58 (72.5%) were male and 22 (27.5%) were female. [Table 1] shows the baseline characteristics of the patients. The average age of enrolled patients was 62 years. Hs-CRP values of <1 mg/L were considered normal and values between 1 and 10 mg/L were considered elevated. Values more than 10 mg/L were not considered due to the possibility of added sources of inflammation or sepsis. Out of 80 cases, eight cases (8.75%) had Hs-CRP in the normal range and 73 cases (91.25%) had Hs-CRP in the elevated range. Among the total subjects, two patients succumbed during their hospital stay. STEMI was the most common diagnosis (57.5%). The most common risk factor was hypertension, present in 72.5% of the study population. Of the number of vessels involved, double-vessel disease was most common (38.8%).

Hs-CRP was elevated in 73 of 80 cases (91.3%). Mean Hs-CRP values in males were 3.99 mg/L, whereas the mean Hs-CRP value in females was slightly higher at 4.56 mg/L, but the difference was statistically not significant ($P > 0.05$). Furthermore, there was no significant difference in mean LDL levels in patients with elevated Hs-CRP ($P > 0.05$).

[Table 2] shows the distribution of patients by diagnosis and mean Hs-CRP levels in each group. The Hs-CRP level is elevated in all groups with mean values being slightly higher in NSTEMI and STEMI as compared to UA but is not statistically significant ($P > 0.05$).

[Table 3] shows the distribution of patients by the number of vessels involved and mean Hs-CRP levels in each group. In multiple comparison test, elevation in Hs-CRP between SVD, DVD, and TVD groups is statistically significant ($P < 0.01$), thereby showing that an increase in Hs-CRP level is associated with an increase in the number of vessels involved, however, between TVD and LM+TVD groups, the elevation was not significant ($P = 0.41$).

Table 1: Baseline characteristics.

Variable	Hs-CRP <1 mg/L (*n*=7)	Hs-CRP ≥1 mg/L (*n*=73)	*P*-value
Age (years)	59±6.16	62.36±10.17	0.44
BMI	24.16±2.70	24.36±2.76	0.85
TC (mg/dL)	162.86±23.39	182.49±35.26	0.15
HDL (mg/dL)	36±9.02	40.7±6.02	0.06
LDL (mg/dL)	100.43±23.91	101±29.79	0.96
HTN	4 (57.14%)	54 (73.97%)	0.34
DM	2 (28.57%)	26 (35.62%)	0.71
Smoker	0	19 (26.03%)	0.122

Hs-CRP: High-sensitivity C-reactive protein, BMI: Body mass index, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HTN: Hypertension, DM: Diabetes mellitus

Table 2: Distribution of mean hs-CRP by diagnosis.

Diagnosis	Hs-CRP (mg/L)		*P*-value (Analysis of variance)
	Mean	Std. Deviation	
UA	2.63	1.485	0.144
NSTEMI	4.45	2.47	
STEMI	4.21	2.063	

Hs-CRP: High-sensitivity C-reactive protein

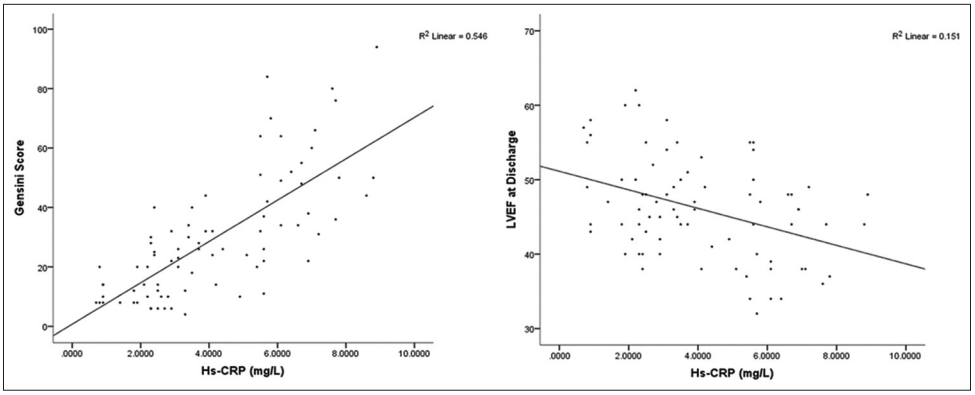


Figure 1: Linear scatter plot showing correlation between hs-CRP and Gensini score and LVEF. Hs-CRP: High-sensitivity C-reactive protein and LVEF: left ventricular ejection fraction.

[Table 4] shows the correlation between Hs-CRP and the severity of coronary stenosis as determined by the Gensini score and the LV ejection fraction at discharge. A significant positive correlation was found between Hs-CRP and Gensini score with a correlation coefficient of 0.74 which is highly significant ($P < 0.005$). The scatter plot [Figure 1] shows a linear correlation. A negative correlation was found between Hs-CRP and LVEF at discharge with a correlation coefficient of −0.39 which is significant ($P < 0.005$). LVEF at discharge was obtained for 78 of the 80 patients as two patients succumbed during the course of treatment. Furthermore, the correlation between Hs-CRP and Gensini score was present irrespective of sex and was statistically significant. However, although correlation between Hs-CRP and LVEF at discharge was present in males and females, the correlation was found to be statistically insignificant in females ($P = 0.45$). This could have possibly been attributed to the lesser number of females in our study.

Table 3: Distribution of mean hs-CRP levels by no. of vessels involved.

No. of vessels involved	Hs-CRP (mg/L)		*P*-value (Analysis of variance)
	Mean	SD	
SVD	2.57	1.524	<0.01
DVD	3.79	1.963	
TVD	5.71	1.897	
LM+TVD	6.44	0.926	

Hs-CRP: High-sensitivity C-reactive protein, SVD: Single vessel disease, DVD: Double vessel disease, TVD: Triple vessel disease, LM: Left main, TVD: Triple vessel disease

Table 4: Correlation between hs-CRP levels and Gensini score and LVEF.

	Gensini score	LVEF at discharge
Hs-CRP (mg/L)		
Pearson Correlation	−0.739	−0.389
n	80	78

LVEF: Left ventricular ejection fraction, Hs-CRP: High-sensitivity C-reactive protein

DISCUSSION

It is well established that Hs-CRP is a sensitive marker of systemic inflammation and, therefore, is being used as risk enhancing marker while guiding the initiation of statin therapy for primary prevention of ASCVD. Numerous studies have established the fact that CRP levels are elevated in patients with angiographically diagnosed CAD. Various reasons are speculated for this rise. CRP may not have a direct causative role in atherosclerosis and may be only a marker of inflammation[3] or it may have a direct role in atherogenesis as evidenced by the following observations: (i) localization of CRP in atherosclerotic lesions, (ii) facilitating LDL uptake by macrophages by binding to the LDL molecules without the need for any enzymatic modification,[4] and (iii) CRP administration in animal model promotes inflammation.[5] CRP has also been found to be a key factor in plaque rupture[6] and that initial and serial measurement of CRP in acute coronary syndrome may help to identify patients with adverse outcomes.[7] Furthermore, a strong correlation has been found between CRP and the occurrence of future coronary events in patients with chronic stable angina.[8]

Another possible mechanism underlying the role of CRP in inflammation could be its inverse relationship with vitamin D. It is thought that vitamin D helps in the regulation of inflammatory cytokines and thereby modulates inflammation.[9] In a large-scale Mendelian randomization analysis, Vitamin D was found to be having a casual effect on CRP meaning that correction of vitamin D could potentially help in abating chronic inflammation which is a major driver for ASCVD.[10]

We observed that Hs-CRP levels did not vary much with the gender or type of ACS and that it correlates well with the

severity of coronary stenosis. It is worthwhile to note that although patients with any of the acute coronary syndromes show an elevation in Hs-CRP, the degree of elevations does not differ significantly between UA, NSTEMI, or STEMI.

In a study by Seyedian *et al*.,[11] Hs-CRP levels were significantly higher in patients with unstable angina than those in patients with stable angina. Furthermore, the level of Hs-CRP in patients with unstable angina was associated with the severity of coronary stenosis. In agreement with the above, our study also revealed that the majority of patients with UA had elevated Hs-CRP and that the values correlated with the severity of stenosis in those patients.

Our decision to use the Gensini scoring was based on the fact that not only it scores the lesion according to the absolute angiographic severity but it also takes into account the location of the lesion within the coronary tree. Left main lesions have the maximum score followed by proximal segments of the left anterior descending and left circumflex coronary. The final score therefore also represents the functional significance of the lesions in terms of the at-risk myocardium. Patients with elevated Hs-CRP had higher Gensini scores, thereby signifying a higher disease burden.

Nyandak *et al*.[12] noted the presence of a correlation between the severity of coronary stenosis and Hs-CRP levels which are consistent with our study. This supports the fact that inflammation is not only an important trigger for plaque rupture acutely but also acts as a driver of chronic atherosclerosis as evidenced by the occurrence of higher Hs-CRP levels with an increasing burden of coronary atherosclerosis.

Elevated CRP levels were correlated with the severity of CAD in a study by Liu *et al*.[13] who found elevated Hs-CRP was an independent predictor of disease burden as evidenced by higher syntax scores in those patients. Although, in our study, the assessment of stenosis was done by the Gensini scoring system, the results were in agreement, with elevated Hs-CRP levels (>1 mg/L) seen in cases with higher Gensini scores. Moreover, patients with CRP levels <1 mg/L had lower stenosis scores.

Attempts have also been made to link Hs-CRP levels with plaque vulnerability by assessing plaque ulceration and inflammation. In a study by Arroyo-Espliguero *et al*.[14] who considered Hs-CRP levels in patients with acute and chronic coronary syndromes, levels were notably higher in patients presenting with ACS compared to those of chronic stable angina. Furthermore, the Hs-CRP levels correlated with the number of complex vulnerable plaques in their study. It highlights the importance of Hs-CRP as a marker of atheromatous plaque vulnerability also.

Therefore, Hs-CRP serves as an important marker for disease burden in patients with ASCVD. Another important marker is the fibrinogen-albumin ratio. Assay of both these markers is widely available and inexpensive. With inflammation, fibrinogen being a positive acute phase reactant rises, while albumin a negative acute phase reactant falls. Several studies have shown a relationship between raised fibrinogen and reduced albumin with increased mortality and morbidity in patients with CAD.[15,16] Combining the two as a ratio has been shown to improve the sensitivity and specificity in predicting the severity of CAD in patients with STEMI.[17]

CONCLUSION

We conclude that Hs-CRP levels are significantly elevated in patients presenting with ACS. Hs-CRP also correlates well with severity of coronary stenosis and the number of vessels involved. However, the degree of elevation does not vary significantly between UA, NSTEMI and STEMI.

Limitations

Although the results of the study were statistically significant, a larger population size is essential to assess the relationship of Hs-CRP levels with the severity of coronary atherosclerosis. The patients were restricted to local geographic region and had limited ethnic diversity. Furthermore, the study is not sufficiently powered to assess the influence of gender on Hs-CRP levels due to to the lesser number of females. Although patients with Hs-CRP >10 mg/L were excluded in view of possible source of sepsis, this may not be the case for all such patients as other supportive evidence such as serum procalcitonin levels and cultures were not obtained before exclusion. The severity assessment of coronaries was based on the visual assessment of luminal stenosis in angiogram which may have interobserver variability. Plaque visualization and assessment was not carried out. Optical coherence tomography or intravascular ultrasound-based coronary assessment in correlation with Hs-CRP levels may be more informative.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tibaut M, Caprnda M, Kubatka P, Sinkovič A, Valentova V, Filipova S, *et al*. Markers of atherosclerosis: Part 1-serological

markers. Heart Lung Circ 2019;28:667-77.
2. Kamath DY, Xavier D, Sigamani A, Pais P. High sensitivity C-reactive protein (HsCRP) & cardiovascular disease: An Indian perspective. Indian J Med Res 2015;142:261-8.
3. Khreiss T, József L, Potempa LA, Filep JG. Opposing effects of C reactive protein isoforms on shear-induced neutrophil-platelet adhesion and neutrophil aggregation in whole blood. Circulation 2004;110:2713-20.
4. Khreiss T, József L, Potempa LA, Filep JG. Conformational rearrangement in C-reactive protein is required for proinflammatory actions on human endothelial cells. Circulation 2004;109:2016-22.
5. Calabro P, Willerson JT, Yeh ET. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation 2003;108:1930-2.
6. Badimon L, Peña E, Arderiu G, Padró T, Slevin M, Vilahur G, *et al*. C-reactive protein in atherothrombosis and angiogenesis. Front Immunol 2018;9:430.
7. Mani P, Puri R, Schwartz GG, Nissen SE, Shao M, Kastelein JJ, *et al*. Association of initial and serial C-reactive protein levels with adverse cardiovascular events and death after acute coronary syndrome: A secondary analysis of the VISTA-16 trial. JAMA Cardiol 2019;4:314-20.
8. Zebrack JS, Anderson JL, Maycock CA, Horne BD, Bair TL, Muhlestein JB, *et al*. Usefulness of high sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol 2002;89:145-9.
9. Liu W, Zhang L, Xu HJ, Li Y, Hu CM, Yang JY, *et al*. The anti-inflammatory effects of Vitamin D in tumorigenesis. Int J Mol Sci 2018;19:2736.
10. Zhou A, Hyppönen E. Vitamin D deficiency and C-reactive protein: A bidirectional Mendelian randomization study. Int J Epidemiol 2022;dyac087.
11. Seyedian SM, Ahmadi F, Dabagh R, Davoodzadeh H. Relationship between high-sensitivity C-reactive protein serum levels and the severity of coronary artery stenosis in patients with coronary artery disease. ARYA Atheroscler 2016;12:231-7.
12. Nyandak T, Gogna A, Bansal S, Deb M. High sensitive C-reactive protein (Hs-CRP) and its correlation with angiographic severity of coronary artery disease (CAD). J Indian Acad Clin Med 2007;8:217-21.
13. Liu Y, Jia SD, Yao Y, Tang XF, Xu N, Jiang L, *et al*. Impact of high-sensitivity C-reactive protein on coronary artery disease severity and outcomes in patients undergoing percutaneous coronary intervention. J Cardiol 2020;75:60-5.
14. Arroyo-Espliguero R, Avanzas P, Cosín-Sales J, Aldama G, Pizzi C, Kaski JC. C-reactive protein elevation and disease activity in patients with coronary artery disease. Eur Heart J 2004;24:401-8.
15. Peng Y, Wang H, Li YM, Huang BT, Huang FY, Xia TL, *et al*. Relation between admission plasma fibrinogen levels and mortality in Chinese patients with coronary artery disease. Sci Rep 2016;6:30506.
16. Suzuki S, Hashizume N, Kanzaki Y, Maruyama T, Kozuka A, Yahikozawa K. Prognostic significance of serum albumin in patients with stable coronary artery disease treated by percutaneous coronary intervention. PLoS One 2019;14:e0219044.
17. Karahan O, Acet H, Ertaş F, Tezcan O, Çalişkan A, Demir M, *et al*. The relationship between fibrinogen to albumin ratio and severity of coronary artery disease in patients with STEMI. Am J Emerg Med 2016;34:1037-42.

How to cite this article: Sharma A. Association of Hs-CRP levels in patients with acute coronary syndromes and it's correlation with angiographic severity of coronary artery stenosis. Indian J Cardiovasc Dis Women 2023;8:37-42.