Section: General Medicine

Original Research Article

RELATIONSHIP OF HIGH-SENSITIVE C-REACTIVE PROTEIN WITH CARDIOVASCULAR RISK FACTORS IN ACUTE CORONARY SYNDROME

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Abstract

Background: Epidemiological studies indicate a rising prevalence of cardiovascular disease (CVD) in India, linked to factors like hypertension, diabetes, and smoking. While conventional risk factors are recognized, not all events can be predicted, prompting interest in novel predictors such as imaging of subclinical atherosclerosis. Inflammation, notably assessed by high-sensitivity C-reactive protein (Hs-CRP), emerges as a key contributor to CVD, serving as a strong predictor in various studies. These findings highlight the ongoing quest for more accurate CVD risk assessment approaches. **Materials and Methods:** Patients admitted to the Intensive Cardiac Care Unit with acute coronary syndrome, excluding those with specific medical histories. Informed consent was obtained, and data from August 2021-August 2022 were collected and analyzed using SPSS. Clinical assessments, biochemical investigations, and various tests were conducted, with defined criteria for conditions like diabetes and hypertension. The study protocol received institutional ethical approval. **Result:** The mean age was 56.54 ± 10.43 years. Female patients exhibited elevated levels of hs-CRP, with 76% registering values exceeding 3 mg/l, in contrast to 56.5% of male patients. The prevalence of elevated hs-CRP (>3 mg/l) was notably higher in the lower SES group (83.33%) compared to the upper SES group (50%, $p < 0.05$). Smokers exhibited a significantly higher proportion of patients with elevated CRP levels (55% with >3 mg/l compared to 20% with <1 mg/l; $p = 0.03$ compared to non-smokers). Similarly, patients with Metabolic Syndrome (MS), central obesity, and periodontitis showed a higher prevalence of elevated hs-CRP levels. **Conclusion:** This study in Indian ACS patients reveals correlations between hs-CRP levels and several CV risk factors, SES, periodontitis, ACS type, and angiographic severity of CAD. The gender-specific variation prompts consideration of distinct cutoff values for hs-CRP in CV risk prediction. Unexpectedly, no significant association was found between hs-CRP levels and HTN, DM, or dyslipidemia, necessitating exploration in future, larger studies.

INTRODUCTION

Epidemiological studies have revealed that the prevalence of cardiovascular disease (CVD) in India is increasing along with the prevalence of conventional risk factors for cardiovascular disease. Present health transition from predominance of infections to the preponderance of cardiovascular disorders, such as Hypertension, Diabetes mellitus and cardiovascular disease is now responsible for higher rates of deaths in India.[1] Indians have one of the highest rates of heart disease in the world. Several modifiable and non-modifiable factors such as hypertension, diabetes mellitus, smoking etc are recognized as major risk factors for CVD and aggressive correction of these play vital role in CVD prevention. However, not all adverse cardiovascular events can be predicted or explained by these conventional risk factors, which limits our ability to accurately identify the individuals who are at "high risk" of developing CVD1. Over the past decade, identification of novel risk factors and predictors for CVD has been an area of major interest in preventive cardiology.[2] Therefore, a host of alternate risk assessment approaches such as imaging of subclinical atherosclerosis, detection of vascular

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inflammation etc are being evaluated to overcome this limitation and to provide more accurate risk estimates in any given individual. Numerous studies have provided the evidence that inflammation plays a central role in the occurrence of CVD. Accordingly, several mediators of the inflammatory response, including acute-phase proteins, cytokines and cellular adhesion molecules have been evaluated as potential indicators of the risk of a first acute atherothrombotic event, as well as of recurrent complications after initial presentation. Hs-crp is the most sensitive of acute reactants.[2] As the prototypical acute-phase reactant, Hs-CRP has been the focus of much of the clinical investigation. Various epidemiological studies have demonstrated that Hs-CRP is a strong predictor of future cardiovascular events.[3]

CRP emerged as the most exquisitely sensitive systemic marker of inflammation and a powerful predictive marker of future cardiovascular risk. CRP's predictive power for vascular risk detection resides between 0.1 to 0.5 mg/dl – a level which is present in most of the healthy individuals without inflammation, whereas, highly sensitive CRP (Hs-CRP) is well standardised and it has limits of detection as low as 0.02mg/dl.[4,5]

Sharad Gupta etal conducted study on 337 patients and demonstrated that in Indian patients presenting with acute coronary syndrome, the Hs-CRP levels correlate with cardiovascular risk factors such as smoking, obesity, lower socio-economic status, the type of acute coronary syndrome and angiographic severity of coronary artery disease1. Ghodke.S.S et al conducted study on 200 patients and concluded that, there is clear trend, that Hs-CRP level correlate significantly with angiographic features of thrombi and eccentric lesions. The inflammation can be implicated in transformation of stable coronary plaque to unstable plaque rupture thrombus.[2] Arslan Masood, Shariq Jafar from department of cardiology Jinnah hospital, Lahore studied on 80 patients and the mean angiographic scores showed increasing trend from lower to higher hs – CRP risk group.[3]

Hasnat MA et al conducted study on total of 90 patients, and concluded that significant positive correlation is observed between the extent of coronary artery disease and hs-CRP level, and is found to be higher in patients with higher degree of angiographic stenosis, this shows that hs-CRP level have a positive correlation with disease burden in coronary artery disease, elevated hs-CRP can predict the coronary atherosclerotic disease burden6. Mohammad Assadpour et al conducted a study which included 85 patients for coronary angiography, 1 (1.2%) patient with hs-CRP less than 1mg/dl ,7(8%) patients with 1-3 mg/dl, 16(18.4%) with more than 3 mg/dl have severe coronary atherosclerosis ($p<0.010$).[5]

The objectives of the study were to correlate the level of Hs-CRP with risk factors like age, sex, family history, smoking, hyperlipidaemia, obesity, hypertension and diabetes mellitus and to correlate the level of Hs-CRP with the type of acute coronary syndrome.

MATERIALS AND METHODS

Patients admitted in the Intensive cardiac Care Unit of Raichur Institute of Medical Sciences, Raichur with ACS- Unstable angina, ST elevation myocardial infarction, non-ST elevation myocardial infarction were included in the study.

Patient with past CABG, PTCA, valvular heart disease, hepatic dysfunction, renal dysfunction, creatinine > 1.5 mg / dL, collagen vascular disease4, recent or ongoing infection, fever or inflammatory disorders and history of recent trauma were excluded from the study.

Patients admitted in the ICCU fulfilling the Inclusion and Exclusion Criteria were selected. The next of kin were informed regarding the aim of study and informed consent will be taken. Information was taken through the prepared proforma from each patient. The data was analyzed by SPSS version 26.0. Patients admitted in the ICCU fulfilling the Inclusion and Exclusion Criteria over the period from August 2021-August 2022 were recruited in the study.

Enrolled patients underwent detailed clinical assessment, biochemical investigations, and coronary angiography. Clinical evaluation covered medical history, conventional cardiovascular risk factors, socio-economic status, physical examination, and dental examination. In this study several investigations were done like Hs-CRP, 2D-Echocardiography, Serum Blood Urea Nitrogen, Serum Creatinine, Serum Sodium, Serum potassium, Liver function test, Renal function test, Complete blood count and Lipid profile.

Defined criteria were used for Diabetes Mellitus (DM), Hypertension (HTN), Smoking, Family history of premature CAD, and Dyslipidemia. MS was defined according to the National Cholesterol Education Program-Adult Treatment Panel III criteria. Socio-economic status (SES) was determined using modified Kuppuswamy's scale. The study protocol received approval from the Institutional Research and Ethical Committee.

RESULTS

The study included 40 subjects, predominantly males (77.5%). The mean age was 56.54 ± 10.43. The distribution of hs-CRP levels and their relationship with gender and SES is presented in Tables 1 and 2, respectively. Notably, female patients exhibited higher hs-CRP levels, and there was a significant association between high hs-CRP and lower SES.

Female patients exhibited elevated levels of hs-CRP, with 76% registering values exceeding 3 mg/l, in contrast to 56.5% of male patients ($p = 0.02$). Among the participants, 12 (30%) were categorized under lower socioeconomic status (SES), 24 (60%) under middle SES, and 4 (10%) under upper SES. The

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prevalence of elevated hs-CRP (>3 mg/l) was notably higher in the lower SES group (83.33%) compared to the upper SES group (50%, $p < 0.05$).

Table 1: Distribution of hs-CRP in relation to gender profile of the patients

Gender	hs-CRP levels			P value
	<1mg/l	1-3mg/l	>3mg/l	
	n=8	n=8	n=24	
Females n=11	1	2	8	<0.05
Males n=29	7	6	16	

Table 2: Distribution of study participants according to the levels of hs-CRP in relation to the socioeconomic status

Risk factor	Hs-CRP categories			P value
	<1 mg/l n = 8	>1-3 mg/l n = 8	>3 mg/l n = 28	
Lower SE Class	1	1	10	<0.01
Middle SE Class	6	5	13	<0.01
Upper SE Class	1	1	2	0.11

Table 3: High Sensitivity C-Reactive Protein (hs-CRP) Levels in Relation to Cardiovascular Risk Factors

Risk factor	n	Hs-CRP categories			P value
		<1 mg/l n = 8	>1-3 mg/l n = 8	>3 mg/l n = 28	
Smoker	20	4	5	11	<0.05
Metabolic syndrome	8	1	2	5	<0.01
Central obesity	14	3	2	9	<0.05
Periodontitis	12	1	2	9	<0.001
Hypertension	16	4	3	9	0.213
Diabetes	12	4	2	6	0.09
Dyslipidemia	23	4	4	15	0.06
Premature CAD	6	1	2	3	<0.01

[Table 3] illustrates the distribution of hs-CRP values concerning various cardiovascular (CV) risk factors. Smokers exhibited a significantly higher proportion of patients with elevated CRP levels (55% with >3 mg/l compared to 20% with <1 mg/l; $p = 0.03$ compared to non-smokers). Similarly, patients with Metabolic Syndrome (MS), central obesity, and periodontitis showed a higher prevalence of elevated hs-CRP levels. Conversely, no statistically significant association was observed between hs-CRP levels and Hypertension (HTN), Diabetes Mellitus (DM), or dyslipidemia.

Overall, 6 patients presented with premature coronary artery disease (CAD) (onset age <45 years), with the majority (80%) having high hs-CRP levels, contrasting with only a few (4%) within normal limits (<1 mg/l; $p = 0.001$).

A higher percentage of patients with ST-Elevation Myocardial Infarction (STEMI) had hs-CRP levels above 3 mg/l compared to those with Unstable Angina/Non-ST Elevation Myocardial Infarction (UA/NSTEMI) (p value < 0.001). Similarly, the majority of patients with Single-Vessel Disease (SVD) had hs-CRP levels <1 mg/l, while most with Triple-Vessel Disease (TVD) exhibited elevated (>3 mg/l) hs-CRP levels ($p < 0.001$).

DISCUSSION

Epidemiological studies highlight the escalating prevalence of cardiovascular disease (CVD) in India, concurrent with traditional risk factors. The shift from infectious to cardiovascular disorders is now a major contributor to 53% of all deaths in India. Indians face one of the world's highest heart disease rates, presenting aggressively at a younger age. Consequently, preventing CVD is a crucial public health challenge. While conventional risk factors like Hypertension, Diabetes, and smoking are recognized, they do not predict all adverse CV events accurately. This limitation prompts exploration of alternate risk assessment approaches, such as imaging of subclinical atherosclerosis and detection of vascular inflammation.

Inflammation plays a pivotal role in CVD occurrence, with numerous studies establishing markers like high-sensitivity C-Reactive Protein (hs-CRP) as potent predictors of future cardiovascular events.[7-9] The present study contributes valuable insights into hs-CRP levels and their relationship with CV risk factors in an Indian context, crucial for daily clinical practice.

In our study, women demonstrated higher hs-CRP levels than men, aligning with previous population studies.[10] The need for gender-specific hs-CRP cutoff values for CV risk prediction may warrant exploration in larger-scale outcome studies.[11]

The study also highlights the association between low Socio-Economic Status (SES) and elevated hs-CRP levels, consistent with established links between SES and increased CAD risk. Similarly, smoking, Metabolic Syndrome, central obesity, and periodontitis correlated with higher hs-CRP levels. Unexpectedly, no significant association was found between hs-CRP levels and HTN, DM, or dyslipidemia. The impact of ongoing therapies, lifestyle modifications, and genetic factors on this relationship merits further investigation.[12-14]

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The study further underscores the significant correlation between hs-CRP levels and the type of ACS, angiographic extent of CAD, and premature CAD. Patients with STEMI exhibited higher peak hs-CRP levels, aligning with existing literature. This correlation reinforces the notion that hs-CRP levels not only indicate ACS presence but also reflect increased disease burden.

CV events, in most instances, have been demonstrated to be independent of major traditional risk factors routinely assessed in clinical practice. Hs-CRP, in terms of clinical utility, emerges as a more robust predictor of CV events compared to LDL cholesterol, providing prognostic information across various calculated Framingham risk levels and metabolic syndrome (MS) categories. Using widely available high-sensitivity assays, hs-CRP levels of ≤1, 1 to 3, and >3 mg/l correspond to low, moderate, and high-risk groups for future CV events.[15,16]

One notable advantage of hs-CRP is its stability, with minimal diurnal variation, making it the most widely used and standardized inflammatory marker for cardiovascular and metabolic disorders. However, limited information is available about hs-CRP levels and their association with CV risk factors or incident cardiovascular disease (CVD) in Indian studies. Our study fills this gap and provides crucial insights into this aspect, pertinent to day-to-day clinical practice.

In our investigation, it was observed that women exhibited higher hs-CRP levels compared to men, aligning with previous population studies indicating elevated hs-CRP levels in women within healthy populations. Whether this implies a need for gender-specific cutoff values for hs-CRP in predicting CV risk warrants evaluation in large-scale outcome studies.[17]

The influence of socioeconomic status (SES) on CVD and mortality rates has been consistent across nations.[18] Our study revealed a significantly higher prevalence of elevated hs-CRP levels in the lower SES group compared to the upper SES group, reinforcing the association between inflammation and increased CVD risk in individuals with low SES. Additionally, our findings indicated that higher hs-CRP levels were associated with smoking, metabolic syndrome (MS), central obesity, and periodontitis. However, contrary to previous literature, we did not find a significant association between elevated hs-CRP levels and hypertension (HTN), diabetes mellitus (DM), or dyslipidemia19-26. Lifestyle modifications and the use of antidiabetic and lipid-lowering agents in some patients might have contributed to this unexpected result.

The study also highlighted a significant correlation between elevated hs-CRP levels and premature CAD, as well as the extent and severity of CAD. Patients with STEMI showed higher peak hs-CRP levels compared to those with UA/NSTEMI, and there was a notable correlation between hs-CRP levels and the complexity of angiographic stenosis.

Despite these insightful findings, further exploration is needed to understand the genetic and environmental determinants of hs-CRP levels, especially concerning HTN, DM, and dyslipidemia. The impact of genetic variants, lifestyle factors, and pharmacological agents on hs-CRP levels requires comprehensive investigation in future studies.

Limitations: The study has limitations, such as the inability to assess the impact of ongoing treatments on hs-CRP levels and the focus on ACS patients rather than stable CAD. Nevertheless, the findings shed light on critical associations between hs-CRP levels and various CAD aspects in Indian patients.

CONCLUSION

This study in Indian ACS patients reveals correlations between hs-CRP levels and several CV risk factors, SES, periodontitis, ACS type, and angiographic severity of CAD. The gender-specific variation prompts consideration of distinct cutoff values for hs-CRP in CV risk prediction. Unexpectedly, no significant association was found between hs-CRP levels and HTN, DM, or dyslipidemia, necessitating exploration in future, larger studies.

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