Original Article

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Correlation between Serum High Sensitivity C-reactive Protein Level and Severity of Coronary Atherosclerosis Assessed by Angiographic Gensini Score in Patients with Acute Coronary Syndrome

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Abstract

Background and Objectives: Atherosclerosis is now known to be an active process of cell activation, inflammation and thrombosis [1]. To study, whether there is any correlation between the serum hs- CRP level, a biomarker of inflammation, and the angiographic severity and extent of coronary artery lesion in patients with acute coronary syndrome, such studies are sparse in India. *Methods:* Patients with ACS who were fulfilling the inclusion criteria, were enrolled prospectively in the study during the period February 2017 to February 2018. The patients were further classified three risk groups according to serum hs-CRP levels. < 1 mg/L - low risk, 1-3 mg/L - average risk and >3 mg/L- high risk. The presence and extension of CAD was assessed according to the modified Gensini scoring system. Mean angiographic Gensini scores were compared among the serum hs-CRP risk groups using ANOVA as the test of significance. Direct correlation between angiographic Gensini scores and serum hs-CRP levels were assessed using Pearson's correlation (2-tailed). A cut-off p value of < 0.05 was set for results to be statistically significant. Independent predictors of Gensini score were assessed with multiple regression analysis. *Results:* A total of 100 patients, with diagnosis of ACS, The mean angiographic Gensini scores significantly associated with the plasma hs-CRP, it showed increasing trend from lower to higher serum hs-CRP risk groups, and high serum hs-CRP was independently associated with Gensini score. *Conclusion:* Our study found that the severity of coronary atherosclerosis significantly associated with the concentration of the plasma hs-CRP and the mean angiographic Gensini scores, also showed increasing trend from lower to higher serum hs-CRP risk groups. Moreover, high serum hs-CRP was associated with Gensini score independent of age, sex, smoking status, hypertension, diabetes, dyslipidemia and Family history of CAD/CVdeath.

Keywords: Coronary Atherosclerosis; Angiographic Gensini Score; Acute Coronary Syndrome.

Introduction

Atherosclerosis, once considered to result from a passive process of lipid accumulation, is now known to be an active process of cell activation, inflamma-tion and thrombosis [1]. Inflammation is the key mechanism in the pathogenesis of the different stages of atherosclerosis, however, the inflammatory process of atherosclerosis is difficult to measure directly. No imaging techniques can assess inflammatory changes, and arterial biopsy to monitor such alterations or therapeutic interventions is neither practical nor ethical. There is therefore a growing interest in biomarkers of inflammation, plasma proteins that can be quantified in peripheral blood.

Over the past decade, identification of novel risk factors and predictors for CVD has been an area of major interest in preventive cardiology. Serum high sensitivity C- reactive protein (hs-CRP), a biomarker of inflammation, has been shown to effectively predict the risk of adverse cardiovascular (CV) events consistently. Despite its initial role as a marker of vascular inflammation, recent research has established the role of serum hs-CRP in athero-genesis. It is involved throughout the devolvement

of atheromatous lesions and is detectible even in the initial phases of plaque development. Serum hs-CRP levels may aid in identifying patients at high risk for a first CV event who might otherwise be missed by screening for lipids and other conventional risk factors alone.

The relationship between levels of serum hs-CRP and the presence and extent of angiographically documented coronary artery disease have seldom been investigated, especially in the Indian context. It is possible that serum hs-CRP is predictive for CAD risk either through a correlation with CAD extent (disease marker) or as an indicator of inflammation that leads to an atherothrombotic event that leads to plaque rupture (a process marker). Defining the relationship between serum hs-CRP and disease markers such as CAD extent as assessed by coronary angiography will enhance our understanding of whether 'inflammation markers' such as serum hs-CRP would be complementary or redundant when combined with clinical risk prediction with other risk markers.

The present study is designed to know if there is any association between the amount of coronary artery disease (strategic lesion location, extent and severity of the angiographic luminal disease) and the most predictive vascular inflammatory marker—serum hs-CRP in patients with acute coronary syndrome.

Aims and Objectives

1. To see the serum hs-CRP level in patients with acute coronary syndrome.
2. To see the angiographic severity and extent of coronary artery lesion in patients with acute coronary syndrome.
3. To see whether there is any correlation between the serum hs-CRP level and the angiographic severity and extent of coronary artery lesion in patients with acute coronary syndrome.

Material and Methods

During the period February 2017 to February 2018, 100 patients with the clinical diagnosis of acute coronary syndrome, and who were fulfill the following criteria, included in the study. The definition of ACS was made according to the 2012 "Third universal definition of myocardial infarction" expert consensus document[2].-

Inclusion Criteria

- Patients with acute coronary syndrome irrespective of risk factors.
- Patient/party willing to give informed consent for active participation in the study.

Exclusion Criteria

- Patients with history of coronary angiography in the recent past (<1 month),
- Patients on statins for more than one month,
- Patients with any systemic infection,
- Patients with malignancies,
- Patients with rheumatologic/autoimmune diseases,
- Patients with chronic inflammatory disorders,
- Patients with renal/hepatic compromise,
- Patients with recent trauma.
- Patients' refusal to give consent.
- Patients with psychiatric illness and those under legal custody.

It was a hospital based non-comparative prospective cross-sectional study. In every patient a focused history from cardiovascular point of view was taken on admission and was subsequently reviewed if required. Similarly a 12 lead ECG with a long lead II, qualitative Trop-T, and Echocardiography was done on admission and was subsequently repeated if required. Serum hs-CRP assessment was performed using the IMMULITE method containing one monoclonal and one polyclonal anti-CRP antibodies. This method provides a measurement range from 0.1 to 500 mg/L.

Patients were divided into three risk groups according to serum hs-CRP levels.

- < 1 mg/L - low risk,
- 1-3 mg/L - average risk
- >3 mg/L- high risk.

Coronary angiography was performed using classic Judkins method after puncture of femoral or radial artery and quantitative analysis of coronary artery stenosis was done and, the presence and extension of CAD was assessed according to the modified Gensini scoring system.

The Gensini score for each patient was inferred from the coronary arteriogram by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic

importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated; reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given scores of 1, 2, 4, 8, 16, and 32, respectively. Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: LM×5; the proximal segment of LAD×2.5; the proximal segment of LCX×2.5; the mid-segment ofthe LAD ×1.5; the RCA, the distal segment of the LAD, the posterolateral artery and the obtuse marginalartery ×1; and others ×0.5 [3].

Results

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Mean angiographic Gensini scores were compared among the serum hs-CRPrisk groups using ANOVA as the test of significance. Direct correlation between angiographic Gensini scores and serum hs-CRP levels were assessed using Pearson's correlation (2-tailed). A cut-off p value of < 0.05 was set for results to be statistically significant. Independent predictors of Gensini score were assessed with multiple regression analysis.

Baseline Characteristics

Table 1 shows the baseline characteristics of study participants.

Table 1: Baseline demographic and clinical data of study patients (n=100).

Characteristic	
Age (Years) (mean± SD, range)	56.61±10.0 (29-86)
Sex	No. (%)
Male	77 (77%)
Female	23 (23%)
Type of Presentation	
STEMI	52 (52%)
NSTEMI	16 (16%)
UA	32 (32%)
Serum hs-CRP Level	
< 1 mg/L - low risk,	7 (7%)
1-3 mg/L - average risk	33 (33%)
>3 mg/L- high risk.	60 (60%)
Risk Factor	
Smoking	69 (69%)
Hypertension	47 (47%)
Dyslipidemia	42 (42%)
Diabetes	29 (29%)
Family h/o CAD/CV death	26 (26%)
Serum hs-CRP levels (mean± SD, range) (mg/L)	4.18±3.30 (0.11-16.3)
Gensini score (mean± SD, range)	48.46±28.64 (3-110)

Table 2: Levels of serum hS-CRP and Type of Presentation

Serum hs-CRP level (mg/l)	UA	NSTEMI	STEMI
<1 mg/l	5	1	1
1-3 mg/l	12	5	13
>3 mg/l	15	10	38
Total	32	16	52
Mean serum hs-CRP levels	2.43±1.67	3.70±2.09	5.41±3.83

Serum hs-CRP Level In Different Subgroups

The mean serum hs-CRP in different risk subgroups (Table 3) was similar in patients with and without many of the study risk factors/profiles (gender; p=0.300, and hypertension; p=0.396), while it was significantly higher in those with hyperlipidaemia (p=0.000), With diabetes (p=0.021) with a family history of CAD/CV death (p=0.017), history of smoking (p=0.001), than in those without.

Gensini Score In Different Subgroups

The mean Gensini score in different risk factors subgroups (Table 3) was significantly higher in those with male sex (p=0.042), dyslipidaemia (p=0.000), with diabetes (p=0.003) with a family history of CAD/CV death (p=0.003), history of smoking (p=0.000), than in those without. While it was similar in patients with and without hypertension (p=0.865).

Table 3: Serum hs-CRP level and Gensini Score in different risk factors subgroups*

Characteristic	Sr. hS-CRP	Gensini Score
Male	4.39±3.20	51.8±26.4
Female	3.51±3.62	35.7±33.3
P value	0.300	0.042
With diabetes	5.65±4.30	62.3±30.2
Without diabetes	3.59±2.61	42.3±26.2
P value	0.021	0.003
With systemic hypertension	3.89±2.99	47.6±27.8
Without systemic hypertension	4.45±3.57	48.5±29.8
P value	0.396	0.865
With dyslipidemia	5.91±3.95	61.5±26.2
Without dyslipidemia	2.94±1.99	38.4±26.7
P value	0.000	0.000
With a family history of CAD/CVdeath	5.75±4.07	62.1±27.5

Without a family history of CAD/CVdeath	3.61±2.79	42.9±27.6
P value	0.017	0.003
With history of smoking	4.83±3.54	55.3±27.0
Without history of smoking	2.76±2.14	31.9±26.1
P value	0.001	0.000

*Data are presented as mean ± standard deviation; data were analyzed by *t* tests

Correlation Between Serum hs-CRP Level And Gensini Score

Patients belonging to serum hs-CRP low-risk group had a mean angiographic Gensini score of 17.29±15.25 (Range: 3-38), moderate-risk group 27.76±18.12 (Range: 4-76) and high-risk group 63.45±24.62 (Range: 4-110) mg/L. (Table 4).

Table 4: Correlation between angiographic Gensini scores and serum hs-CRP levels.

Serum hs-CRP level (mg/L)	Gensini Score (Mean±SD)	Range
< 1 mg/L	17.29±15.25	3 – 38
1-3 mg/L	27.76±18.12	4 – 76
>3 mg/L	63.45±24.62	4 - 110

Using ANOVA as the test of significance, the mean angiographic Gensini scores showed increasing trend from lower to higher serum hs-CRP risk groups (p = 0.000) (Figure 1).

Serum hs-CRP levels showed significant correlation with respective angiographic Gensini scores by Pearson's correlation (2-tailed) (p = 0.000) (Figure 2).

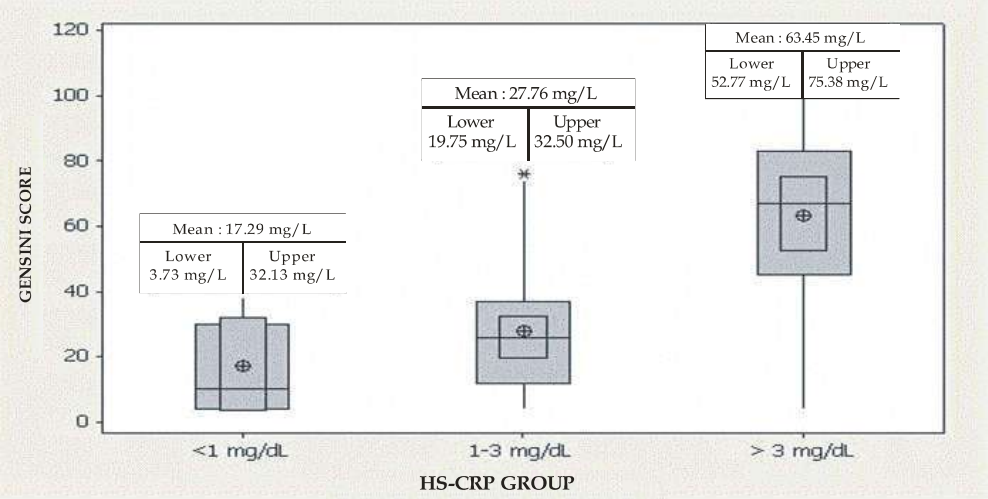

Fig. 1: Mean angiographic Gensini scores among hs-CRP risk groups

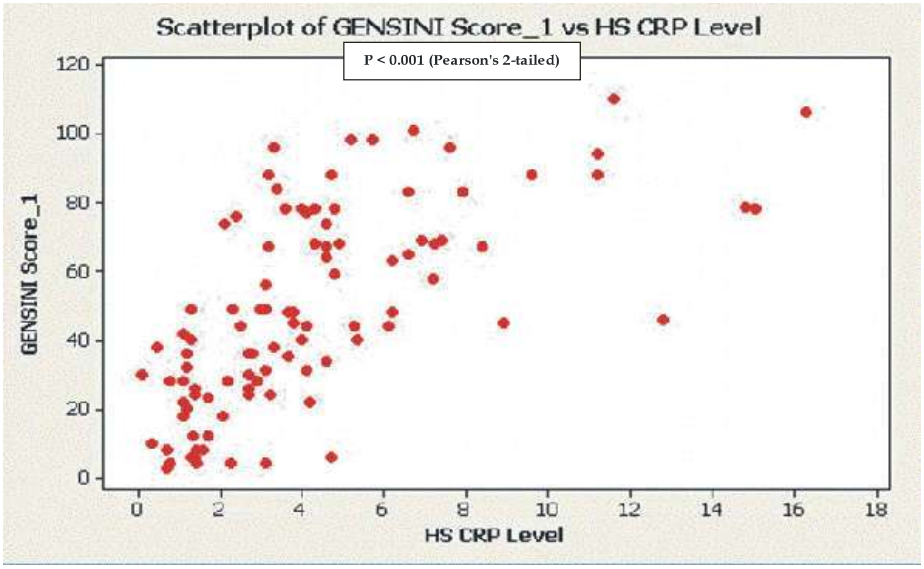

Fig. 2: Correlation between serum hs-CRP levels and angiographic Gensini Score

To examine the independent associations between the Gensini score and serum hs-CRP, multiple linear regression analysis was performed. In this model, the Gensini score was employed as dependent variables and the independent variables including serum hs-CRP, age, sex, smoking status, hypertension, diabetes, dyslipidemia, and family history of CAD/CV death. In the final model (Table 5), diabetes (p=0.040) and serum hs-CRP (*P*=0.000) significantly independently associated with the Gensini score.

Table 5: Predictor of Gensini Score for multiple linear regressions among patients.

Variable	Coef	SE Coef	T value	P value
Constant	0.84	26.77	0.03	0.975
Age	-0.2097	0.2205	-0.95	0.344
Sex	-3.322	8.184	-0.41	0.686
Hypertension	1.195	4.341	0.28	0.784
Diabetes	10.680	5.127	2.08	0.040**
Dyslipidemia	4.068	4.996	0.81	0.418
Smoking	10.802	7.590	1.42	0.158
F/H/O CAD/CV death	4.020	5.124	0.78	0.435
Serum hs-CRP level	4.4228	0.7918	5.59	0.000**

** Significant

Discussion

In recent decades, over 30 epidemiological studies have shown that CRP is associated with cardiovascular risk [4], and there is growing evidence that CRP is not merely a marker of inflammation, but also plays an active role in atherogenesis [5,6]. Studies discussing serum hs-CRP and its correlation with angiographic severity of coronary artery disease (CAD) in patients with acute coronary syndrome are sparse in India.

Serum hs-CRP Level

In our study we showed, the mean value of the serum hs-CRP levels in Indian subjects were 4.18±3.30 mg/L, which is higher to those reported in other ethnic groups [7,8], and is much higher than that reported in Japanese subjects [9], consistent with studies to suggest that the concentration of serum hs-CRP is high in Indians [10-14].

In our study, majority of the patients were having serum hs-CRP level >3 mg/l putting them in high risk category, increased serum hs-CRP serum level in patients with acute coronary syndrome support to a role of serum hs-CRP in plaque vulnerability, which is consistent with another study done by Espligureal R *et al.*, showed that, serum hs-CRP was significantly higher in patients with acute coronary syndrome compared to chronic stable angina (p=0.004) and correlate with complex angiographic lesion (p=0.001) [15].

Serum hs-CRP Level In Different Subgroups

With serum hs-CRP gaining importance as a marker for future cardiovascular events, interest has developed in patient characteristics as well as life-style factors associated with reduced or elevated systemic inflammatory activity.

There are a variety of factors that can influence the concentration of serum hs-CRP. Elevated blood pressure, obesity, smoking, diabetes mellitus, metabolic syndrome, dyslipidaemia and hormone use are the individual characteristics that can increase level of serum hs-CRP along with chronic infection of inflammation. Moderate alcohol consumption, improved fitness, weight loss and medications like statins, fibrates, niacin, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) can decrease the level of hsCRP [16]. Extraneous factors that can influence the concentration are seasonal variation, diurnal influence, age, gender and ethnic differences.

In our study, mean serum hs-CRP in different risk subgroups was significantly higher in those with dyslipidaemia (p=0.000), With diabetes (p=0.021) with a family history of CAD/CVdeath (p=0.017), and with history of smoking (p=0.001), which is consistent with other studies, while it was similar in patients with and without many of the study risk factors/profiles (gender; p=0.300, and hypertension; p=0.396).

Our study cannot prove significant association that history of hypertension is related to the mean serum hs-CRP level , although hypertension was identified as an important risk factor that can increase level of serum hs-CRP [16]. The non-significant association might be attributable to the relatively unawareness of patients to therefore a self-reported history of hypertension can underestimate the diagnosis of hypertension, as found in a recent hypertension survey also [17] and this study was conducted after an ACS, a fact that might have contributed to lower blood pressure than in stable clinical conditions before the ACS.

Regarding sex, men tend to have lower CRP concentrations, (Frohlich et al. [18], Geffken et al. [19]; Hutchinson et al. [20]; Imhof et al. [21]) however some authors report no difference of the CRP concentration by gender (Garcia-Lorda et al. [22]). In our study,

there was no difference of the CRP concentration by gender (p=0.300)

Gensini Score in Different Subgroups

In our study, the mean Gensini score in different risk factors subgroups was significantly higher in those with male sex (p=0.042), with dyslipidaemia (p=0.000), with diabetes (p=0.003) with a family history of CAD/CVdeath (p=0.003), with a history of smoking (p=0.000), than in those without, which is consistent with other studies.

Our study cannot prove that hypertension is related to the mean Gensini score, (p=0.865) although hypertension was identified as an important risk factor for atherosclerosis. The non-significant association might be attributable to the relatively unawareness of patients to therefore a self-reported history of hypertension can underestimate the diagnosis of hypertension, as found in a recent hypertension survey also [17] and this study was conducted after an ACS, a fact that might have contributed to lower blood pressure than in stable clinical conditions before the ACS.

Serum hs-CRP and Coronary Atherosclerotic Burden

The association between the plasma serum hs-CRP levels and the extent of coronary stenosis in subjects remains controversial.

Azar et al. [23] reported no correlation of the serum hs-CRP levels with the extent score and the number of stenotic vessels in 98 patients. However, the correlations were assessed by simple linear correlations.

Zebrack et al. [7] reported the correlations with the numbers of stenotic vessels and segments and the extent score in 2554 patients, but the correlation coefficients were very low (0.02-0.08), and the correlations were evaluated by simple linear correlations.

Erren et al. [24] reported the serum hs-CRP levels to correlate with the extent score using Spearman's rank correlation test, and the correlation coefficient was 0.29. However, these strong univariate associations of markers of inflammation and atherosclerosis were lost in multivariate analysis once age, sex, high density lipoprotein cholesterol, and fibrinogen were taken into account.

Taniguchi et al. [25] reported that after the exclusion of patients with statins, the serum hs-CRP levels were found to correlate with the number of stenotic vessels and better with the numbers of stenotic segments and the extent score (r=0.30 - 0.32). However, in that study, the median value of the serum hs-CRP levels in Japanese patients with coronary heart disease was 0.70 mg/L, which was much lower than those reported in other ethnic groups.

Avanzas et al. [26] correlated CRP level with the number of complex stenosis (irregular border, ulceration or filling defect).

Zairis et al. [27] demonstrated that with increasing of CRP tertile a significant increase in either the number of multiple complex lesions or presence of apparently thrombus containing lesions.

Hasnat MA et al. [28] conducted a study at Dhaka medical college hospital, Bangladesh and showed that high serum hs-CRP associated with angiographically severe coronary artery disease.

Tenzin Nyandak et al. conducted a study at the cardiology department of Safdarjung Hospital New Delhi and showed that high serum hs-CRP associated with angiographically severe coronary artery disease [29].

Ghazala Irfan et al. conducted a study at the department of cardiology, Liquat National Hospital, Karachi, Pakistan and showed that among patients with acute coronary syndrome increased levels of serum hs-CRP correlates with specific high risk coronary artery lesions [30].

Arslan Masood et al. conducted a study at the department of cardiology, Jinnah Hospital, Lahore, Pakistan and showed that Serum hs-CRP levels show significant correlation with the severity [31].

In our study, one hundred ACS patients who underwent coronary angiography were recruited, and Gensini's score was used to define the angiographical characteristics of coronary atherosclerosis. Subjects were assigned to 3 groups according to their serum hs-CRP level. The results of this study indicated that the severity of coronary atherosclerosis significantly associated with the concentration of the plasma hs-CRP by Pearson's correlation (2-tailed) (p = 0.000).

Using ANOVA as the test of significance, the mean angiographic Gensini scores showed increasing trend from lower to higher serum hs-CRP risk groups (p= 0.000).

Moreover, multiple stepwise linear regression analysis demonstrated that high serum hs-CRP was associated with Gensini score independent of age, sex, smoking status, hypertension, diabetes, dyslipidemia and Family history of CAD/CV death.

So far, the correlation of serum hs-CRP level and angiographic score was studied in other ethnic groups. Since in this study, subjects were Indians, the correlation that we observed between serum

hs-CRP and Coronary Atherosclerotic Burden disease in ACS patients is noteworthy, which seems to be in accordance to many studies in Asian Indians where it was found that, as compared to western population, the Asian Indians have diffuse angiographic as well as premature CAD. And this is due to a genetic susceptibility, which magnifies the adverse effects of lifestyle factors associated with urbanisation, affluence, and changes in diet.

Conclusion

Our study found that the severity of coronary atherosclerosis significantly associated with the concentration of the plasma hs-CRP and the mean angiographic Gensini scores, also showed increasing trend from lower to higher serum hs-CRP risk groups. Moreover, high serum hs-CRP was associated with Gensini score independent of age, sex, smoking status, hypertension, diabetes, dyslipidemia and Family history of CAD/CVdeath.

Limitations of our study

Although the results of this study support the hypothesis, there are some facts to be considered which might affect the results:

- Number of study population was limited.
- Angiography could not be done very early after admission.
- Difference of CAG findings between thrombolytic recipients and non-recipients was not compared.
- Angiography was evaluated by visual estimation so there was chance of inter observer and intra observer variation of interpretation of the severity of stenosis.
- Moreover, other putative factors that could affect the predictive power of serum hs-CRP (e.g. nutritional status and physical activity) were not included in the regression analyses.
- This study was conducted after an ACS, a fact that might have contributed to lower lipid levels and blood pressure than in stable clinical conditions before the ACS. In addition, at this time, high fasting glucose levels could be related to stress-induced

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