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Original Research Article

High-sensitivity C-reactive protein and interleukin-6 as risk predictors in patients with stable angina pectoris

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ABSTRACT

Background: Cardiovascular diseases are a leading cause of morbidity and mortality especially in developing countries such as India. Biomarkers such as high-sensitivity C-reactive protein (Hs-CRP) and interleukin-6 (IL-6) can help in risk stratification and better management of patients with stable angina.
Methods: This was a prospective observational study wherein symptomatic patients with stable angina were enrolled. Coronary angiogram was done in those consenting to the procedure. Severity of coronary stenosis was graded as per the modified Gensini score (mGS). Hs-CRP and IL-6 levels were determined pre-procedure and 24 hours post percutaneous coronary intervention (PCI). Based on angiographic profile, patients were subdivided into four groups: group 1: normal coronaries, group 2: single vessel disease, group 3: double vessel disease and group 4: triple vessel disease. Primary outcome was occurrence of major adverse cardiovascular events over one-year period.
Results: A total of 158 patients completed the study with a mean age of 62.8±9.6 years. A significant difference was observed between the four groups in terms of age, Hs-CRP and IL-6 levels. Of the 124 patients undergoing PCI, significant difference was observed in terms of pre and post procedure Hs-CRP ($P<0.0001$) and IL-6 levels ($P<0.0001$). Strong positive correlation was seen between Hs-CRP and IL-6 levels with modified Gensini scoring (mGS). Patients with MACE (15/158; 9.4%) had significantly higher levels of Hs-CRP and IL-6. Multivariate logistic regression analysis revealed that Hs-CRP, IL-6, ΔHs-CRP and ΔIL-6 were independent predictors of major adverse cardiovascular events (MACE).
Conclusions: Hs-CRP and IL-6 levels were independent predictors of outcomes and can be used for risk stratification in these patients.

Keywords: Angina pectoris, Biomarkers, Coronary angiogram, Coronary artery disease, Interleukin-6, High sensitivity C-reactive protein

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading cause of death worldwide accounting for nearly one-third of all the deaths.[1] In India, CVD accounts for nearly a quarter (24.8%) of all deaths with a majority of them (52.4%) occurring below 70 years of age.[2] Atherosclerosis, the underlying pathology responsible for CVD, is a chronic inflammatory process.[3] It has been seen that atherosclerosis is often characterized by the presence of a low-grade inflammation which alters the endothelial lining of the coronary arteries.[4] This is associated with an increase in the level of various inflammatory markers such as acute phase proteins and cytokines. Previous studies

have suggested that inflammation both at local and systemic levels has an important role to play in the destabilization and rupture of atherosclerotic plaques leading to acute coronary events.[5] Recently the focus has shifted from a risk factor based assessment to the use of blood based biomarkers of inflammation in order to improve the risk stratification and determine patient groups who would readily benefit from a particular treatment strategy. Among these, high sensitivity C-reactive protein (Hs-CRP), a prototype marker of the inflammatory process, has been the most studied factor both for the causation as well as the prediction of CVD.[6] In addition, cytokines such as interleukin-6 (IL-6) plays an important role in the chronic inflammatory process and development of atheromatous plaques.

Hs-CRP and IL-6 both are pleiotropic cytokines with a wide impact on cellular and humoral immune response thus serving as marker of inflammation, host defence and tissue injury. IL-6 is a proinflammatory cytokine which has stimulatory effects on T- and B-lymphocytes and leads to the synthesis of acute-phase proteins such as CRP and fibrinogen. In addition, IL-6 leads to increased production of major chemoattractant protein-1 which is a major chemoattractant for monocytes and hence plays a role in lymphocyte activation. All of these suggest that both Hs-CRP and IL-6 can be a marker for inflammatory states in patients with stable angina.[4-6]

This study aims to determine the serum levels of Hs-CRP and IL-6 in patients with stable angina pectoris and its correlation with severity of the disease. In addition, we also envisaged to determine the short-term prognostic significance of Hs-CRP and IL-6 pre and post coronary angioplasty in patients with stable angina pectoris.

METHODS

This was a single center prospective observational study carried over a two-year period in the Department of Cardiology, SMS Medical College, Jaipur. All patients >18 years diagnosed with chronic stable angina (Canadian Cardiovascular Society class 3 or more) which was defined as chest pain brought on by exertion and relieved on rest, with symptoms persisting despite optimal medical therapy. All the enrolled patients had a positive electrocardiogram (ECG) exercise stress test response (>1 mm ST-segment depression). The following patients were excluded: features suggestive of acute coronary syndrome (ACS) at screening or a history of ACS in previous three months; history of previous coronary artery bypass grafting, percutaneous coronary intervention, surgery or trauma in the past three months; valvular heart disease, heart failure or left ventricular ejection fraction (LVEF) <30%; chronic kidney disease, hepatic dysfunction, acute and chronic infections; anemia, peripheral vascular disease or history of autoimmune diseases; inability to provide informed consent or to follow-up after discharge; and co-existing conditions associated with a limited life expectancy of less than six months.

In all these patients, detailed clinical history including symptomatology, presence of CVD risk factors, family history and prior evidence of CVD were recorded. In addition, blood samples for routine hematological and biochemical parameters were collected on admission. Twelve lead electrocardiogram and echocardiographic assessment were carried out with LVEF being estimated using the bi-plane Simpson's method. Coronary angiogram was performed in all patients consenting for the procedure and revascularization (percutaneous coronary intervention [PCI]) in those as deemed necessary by the treating physician based on clinical risk assessment and severity of the lesion. Standardized definitions of all patient-related variables and clinical diagnoses were used.

Hs-CRP and IL-6 assessment

Serum levels of Hs-CRP (diagnostics Biochem Canada Inc.) and IL-6 (diaclone immunoassay, France) were determined using the enzyme linked immunosorbent assay (ELISA) techniques.[7,8] Commercially available ELISA kits were used for both Hs-CRP and IL-6 levels determination with the sensitivity of the Hs-CRP ELISA kit being 10 ng/ml and that of IL-6 being <2 pg/ml. In all these patients, after an overnight fast, 5 ml of venous blood sample was taken in the morning prior to the performance of an angiogram. Samples were allowed to form clot at room temperature following which they will be transferred to laboratory on ice and centrifuged at 3000 cycles/minute within half an hour. The supernatant from the centrifuge were divided into two aliquots and stored at -80°C until the time of analysis. In addition in all those patients undergoing PCI and consenting to be a part of the study, a repeat 5 ml of venous blood sample was withdrawn 24 hours post PCI.

Angiographic analysis

Angiographies were performed according to the standard Judkins technique in all patients post a written informed consent regarding the procedure. Images of the coronary tree were obtained in routine projections in all patients and reviewed separately by two experienced cardiologists who were unaware of the patient's details including the results of immunoassays. Coronary stenosis was considered only if there was more than 50% reduction in luminal diameter of coronary artery. Based on the presence or absence of coronary stenosis in major coronary arteries, patients subdivided into four groups: group 1: those without CAD, if no coronary artery showed a reduction in lumen diameter ≥ 50%; group 2: those with single vessel disease (SVD), if stenosis was detected in only one coronary artery; group 3: those with double vessel disease (DVD), if stenosis was detected in two coronary arteries and; group 4: those with triple vessel disease (TVD), if stenosis was detected in three coronary arteries. The severity of the coronary artery disease was quantified using the modified Gensini scoring (mGS) system.[9] This is an angiographic scoring system which determines the degree of coronary artery involvement based on the stenosis severity of eight major

coronary branches. These would include left main stem, left anterior descending, diagonal branch, 1st septal perforator, left circumflex artery, marginal or posterolateral branch, right coronary artery and main posterior descending artery. The scoring system is: 0 for no stenosis; 1 for 1-49% stenosis; 2 for 50-74% stenosis; 3 for 75-99% stenosis and 4 for total occlusion. Based on the degree of stenosis, all the vessel scores were summed and a total angiographic score between 0-32 was assigned to each individual.[9]

Outcomes

All the patients were followed up for a period of one year to determine major adverse cardiovascular events (MACE) which was defined as occurrence of either death, myocardial infarction, unstable angina or and any coronary revascularization (surgery and/or PCI). A written informed consent was obtained from all eligible patients prior to inclusion in the study which was approved by the institutional review board.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean value and standard deviation while count variables were expressed as frequencies and percent values. The normality of distribution of data was assessed through the Shapiro-Wilks test. Statistical comparison of baseline characteristics was performed using the chi-square test for categorical variables while one-way analysis of variance (ANOVA) was used for the continuous variables. In addition, post-hoc analysis was performed by the Tukey multiple comparison tests. Correlation between Hs-CRP as well as IL-6 levels were performed by the Pearson product-moment correlation coefficients. Univariate and multivariate logistic regression analysis was used to assess the association between Hs-CRP and/or IL-6 levels with the outcome while adjusting for other potential confounders. In addition, receiver operating characteristic (ROC) curves were computed to relate the Hs-CRP and IL-6 levels with outcome. Area under the curve (AUC), or c-statistic was used as a measure of the predictive accuracy of these biomarkers with the diagnostic ability of classified as "excellent" if AUC, or c-statistic values were ≥0.9, "good" if AUC were ≥0.80, "fair" if AUC were ≥0.70 and "poor" if AUC were <0.7010. Data analysis was done using the Statistical Package for the Social Sciences (SPSS) software package version 24 (SPSS, Chicago, Illinois, USA). P values <0.05 shall be considered significant.

RESULTS

A total of 172 patients were enrolled in the study of whom 14 patients were excluded as a result 158 patients completed the study. The mean age of the patients was 62.8±9.6 years (range: 40-88 years) with a male predominance (57.6%). Hypertension was the most common co-morbidity seen in 51 (32.2%) patients followed by diabetes in 16 (26.5%) and dyslipidaemia in 32 (20.2%). The mean Hs-CRP levels were 3.44±1.00 mg/l in the study population while the mean IL-6 levels were 87.80±12.25 pg/ml. All the patients underwent coronary angiogram with normal epicardial coronaries reported in 15 (9.6%) subjects. SVD was the most common abnormality in 50 (31.6%) patients followed by triple vessel disease in 47 (29.7%) and double vessel disease in 46 (29.1%) subjects. Left anterior descending artery (LAD) was the most commonly involved coronary artery in 110 (39.9%) patients followed by right coronary artery (RCA) in 79 (28.7%), left circumflex artery (LCX) in 68 (24.3%) and left main coronary artery (LM) in 21 (7.1%) subjects. The mean mGS in the study population was 4.93±4.30 with 124/158 (78.5%) subjects undergoing PCI. Based on the coronary angiographic profile, patients were subdivided into four groups: group 1: normal epicardial coronaries (n= 15), group 2: SVD (n= 50), group 3: DVD (n= 46) and group 4: TVD (n=47) (Table 1).

Table 1: Demographic parameters of all patients with stable angina (n=158).

Parameters	Patients
Mean age (in years)	62.8±9.6 (40-88)
Male/females	91 (57.6%)/67 (42.4%)
Smoking	65 (41.1%)
Hypertension	51 (32.2%)
Diabetes mellitus	16 (26.5%)
Dyslipidemia	32 (20.2%)
Hs-CRP (mg/l)	3.44±1.00 (0.57-6.81)
IL-6 (pg/ml)	87.80±12.25 (55.54-120.06)
Total cholesterol (mg/dl)	180.59±34.27
Triglyceride (mg/dl)	148.06±70.9
LDL cholesterol (mg/dl)	89.81±21.04
HDL cholesterol (mg/dl)	54.03±11.76
Coronary angiogram	158 (100%)
Lesion profile	
Normal epicardial coronaries	15 (9.6%)
Single vessel disease	50 (31.6%)
Double vessel disease	46 (29.1%)
Triple vessel disease	47 (29.7%)
Vessels involved	
Left main	21 (7.1%)
Left anterior descending	110 (39.9%)
Left coronary circumflex	68 (24.3%)
Right coronary artery	79 (28.7%)
Modified Gensini score	4.93±4.30 (0-32)
Undergoing percutaneous coronary intervention	124/158 (78.5%)

*HDL: high density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; IL-6: interleukin-6; LDL-C: low density lipoprotein; mg/dL: milligram per decilitre; mg/L: milligram per litre; pg/mL: picogram per millilitre

There was a significant difference between the four groups in terms of age, baseline Hs CRP and IL-6 as well as the mGS. Patients with TVD has significantly higher baseline levels of Hs-CRP and IL-6. No difference was observed between the three groups in terms of sex distribution, co-morbidities such as hypertension or diabetes and smoking status. In addition, haematological and biochemical parameters such as haemoglobin, total leucocyte counts, blood urea, serum creatinine and electrolytes were similar between the four groups (Table 2). Post-hoc analysis revealed that there was a significant difference between all the groups in terms of Hs-CRP (group 1 versus 2: p<0.0001; group 1 versus 3: p<0.0001; group 1 versus 4: p<0.0001; group 2 versus 3: p<0.0001; group 2 versus 4: p<0.0001 and group 3 versus 4: p=0.008), IL-6 levels (group 1 versus 2: p<0.0001; group 1 versus 3: p<0.0001; group 1 versus 4: p<0.0001; group 2 versus 3: p<0.0001; group 2 versus 4: p<0.0001 and group 3 versus 4: p=0.006) and mGS (group 1 versus 2: p=0.03; group 1 versus 3: p<0.0001; group 1 versus 4: p<0.0001; group 2 versus 3: p<0.0001; group 2 versus 4: p<0.0001 and group 3 versus 4: p<0.0001).

Pre and post-procedure Hs-CRP and IL-6

Of the 158 patients, PCI was done in 124 (78.5%) of them. There was a significant difference in terms of pre and post procedure Hs-CRP (pre-procedure: 3.60±0.86 versus post-procedure: 8.93±2.83; p<0.0001) and IL-6 levels (pre-procedure: 89.48±11.17 versus post-procedure: 142.89±18.91; p<0.0001). Both the post-procedure Hs-CRP and IL-6 levels were significantly different among the three groups with the highest levels reported in patients with TVD. In addition, the mean difference i.e. ΔHs-CRP (calculated as the difference between post-procedure and pre-procedure Hs-CRP) and ΔIL-6 (calculated as the difference between post-procedure and pre-procedure IL-6) were significantly higher among patients with TVD as compared to the other two groups (Table 2).

Correlation: IL-6 and Hs-CRP levels

There was a very strong positive correlation seen between baseline Hs-CRP and IL-6 levels [Figure 1] which was highly significant (r=0.978 [95% CI: 0.970-0.984]; p<0.0001) and a strong correlation between baseline Hs-CRP and modified Gensini score (r=0.754 [95% CI: 0.678-0.814]; p<0.0001) as well as baseline IL-6 and modified Gensini score (r=0.748 [95% CI: 0.670-0.809]; p<0.0001) (Figure 1, 2a and 2b).

Outcomes

MACE was observed in 15/158 (9.4%) patients with a significantly higher frequency seen among diabetics and patients with prior history of stroke. Patients with MACE had significantly higher levels of baseline Hs-CRP and IL-6. In addition, among those patients who underwent PCI and had MACE, post-procedure Hs-CRP and IL-6 as well as Δ Hs-CRP and Δ IL-6 levels were significantly higher than those without MACE (Table 3). A ROC curve was plotted to evaluate the predictive ability and cut-off values of baseline Hs-CRP and IL-6 levels as well as that for Δ Hs-CRP and Δ IL-6 levels for prediction of MACE (Figure 3 and 4). ROC analysis showed that the AUC for Hs-CRP was 0.70 (p=0.01) while that of IL-6 was 0.67; (p=0.03). The cut-off levels of Hs-CRP for prediction of MACE was 3.4 mg/l with a sensitivity of 80% and a specificity of 52.3%. Similarly, the cut-off levels of IL-6 were 85.86 pg/ml with a sensitivity of 73.3% and a specificity of 51.7%. The AUC values for Δ Hs-CRP was 0.741 (p=0.003) and that for Δ IL-6 levels was 0.761 (p=0.001). The cut-off levels of Δ Hs-CRP was 6.09 with a sensitivity of 80% and a specificity of 72.5% while that for Δ IL-6 levels was 50.1 pg/ml with a sensitivity of 80% and a specificity of 52.3% (Figure 3).

Univariate logistic regression analysis showed that TVD (OR: 1.49; 95% CI: 0.91-1.95; p=0.05), mGS (OR:1.15; 95% CI:1.05-1.26; p=0.002), serum creatinine (OR: 1.40; 95% CI: 1.15-5.54; p=0.001), baseline IL 6 (OR: 1.06; 95% CI: 1.04-1.11; p=0.015), baseline Hs CRP (OR: 2.42; 95% CI: 1.30-4.50; p=0.005), post procedure Hs-CRP (OR: 1.41; 95% CI: 1.13-1.76; p=0.002), post procedure IL-6 (OR: 1.26; 95% CI: 1.1-1.42; p=0.002), Δ Hs-CRP (OR:1.54; 95% CI: 1.17-2.03; p=0.002) and Δ IL-6 (OR: 1.19; 95% CI: 1.1-1.35; p=0.002) were independent predictors of MACE. Multivariate logistic regression analysis revealed that baseline Hs-CRP, baseline IL-6, ΔHs-CRP and ΔIL-6 were independent predictors of MACE (Table 4).

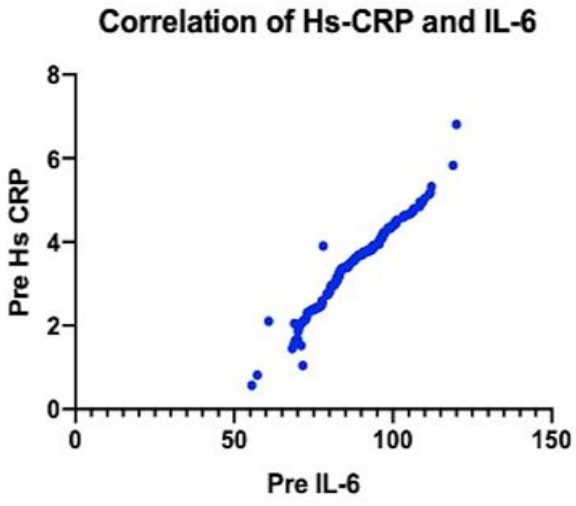

Figure 1: Scatterplot showing correlation between baseline Hs-CRP and IL-6 levels.

Table 2: Comparison of demographic, clinical and biochemical parameters between the groups.

Parameters	Normal coronaries	Single vessel disease (n=50)	Double vessel disease (n=46)	Triple vessel disease (n=47)	P-value
Age	56.6±7.4	61.9±9.9	65.4±9.5	63.4±9.2	0.015
Male	7 (46.6%)	26 (52%)	30 (65%)	28 (59.5%)	0.46
Female	8 (53.4%)	24 (48%)	16 (35%)	19 (40.5%)	0.46
Smoking	4 (26.6%)	18 (36%)	23 (50%)	20 (42.5%)	0.37
Hypertension	4 (26.6%)	14 (28%)	20 (43.4%)	13 (27.6%)	0.20
Diabetes Mellitus	1 (6.6%)	11 (22%)	9 (19.5%)	11 (23.4%)	0.31
Dyslipidemia	4 (26.7%)	6 (12%)	11 (23.9%)	11 (23.4%)	0.16
Stroke	0(0%)	2 (3.1%)	1(2.1%)	3 (6.3%)	0.14
MACE	0	1(2%)	6 (13%)	8 (17%)	0.009
Baseline Hs-CRP (mg/l)	1.82±0.72	2.92 ± 0.70	3.73±0.63	4.20±0.73	<0.0001
Baseline IL-6 (pg/ml)	70.49±7.19	81.25±8.80	90.97 ± 8.52	97.17±9.93	<0.0001
Modified Gensini Score	0	2.8±1.1	5.4±2.1	8.3±5.7	0.0001
Haemoglobin (g/dl)	13.8±1.9	13.5±1.6	13.7±1.8	13.6±2.0	0.88
Total leucocyte count (per mm^3)	9.5±3.1	9.8±1.9	12.8±1.9	12.8±1.9	0.80
Platelet count (lakh/mm3)	1.9±0.7	2.3±0.8	2.1±0.7	2.1±0.7	0.34
Haematocrit (%)	44.4±5.2	44.7±4.1	45.2±5.0	44.6±5.1	0.99
Random blood sugar (mg/dl)	135.4±68.5	140.1±73.1	140.5±77.1	144.8±62.7	0.97
Urea (mg/dL)	36.8±16.3	33.7±14.6	32.1±10.4	40.1±31.1	0.25
Serum Creatinine (mg/dl)	1.2±0.3	1.1±0.3	1.1±0.2	1.2±0.4	0.40
Serum sodium (mEq/l)	137.3±2.5	137.8±3.9	137.7±4.0	138.8±4.4	0.98
Serum potassium (mEq/l)	4.4±0.2	4.3±0.4	4.2±0.4	4.3±0.4	0.68
Post procedure Hs-CRP (mg/l)		6.1±1.4	9.7±1.8	11.3±2.3	<0.0001
Post procedure IL-6 (pg/ml)		124.4±12.7	148.6±10.8	157.9±14.0	<0.0001
ΔHs-CRP (mg/l)		3.1±1.1	5.9±1.5	7.1±1.8	<0.0001
ΔIL-6 (pg/ml)		42.8±9.7	57.5±8.5	61.1±9.3	<0.0001

*MACE: major adverse cardiovascular event; mEq/L: milli-equivalent per litre;

Table 3: Comparison of the parameters between MACE and no MACE sub-groups.

	MACE (n=15)	No MACE (n=143)	P-value
Mean age (in years)	63.86 ± 10.61	62.76 ± 9.52	0.673
Sex (males)	10/15(66.7%)	81/143(56.6%)	0.455
Smoking	5/15(33.3%)	60/143(41.9%)	0.518
Hypertension	4/15(26.7%)	47/143(32.8)	0.625
Diabetes Mellitus	6/15(40%)	26/143(18.19)	0.045
Dyslipidemia	1/15(6.6%)	31/143(21.7%)	0.169
History of stroke	2/15(13.3%)	4/143(2.8%)	0.042
Pre Hs-CRP (mg/l)	4.16±1.07	3.36±0.97	0.001
Pre IL-6 (pg/mL)	95.28±13.38	87.01±11.90	0.012
Post Hs-CRP* (mg/l)	11.23±2.88	8.61±2.68	0.003
Post IL-6* (pg/ml)	157.74±18.68	140.84±18.09	0.001
Δ hs-CRP* (mg/l)	7.07±2.17	5.08±2.11	0.001
Δ IL-6* (pg/ml)	62.45±11.33	52.11±11.79	0.002

Table 4: Independent predictors of MACE: multivariate logistic regression analysis.

	Odds Ratio	95% Confidence Interval	P-value
Baseline IL-6 (pg/mL)	2.81	1.56-4.46	0.023
Baseline Hs-CRP (mg/L)	3.84	1.23-5.32	0.012
Triple vessel disease	0.90	0.21-3.89	0.891

Continued.

	Odds Ratio	95% Confidence Interval	P-value
Modified Gensini score	1.03	0.85-1.25	0.721
Serum Creatinine (mg/dL)	1.11	0.89-2.01	0.041
Δ Hs-CRP (mg/L)	1.84	1.17-2.42	0.011
Δ IL-6 (pg/mL)	1.55	1.13-1.82	0.032

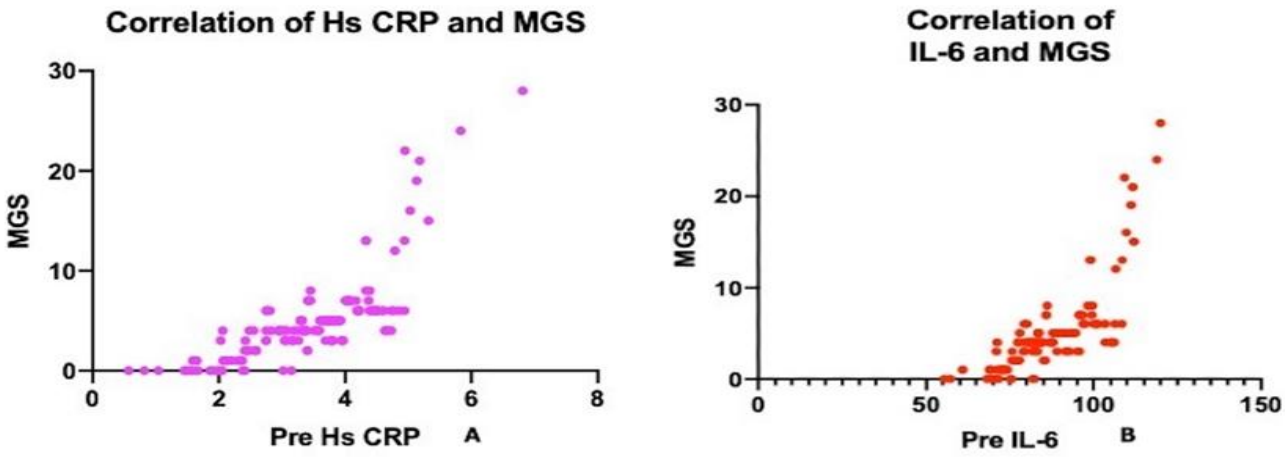

Figure 2: Scatterplot showing correlation between baseline (a) Hs-CRP and modified Gensini scores, (b) IL-6 levels and modified Gensini scores.

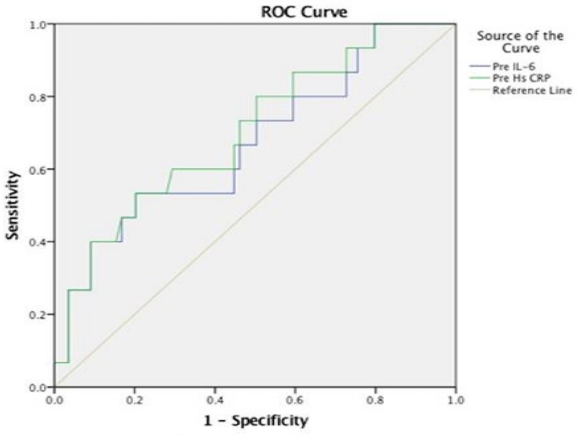

Figure 3: Receiver operating curve analysis for Hs-CRP and IL-6 as a predictor of MACE.

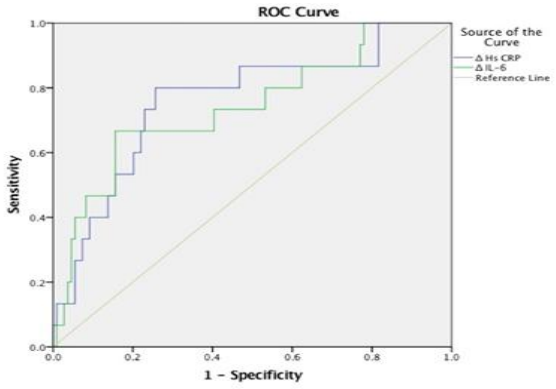

Figure 4: Receiver operating curve analysis for ΔHs-CRP and ΔIL-6 as a predictor of MACE

DISCUSSION

Hs-CRP and IL-6 have been extensively evaluated in patients with acute coronary syndrome (ACS), however data regarding its role in patients with stable angina pectoris seems to be conflicting. The findings in our study showed that both Hs-CRP and IL-6 increased with an increase in severity of CAD. In addition, baseline levels of both Hs-CRP and IL-6 were independent predictors of MACE. This highlights the putative role of these inflammatory biomarkers in patients with stable angina and its impact on outcomes. Although uncertainty exists in few studies regarding Hs-CRP as a marker of severity in patients with stable angina, case-control and cross-sectional studies have shown a strong association.[11-16] However, a meta-analysis clearly indicated that even after the correction of a number of important factors in heart disease, Hs-CRP remained a risk factor and a powerful predictor of CV events.[17] The role of Hs-CRP as a prognostic marker has been highlighted in the studies by Sinning et al which showed that Hs-CRP has some prognostic benefit however, it adds little to the risk stratification compared with the traditional risk factors.[18] Similarly, a sub study of the prevention of events with angiotensin-converting enzyme inhibition (PEACE) trial comprising 3771 patients showed that a baseline Hs-CRP >1mg/L was associated with significantly higher risk of cardiovascular death, myocardial infarction (MI) and stroke.[19] Mokhtar et al proposed a cut-off level of >5 mg/L for Hs-CRP for prediction of MACE (sensitivity: 93.7% and specificity: 100%).[20] In this study, baseline Hs-CRP >3.4 mg/L had a sensitivity of 80% and a specificity of 52.3% to predict MACE. In patients with stable angina, elevated IL-6 levels occur due to release from various cells

including the vascular smooth muscle cells as well as the macrophage and the foam cells in atheromatous plaques. In the study by Mokhtar et al, a significant increase in serum level of IL-6 was seen in patients with stable CAD as compared to non-CAD patients.[20] This finding was consistent with those of Sarrafzadegan et al, Tang et al and Caselli et al who too had reported higher concentrations of IL-6 in patients with stable angina.[21-23] In addition, IL-6 levels also reflect the degree of vascular inflammation and the severity of CAD. Mokhtar et al found significant increase in serum level of IL-6 in MVD and SVD patients as compared with non-CAD patients, a finding seen in our patients too.[20] This finding is in accordance with that of Liu et al who too had reported higher serum levels of IL-6 in patients with multivessel disease as compared with control group.[24] In our study, we observed a significant correlation with IL-6 levels and mGS, a finding reported by Tanidi et al.[25] However, Mohktar et al found no association between IL-6 levels and the Gensini score.[20]

Prognostic significance of Hs-CRP and IL-6 pre and post angioplasty

Acute inflammatory response is an initial consequence of PCI due to the exposure of the thrombogenic surface of the vessel wall to circulating leucocytes and through the recruitment of inflammatory cells from the overstretched adventitia.[4] PCI especially stent implantation stimulates the arterial intimal cellular proliferation and extracellular matrix synthesis which is mediated largely by inflammatory processes.[4,6] In addition, stent deployment can cause a foreign body reaction further amplifying the inflammatory response. It is still not clear in stable CAD patients whether the magnitude of increase in Hs-CRP post PCI is an independent prognostic marker. In the study by Gach et al, of the 89 stable CAD patients treated by PCI, MACE was observed in 36 patients. Multivariate analysis reported that a prior history of myocardial infarction and a significant increase in Hs-CRP post PCI (P=0.004 and 0.003, respectively) were independent predictors of MACE. In this study, the authors found that a significant increase in Hs-CRP post PCI (ΔHs-CRP) was more predictive of MACE than levels of Hs-CRP pre and post PCI.[26] In our study, both baseline Hs-CRP levels and increase post PCI (ΔHs-CRP) were independent predictors of MACE.

Previous studies have shown a significant association between pre-procedural CRP levels and subsequent cardiac events in patients treated with bare metal stent (BMS).[27,28] However, the predictive role of Hs-CRP for adverse outcomes in patients implanted with mixed BMS and drug-eluting stent (DES) or only DES implantations has been controversial.[29,30] In a study among 513 patients undergoing non-urgent PCI, high levels of Hs-CRP was associated with a greater risk of periprocedural MI but not mortality. Xu et al investigated the role of Hs-CRP level both at admission and follow-up in 303 patients with stable angina to determine its predictive value for in-stent restenosis (ISR). The authors concluded that plasma Hs-CRP levels both at admission and on follow-up were independent predictors of ISR in stable CAD patients with DES implantation.[31] Similarly, a meta-analysis comprising six studies reported that high levels of Hs-CRP were associated with an increased risk of ISR.[32] Previous studies done in patients with unstable angina have shown that elevated levels of IL-6 post PCI was an independent predictors of cardiac death or MI and MACE.[33] However, its role as a predictive tool for MACE post PCI is less clear. Hojo and colleagues had for the first time demonstrated a correlation between the rise of IL-6 concentration post PCI and the risk of late restenosis.[34] However, a limited sample size (32 subjects) was one of the major study limitations. In a study among 216 patients with stable CAD undergoing elective PCI, baseline IL-6 levels were not predictive of ISR.[35] In our study, we found both baseline IL-6 levels as well as increase in IL-6 levels post PCI (ΔIL-6) to be independent predictors of MACE. We also for the first time proposed a cut-off level of IL-6 as well as ΔIL-6 as a predictor of MACE.

One of the important limitations of our study was that it was a single center study with a limited sample size. Since, we had enrolled only patients with stable angina (CCS class III or more) who were symptomatic despite being on GDMT over a short enrollment period, our sample size was small. Another limitation to our study was a short duration of follow-up. Multiple multicentric studies are needed in order to support the hypothesis regarding the role of Hs-CRP and IL-6 as one of the risk predictors in stable CAD patients.

CONCLUSION

A strong quantitative correlation was observed between increased Hs-CRP and IL-6 levels with future major adverse cardiac events in a population with stable angina. Quantitative determination of these biomarkers were found which might contribute to a better risk stratification over and above the traditional risk factors in these patients. These biomarkers can be developed as a prognosis indicator post PCI however, there is a need of larger multi-centric studies to further validate the cut-offs values of Hs-CRP and IL-6 proposed by us.

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