Exploring the Association of Fibrinogen and CRP with the Clinical Spectrum of CAD and Periprocedural Outcomes in Patients Undergoing Percutaneous Coronary Interventions

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ABSTRACT

Background: The pathophysiology of an atherosclerotic plaque is mediated by the mechanisms involving thrombus formation and systemic inflammation. While C-reactive protein (CRP) levels are useful in predicting a cardiovascular event in intermediate risk population, the usefulness of routinely measuring fibrinogen in patients with acute coronary syndrome (ACS) is debatable. Also, data on the association of these markers with periprocedural outcomes in patients undergoing percutaneous coronary interventions (PCI) is scarce.

Aims: The study aimed to determine whether the levels of fibrinogen and CRP vary across the different spectra of CAD and whether they have any correlation with cardiac Troponin I levels.

Materials and Methods: A total of 284 patients with coronary artery disease undergoing percutaneous coronary intervention were included in the study. Complete blood count, serum lipid profile, serum CRP, fibrinogen, and troponin I were measured for all patients.

Results: Patients with STEMI had significantly higher levels of CRP as compared to those with unstable angina (USA) and chronic stable angina (CSA). Patients presenting with ACS had significantly higher baseline fibrinogen as compared to those with CSA. A significant positive correlation between CRP and admission Troponin I ($r = 0.50; P < 0.05$) as well as fibrinogen and admission troponin I ($r = 0.30; P < 0.05$) was observed.

Conclusions: The levels of the markers of inflammation and atherothrombosis vary with presentation across varied spectra of CAD with generally higher levels in acute presentation and in those who develop periprocedural MI.

Keywords: CRP, fibrinogen, percutaneous coronary interventions, troponin

INTRODUCTION

The pathophysiology of an atherosclerotic plaque is thought to be mediated by the mechanisms including accumulation of lipids within the vessel wall, thrombus formation, increased concentrations and activity of coagulation factors, and decreased activity of antithrombotic factors and fibrinolytic system.$^{[1,2]}$ Some data also implicate the underlying systemic and coronary inflammations leading to accelerated progression and precipitation of atherothrombosis.$^{[3,4]}$ Autopsy studies have revealed active inflammation at the sites of plaque rupture in patients
with acute coronary syndromes (ACS) which is also associated with the increased markers of inflammation and atherothrombosis like fibrinogen and C-reactive protein.[5-7]

As an acute phase reactant involved in the final common pathway of the coagulation cascade and as an essential component of platelet cross-linking in thrombus formation, fibrinogen possesses a clear biological mechanism for potentially having adverse cardiovascular effects. Although studies have investigated the relationship of biological markers of inflammation like fibrinogen and CRP with cardiovascular (CV) events and future CV risk, whether the use of these markers provides any incremental risk prediction beyond that provided by cardiovascular risk factors is still not clear.[8-13] The elevated levels of such acute phase reactants in patients with ACS could very well be a marker of widespread underlying vascular inflammation and hyperresponsiveness of the inflammatory system leading to plaque instability.

While the measurement of the CRP levels is considered useful in the stratification of patients at intermediate risk for a cardiovascular event, the usefulness of routinely measuring fibrinogen and other biomarkers of inflammation in patients with ACS is debatable.[14,17]

Apart from concerns about precisions in assay analysis and standardization, it is not clear whether measuring fibrinogen provides additive value over and above that conferred by hs-CRP, given the positive intercorrelation between these inflammatory biomarkers. The fibrinogen levels may reflect both an inflammatory and a prothrombotic state because the risk associated with higher fibrinogen levels was only partially accounted for by the higher hs-CRP levels. Attenuation of the risk associated with fibrinogen after adjustment for hs-CRP, and vice versa, may be explained by potential confounding, or possible mediation, of some of the effect of fibrinogen via inflammation.

Although previous studies have assessed the relationship of fibrinogen and CRP with existent or future development of CVD, data on their association with the clinical spectrum of CAD and periprocedural outcomes in patients undergoing percutaneous coronary interventions (PCI) are scarce.

The aim of the current study was to determine
1. Whether the markers of vascular thrombosis and inflammation viz. fibrinogen levels and CRP are different in patients across the clinical spectrum of CAD and have any correlation with cardiac troponin I which is a known marker of myocardial injury.
2. Whether the elevated baseline levels of fibrinogen and CRP are helpful in predicting the outcomes (including per-procedural MI or major adverse cardiac events at follow up) among patients undergoing PCI.

MATERIALS AND METHODS

A total of 284 patients admitted at our institute between December 2016 and November 2018 who were scheduled to undergo PCI were included in the study. Patients with unstable angina pectoris, ST-elevation myocardial infarction, or non-ST-elevation myocardial infarction were considered to have acute coronary syndrome (ACS).

We excluded individuals who had a history of recent surgery, trauma, peripheral arteriopathy, hepatic insufficiency, renal insufficiency (creatinine >1.5 mg/dl), malignancy, febrile disorders, or acute or chronic inflammatory disease; persons who had autoimmune diseases with or without immunosuppressive therapy, and anyone who was on anticoagulant treatment.

Baseline demographic information and laboratory data including complete blood count (TLC, ESR, and platelet counts), complete lipid panel, serum C-reactive protein (CRP), fibrinogen and troponin I were obtained from all subjects. Troponin-I levels were measured every 8 h following PCI until hospital discharge or up to 24 h to assess the degree of myocardial injury, if any. All patients underwent PCI as per institutional protocol. Periprocedural MI was defined according to the 2018 Fourth Universal Definition of Myocardial Infarction.[18]

Plasma fibrinogen levels were determined via the Clauss method and by using a BBL semiautomated fibrometer (BD Diagnostic Systems; Sparks, Maryland). CRP was measured by the nephelometric method by using a Siemens nephelometer. A cut-off of ≤0.3 mg/dl for CRP and <350 mg/dl for fibrinogen were considered as the upper limits of normal.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. The study conformed to the institutional ethical guidelines and all patients were included after obtaining informed consent.

Statistical analysis

All laboratory data were collected from the patients’ records. Data were expressed as mean ± SD. Continuous variables among the four groups were compared via one-way ANOVA for parametric data. Frequency variables were
compared by means of the c2 test. The variables in the study were age, sex, CRP level, white blood cell (WBC) count, plasma fibrinogen level, diabetes mellitus, dyslipidemia, arterial hypertension, smoking, and troponin-I. Plasma fibrinogen level and CRP were dichotomized into binary predictors. The cutoff points were ≥0.3 mg/dl mg/dl for CRP and ≥350 mg/dl for plasma fibrinogen level. The confidence intervals (CIs) corresponded to the 95% level. Differences were considered to be significant when the P value was less than 0.05. The data conformed to each test by which they were analyzed. All statistical analyses were performed by using SPSS version 23.0 software (SPSS, Inc.; Chicago, Ill) on a Windows XP platform.

RESULTS

Baseline characteristics of study population
Table 1 depicts the baseline demographic data of the study population (mean age 57.5 ± 10.36 yr, range 24-94 yr, 71% males). While 20% of the patients were younger than 50 years, 12% belonged to the age group >70 years. Of all 284 study participants, 135 had arterial hypertension (47%), 98 had diabetes mellitus (34%), and 82 patients (29%) were smokers. Mean LDL, HDL, total cholesterol, triglyceride, and VLDL levels were 110.13 ± 37.89; 45.52 ± 9.70; 183.97 ± 39.98; 110.13 ± 37.89; and 27.97 ± 6.97 mg/dl, respectively. Nearly half of the patient population (130; 46%) presented with STEMI [78 (60%) had anterior wall MI, 49 (38%) had inferior wall MI and 3 patients presented with posterior wall MI] and 85 (30%) had chronic stable angina upon presentation. Of all the STEMI (n = 130), majority (98/130) presented after 48 hours of presentation and only 24.6% (32 / 130) presented within the first 48 hours of MI. The mean troponin-I level of the overall patient population was 19.67 ± 11.12 ng/ml.

Coronary angiography revealed single vessel disease in 185 (65%) patients (LAD-111/185: 60%, RCA-49/185: 26.5%, LCx/OM-25/185: 13.5%), double vessel disease in 76 (23%), triple vessel disease in 17 (5.98%) while 6 (2.11%) patients had left main disease.

CRP levels and modes of clinical presentation, [Table 2]
Mean CRP for those with ACS (STEMI, NSTEMI, and USA) was 0.85 ± 0.70 mg/dl as compared to 0.52 ± 0.38 mg/dl in those with CSA (P < 0.001). The CRP levels of the four groups, Group 1 (STEMI), Group 2 (NSTEMI), Group 3 (USA), and Group 4 (CSA) were compared. The mean baseline levels upon hospital admission were 0.95 ± 0.77 mg/dl in the STEMI group, 0.73 ± 0.57 mg/dl in the NSTEMI group, 0.54 ± 0.32 mg/dl in the USA group, and 0.52 ± 0.38 mg/dl in the CSA group. Patients with STEMI had significantly higher CRP levels as compared to Groups 3 and 4 (USA and CSA, both P < 0.05); the difference between STEMI and NSTEMI groups for baseline CRP levels were not significantly different. Although patients with NSTEMI had numerically higher CRP levels as compared to those with USA and CSA, the difference was not statistically significant.

Fibrinogen levels and modes of clinical presentation, [Table 3]
Mean fibrinogen levels for those with ACS (STEMI, NSTEMI, and USA) were 280.99 ± 79.22 mg/dl as compared to 207.54 ± 56.93 mg/dl in those with CSA (P < 0.001). The mean baseline levels at hospital admission were

| Table 1: Baseline characteristics of study population |
|-----------------------------------------------|
| Ya| Age (yrs) | No (%)|
|----|---------|-----|
| 20‑49 yrs | 59 (20.77)|
| 50‑59 yrs | 97 (34.15)|
| 60‑69 yrs | 93 (32.74)|
| ≥70 | 35 (12.32)|
| Sex | Male | 203 (71)|
| | Female | 81 (29)|
| Smoker | Yes | 82 (28.9)|
| | No | 202 (71.1)|
| Diabetes | Yes | 98 (34)|
| | No | 186 (66)|
| Hypertension | Yes | 135 (47)|
| | No | 149 (53)|
| Lipid level (mg/dl) | LDL (mean±sd) | 110.13±37.89|
| | HDL (mean±sd) | 45.52±9.70|
| | Total cholesterol | 183.97±39.98|
| | Triglycerides (mean±sd) | 110.13±37.89|
| | VLDL (mean±sd) | 27.97±6.97|
| Clinical presentation | Stable angina | 85 (30)|
| | Unstable angina | 23 (8)|
| | NSTEMI | 46 (16)|
| | STEMI | 130 (46)|
| Angiogram finding | SVD | 185 (65)|
| | DVD | 76 (23)|
| | TVD | 17 (5.98)|
| | LM | 6 (2.11)|

SVD: Single Vessel Disease, DVD: Double Vessel Disease. TVD: Triple Vessel Disease, LM: Left Main

| Table 2: CRP levels and clinical presentation |
|------------------|---|---|---|---|
| Clinical presentation | n | Mean±SD | P | Multiple comparison | P<0.05 |
|----------|-----|--------|---|-----------------|
| STEMI | 130 | 0.95±0.77 | <0.05 | CSA-STEMI |
| NSTEMI | 46 | 0.73±0.57 | USA-NSTEMI |
| USA | 23 | 0.54±0.32 | |
| CSA | 85 | 0.52±0.38 | |
| Total | 284 | 0.75±0.64 | |
291.72±76.63 mg/dl in the STEMI group, 263.5 ± 81.98 mg/dl in the NSTEMI group, and 207.54 ± 56.93 mg/dl in the USA group, and 255.39 ± 79.19 mg/dl in the CSA group. Similar to that observed for CRP, patients with STEMI had significantly higher levels of fibrinogen as compared to groups 3 and 4 (USA and CSA, respectively, both P < 0.05).

In contrast to what was observed for CRP, patients with STEMI had significantly higher levels of fibrinogen as compared to groups 3 and 4 (USA and CSA, respectively, both P < 0.05). In contrast to what was observed for CRP, patients with NSTEMI and USA also had significantly higher fibrinogen levels as compared to those with CSA (P < 0.05). Hence, patients presenting with ACS (whether STEMI, NSTEMI, or USA) uniformly had significantly higher baseline fibrinogen as compared to those with CSA.

Dichotomization of CRP into arms with levels less than or more than 0.3 mg/dl
Overall 112/284 (39.4%) and 172/284 (60.56%) had CRP levels less than and more than 0.3 mg/dl, respectively. Interestingly, nearly 2/3rd of the patients with ACS (STEMI: 66.9%, NSTEMI: 67.3%, and USA: 65.2%) had CRP >0.3 mg/dl. In those presenting with CSA, only 45% had values >0.3 mg/dl [P < 0.01 for comparison between CSA and ACS, Table 4].

Dichotomization of fibrinogen into arms with levels less than or more than 350 mg/dl
Overall 224 (78.87%) and 60 (22.53%) had fibrinogen levels less than and more than 350 mg/dl, respectively. We observed that significantly higher percentage of patients with STEMI (33%), NSTEMI (20%), and USA (21%) had fibrinogen >350 mg/dl as compared to those with stable angina patients [only 3.5% had fibrinogen >350 mg/dl, P < 0.001, Table 4].

This association of CRP and fibrinogen with clinical presentation was borne out by the correlation analysis of these markers with Troponin-I. A significant positive correlation between CRP and admission troponin I (r= 0.50; P < 0.05) and fibrinogen and admission troponin I (r = 0.30; P < 0.05) was observed [Figures 1 and 2].

Periprocedural MI-CRP and fibrinogen levels
A total of 15 patients developed periprocedural MI (5.28%). The mean baseline CRP levels were significantly higher in these 15 patients as compared to those who did not develop periprocedural MI (1.27 ± 1.01 mg/dl v/s 0.72 ± 0.60 mg/dl; P < 0.005). Of these 15 patients, 12 had CRP >0.3 mg/dl.

Although the mean fibrinogen level was also higher in patients with periprocedural MI, the difference was not statistically significant (287.13 ± 82.17 v/s 257.44 ± 80.32 mg/dl P = 0.19). Overall, seven out of 15 had fibrinogen levels >350 mg/dl.

CRP and fibrinogen levels vs conventional risk factors, lipids, and leucocyte count
No significant differences in CRP and fibrinogen were found with respect to diabetes or smoking, although both CRP and fibrinogen were found to be significantly higher in nonhypertensive patients (P<0.05) (CRP-0.64 ± 0.51 mg/dl v/s 0.84 ± 0.74 mg/dl; fibrinogen- 248 ± 78 mg/dl v/s 268 ± 82 mg/dl).

We found a significant negative correlation of CRP with HDL cholesterol and positive correlations with LDL, total cholesterol, triglyceride, LDL: HDL ratio,
and total cholesterol: HDL ratio [Table 5]. We found no significant correlation between fibrinogen and the other lipid parameters. Significant positive correlations between both CRP and total leukocyte count ($r = 0.14; P = 0.02$) and fibrinogen and total leukocyte count were observed ($r = 0.12; P = 0.04$).

**CRP, fibrinogen levels, and the development of clinical events**

During a mean follow-up period of 6 months (range 3–9 months), 10 patients (3.4%) had MACEs. These included two admissions for heart failure, one death and two cases of reocclusion in the first 30 days ($n = 5$) and one case of reocclusion and three admissions for heart failure ($n = 5$) at 6 months. We found no statistically significant difference in CRP and fibrinogen values in patients who developed clinical events in comparison to patients who remained free of events at 6 months of follow up. Overall six and five patients, respectively, among these 10 patients had CRP >0.3 mg/dl and fibrinogen >350 mg/dl.

**DISCUSSION**

In this study of 284 patients of CAD undergoing PCI across the spectrum of CAD, we assessed the relationship, if any, between the plasma levels of fibrinogen and CRP with different clinical presentations including STEMI (46%), NSTEMI (16%), USA (8%), and CSA (30%). Patients with STEMI had significantly higher CRP levels ($0.95 \pm 0.77$ mg/dl) as compared to those with USA ($0.54 \pm 0.32$ mg/dl) and CSA ($0.52 \pm 0.38$ mg/dl), $P < 0.05$. Although patients with NSTEMI had higher CRP level ($0.73 \pm 0.57$ mg/dl) as compared to those with USA and CSA, the difference was not statistically significant.

The mean levels of fibrinogen at baseline were significantly higher in all patients with ACS (STEMI: $291.72 \pm 76.63$ mg/dl), NSTEMI ($263.5 \pm 81.98$ mg/dl), and USA ($255.39 \pm 79.19$ mg/dl) as compared to those with CSA ($207.54 \pm 56.93$ mg/dl). Therefore, patients presenting with ACS had significantly higher baseline fibrinogen as compared to those with CSA.

**Fibrinogen and CRP** are nonspecific acute-phase reactants that play an important role in the inflammation–coagulation cascade. While studies have linked elevated fibrinogen levels to cardiovascular risk factors, cardiovascular disease (CVD), and even mortality, the routine measurement of fibrinogen or other acute-phase reactants is not recommended. Although various biomarkers of inflammation, coagulation, and increased blood viscosity have been implicated as the risk factors for CVD; however, the direct causality of these associations with CVD events is debatable.[19‑24]

We further observed that nearly 2/3rd of all patients with ACS had CRP >0.3 mg/dl as compared to only 45% of those with CSA ($P = 0.02$). Similarly, more patients with ACS had fibrinogen >350 mg/dl (20-33%) vs only 3.5% amongst those with CSA ($P = 0.01$). Both markers have a significant positive correlation with admission troponin I (CRP: $r = 0.50$; $P < 0.05$, fibrinogen: $r = 0.30$; $P < 0.05$).

Similar to what has been observed by us, The Emerging Risk Factors Collaboration study, also studied the value of adding CRP or fibrinogen levels to conventional risk factors for the prediction of cardiovascular risk after analyzing data from the 52 prospective studies that included 246,669 participants without previous history of cardiovascular disease. Assessment of CRP or fibrinogen level in these patients with intermediate CV risk could help prevent an additional event over a period of 10 years for every 400 to 500 people screened.[25]

**Table 5: Correlation of CRP, Fibrinogen, and Lipid parameters**

| Correlation | HDL | LDL | TCHL | TG | LDL/HDL | TCHL/HDL |
|-------------|-----|-----|------|----|---------|----------|
| CRP $r$     | -0.205 | 0.186 | 0.157 | 0.136 | 0.280 | 0.303 |
| $P$         | 0.001 | 0.002 | 0.008 | 0.021 | 0.001 | 0.001 |
| Fibrinogen $r$ | -0.057 | 0.024 | 0.002 | 0.03 | 0.038 | 0.0020 |
| $P$         | 0.335 | 0.683 | 0.970 | 0.584 | 0.683 | 0.970 |

$r$: Correlation coefficient

![Figure 2: Correlation of fibrinogen and admission Trop I](image-url)
Ridker et al. reported that the increasing levels of fibrinogen were a significant predictor of developing future peripheral vascular disease, although the association with CRP was stronger. The authors also observed that upon the addition of both inflammatory markers markedly improved the predictive models based on traditional risk factors.[27]

Mora et al. observed a significant positive correlation between high levels of immunoassay-measured fibrinogen and hs-CRP, with incident CVD over a 10-year follow-up period in 27742 initially healthy females. While the predictive value of fibrinogen was similar in magnitude and additive to that of hs-CRP, a distinct joint association was observed: high levels of both biomarkers were associated with the highest CVD risk.[4]

Data from the Edinburgh Artery Study also reported that the baseline levels of CRP, IL-6, leukocyte elastase, fibrinogen, D-dimer, t-PA, vWF, and plasma viscosity were significantly higher in those who developed future CVD, MI, and stroke compared with those who did not. The HR for CVD events with fibrinogen was significant (1.76, 95% CI 1.35–2.31) even after the adjustment of conventional CVD risk factors.[28]

However, in contrary to what has been observed by us and as reported previously, others have not consistently shown a positive association between thrombo-inflammatory markers and CVD. In a sub-study of the prospective AtheroGene registry, (n = 1806 patients with stable angina), although C-reactive protein and fibrinogen were predictive for future cardiovascular risk, they did not provide further information on top of that obtained from traditional risk factors.[29]

Similar findings were reported in the PRIME study, where both CRP and fibrinogen lost significance as predictors for MI and CHD death, when adjusted for traditional risk factors.[30]

A meta-analysis of published data from 18 such studies, involving about 4000 CHD cases, indicated a relative risk of 1.8 (95% confidence interval [CI], 1.6–2.0) per 1-g/L increase in plasma fibrinogen level.[19] Danesh et al. in a recent meta-analysis reported a moderately strong association between the plasma fibrinogen levels and the risk of CHD, even after adjustment for risk factors. Within each age group considered (40–59, 60–69, and >70 years), there was an approximately log-linear association with usual fibrinogen levels for the risk of any CHD, any stroke, other vascular mortality, and nonvascular mortality, and the hazard ratio for the risk prediction for fibrinogen were unaffected after adjustment for either CRP or traditional CV risk factors.[3]

Although we did not find any significant association of CRP and fibrinogen with traditional risk factors like diabetes, hypertension, and smoking, significant correlations of CRP only were observed with various lipid subfractions (negative correlation with HDL cholesterol and positive correlation with LDL, total cholesterol, triglyceride, LDL: HDL ratio and total cholesterol: HDL ratio).

While all these previous studies have assessed the relationship of fibrinogen and CRP with existent or future development of CVD, data on their association with the clinical spectrum of CAD and periprocedural outcomes in patients undergoing PCI is scarce. We observed that periprocedural MI developed in 15 patients and both CRP (1.27 ± 1.01 mg/dl v/s 0.72 ± 0.60 mg/dl; P < 0.005) and fibrinogen (287.13 ± 82.17 v/s 257.44 ± 80.32 mg/dl, P = 0.19) were higher in these patients, trends were significant only for CRP. Of these 15 patients, nearly 50-75% had CRP >0.3 mg/dl and fibrinogen >350 mg/dl. We did not find any significant difference between mean CRP and fibrinogen values amongst patients who developed clinical events at follow up as compared to patients who remained free of clinical events, although nearly half of them had values above the normal cut-off.

Limitations
A single center study with limited patient numbers and only a short term follow up with low number of clinical events reflects a major limitation of this study. Moreover, a single point measurement of both fibrinogen and CRP is also a limitation, since we were unable to examine whether serial determination of these biomarkers have a relevance.

CONCLUSIONS
Fibrinogen and CRP potentially reflect different pathophysiological aspects of atherothrombosis, namely, prothrombotic and proinflammatory pathways. In this study, we observed that patients with ACS had significantly higher fibrinogen levels as compared to those presenting with CSA. On the other hand, higher CRP levels were only observed in the STEMI patients as compared to other groups. The proportion of patients having CRP >0.3 mg/dl and/or fibrinogen >350 mg/dl was also higher amongst those with ACS, with both these markers also demonstrating a significant correlation with admission troponin-I levels. Of all patients undergoing PCI, patients who developed periprocedural MI also had higher CRP and fibrinogen levels, although the
trends were significant only for CRP. No significant association between CRP and fibrinogen was observed with MACE at follow up of 6 months, perhaps due to the limited patient numbers and short-term follow up. Future studies with larger patient numbers are required to evaluate whether the routine use of these markers have a potential clinical use.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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