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ORIGINAL PAPER
Diseases of systemic circulation

Association of fibrinogen and D-dimer levels with severity of acute coronary syndromes (RDC code: VIII-6)

Mukhyaprana M. Prabhu[1]*, Jagadish Madireddy[2], Ranjan K. Shetty[3], Weena Stanley[1]

[1] Department of Medicine, Kasturba Medical College, Manipal, Karnataka, India; [2] Sri Jayadeva Institute of Cardiology, Bengaluru, India; [3] Manipal Hospital, Bengaluru, India

Abstract

Background: Acute coronary syndromes (ACSs) are the primary cause of mortality worldwide. The aim of the study was to assess the associations of serum fibrinogen and plasma D-dimer levels with angiographic severity of atherosclerotic lesions as well as the presence of in-hospital complications and complications at 30-day follow-up in patients with ACS. **Methods:** This was a prospective study including 107 patients with ACS. Severity of CAD was assessed by the Gensini score. Correlations of D-dimer and fibrinogen levels with complications such as heart failure, arrhythmia, recurrent angina, and cardiac death were assessed using the Pearson correlation coefficient and the receiver operating characteristic curve analysis. **Results:** The mean age of patients was 61±10.9 years. Mean serum fibrinogen levels were higher in individuals with severe left ventricular (LV) dysfunction than in those with moderate and mild LV dysfunction (444 mg/dl, 404 mg/dl, and 330 mg/dl, respectively). Similarly, the mean plasma D-dimer level was higher in individuals with severe ACS (1.03 µg/ml) than in those with moderate (1.88 µg/ml) and mild ACS (3.5 µg/ml). **Conclusion:** Our study revealed that patients with higher serum fibrinogen levels tend to have more severe ACS, greater LV dysfunction, and a higher rate of complications. Therapies aimed at reducing fibrinogen levels might help reduce mortality and morbidity in patients with ACS. JRCD 2021; 4 (5): 109–114

Key words: coronary artery disease, acute coronary syndromes, serum fibrinogen, D-dimer

Background

Acute coronary syndromes (ACSs) are the primary cause of mortality worldwide [1]. The underlying pathological mechanism of ACS is thrombosis, which manifests as impaired fibrinolysis and blood coagulation [2]. A few clinical studies have assessed the relationship between the levels of D-dimer or fibrin and fibrinogen degradation product and the short-term prognosis of individuals with ACS; however, none of them have identified a single marker that would have sufficient sensitivity to predict the outcome of ACS patients [3,4]. The current study aimed to assess the association of serum fibrinogen and plasma D-dimer levels with the severity of coronary artery disease and the presence of complications due to ACS.

Methods

This was a prospective study including 107 patients with ACS treated at Kasturba Hospital, Kasturba Medical College, Manipal Academy of Higher Education, Karnataka, India.

We enrolled patients older than 18 years presenting with the first episode of ACS. The exclusion criteria were as follows: coronary revascularization, cerebrovascular disease, or acute ischemic syndromes within the previous 6 months; history of deep vein thrombosis; and comorbid conditions known to alter the activity of the coagulation system (renal or hepatic insufficiency).

On admission, a family history was obtained and clinical examination was performed.

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* Corresponding author: Department of Medicine, Kasturba Medical College, Manipal, Karnataka, India, Tel: 09 449 592 986; E-mail: mm.prabhu@manipal.edu
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Smoking was defined according to the Centers for Disease Control and Prevention guidelines. Individuals who reported smoking a minimum of 100 cigarettes in their lifetime and who, at the time of the survey, smoked either every day or on some days were considered as current smokers. On the other hand, individuals who reported smoking of at least 100 cigarettes in their lifetime and who, at the time of the survey, did not smoke at all were considered as former smokers. Finally, individuals who reported never having smoked at least 100 cigarettes were defined as never smokers.[5]

All patients underwent electrocardiography (ECG). If the ECG recording showed ST-segment elevation, ST-segment elevation myocardial infarction (STEMI) was diagnosed. On the other hand, if there was no ST-segment elevation++ but ST-segment changes such as ST-segment depression or T-wave inversion were noted, or if the patient showed no abnormalities on ECG, then the levels of the cardiac biomarker troponin T were assessed using the chemiluminescence method. A value of more than 0.02 ng/ml was considered positive. Unstable angina was defined as angina pectoris or equivalent ischemic discomfort with at least one of the following three features: 1) it occurred at rest (or with minimal exertion) and usually lasted >10 minutes; 2) it was severe and of new onset (i.e., within the previous 4–6 weeks); and/or 3) it occurred with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent). The diagnosis of non-STEMI (NSTEMI) was established if a patient with the clinical features of unstable angina developed evidence of myocardial necrosis, as reflected by elevated levels of cardiac biomarkers.

Blood samples for the analysis of fibrinogen and D-dimer levels were obtained from all patients who met the inclusion criteria. The fasting lipid profile was assessed by an enzymatic colorimetric test, and low-density lipoprotein cholesterol (LDL-C) levels, by the Friedewald formula. High-density lipoprotein cholesterol (HDL-C) levels were also assessed. Low HDL-C levels were defined as the levels of 50 mg/dl or lower for women and of 40 mg/dl or lower for men, according to the Adult Treatment Panel III (ATP III) guidelines.

Complications were assessed based on ejection fraction (EF) measured by echocardiography; the presence of pulmonary edema diagnosed based on signs, symptoms, chest radiograph, and recurrent chest pain; and the presence of arrhythmia diagnosed by ECG. The main adverse cardiac events that were assessed at 30-day follow-up included mortality, recurrent ischemia, and reocclusion of the infarct-related artery. Cardiogenic shock was defined as end-organ hypoperfusion due to cardiac failure and was diagnosed on the basis of the following signs and symptoms: persistent hypotension (systolic blood pressure <80 to 90 mm Hg or mean arterial pressure drop of 30 mm Hg compared with baseline) with a significant reduction in cardiac index (<1.8 l/min/m^2 without inotropic support [and, in some cases, an intra-aortic balloon pump] or -2.0 to 2.2 l/min/m^2 with support) and normal or elevated filling pressure.

Gensini score calculation

The Gensini score was calculated based on the number of stenotic segments along with their respective degrees of luminal narrowing and localization within the coronary tree. A reduction in the lumen diameter of 25%, 50%, 75%, 99%, and 100% was assigned a value 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: the left main coronary artery × 5; the proximal segment of left anterior descending coronary artery (LAD) × 2.5; the proximal segment of the circumflex artery × 2.5; the mid-segment of the LAD × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and others × 0.5. The Gensini score was calculated as follows: severity score × segment location multiplying factor × collateral adjustment factor.

Ethical issues

The study was approved by the ethical committee at Kasturba Hospital (Manipal, India). Informed consent was obtained from all participants.

Statistical analysis

Normally distributed parameters, including age, the levels of total cholesterol, triglycerides, HDL-C, and LDL-C, and the ratio of total cholesterol to HDL-C were presented as mean ± standard deviation. Skewed data were assessed using the Kruskal-Wallis test, while categorical variables, using the χ^2 test. The Pearson correlation coefficient was used to measure the strength of linear correlations between fibrinogen and D-dimer levels and the Gensini score. The receiver operating characteristic (ROC) curve analysis was performed to assess associations of fibrinogen and D-dimer levels with complications. A P value of less than 0.05 was considered significant. Statistical analysis was performed with the SPSS Statistics 20 software (IBM, Armonk, New York, United States).

Results

Baseline demographic and clinical characteristics of patients

We enrolled a total of 148 patients, of whom 39 were excluded based on prespecified exclusion criteria and 2 others withdrew their consent to participate in the study. The final sample size included 107 patients (78 men [72.9%] and 29 women [27.1%]). Most patients presenting with the first episode of ACS were in the age group of 51 to 60 years (37 patients), followed by those aged from 61 to 70 years (32 patients). The mean age of the study group at presentation was 61±10.9 years (61±11.36 years for men and 60±9.88 years for women). Of the included patients, 34 had unstable angina, 35 were diagnosed with NSTEMI, and 38 had STEMI. Chest pain was the most common presenting symptom reported in 102 patients, followed by sweating in 26 patients, dyspnea in 17 patients, and palpitations in 12 patients.

Based on the Gensini score, patients were classified into groups with mild (score ≤43), moderate (score, 44–76), and severe (score ≥77) ACS. Severe ACS was present in 30 of the 38 patients (81.1%) with STEMI, and in 7 of the 35 patients (18.9%) with NSTEMI. None of the patients with unstable angina presented with severe ACS.

Table 1. Baseline characteristics of patients depending on the severity of coronary artery disease based on the Gensini score

Parameter	Severity of CAD (Gensini score)			
	Mild (≤43) n=35	Moderate (44–76) n=35	Severe (≥77) n=37	P value
Sex (male/female), n	28/7	26/9	24/13	0.34
Hypertension, n (%)	11 (31)	19 (54)	22 (60)	0.04
Diabetes, n (%)	12 (34)	14 (40)	18 (49)	0.45
Alcohol use, n (%)	5 (14)	4 (11)	2 (5)	NA*
Smoking, n (%)	3 (8)	5 (14)	6 (16)	NA*
Family history, n (%)	1 (2.8)	0 (0)	2 (5)	NA*

A P value of less than 0.05 was considered significant.
* P values were not calculated owing to a small number of patients in the study population.
Abbreviations: CAD, coronary artery disease; NA, not applicable

Among the common risk factors for CAD, age older than 45 years was noted in 100 patients; male sex, in 78 patients; hypertension, in 52 patients; and diabetes, in 44 patients. Only hypertension was positively associated with the severity of ACS, while no associations were noted for other factors such as diabetes or sex (P>0.05). For the remaining risk factors such as alcohol use, smoking, and family history, associations were not assessed due to a small number of patients. Detailed data are presented in Table 1.

Lipid profile

The fasting lipid profile was assessed in all participants. Among the 107 patients, 83 had dyslipidemia, of whom 56 had LDL-C levels higher than 100 mg/dl and 56 patients had HDL-C levels lower than 40 mg/dl, while 26 patients had triglyceride levels higher than 200 mg/dl and 24 patients had triglyceride levels higher than 100 mg/dl. The mean serum triglyceride concentration was 121.82 mg/dl; HDL-C, 41.65 mg/dl; and LDL-C, 107.28 mg/dl. Only 4 patients in our study had received prior statin therapy. Non-HDL-C levels were lower than 100 mg/dl in 27 patients, between 100 and 130 mg/dl in 36 patients, and higher than 130 mg/dl in 44 patients. The mean non-HDL cholesterol in the study population was 130.14 mg/dl.

Association of fibrinogen and D-dimer levels with acute coronary syndrome

Fibrinogen and D-dimer levels were positively correlated with the Gensini score (Figure 1a and 1b). The mean serum fibrinogen levels were significantly higher in patients with severe ACS than in those with moderate or mild ACS (418±46.56 mg/dl *vs* 332±57.83 mg/dl *vs* 257±66.96 mg/dl, Figure 2a). Serum fibrinogen levels were also higher in patients with STEMI than in those with NSTEMI or unstable angina (428±30 mg/dl *vs* 340±33 mg/dl *vs* 233±40 mg/dl; P<0.001 for both comparisons).

The mean D-dimer level was higher in individuals with severe ACS than in those with moderate or mild ACS (4.10±1.85 ng/dl *vs* 1.88±1.49 ng/dl a *vs* 1.035±1.01 ng/dl, Figure 2b). The mean D-dimer levels in patients with unstable angina, NSTEMI, and STEMI were 0.4 ng/dl, 1.5 ng/dl, and 4.3 ng/dl, respectively. The differences between the groups were significant (P<0.05 for unstable angina *vs* NSTEMI and P<0.01 for NSTEMI *vs* STEMI).

Serum fibrinogen levels and left ventricular function

Patients were classified into 4 groups based on left ventricular (LV) function: normal LV (ejection fraction [EF], 50%-70%) mild dysfunction (EF, 40%-50%), moderate dysfunction (EF, 30%-39%), and severe LV dysfunction (EF <30%). The mean serum fibrinogen levels were significantly higher in individuals with severe LV dysfunction than in those with moderate or mild LV dysfunction (Figure 3).

Fibrinogen and D-dimer levels and the presence of complications

The rates of in-hospital complications and those occurring at 30-day follow-up were assessed. Complications were noted in 27 patients (25%). Mean serum fibrinogen levels were higher in patients with complications than in those without complications: for shock, 457 mg/dl *vs* 329 mg/dl; for pulmonary edema, 421 mg/dl *vs* 324 mg/dl; for arrhythmia, 414 mg/dl *vs* 322 mg/dl; for recurrent chest pain, 451 mg/dl *vs* 329 mg/dl; and for reocclusion, 474 mg/dl *vs* 333 mg/dl (Figure 4).

The ROC curve for the association between fibrinogen levels and the presence of complications is shown in Figure 5a. The area under the curve was 0.836 (P<0.001). The sensitivity and specificity of fibrinogen levels for predicting complications were as follows: for the level of 335 mg/dl, 90% and 56%, respectively; for the level of 370 mg/dl, 78% and 69%, respectively; and for the level of 408 mg/dl, 63% and 88%, respectively.

The ROC curve for the association between D-dimer levels and the presence of complications is shown in Figure 5b. D-dimer levels were higher in individuals with complications than in those with-

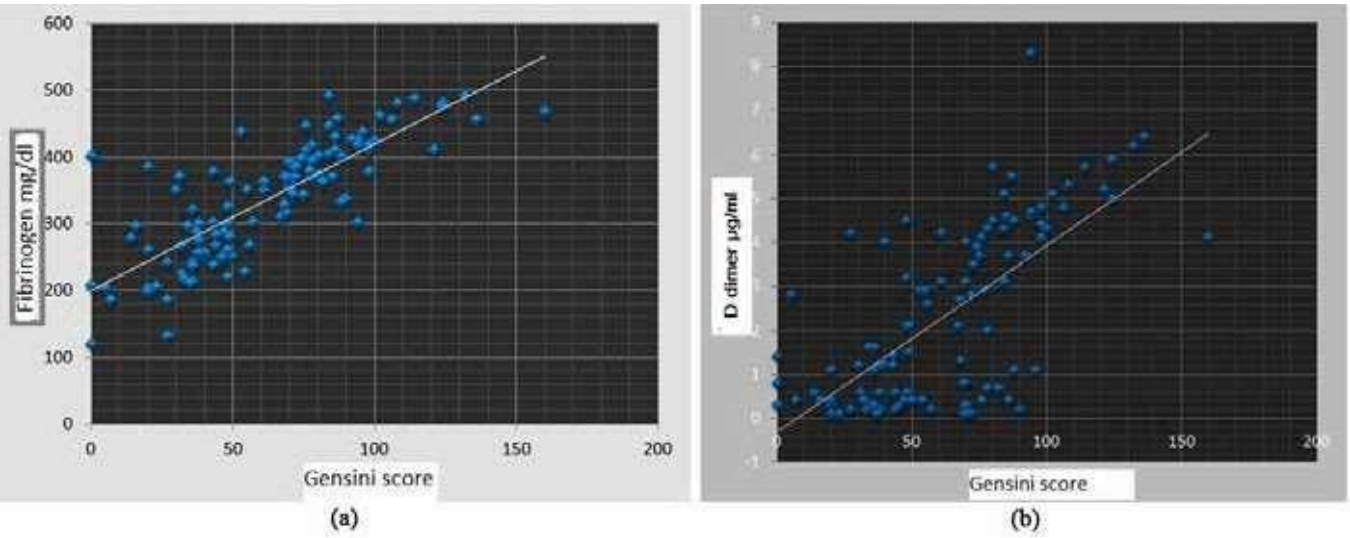

Figure 1. Correlations of serum fibrinogen (a) and plasma D-dimer levels (b) with the Gensini score

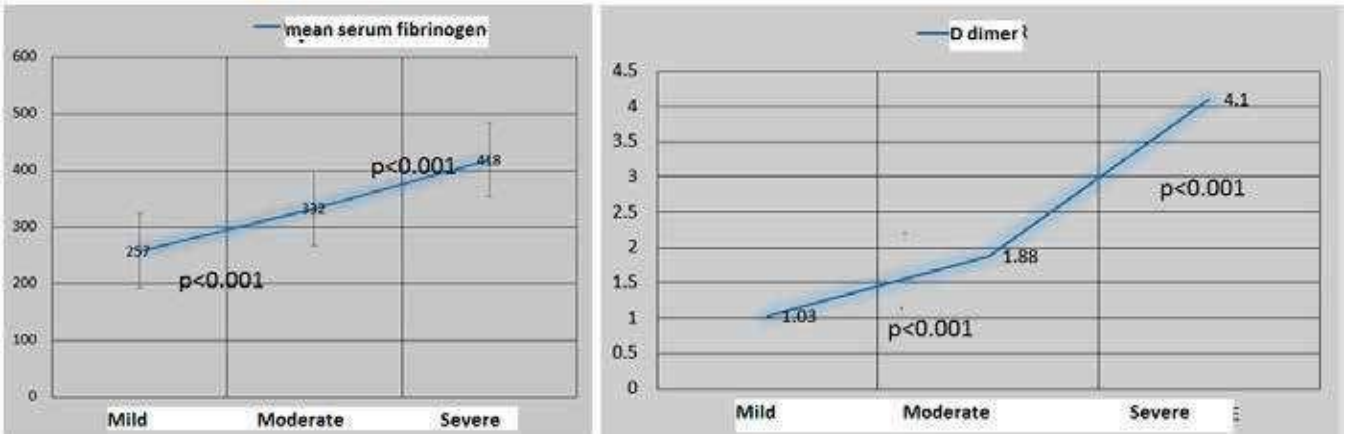

Figure 2. Associations of serum fibrinogen (a) and plasma D-dimer levels (b) with the severity of acute coronary syndrome

out. The area under the curve was 0.815 (P<0.001). The sensitivity and specificity of D-dimer levels for predicting complications were as follows: for the level of 1.55 µg/ml, 85% and 61%, respectively; for the level of 2.85 µg/ml, 78% and 71%, respectively; and for the level of 4.25 µg/ml, 60% and 89%, respectively.

Discussion

Cardiovascular disease is the primary cause of mortality worldwide, and most deaths are due to myocardial infarction. Associations between acute phase reactants and the severity of ACS have been widely studied. Two such reactants that have long attracted a considerable interest are fibrinogen and D-dimer. Inflammation, thrombosis, and endothelial dysfunction play a crucial role in atheroma formation and progression. Proinflammatory cytokines, such as interleukin 6 and tumor necrosis factor α, released from the endothelium and macrophages, induce fibrinogen production in the liver. This is partly explained by a reduction in fibrinolytic activity and plasminogen concentrations. Fibrinogen and its metabolites lead to endothelial dysfunction. The fibrin metabolite is a major component of atherosclerotic plaque. Fibrin stimulates the proliferation of cells in the intima as well as promotes the cross-linking of low-density lipoprotein with cholesterol. All these processes lead to the formation and progression of plaque. The Northwick Park Heart Study, Framingham Study, PROCAM study, and the ECAT study have found that fibrinogen is an independent risk factor for myocardial infarction [6–8].

The current study showed a significant prevalence of ACS in men as compared with women. The results are consistent with several population studies showing the higher prevalence of ACS in men. The multicenter prospective registry CREATE showed a 76% prevalence of ACS among Indian males [9]. Singh et al. [10] and Misiriya et al. [11] reported a similar prevalence, of 73% and 75%, respectively.

The mean age at presentation with the first episode of ACS in our study population was 61.10 years. Acute coronary syndrome was found to occur at an older age in our population when compared with other Indian studies, such as CREATE (57.5 years) and the study by Misiriya et al. [11] (58.3 years). This could be explained

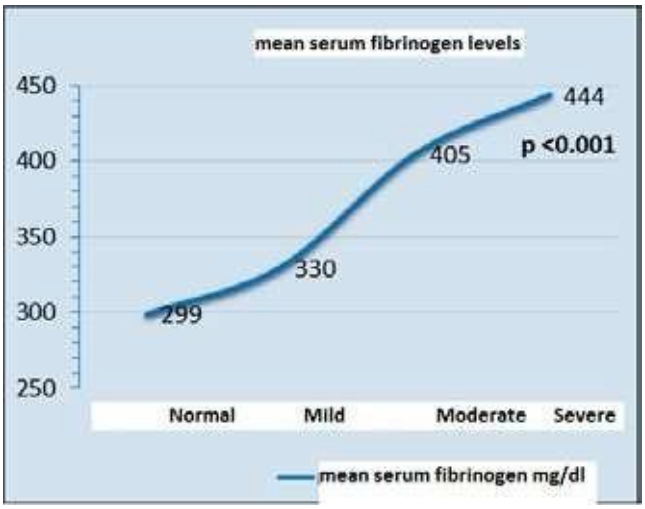

Figure 3. Association of serum fibrinogen levels with left ventricular function

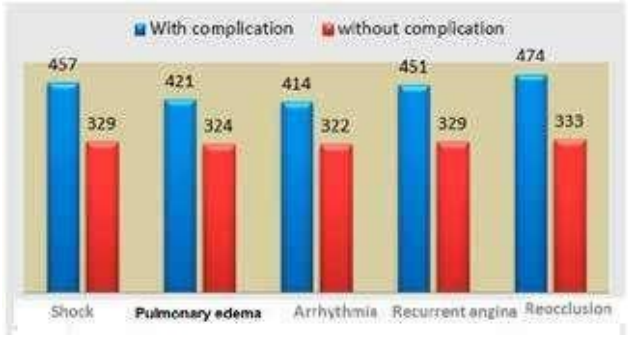

Figure 4. Differences in serum fibrinogen levels between patients with and without complications

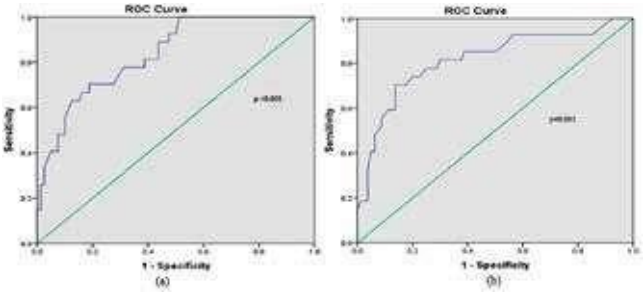

Figure 5. Receiver operating characteristic curve for the association of fibrinogen (a) and D-dimer (b) with the rate of complications

by the higher literacy rate and socioeconomic status of the local population, which might have promoted health consciousness, resulting in early screening and prompt treatment for diabetes, hypertension, and dyslipidemia.

Hypertension is a well-established risk factor for ACS and its complications. In our study, hypertension was defined according to the Joint National Committee guidelines. Approximately 49% of our participants were found to have hypertension, which is in line with the finding reported by Foussas et al. [12] (51%).

In our study, about 41.5% of patients had diabetes as a risk factor for ACS, as compared with 33% in the study by Babu et al.[13] Apart from the increased incidence of ACS, patients with diabetes also have worse outcomes than those without diabetes. Given that the incidence of diabetes is expected to double in the next 25 years, the prevalence of ACS is also expected to increase in the years to come.

Lipid abnormalities

In our study, most patients had dyslipidemia, including abnormal levels of LDL-C, HDL-C, and triglycerides. Our results are in line with those of Tenzin Nyandyak et al. [14], who reported mean triglyceride levels of 126.13 mg/dl, HDL-C of 43.94 mg/dl, and LDL-C of 104.35 mg/dl [15], as well as with those reported by another study from the same center, in which triglyceride, LDL-C, and HDL-C levels were 129 mg/dl, 116 mg/dl, and 39 mg/dl, respectively. Our study also showed that most patients with ACS (75.76%) had non-HDL-C levels higher than 100 mg/dl.

Elevated serum cholesterol levels are an independent risk factor for ACS. High cholesterol levels can induce plaque formation even in the absence of other potential risk factors. Low-density lipoprotein cholesterol is the major component of total cholesterol and acts as a vehicle for the transport of cholesterol to peripheral tissues. On the other hand, HDL-C acts in an opposite manner, mobilizing cholesterol from peripheral tissues to be excreted by the liver as bile. Statins have been shown to significantly reduce the risks associated with elevated serum cholesterol levels and facilitate plaque stabilization. The beneficial effects of statins in atherosclerosis are well established. A meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaborators showed that statins reduced the 5-year incidence of major coronary events by approximately 25% for each 39-mg/dl reduction in LDL-C levels (P<0.0001) [15].

In the present study, 14% of individuals were smokers and approximately 11% were alcohol users. The incidence of smoking was found to be lower in our study. This may be attributed to the fact that patients did not report smoking for the sake of health insurance claims. The incidence of ACS in women and men was shown to increase by 6- and 3-fold, respectively, when compared with non-smokers [16].

Fibrinogen and the Gensini score

In our study, individuals with higher serum fibrinogen levels were found to have more severe CAD, as assessed by the Gensini score. We found a significant association between mobilizing cholesterol and the Gensini score (P<0.001). The Pearson correlation coefficient for fibrinogen and Gensini score was 0.808. The results of our study are consistent with those reported by Hong et al. [17], who also showed that the mean serum fibrinogen levels were the highest in patients with severe ACS as compared with those with moderate and mild ACS (333 mg/dl, 324 mg/dl, and 310 mg/dl, respectively). The mean fibrinogen levels in each group were higher in our study than in the study of Hong et al. [17], which may be explained by the fact that our institution is a tertiary health center admitting more cases of severe ACS. This is reflected by the Gensini score of our study population, which was higher than that reported by Hong et al. [17]

In our study, serum fibrinogen levels were significantly higher in patients with STEMI as compared with those with NSTEMI or

unstable angina. Similar results were reported by Omran et al. [18] and Zheng et al. [19], who found the mean serum fibrinogen level to be higher in patients with STEMI and NSTEMI compared with those with unstable angina.

Our study also showed that the mean serum fibrinogen level was higher in individuals with complications than in those without. A similar result was reported by Shi et al., who found that the mean serum fibrinogen level was higher in individuals with reocclusion and cardiac death [20]. However, unlike Shi et al. [20], we also assessed other complications such as shock, pulmonary edema, arrhythmia, and recurrent chest pain.

Our study revealed that patients with higher serum fibrinogen levels tend to have more severe ACS, as assessed by the Gensini score. For each 1-mg/dl increase in serum fibrinogen levels, the severity of ACS increased by 0.3 Gensini score. However, so far, no drug has been approved for the reduction of serum fibrinogen levels, and no large-scale study has been conducted to assess if the therapeutic reduction of fibrinogen provides any benefits in terms of mortality and morbidity.

D-dimer levels and the Gensini score

In our study, individuals with higher D-dimer levels had a significantly higher Gensini score. A similar correlation was demonstrated by Zheng et al. [19] and Xiong et al. [21] Orak et al. [22] revealed a significant correlation between D-dimer levels and different types of ACS. The mean D-dimer levels were 0.65 μg/ml, 2.92 μg/ml, and 2.99 μg/ml in patients with unstable angina, NSTEMI, and STEMI, respectively. In a study by Bayes-Genis et al. [23], a D-dimer level of more than 5 μg/ml had a sensitivity of 65% and specificity of 80% for differentiating unstable angina from NSTEMI and STEMI.

Limitations

Our study revealed a significant correlation of serum fibrinogen and D-dimer levels with the severity of ACS. However, as this was a nonrandomized observational study, further research, including randomized trials, is required to confirm this relationship. Moreover, although we detected a significant effect of fibrinogen levels on 30-day clinical outcomes, the correlation between serum fibrinogen levels and long-term clinical outcomes was not assessed and requires further research. Finally, coronary angiographic assessment was based on luminal assessment and lacks plaque visualization.

Conclusions

Our study showed a significant correlation of serum fibrinogen and plasma D-dimer levels with the severity of CAD, as assessed by the Gensini score. Moreover, in patients presenting with the first episode of ACS, elevated serum fibrinogen levels were correlated with a higher rate of in-hospital complications as well as complications at 30-day follow-up.

In conclusion, patients with higher serum fibrinogen levels tend to have more severe ACS, greater LV dysfunction, and a higher rate of complications. However, further large-scale studies are needed to assess if serum fibrinogen levels could be used as a predictor of outcome in patients with ACS and to investigate if the therapeutic reduction of fibrinogen levels provides any benefits in terms of mortality and morbidity.

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