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RESEARCH ARTICLE

Prognostic value of inflammatory markers in patients presenting with acute coronary syndrome

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Abstract

Objective: The objective of the study is to study the use of IL6, IL10, TNF, CRP, neutrophil-lymphocyte ratio (NLR) as a prognostic biomarker for patients presenting with the acute coronary syndrome.

Background: ACS is the most common cause of death worldwide, but mortality due to Coronary artery disease slowly came down and reached a plateau. ACS occurs in response to inflammation, plaque rupture and subsequent thrombosis, progressive mechanical obstruction, and dynamic obstruction.

Methods: It is a Prospective study of 100 patients, both Male and Female with ACS admitted to the SJICR with ACS, were subjected to the Full clinical evaluation including history and physical examination with particular emphasis on risk factors.

Results: Most of the patients studied were STEMI; only seven patients of NSTEMI were included. The male to female ratio was 3.55. The most commonly associated risk factors were smoking, diabetes mellitus, hypertension. STEMI patients had a shorter window period compared to NSTEMI. The mean duration of hospitalization was three days. Inflammatory markers were compared across various TIMI risk scores. When compared to the TIMI score of <4 to >4, HsCRP shows a significant correlation. While other inflammatory markers showed higher values with higher TIMI scores but P value was not significant.

Conclusion: NLR, HsCRP, IL6, IL10 are significantly associated with TIMI, GRACE, KILLIP risk scoring systems. Inflammatory markers except TNF, shows the correlation with mortality, morbidity, the extent of CAD. These markers explain other domain of pathogenesis in ACS which is a potential target for newer therapeutics.

Keywords: Inflammatory markers, Acute Coronary Syndrome, STEMI

Background

ACS is the most common cause of death worldwide, but mortality due to Coronary artery disease slowly came down and reached a plateau. Now even with effective interventions and better prognostic scoring systems, we were unable exactly prognosticate due to the multifactorial pathogenesis of ACS. One crucial dimension which was less explored was inflammation. Acute coronary syndromes (ACS) occur in response to inflammation, plaque rupture and subsequent thrombosis, progressive mechanical obstruction, and dynamic obstruction. ACS spectrum range from non–ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI). ECG findings and markers of myocyte necrosis are used to differentiate the type of ACS and reperfusion strategy. However, significant uncertainty remains regarding long-term risk and optimal secondary prevention for

individual patients. Among potential biomarkers, much interest has focused on biomarkers of inflammation. The process that leads to eventual plaque erosion or rupture involves several inflammatory mechanisms, including endothelial dysfunction, leukocyte migration, extracellular matrix degradation, and platelet activation. The optimal inflammatory biomarker would provide a method for quantitating systemic and cardiac-specific inflammation, thereby predicting the risk of recurrent coronary events and its clinical sequelae. Because they address a different aspect of ACS pathophysiology, biomarkers of inflammation may provide unique information to the clinician separate from that provided by conventional biomarkers.[1]

Objective of the study

To study the use of IL6, IL10, TNF, CRP, neutrophil-lymphocyte ratio (NLR) as a prognostic biomarker for patients presenting with the acute coronary syndrome, and to assess its prognostic value in predicting CAD severity, clinical course and short term, long term mortality and morbidity

Methods

Method of collection of data

One hundred patients, both Male and Female, with ACS admitted to Sri Jayadeva Institute of cardiovascular sciences & research.

Inclusion criteria

- Patients with Acute STEMI, NSTEMI, both Male and Female above 18 years of age.
- Myocardial infarction diagnosed by:
- Detection of a rise and/or fall in cardiac biomarkers values preferably cTn, with at least one value above the 99th percentile of the URL and with at least one of the following:
  1. Symptoms of ischemia
  2. New or presumed new significant ST-T wave changes or new LBBB.
  3. Development of the pathologic Q wave in the ECG.
  4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  5. Identification of an intracoronary thrombus by angiography.

Exclusion criteria

- Patients under the age of 18 were excluded from the study.
- Chronic illness, e.g., chronic liver disease, chronic renal failure.
- Acute or chronic inflammatory diseases, e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.
- Active infection, e.g., Pneumonia, UTI, malignancy.
- Acute coronary insufficiency secondary to any shock state or secondary to traumatic injury to the heart were also excluded from the study.
- Post CABG, post-PTCA patients with the acute coronary syndrome.
- Patients who suffered from previously documented Acute Coronary Syndrome were also excluded from the study.

Study design

This study is a Prospective study of patients admitted to Sri Jayadeva hospital with ACS. All patients were subjected to the following – Full clinical evaluation including history and physical examination with particular emphasis on risk factors (diabetes mellitus, hypertension, family history, and smoking). Patients were classified according to Killip Classifications into, – Class I – with no clinical signs of heart failure, Class II – with rales or crackles in the lungs, S3 or elevated venous pressure, Class III – with frank pulmonary edema, Class IV – cardiogenic shock or hypotension and evidence of peripheral vasoconstriction. Laboratory investigations – Routine laboratory investigation for assessment of liver and kidney functions, blood sugar, were done for all patients. Cardiac biomarkers and inflammatory markers are done at the time of admission.

Associated Imaging studies

Echocardiography: for assessment of the ejection fraction (EF) and the presence of RWMA, Cardiac catheterization, and percutaneous coronary intervention with particular attention to collect the following data: (a) TIMI flow grade before any procedure and after final adjunctive interventions (b) Number of vessels affected and (c) Severity of the lesions requiring emergency bypass surgery or emergency stenting.

Follow Up

All patients were followed up for a total period of 1 month and six months for the following:

recurrence of chest pain, arrhythmias either primary or secondary that require pharmacological or interventional treatment, readmission by recurrent myocardial ischemia, either unstable angina or myocardial infarction, revascularization either by PCI or CABG, heart failure defined by symptoms and signs of pulmonary congestion requiring the use of specific therapy as diuretics, vasodilators, and inotropic supports, or death.

Results

We have collected the data of 100 ACS patients admitted to SJICR for treatment; demographic data was shown in Table 1. The Hospital out course and timeline are shown in the flow chart [Figure 1]. Out of 100 patients studied, 93 were STEMI, only seven patients of NSTEMI were included. We have included 78 Male patients and 22 female patients. The most commonly associated risk factors were smoking, Diabetes mellitus, hypertension. STEMI patients had a shorter window period compared to NSTEMI (11.74 hours vs. 28.57 hours) Table 1. The mean duration of hospitalization was three days. TIMI risk score and mortality, the mace was compared and shown in Table 2. Inflammatory markers were compared across various TIMI risk scores in Table 3. When compared to the TIMI score of <4 to >4, HsCRP shows a significant correlation (5.15 SD2.2 vs. 7.36 sd 6.4, P-value 0.01). While other inflammatory markers showed higher values with higher TIMI scores but P value was not significant. Grace Risk Score and Mortality, Mace was shown in Table 4. Inflammatory markers are compared with GRACE risk scoring, and results were shown in Table 5. Patients are classified into two groups

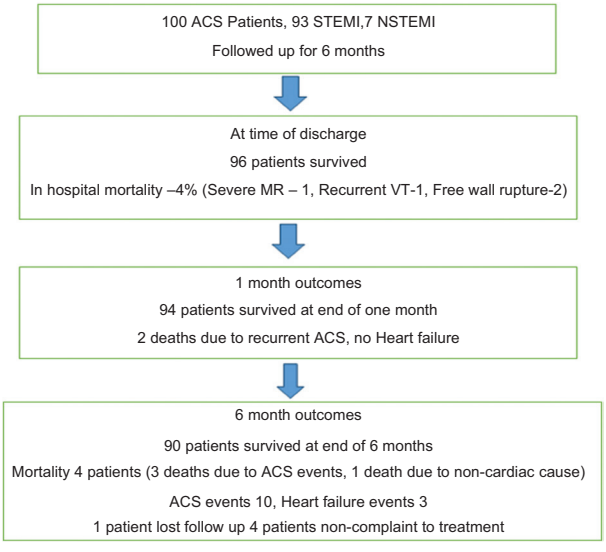

Figure 1 Flow chart of study.

Table 1 Basic Demographics Data

	STEMI	NSTEMI
Age	53 (SD 12.2)	64 (SD 15.8)
Sex		
Male	73	5
Female	20	2
Risk factors		
DM	17	3
Smoking	22	2
Baseline HB	13.28 (SD-2.2)	13.08 (SD-2.6)
S. CREAT	1.08 (SD-0.2)	1.17 (SD-2)
Hypertension	16	2
Window period	11.74 (SD-15.3)	28.57 (SD-10.6)
CAD		
Insignificant CAD	5	1
SVD	51	0
DVD	13	3
TVD	20	1
Duration of hospitalisation (days)	3.55 (SD-1.1)	3 (SD-0)
Killip class I	77	6
II	8	1
III	3	0
IV	5	0
Timi score	3.5 (SD-2.4)	3.7 (SD-1.3)
Grace score	109.2 (SD-30.7)	—

Table 2 TIMI Risk Score and Mortality, Mace

	TIMI score <4	TIMI score >4
Death at the end of 6 months	1 death out of 64 patients	9 out of 36 patients
Death and mace at the end of 6 months	8 events out of 64 patients	11 out of 36 patients

Table 3 Comparison of inflammatory markers with TIMI Score

	TIMI 1-2	TIMI 3-4	TIMI >4	P-value
NLR mean	5.15	5.91	7.36	0.101
SD	2.2	3.1	6.4	
HSCRP mean	9.2	10	13.2	0.01
SD	4.5	5.6	5.8	
IL6 mean	19.4	24.1	50.4	0.163
SD	60	44	94	
IL 10 mean	4.9	10.2	21.6	0.075
SD	14.5	25.5	45.6	
TNF	0.09	0.18	8.68	0.249
SD	0.09	0.1	8.5	

Table 4 Grace Risk Score and Mortality, Mace

	GRACE score 49-125	GRACE score 126-154	GRACE score >155
Death	1 in 70 patients	4 in 18 patients	3 in 5 patients
Death and MACE at the end of 6 months	8 in 70 patients	5 in 18 patients	4 in 5 patients

according to GRACE scores. Compared to the lower GRACE score (<125), higher GRACE sore (>155) had significantly higher values of HsCRP and IL6. Even IL10 showed a higher value, but the P-value was not significant. When compared across Killip class to inflammatory markers, which showed a significant correlation between Killip class and NLR, HsCRP, IL6, IL10, which is shown in Table 6, scatter plots analyzing window period to inflammatory marker concentration shown in Figure 2. Concentrations of inflammatory markers are not influenced by window periods. Except for HsCRP, all other inflammatory markers did not show any correlation with the extent of Coronary artery disease shown in Table 7. Inflammatory markers like NLR and IL-6 showed a significant correlation between LV function (EF) shown in Table 8. Comparison of the difference in the level of inflammatory markers between dead and alive patients shown in Table 9, comparison of the difference in inflammatory markers between patients with MACE and no MACE shown in Table 10.

Table 5 Comparison of inflammatory markers with GRACE categories

	GRACE 49-125	GRACE 126-154	GRACE 155-319	P-value
NLR mean	5.9	5.3	9.5	0.12
SD	4.1	2.5	7	
HSCRP mean	9.9	12.1	18.7	0.01
SD	5.1	4.5	4.1	
IL6 mean	22.1	34.3	132.5	0.02
SD	55	83	119	
IL 10	9.4	8.6	38.4	0.09
	29.3	19.3	46.8	
TNF	3.3	0.17	0	0.84
	26.8	0.72	0	

Table 6 Comparison of Killip class and inflammatory markers

Killip	1	2	3	4	P-value
NLR mean	5.4	5.8	8.6	14.1	<0.0005
SD	2.5	4	2.3	12	
HSCRP mean	9.7	11	14.5	19.6	<0.0005
SD	5	4.8	6.2	4.9	
IL6 mean	24.6	9.3	6	152.8	<0.0005
SD	62.8	9.9	3.5	100	
IL 10	7.4	9.8	1.9	78.4	<0.0005
SD	20	18.4	3.38	79.6	
TNF	0.11	25	0	0	0.015
SD	0.56	74.1	0	0	

Discussion

In our study, many of the patients were STEMI; this is because many of NSTEMI patients were already treated before reaching our center. In-hospital mortality was 4%, and six months mortality 10%. Men were more commonly affected than women. In 6 months of follow-up, ten recurrent ACS events and three heart failure related recurrent hospital admissions happened. According to estimates from AHA, the short term mortality rate of patients with STEMI ranges from 5-6% during initial hospitalization and 7–18% at one year.[2] In our study, higher CRP levels were associated with higher TIMI, GRACE, Killip risk score, and extent of coronary artery disease. Those with TIMI risk score >4 mean CRP level was 13.2(SD 5.8) in comparison to TIMI score <2 with a mean CRP level of 9.2 (SD 4.5). Higher CRP levels were associated with more ACS and heart failure events. Only a single value before treatment was taken, so release patterns and treatment response cannot be analyzed. Peak CRP levels were associated in 6 months follow up with an increased incidence of major adverse cardiac events (MACEs) in patients with STEMI(HR1.1649,95% C.I.1.0197–1.3307,p <0.05), CRP plasmatic concentrations showed a different release curve in patients with STEMI in Comparison with patients with NSTEMI and with UA. CRP peak concentrations did not correlate with ejection fraction and angiographic findings but correlate with the incidence of MACE.[1] Delhaye et al. assessed the predictive value of CRP in patients undergoing elective PCI. They showed that high pre-procedural CRP levels were

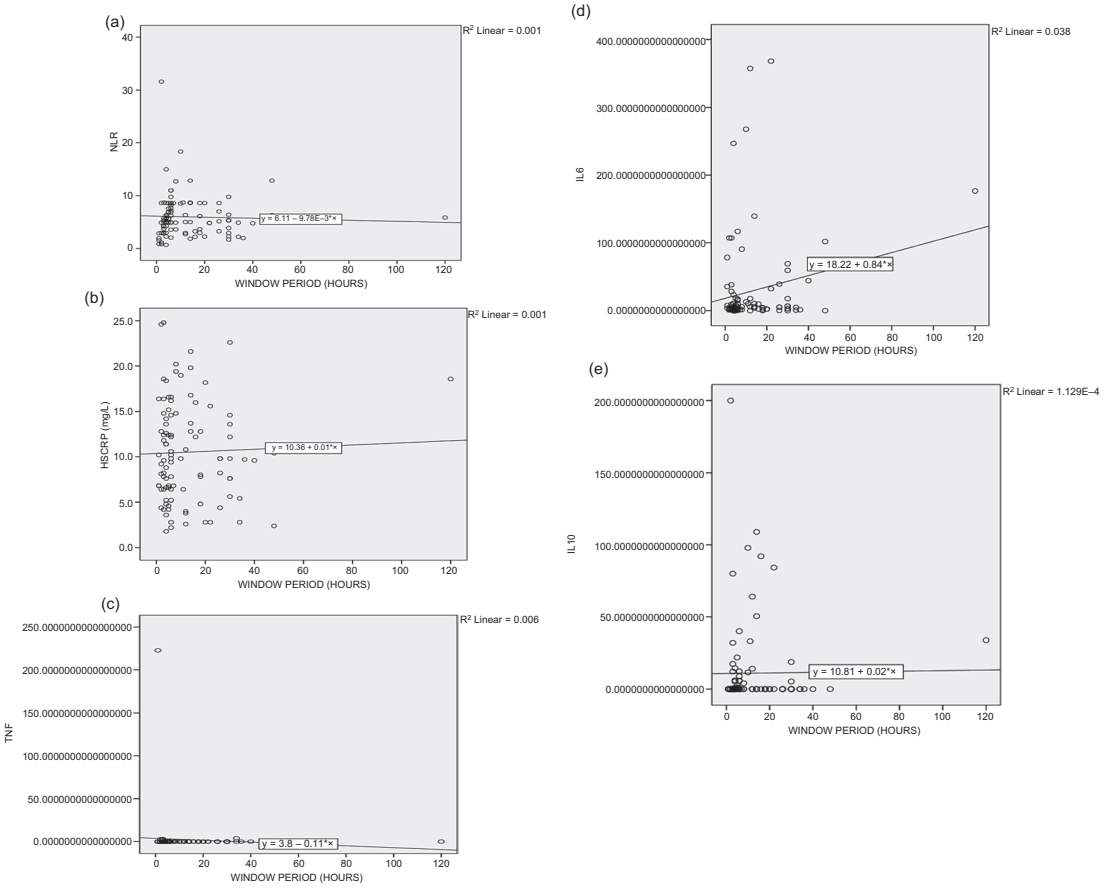

Figure 2 Scatter plots of Inflammatory markers and the window period.

Table 7 Inflammatory markers and the extent of CAD

Inflammatory markers	Insignificant CAD	SVD	DVD	TVD	P-Value
HsCRP	4.06 (1.63)	9.69 (4.63)	11.97 (2.82)	12.73 (6.34)	0.001
NLR	4.52 (1.86)	5.96 (3.1)	5.78 (2.47)	4.99 (2.57)	0.430
IL 6	20.45 (30.89)	25.88 (67.08)	6.14 (5.36)	39.31 (79.34)	0.522
IL 10	2.02 (4.96)	5.97 (14.23)	8.40 (17.27)	16.16 (33.75)	0.228
TNF	0.35 (0.87)	4.57 (31.17)	0 (0)	0 (0)	0.834

Table 8 Inflammatory markers and LV dysfunction

Inflammatory markers	Mild LV dysfunction EF > 45%	Moderate LV dysfunction EF 35-44%	Severe LV dysfunction EF < 35%	P-value
HsCRP	10.17 (SD-5.77)	10.91 (SD-4.69)	19	0.242
NLR	5.4 (SD-2.82)	6.76 (SD-5.42)	18.39	0.002
IL 6	28.57 (SD69.36)	23.14 (SD49.98)	267.79	0.001
IL 10	9.05 (SD-23.88)	12.30 (SD35.39)	97.85	0.010
TNF	0.09 (SD- 0.57)	6.74 (SD-38.18)	0.00	0.378

associated with a higher risk of mortality or MI, but are not related to target vessel revascularization or stent thrombosis.[3] Birbek et al. did a comprehensive meta-analysis., including over 34,000 patients that underwent PCI for different conditions, showed that high CRP levels were associated with increased MACE, all-cause mortality, myocardial infarction, coronary revascularization, and clinical restenosis, and concluded that every 1 mg/L in the CRP value was associated with 12% increase in the risk of

Table 9 Difference in levels of inflammatory markers between dead and alive patients

	Alive	Dead	P-Value
NLR	5.74	8.13	0.08
SD	2.9	2.9	
CRP	9.83	16.68	<0.0001
SD	4.9	6.5	
IL 6	24.9	66.2	0.06
SD	64.5	82	
IL 10	6.46	52.4	<0.0001
SD	17.3	66.2	
TNF	2.64	0	0.72
SD	23.6		

Table 10 Difference in Inflammatory Markers between patients with MACE and no MACE

	No MACE	MACE	P-Value
NLR	5.8	6.6	0.43
SD	4.1	3.9	
CRP	9.4	15	<0.0001
SD	4.8	5.5	
IL 6	21.7	60	0.025
SD	55	100	
IL 10	6.9	28.5	0.004
SD	24.5	41.3	
TNF	2.9	0	0.6
SD	24.8		

MACE.[2] Ahmed Mowafy et al. analyzed 106 young ACS patients with IL6 levels. The level of IL-6 level showed a marked difference between randomized patients and the control group (mean ± SD) IL-6 level was proportional to the severity of the lesions in the coronary anatomy. It was significantly higher in patients with significant lesions in the angiography (92 patients) than that of those with the non-significant lesion (18 patients) and that of the control group (30 patients), (mean ± SD "Range" 45.5 Vs. 9.22 Vs. 3.83 respectively with P <0.001). Also, there was no statistically significant difference in IL-6 level regarding gender, smoking status, or family history. However, the IL-6 level was statistically higher in diabetic patients compared to non-diabetics and lowered in those with a history of hypertension. Moreover, there was a statistically significant positive correlation between IL-6 level (39.56 pg/ml) and BMI means (27.04). The mean IL-6 level was statistically significantly higher in those with Killip class III compared to those with Killip class II or I. The mean level of IL-6 was higher in those with +ve troponin test compared to those with -ve troponin. The IL-6 level was statistically significantly higher in non-survivals compared to the survived group (mean 92.33Vs 38.08 with P <0.001).The optimal cutoff value for the IL-6 level to predict morbidity was 41 pg/ml. This cutoff value has a sensitivity of 100%, a specificity of 66%, a positive predictive value of 25%, a negative predictive value of 100%, and a diagnostic accuracy of 69%.

In our study IL6 significantly higher in patients with TIMI score >4 (mean value 50.4 SD 94, p-value 0.16), in patient with GRACE score > 155 with mean value of 132,SD 119 (p-value 0.02). Unlike previous studies, IL6 levels were not correlating with the extent of coronary artery disease. Those patients who were in Killip class IV had significantly higher IL 6 value (152, p-value <0.005). Those patients who were having higher LV dysfunction showed higher IL6 values. Patients with EF<35% were having a mean value of 267.79. A nested case-control design was used to compare TNF-a levels obtained an average of 8.9 months after initial MI among 272 participants in the Cholesterol And Recurrent Events (CARE) trial who subsequently developed recurrent nonfatal MI or a fatal cardiovascular event (cases) and from an equal number of participants with age- and sex-matched who remained free of these events during follow-up (controls). Overall, TNF-a levels were significantly higher among cases than controls (2.84 versus 2.57 pg/mL, P50.02). The excess risk of recurrent coronary events after MI was predominantly seen among those with the highest levels of TNF-a, such that those with levels over 4.17 pg/mL (the 95th percentile of the control distribution) had a '3-fold increase in risk (RR 2.7, 95% CI 1.4 to 5.2, P<0.004).[5] In contrast to the above study in our study, there no correlation between TNF alfa values and coronary events. Most of the patients had undetectable TNF values. Idrus alwi et al. did an observational study, as many as 146 subjects were analyzed, consisting of 84 ACS patients and 62 coronary artery disease (CAD). The IL-10 level was higher in the group of ACS patients (7.37 pg/mL ±7.81, CI 95% 5.68-9.07) than that in CAD patients (1.59 pg/mL ±1.55, CI 95% 1.2-1.98). The optimal cut-off point for serum IL-10 level is >1.95 pg/mL, with 79.76 % sensitivity and 77.42 % specificity.[6] Based on ROC analysis, the optimal cut point that provided the maximal sensitivity and specificity for predicting adverse cardiovascular events was 4.9 pg/mL. By using this cut point, the study population was stratified into

two groups (i.e., >4.9 pg/mL vs. <4.9 pg/mL). There was a higher incidence of C-reactive protein elevation and a higher percentage of patients who had myocardial infarction on presentation in patients with high IL-10 plasma levels compared with those with low IL-10 plasma levels. Otherwise, baseline characteristics did not significantly differ between patients in the two groups. Specifically, we found that elevated plasma levels of IL-10 were associated with an increased risk of subsequent death or nonfatal myocardial infarction to 5 years after an index event, even after adjustment for clinically significant covariates, including other established biomarkers such as hs-CRP and NT-proBNP.[7]

In our study IL 10 levels significantly elevated in patients with TIMI risk score >4 (21.6 , SD 45.6, p-value 0.075),GRACE risk score > 155 (38.4, SD 46.8 , p-value 0.09), Killip class IV (78.4,SD 79.6, p-value <0.0005). Higher IL 10 levels are associated with severe LV dysfunction (EF<35%) mean value of 97.5(p-value 0.01). The GRACE risk score was significantly higher in the group with high NLR values compared to those with moderate or low NLR (161.5±40.3, 130.5±32.3, and 123.9±34.3, respectively, p<0.001). Similarly, the SYNTAX score was significantly higher in the group with higher NLR.[8] Arbel et al. found that increased NLR was associated with increased severity of CAD, thereby providing additive predictive value to conventional risk factors and commonly used biomarkers, e.g., C-reactive protein (CRP) and total WBC count.[9]

In our study, NLR increased with increasing TIMI, GRACE score but P value was not significant, and it was not associated with the extent of coronary artery disease.

Limitations of the study

A small sample of cases studied, followed up for six months, Only one sample of inflammatory markers are analyzed, follow up response to treatment was not analyzed. Treatment modalities were different based on patient references. Drug compliance was not objectively assessed.

Conclusions

NLR, HsCRP, IL6, IL10 are significantly associated with TIMI, GRACE, KILLIP risk scoring systems. Inflammatory markers studied above, except TNF, shows a correlation with mortality, morbidity, the extent of coronary artery disease. These markers explain other domain of pathogenesis in ACS which is a potential target for newer therapeutics.

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