

## “A Retrospective Study on the Utility of GRACE and TIMI Score to Predict Coronary Revascularization among Patients with Acute Coronary Syndrome”

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**Abstract:** GRACE and TIMI score are risk stratification tools that are able to predict the short term and long term mortality in patients with Acute Coronary Syndrome (ACS). There is insufficient evidence from the literature on the value of risk scores in predicting need for coronary revascularization. Hence, we performed the study to assess the utility of GRACE and TIMI score to predict the requirement for coronary revascularization. A total of 515 patients with ACS participated in the study. Patients with co-morbid medical conditions were excluded. Baseline characteristics of all the patients were recorded. GRACE and TIMI score were calculated for the patients using web based calculator and their in-hospital mortality was also recorded. Based on angiographic data the need for coronary revascularization was assessed. The ability of GRACE and TIMI score to predict coronary revascularization was estimated by plotting ROC curves. The cut off for GRACE score, to predict the need for revascularization was 121.5 (AUC of 0.624;  $p = 0.001$ , 95% CI= 0.55-0.68) with a sensitivity of 61%, specificity of 60%; the cut-off for TIMI risk score was 2.5 (AUC of 0.59,  $p = 0.01$ , 95% CI- 0.51-0.65) with a sensitivity of 66%; and specificity of 47%. The GRACE score showed a marginal potential of predicting the need for coronary revascularization in ACS patients and may be a useful, preliminary screening tool in the cardiac catheterization laboratory.

**Keywords:** Acute Coronary syndrome, co-morbid, GRACE, in-hospital mortality, revascularization, Thrombolysis in Myocardial Infarction (TIMI).

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### I. Background

Acute Coronary syndrome, the most severe form of coronary artery continues to have high mortality and morbidity [1, 2]. It includes patients with ST-Elevation Myocardial Infarction (STEMI), Non ST-Elevation Myocardial Infarction (NSTEMI) and unstable angina (UA). The prognosis of patients is considerably varied with respect to both short term and long term outcomes [3]. Although there is sufficient correlation between clinical symptoms and the severity of the disease, it is not well known if knowledge of the clinical profile of the patient could successfully predict the need for coronary intervention such as coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Using the clinical characteristics of the patients, several prognostic scores have been defined such as GRACE (Global Registry of Acute Coronary Events), TIMI (Thrombolysis in Myocardial Infarction), CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) and PAMI scores ( Primary Angioplasty in Myocardial Infarction) [ 4, 5 ].

The GRACE score has been derived from several large databases across the globe and has been shown to accurately reflect the in-hospital mortality as well as six month mortality in ACS patients [6-9]. The score requires eight independent risk factors such as age, systolic blood pressure at presentation, creatinine level, heart rate at presentation, Killip class for congestive heart failure, presence of cardiac arrest, ST-segment deviation on the index ECG and elevated cardiac enzyme levels on admission for measurement [16]. The GRACE score has been found to be superior to even sophisticated tools such as dobutamine stress echocardiography and myocardial perfusion scanning in predicting long term CV mortality [10]. Since the GRACE score predicts mortality, theoretically it should be an excellent tool to even predict if a patient is likely to have an angiographic lesion that warrants treatment. Although a decision on taking up a patient for invasive procedures is dependent on several other factors besides the angiographic lesion such as patient preference, cost factor, operator intuition

and judgement, it is still worthwhile to have a preliminary idea if a patient is likely to have a lesion that requires immediate invasive procedures such as CABG or PCI [11, 12].

The TIMI (Thrombolysis in Myocardial Infarction) score is a potential seven point risk score which not only predicts the risk of developing an adverse cardiac outcome like death, re-infarction, or recurrent severe ischemia requiring revascularization in patients within 14 days of presentation with ACS but it also anticipates specific therapies with increasing risk for patients which is of great benefit [13-15]. The parameters included for assessment of TIMI score are age, presence of at least 3 classical risk factors for coronary artery disease (CAD), known CAD, use of aspirin in the past 7 days, severe angina in the past 24 hours, elevated cardiac markers and ST-deviation >0.5 mm. This seven point tool for risk assessment divides patients into low (score 0-2), intermediate (score 3-4), high (score 5-7) [16]. In a study done by Charles V. Pollack Jr et al TIMI risk score proved to be successful tool for risk stratification of ED patients with chest pain syndrome [13]. The TIMI score has also been shown to be useful in undertaking invasive strategies in patients with STEMI [17]. However the utility of TIMI score in predicting the need for revascularization in ACS patients is not widely studied.

Hence the aim of the study was to assess the utility of GRACE & TIMI score in predicting the need for coronary revascularization as assessed by coronary angiography. The study also attempted to look at the prognostic value of the GRACE and TIMI score in the Indian population as there is only one published study so far in the Indian population.

## **II. Methods**

The study was a retrospective study performed in the Dept of Cardiology, SRM Medical College Hospital, Kanchepuram, India. The data was collected from the records of another study to assess the utility of multiple biomarkers in Acute Coronary Syndrome. The study was conducted from September 2014 – October 2015. The study was approved by the Institute Ethics Committee of the hospital and was carried out in accordance with the Declaration of Helsinki guidelines (Amended version 2013). We included patients admitted with the diagnosis of Acute Coronary Syndrome within 48 hours of admission from the time of initial symptoms. We excluded patients with co-morbid medical conditions that could affect the mortality. All the baseline characteristics of the study patients were recorded such as age, gender, risk factors such as diabetes, hypertension, family history of CAD and vital parameters such as blood pressure, heart rate, laboratory parameters such as lipid profile, serum creatinine, Hb, total count, cardiac biomarkers such as troponin, CPK-MB. Based on the characteristics of the patient, the GRACE and TIMI score were calculated using a web based calculator. The in-hospital mortality of patients was also recorded. Based on the angiography characteristics and clinical presentation, the decision regarding need for revascularization was made by blinded cardiologists.

### **Statistical analysis**

Data are represented as mean  $\pm$  SD or median with interquartile range or frequency with percentages. Based on the GRACE-in hospital score, patients were divided into three tertiles- lower, intermediate and higher tertiles. As the GRACE score increases the risk of mortality increases. Thus the division of the study population based on tertiles into low risk, intermediate risk, and high risk was performed. All patient characteristics were compared between the three groups using ANOVA or Chi-square test. An ROC curve was plotted for GRACE hospital score & TIMI score vs. in-hospital mortality. ROC curve was also plotted between the various subsets of patients. Pearson correlation was performed between GRACE score, TIMI score and the other clinical characteristics of the patient. An ROC was plotted to find the cut-off GRACE score that could accurately predict the need for coronary revascularization. Data were analyzed using SPSS v.17.0. A P value of <0.05 was considered statistically significant.

## **III. Results**

We screened 587 patients for the above study. However 63 patients were unwilling to participate in the study. Nine patients were discharged against medical advice and their data were unavailable. Thus a total of 515 patients were available in the present study. Among the 515 patients who were the part of the study, angiography was performed in 391 patients, of which 265 patients were advised angioplasty or CABG. 126 patients were advised medical management. This decision was based on lesion severity, ischemic burden and clinical representation of the patient. GRACE in-hospital score and the TIMI risk scores were calculated using the data available. Based on the GRACE in-hospital scores, patients were divided into 3 tertiles; low risk (Tertile 1/T1) cut off from 0-113, intermediate risk (Tertile 2/T2) cut off from 113-143 and high risk (Tertile 3/T2) greater than 143. When baseline values were calculated (Table 1), age (p=0.001), body mass index/BMI (p=0.001), heart rate (p=0.001), bloodpressure/BP(p=0.001),ejection fraction/ EF(p=0.001), triglycerides/ TGL(p=0.041),urea(p=0.001),creatinine(p=0.003), haemoglobin (p=0.001), creatine phosphokinase/ CK(p=0.031), creatine phosphokinase myocardial band/CPK-MB(p=0.020), GRACE in-hospital(p=0.001),

TIMI risk score( $p=0.001$ ) and overall death( $p=0.001$ ) were found to be significantly different between the groups. From the table it is evident that patients in the T3 group were older in age( $64.59\pm 9.48$ ), higher BMI( $29.25\pm 13.09$ ), higher number of STEMI diagnosis [131(80.9%)], higher heart rate ( $86.12\pm 19.89$ ), lower EF( $44.48\pm 11.64$ ), lower triglyceride levels( $132.36\pm 85.58$ ), higher creatinine( $1.29 \pm 0.81$ ), highest levels of biomarkers: CPK( $1580.81\pm 1811.54$ ) and CPK-MB( $191.08\pm 268.84$ ), and higher risk scores: GRACE in-hospital( $178.86 \pm 32.45$ ), TIMI( $4.89 \pm 2.25$ ) as compared to the other two tertiles. There was no statistically significant difference among the three tertiles of grace scores with respect to their angiographic features.

ROC curves were plotted between GRACE in-hospital score and in-hospital mortality which showed an AUC of 0.85 ( $p=0.0001$ , 95 % CI- 0.79 to 0.92) and the cut-off value of GRACE score to predict mortality were 143.5 with a sensitivity of 86 % and specificity 73% (Fig.1a), TIMI risk score and in-hospital mortality showed an AUC of 0.79 ( $p= 0.0001$ , 95% CI ; 95% CI - 0.70 to 0.88) optimal cut-off 4.5 with a sensitivity of 65 % and specificity of 79 % (Fig.1b).

We also plotted ROC curves for GRACE in hospital and TIMI risk score to see the ability to predict the need for revascularization. The cut off for GRACE score, to predict the need for revascularization was 121.5 (AUC of 0.624;  $p = 0.001$ , 95% CI= 0.55-0.68) with a sensitivity of 61%, specificity of 60% (Fig. 2A). Whereas TIMI risk score yielded an AUC 0.59 ( $p = 0.01$ , 95% CI- 0.51-0.65) optimal cut off 2.5 with a sensitivity of 66%; and specificity of 47% (Fig. 2b). Age and Creatinine were the strongest predictors for the need of revascularization ,[AUC of 0.64( $p$  value=0.006) and 0.65 ( $p = 0.004$ ) respectively]

ROC curves were also plotted between GRACE in-hospital score/TIMI risk score and in-hospital death for comparing patients with STEMI risk factors like Diabetes mellitus (DM), Hypertension (HT) and without risk factors, STEMI patients who had undergone thrombolysis and not undergone thrombolysis, patients who visited the hospital within 12 hours of presentation of myocardial infarction/MI and patients who took more than 12 hours and age below 65 and above 65 (Table 2). There were no differences between study sub groups in the ability of GRACE and TIMI score to predict in hospital death in STEMI patients. GRACE and TIMI score did not show predictive ability for in hospital mortality in NSTEMI patients.

The correlation between GRACE scores and TIMI scores was done with demographic characteristics: age, height, weight and BMI, clinical Variables: heart rate, systolic blood pressure/SBP and diastolic blood pressure/DBP, laboratory parameters: Total TC, HDL, VLDL, LDL, TGL, Urea, Creatinine, Hb and TC, and ejection fraction. EF negatively correlated with both GRACE in-hospital score( $r=-.380$ ,  $p=0.001$ ) as well as with TIMI risk score( $r=-0.43$ ,  $p=0.001$ ) (Fig.3a and 3b). Similarly GRACE in-hospital score correlated negatively with haemoglobin levels( $r=-0.20$ ,  $p=0.001$ ), while it positively correlated with total count( $r= 0.32$ ,  $p=0.001$ ) (Fig. 4a and 4b). There was a good correlation between GRACE and TIMI score ( $r= 0.662$  and  $p= 0.0001$ ).

#### IV. Discussion

The Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk model study done in our centre is the first study to look into the utility of GRACE and TIMI risk score in assessing the need for coronary revascularization in ACS patients in the Indian community. Our study showed that GRACE score did have a marginal ability to predict the need for coronary revascularization in patients with ACS. In a previous study, GRACE risk score was higher in NSTEMI patients with high-risk coronary anatomy (HRCA) than in low-risk coronary anatomy (LRCA) and the former group were more likely to have a lesion requiring CABG treatment [18]. However the ability of GRACE scores to predict HRCA was minimal as seen by the small AUC. In contrast, a study by Zhou et al showed that GRACE had a strong ability in predicting the need for PCI in NSTEMI patients .4 In patients with a GRACE score of greater than 140, early intervention within 24 hours was more effective in reducing cardiovascular outcomes than delayed revascularization in non ST-ACS. In contrast in patients with low and intermediate risk, there was no difference in outcomes between early and delayed revascularization [19]. There are also been reports of situations in which there was a greater likelihood of PCI among people with low risk than high risk patients according to GRACE score in both STEMI and NSTEMI [20]. Having a non-invasive method such as the GRACE score to predict the severity of the disease that warrants an invasive procedure would certainly be a valuable tool in the hands of the interventional cardiologist. It could possibly be used as a screening method to identify the patients with high risk lesions even before an angiography is performed. At times it is common for patients to receive thrombolysis in hospital and opt for PCI/angiography at a later date. During these situations, knowing that a patient is likely to have a high risk lesion would give a stronger case for avoiding such inappropriate delays.

The GRACE score was created based on the data derived from 14 countries comprising principally of the Caucasian population. There is only one other study done in the Indian population which showed that higher GRACE score was able to predict the risk of major in-hospital events and increased severity of CAD [21]. The cut off value in GRACE score to predict hospital events in this study was 217. In another study a cut off of GRACE risk score of >155 manifested the high risk group [22]. In contrast our study revealed a cut off of 146.5 to predict in-hospital mortality. The difference in the cut-off values between our study and the earlier published

study could be attributed to the difference in demographic profile of the patients. In our study most of the patients belonged to the rural and sub-urban population and it was well possible that patients in the high risk group who had high risk of events did not survive even to reach the hospital visit because of the delay in seeking medical care.

The AUC for GRACE score was much higher than that seen with the TIMI score. This is not surprising considering the fact that GRACE score takes into account several additional features such as creatinine, cardiac biomarker elevation and presence of cardiac arrest. Nevertheless both GRACE and TIMI score serve as useful tools to predict the in hospital mortality risk in the Indian population as seen by their AUC.

The GRACE score was found to inversely correlate with ejection fraction from our study. The GRACE score was evaluated to see if it could accurately predict heart failure following an ACS in an earlier study. High- and moderate-GRACE risk score had a six fold and two fold increased risk of HF respectively [23]. In a study by McAllister et al, the GRACE score was used to predict the risk of CHF admissions. It was observed that compared to the lowest quintile, patients in the highest GRACE score quintile had more CHF admissions (116 vs. 17) [24]. Thus there seems to be a distinct relationship between the GRACE score and the left ventricular function of the patient with ACS. Although, we did not study the development of HF after discharge from hospital in our study population, the negative correlation that was observed between EF and GRACE score does reiterate the trend observed in earlier studies. In comparison to the TIMI score, the GRACE score had a better ability to predict in-hospital mortality and need for revascularization. These findings are in agreement with an earlier study that showed the TIMI score to be less discriminative than the GRACE score in prediction of in-hospital mortality [25].

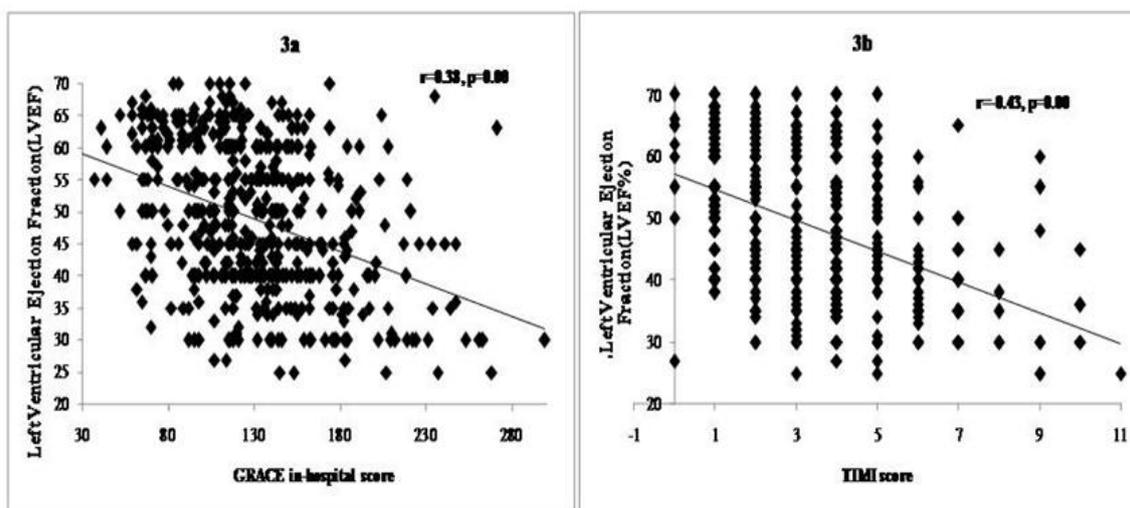
#### **Limitations of the study:**

The number of events among NSTEMI was inadequate to assess the utility of this tool in this population in predicting the risk of mortality. We could not obtain sufficient long term follow-up data of these patients which could have strengthened the value of these models in long term risk prediction in the Indian population. As this was a single centre study some of the findings could reflect more of the prevalent practice pattern in the site and may be less transposable to the general community.

#### **V. Conclusion**

Our study has shown that, the GRACE score does have a modest ability as a preliminary screening tool to predict the need for interventional procedures among patients with acute coronary syndrome.

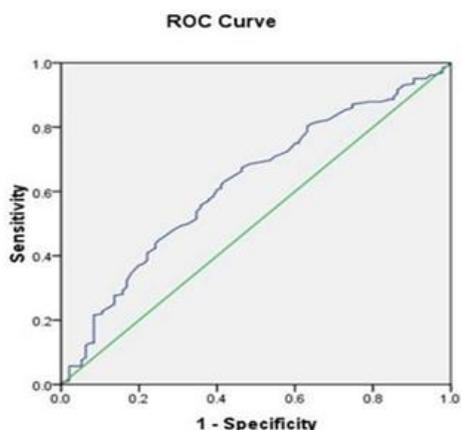
**Figure 3. Correlation plots for (a) GRACE in-hospital (b)TIMI scores vs. ejection fraction**



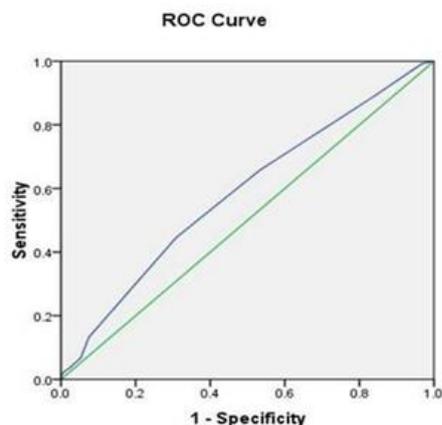
**3a. GRACE in-hospital score vs. Left Ventricular Ejection Fraction(LVEF)**

**3b. TIMI score vs. Left Ventricular Ejection Fraction(LVEF%)**

**Fig 2. Receiver operating characteristics (ROC) for GRACE & TIMI score to predict need for revascularization.**

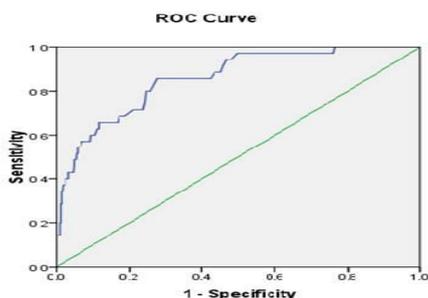


**Fig 2(a) GRACE score AUC=0.62 , p = 0.001, 95% CI= 0.55-0.68 ; Cut off= 121.5; Sensitivity= 61%; Specificity=60%).**

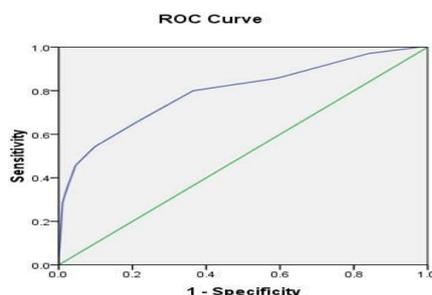


**Fig 2(a) TIMI score. (AUC=0.59, p = 0.01, 95% CI= 0.51-0.65 ; Cut off= 2.5; Sensitivity= 66%; Specificity=47%)**

**1. Receiver operating characteristics (ROC) for (a) GRACE in-hospital score (b) TIMI score vs. In-hospital death**

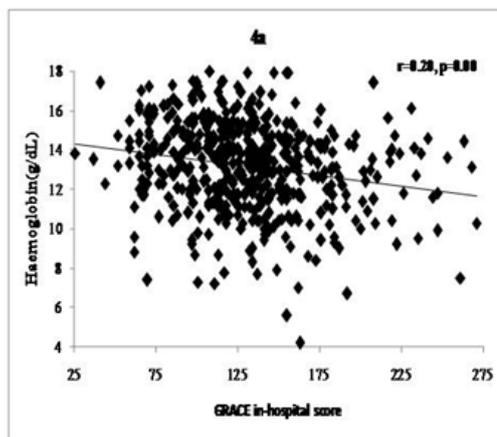


**For 1(a): AUC = 0.85; 95% CI- 0.79 to 0.92; p=0.0001; optimal cutoff 143.5; sensitivity 86%; specificity 73%.**

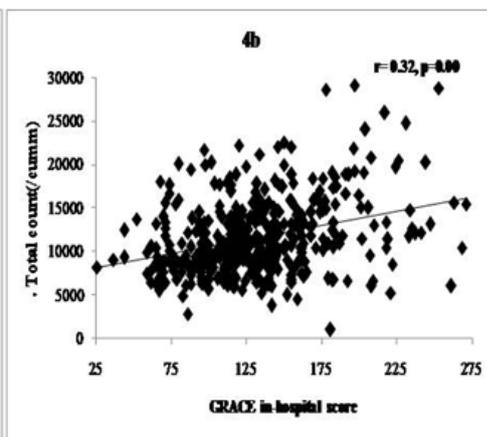


**For 1(b): AUC = 0.79; 95% CI-0.70 to 0.88; p=0.0001; optimal cutoff 4.5; sensitivity 65%; specificity 79%.**

**Figure 4. Correlation plots for GRACE in-hospital score vs. (a) Haemoglobin and (b) Total count**



**4a. GRACE in-hospital score vs. Haemoglobin (Hb) levels (g/dL)**



**4b. GRACE in-hospital score vs. Total count (/cumm)**

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### Conflict of Interest:

We declare that we do not have any conflict of interest.

### Financial Disclosure:

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**Table 1.** Baseline characteristics of study patients.

Characteristics	Total(N=515)	T1(N=179)	T2(N=184)	T3(N=152)	P-value
Age	56.5 ± 11.7	48.66 ± 10.15	57.34 ± 9.56	64.6 ± 9.69	0.001
Sex (%)	376(72.9)	135(75.4)	136(73.9)	105(69.1)	0.28
BMI (kg/m <sup>2</sup> )	26.82±8.36	26.17 ± 5.46	25.49 ± 4.26	29.4 ± 13.42	0.001
Delayed presentation (%)	104(20.2)	28(15.6)	34(18.5)	42(27.6)	0.38
Thrombolysed (%)	154(29.8)	36(20.1)	60(32.6)	57(37.5)	0.65
Heart rate (beats/ min)	82.79±15.8	81.28 ± 12.77	81.29 ± 14.02	86.28 ± 20.06	0.005
SBP (mm Hg)	130±25.22	140.95 ± 23.11	129.66 ± 22.93	117.02 ± 23.8	0.001
DBP (mm Hg)	81.82±12.57	86.47 ± 12.1	80.89 ± 11.06	77.18 ± 12.67	0.001
DM (%)	248(48.1)	79(44.1)	93(50.5)	75(49.3)	0.51
HT (%)	234(45.3)	82(45.8)	86(46.7)	65(42.8)	0.94
EF (%)	48.91±11.39	53.66 ± 10.45	48.15 ± 10.24	44.39 ± 11.72	0.001
TC (mg / dL)	184.04±49.06	184.71 ± 46.48	186.99 ± 46.11	179.44 ± 55.45	0.56
HDL (mg / dL)	38.49±12.14	37.65 ± 11.96	37.95 ± 9.82	40.19 ± 14.7	0.23
LDL (mg / dL)	32.29±39.76	32.91 ± 18.69	35.5 ± 61	27.43 ± 17.78	0.18
VLDL (mg / dL )	118.11±43.22	119.72 ± 41.81	120.88 ± 40.58	112.62 ± 47.82	0.43
TG (mg / dL)	148.25±85.48	156.32 ± 78.98	152.34 ± 88.38	133.18 ± 87.97	0.04
Urea (mmol / L)	28.92±16.01	24.37 ± 9.63	26.59 ± 11.81	37.25 ± 22.41	0.001
Creatinine (mmol / L)	1.12±0.89	0.96 ± 0.3	1.11 ± 1.23	1.31 ± 0.82	0.003
Hemoglobin (g/dL)	13.3±2.49	13.85 ± 2.36	13.25 ± 2.49	12.72 ± 2.51	0.001
Total count (/ mm <sup>3</sup> )	11617.39±4231.58	10275 ± 3543.92	11265.03 ± 3332.81	13553.49 ± 5189.73	0.001
GRACE in hospital score	130.6±42.6	88.93 ± 18.32	129.38 ± 9.66	181.15 ± 32.2	0.001
TIMI	3.37±1.99	2.22 ± 1.23	3.15 ± 1.45	4.96 ± 2.25	0.001
Angiography (%)	383(74.2)	140(78.2)	137(74.5)	236 ± 1.23	0.23
Overall death (%)	49(9.5)	6(3.4)	9(4.9)	33(21.7)	0.001
In hospital death (%)	30(5.8)	1(0.6)	2(1.1)	27(17.8)	0.001

BMI- body mass index, DBP- diastolic blood pressure, DM- diabetes mellitus, EF- ejection factor, GRACE- global registry of acute coronary events, HDL- High-density lipoprotein, HT- hypertension, LDL-Low density lipoprotein, TC-total cholesterol, TG- triglycerides, TIMI- Thrombolysis in Myocardial Infarction, VLDL-very low density lipoprotein.

**Table 2:** Assessment of GRACE and TIMI Score within Subgroups Population.

Category	AUC (with 95% confidence interval)	P value	Category	AUC (with 95% confidence interval)	P value
Age below 65-GRACE vs. In-hospital death	0.74(0.63,0.85)	0.001	Age above 65-GRACE vs. In-hospital death	0.77(0.62,0.92)	0.001
Age below 65-TIMI vs. In-hospital death	0.70(0.60, 0.80)	0.001	Age above 65-TIMI vs. In-hospital death	0.71(0.56,0.87)	0.005
Diabetic-GRACE vs. In-hospital death	0.78(0.68, 0.88)	0.001	Non-Diabetic-GRACE vs. In-hospital death	0.77(0.65,0.90)	0.001
Diabetic-TIMI vs. In-hospital death	0.73(0.62,0.83)	0.001	Non-Diabetic-TIMI vs. In-hospital death	0.74(0.62,0.86)	0.001
HT-GRACE vs. In-hospital death	0.79(0.69,0.88)	0.001	Non-HT-GRACE vs. In-hospital death	0.76(0.63,0.89)	0.001
HT-TIMI vs. In-hospital death	0.72(0.61,0.82)	0.001	Non-HT-TIMI vs. In-hospital death	0.75(0.63,0.86)	0.001
STEMI-Thrombolysed GRACE vs. In-hospital death	0.87(0.78,0.96)	0.001	STEMI-Not Thrombolysed GRACE vs. In-hospital death	0.67(0.51,0.83)	0.01
STEMI-Thrombolysed TIMI vs. In-hospital death	0.76(0.65,0.87)	0.001	STEMI-Not Thrombolysed TIMI vs. In-hospital death	0.65(0.49,0.81)	0.08
STEMI-DP GRACE vs. In-hospital death	0.66(0.47, 0.84)	0.04	STEMI-NDP GRACE vs. In-hospital death	0.87(0.77,0.99)	0.001
STEMI-DP TIMI vs. In-hospital death	0.60(0.41,0.79)	0.09	STEMI-NDP TIMI vs. In-hospital death	0.79(0.65,0.93)	0.001

DP – delayed presentation, GRACE- global registry of acute coronary events, HT- hypertension, NDP- non delayed presentation, NSTEMI- Non ST-segment elevation myocardial infarction, STEMI- ST-segment elevation myocardial infarction