

Correlation between Thrombolysis in Myocardial Infarction and The Global Registry of Acute Coronary Syndromes Risk Scores and Severity of Coronary Artery Disease in Patients with Non-ST Elevation Acute Coronary Syndrome

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ABSTRACT

Background: the prognosis of non-ST elevation acute coronary syndrome (NSTEMACS) patients is frequently done by using thrombolysis in myocardial infarction (TIMI) and global registry of acute coronary events (GRACE) risk scores. Only few studies were done for prediction ability of the scores with coronary artery disease. **Methods:** this prospective cross-sectional study included 100 patients was conducted at Mabaret Misr Alqadema and Al-Azhar University Hospitals from May 2017 till September 2018. We calculated the TIMI and the GRACE risk scores for all patients on admission then patients had coronary angiography to detect the extent of the coronary artery disease (CAD). We assessed the severity of CAD by using Gensini score and vessel score. **Results:** the TIMI and GRACE scores have an acceptable predictive value in identifying the extent of the CAD. A TIMI score ≥ 3 and GRACE score ≥ 102 was significantly associated with 3 vessel disease and left main disease ($p < 0.014$ for TIMI and $p < 0.007$ for GRACE). On comparison of the two risk scores, the discriminatory accuracy of the GRACE score was non-significantly superior to the TIMI score in predicting 3 vessel and left main (LM) diseases but the combination of both scores has a higher accuracy ($p < 0.006$). **Conclusions:** the CAD is more extensive by coronary angiography in patients with NSTEMACS who had higher TIMI or GRACE risk scores, as they have a good predictive value. However, when both compared, the GRACE score has a non-statistically significant superiority with multivessel and LM disease, and combination of both scores has a higher accuracy.

Keywords: NSTEMI-ACS, TIMI risk score, GRACE risk score, Gensini risk score, CAD.

INTRODUCTION

Globally, ischemic heart disease remains the number one cause of mortality⁽¹⁾. NSTEMACS is more frequent than STEACS with annual incidence is about 3 per 1000 inhabitants⁽²⁾, with similar mortality as STEMI at 6 months⁽³⁾ and higher with a two-fold difference at 4 years⁽⁴⁾.

Risk models as GRACE and TIMI scores predict a probability for adverse outcomes based on combinations of clinical, ECG, and laboratory data available at presentation assist in identifying patients at risk for recurrent ischemia and death events^(5,6). the GRACE and TIMI RSs are the most widely used⁽⁷⁾, GRACE is more accurate than TIMI score but it is more complex^(8,9).

PATIENTS AND METHODS

Study population and method: This was a prospective observational study, which involved 100 NSTEMI patients, during the period from May 2017 till September 2018. **After approval of the ethical committee of the faculty and after individual written consent**, patients had coronary angiography then we divided the study population into 2 groups: Single or two-vessel CAD group and 3 vessel or LM

CAD group then compared both groups against TIMI and GRACE risk scores.

We excluded from the study patients who had previous coronary artery bypass surgery, myocardial infarction, or previous percutaneous coronary intervention (PCI), patients whose systolic blood pressure (SBP) was more than 180 mm Hg or diastolic blood pressure (DBP) was more than 110 mm Hg and patients with a missing data for calculating the GRACE RS and TIMI RS.

For each enrolled patient, we collected the following data; clinical data (full history, cardiac risk factors and clinical examination), ECG, conventional echocardiographic, laboratory data (CBC, serum creatinine, CK-MB, troponin, coagulation profile and lipid profile) and CA data.

Calculation of the GRACE and the TIMI risk scores

GRACE risk score (GRS); It was calculated by using specific variables (age, heart rate, SBP, creatinine, Killip class, elevated cardiac markers, ST-segment deviation, cardiac arrest at admission) gathered at admission, and accordingly patients were divided into low (GRS < 108), intermediate (GRS 109-140) and high (GRS > 141) risk groups.

TIMI risk score (TRS); at admission the data was gathered: Age ≥ 65 , aspirin use in the last 7 days, at least 2 angina episodes within the last 24 hrs., ST segment deviation of 0.5 mm or more on admission ECG, elevated cardiac biomarkers, at least 3 risk factors for CAD and known coronary artery disease (CAD) (coronary stenosis $\geq 50\%$), scored 1 point for each⁽¹⁰⁾. Based on TRS values, the study population was divided into Low (TRS 0-2), intermediate (TRS 3-4), and high-risk Groups (TRS 5-7).

Coronary arteries anatomies were assessed by cardiac catheterization, a vessel score according to the presence of vessel disease $> 70\%$ in the major epicardial vessels (LAD, LCX and RCA, a large diagonal branch or obtuse marginal also considered in the major epicardial vessels) or presence of left main disease $> 50\%$. The extent of CAD was defined as single vessel disease, two vessel disease or three vessel disease CAD.

A quantitative analysis was performed by using the Gensini score, a score that depends on the lesion stenosis and area supplied by coronary artery, each gets a score, where stenosis diameter (0-25% = 1; 26%-50% = 2; 51%-75% = 4; 76%-90% = 8; 91%-99% = 16; 100% = 32 points) and the vessel scored according to anatomical importance (ranging from 0.5 to 5), then multiplied by each other, and all are summed to get a final score.⁽¹¹⁾

Statistical analysis; We analyzed data using Statistical Program for Social Science (SPSS) version 23, NCSS version 12 and MedCalc version 15.4.

Quantitative data were clarified by mean \pm standard deviation (SD). While qualitative data were cleared using the chi-square test, or Fisher's exact test when the chi-square test was not appropriate. The normality of distribution of quantitative variables was assessed by calculating kurtosis and skewness coefficients and by the Kolmogorov-Smirnov test. Student's t test was the test of comparisons for normal distributions, otherwise the Mann-Whitney test was used.

Receiver operating characteristic (ROC) curves were used to determine the predictive accuracy of the risk scores regarding obstructive and severe CAD (presence of LM or 3 VD). Criteria to qualify for AUC were as follows: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at point of maximum accuracy.

RESULTS

The mean age of studied population was 57.4 ± 7.8 years (ranged from 38-79 years). Males represented 70% (70 patients) of the study population while females represented 30% (30 patients). Forty four percent (44 patients) were hypertensive while fifty

two percent (52 patients) were diabetic and forty seven percent (47 patients) were smokers. (Table 1).

Coronary angiography showed that forty nine percent (49 patients) had a single vessel disease, twenty six percent (26 patients) had two vessels disease and twenty five percent (25 patients) had LM or three vessels disease. The mean Gensini score was 38.7 ± 35.3 (ranged from 0 – 178).

The TIMI risk score among the study population; the study population mean TIMI score was 2.6 ± 1.2 ranging from (1- 6). Fifty patients (50%) had a low TIMI score (0-2), forty two patients (42%) had an intermediate TIMI risk score (3-4) and eight patients (8%) had high TIMI risk score (5-6).

The GRACE risk score among the study population; the mean GRACE risk score was 96.5 ± 20.4 ranging from (46 – 156). Seventy one patients (71%) of the study population had a low GRACE risk score (≤ 108), twenty six patients (26%) had an intermediate GRACE risk score (109 – 140) and three patients (3%) had high GRACE risk score (≥ 141).

We divided the study population into two groups LM or 3 vessel group and Single or two vessels group.

There were significant differences between low risk, intermediate risk and high risk TIMI scores as regard Gensini score (28.8 ± 29 vs. 42.8 ± 35.9 vs. 81.0 ± 33.8 respectively, p value <0.001) with significant positive correlation between both scores (r 0.374, p value <0.001). (Figure 1)

There were significantly differences between low risk, intermediate risk and high risk GRACE scores as regard Gensini score (30.9 ± 31.2 vs. 54.8 ± 36.4 vs. 87.3 ± 37.8 respectively, p value <0.001) with significant positive correlation between both scores (r 0.408, p value <0.001). (Figure 2)

The LM or three vessels disease group had higher TIMI risk score (3.2 ± 1.4 vs. 2.5 ± 1.0 , p value 0.014) (Table 2), GRACE Risk score (105.4 ± 23.8 vs. 93.5 ± 18.4 , p value 0.011) (Table 3) and Gensini score (82.9 ± 41.9 vs. 24.1 ± 14.1 , p-value 0.001).

ROC curve analysis for different scores in predicting LM or three-vessel disease: In our study the TIMI risk score at value 3 showed moderate sensitivity (72%) and low specificity (57.3%) and good negative predictive value of (86%) while GRACE risk score showed moderate specificity (62%) and sensitivity (68%) and good negative predictive value (NPV) of (85.5%). The combination of both scores had a moderate sensitivity (68%), good specificity (62.7%), moderate positive predictive value (PPV) (56.7%) and good negative predictive value (88.6%) so the combination of both scores showed higher accuracy as it had best PPV (56.7%) and specificity (82.7%) with good NPV (88.6%) and moderate sensitivity (68%) (Table 4 and Figure 3).

Table (1): Demographic data of study population

| Demographic data Count (%) | All patients 100 (100%) |
|--------------------------------|-------------------------|
| Age (years) | |
| Mean ± SD | 57.4 ± 7.8 |
| Median (Range) | 57 (38 – 79) |
| Gender | |
| Male | 70 (70%) |
| Female | 30 (30%) |
| Risk factors | |
| HTN | 44 (44%) |
| DM | 52 (52%) |
| Smoking | 47 (47%) |
| Hypercholesterolemia | 39 (39%) |
| Family history of IHD | 16 (16%) |
| Known CAD | 2 (2%) |
| Number of risk factors | |
| Less than 3 CAD risk factors | 75 (75%) |
| Three or more CAD risk factors | 25 (25%) |

Table (2): Comparison between the studied groups regarding the TIMI risk items and score

| TIMI risk items and score | LM or three-vessel disease | Single or two-vessel disease | Test | P-value (Sig.) |
|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|------------------------------|----------------------|----------------|
| Count (%) | 25 (25%) | 75 (75%) | | |
| Item | | | | |
| Age ≥ 65 years | 18 (72%) | 65 (86.7%) | 2.858 ‡ ^F | 0.123(NS) |
| Three or more CAD risk factors | 11 (44%) | 14 (18.7%) | 6.418 ‡ | 0.011(S) |
| Known CAD | 1 (4%) | 1 (1.3%) | 0.680 ‡ ^F | 0.439(NS) |
| ASA use in past 7 days | 8 (32%) | 13 (17.3%) | 2.431 ‡ | 0.119(NS) |
| Severe angina (≥2 episodes in 24 hours) | 14 (56%) | 41 (54.7%) | 0.013 ‡ | 0.908(NS) |
| ECG changes | 22 (88%) | 63 (84%) | 0.235 ‡ ^F | 0.755(NS) |
| Positive cardiac biomarkers | 23 (92%) | 67 (89.3%) | 0.148 ‡ ^F | 1.00(NS) |
| TIMI score | | | | |
| Mean ± SD | 3.2 ± 1.4 | 2.5 ± 1.0 | 2.460 • | 0.014(S) |
| Median (Range) | 3 (1 – 5) | 2 (1 – 6) | | |
| TIMI risk stratification | | | | |
| Low (≤ 2) | 7 (28%) | 43 (57.3%) | 10.02 ‡ | 0.007(S) |
| Intermediate (3 – 4) | 13 (52%) | 29 (38.7%) | | |
| High (≥ 5) | 5 (20%) | 3 (4%) | | |
| * Independent samples Student's t-test. • Mann Whitney U test. ‡ Chi-square test. ‡ ^F Fisher's Exact test. p < 0.05 is significant. | | | | |

(The meaning of these signs “‡^F •” should be written)

Table (3): Comparison between the studied groups regarding the GRACE risk items and score

| <i>GRACE risk items and score</i> | LM or three-vessel disease | Single or two-vessel CAD | Test | P-value (Sig.) |
|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------|----------------------|-----------------------|
| Count (%) | 25 (25%) | 75 (75%) | | |
| Age (years) | | | | |
| <i>Mean ± SD</i> | 59.6 ± 8.4 | 56.7 ± 7.4 | 1.668 * | 0.098 (NS) |
| <i>Median (Range)</i> | 59 (42 – 79) | 57 (38 – 74) | | |
| Pulse (beat/min) | | | | |
| <i>Mean ± SD</i> | 86.8 ± 10.2 | 84.7 ± 9.6 | 0.961 * | 0.339 (NS) |
| <i>Median (Range)</i> | 89 (65 – 110) | 85 (65 – 110) | | |
| SBP (mmHg) | | | | |
| <i>Mean ± SD</i> | 143.6 ± 18.9 | 134.9 ± 21.4 | 1.647 • | 0.100 (NS) |
| <i>Median (Range)</i> | 140 (110 – 180) | 140 (90 – 180) | | |
| Creatinine (mg/dL) | | | | |
| <i>Mean ± SD</i> | 1.12 ± 0.27 | 1.04 ± 0.22 | 1.549 • | 0.121 (NS) |
| <i>Median (Range)</i> | 1.1 (0.7 – 1.8) | 1.0 (0.6 – 1.6) | | |
| Killip class | | | | |
| <i>Class I</i> | 19 (76%) | 73 (97.3%) | 12.483 ‡ | 0.002 (S) |
| <i>Class II</i> | 5 (20%) | 1 (1.3%) | | |
| <i>Class III</i> | 1 (4%) | 1 (1.3%) | | |
| ST-segment deviation on ECG | 22 (88%) | 63 (84%) | 0.235 † ^F | 0.755 (NS) |
| Abnormal cardiac enzymes | 23 (92%) | 67 (89.3%) | 0.148 † ^F | 1.00 (NS) |
| Cardiac arrest on admission | 0 (0%) | 0 (0%) | - | - |
| GRACE score | | | | |
| <i>Mean ± SD</i> | 105.4 ± 23.8 | 93.5 ± 18.4 | 2.579 * | 0.011 (S) |
| <i>Median (Range)</i> | 109 (57 – 156) | 94 (46 – 143) | | |
| GRACE risk stratification | | | | |
| <i>Low (≤108)</i> | 12 (48%) | 59 (78.7%) | 9.415 ‡ | 0.009 (S) |
| <i>Intermediate (109 – 140)</i> | 11 (44%) | 15 (20%) | | |
| <i>High (≥141)</i> | 2 (8%) | 1 (1.3%) | | |
| * Independent samples Student's t-test. • Mann Whitney U test. ‡ Chi-square test. † Fisher's Exact test. p < 0.05 is significant. | | | | |

Table (4): The predictive performance of different scores; ROC curve analysis

| Cut-off values | SN % (95% CI) | SP % (95% CI) | PPV % (95% CI) | NPV % (95% CI) | AUROC (95% CI) | Z statistic | P-value (Sig.) |
|-------------------------|--------------------------|----------------------------|----------------------------|----------------------------|------------------------------|--------------------|-----------------------|
| TIMI score ≥3 | 72% (50.6 – 87.9) | 57.3% (45.4 – 68.7) | 36% (22.9 – 50.8) | 86% (73.3 – 94.2) | 0.659 (0.494 – 0.778) | 2.203 | 0.014 (S) |
| GRACE score ≥102 | 68% (46.5 – 85.1) | 62.7% (50.7 – 73.6) | 37.8% (23.8 – 53.5) | 85.5% (73.3 – 93.5) | 0.672 (0.511 – 0.787) | 2.459 | 0.007 (S) |
| TIMI with GRACE | 68% (46.5 – 85.1) | 82.7% (72.2 – 90.4) | 56.7% (37.4 – 74.5) | 88.6% (78.7 – 94.9) | 0.684 (0.511 – 0.803) | 2.491 | 0.006 (S) |

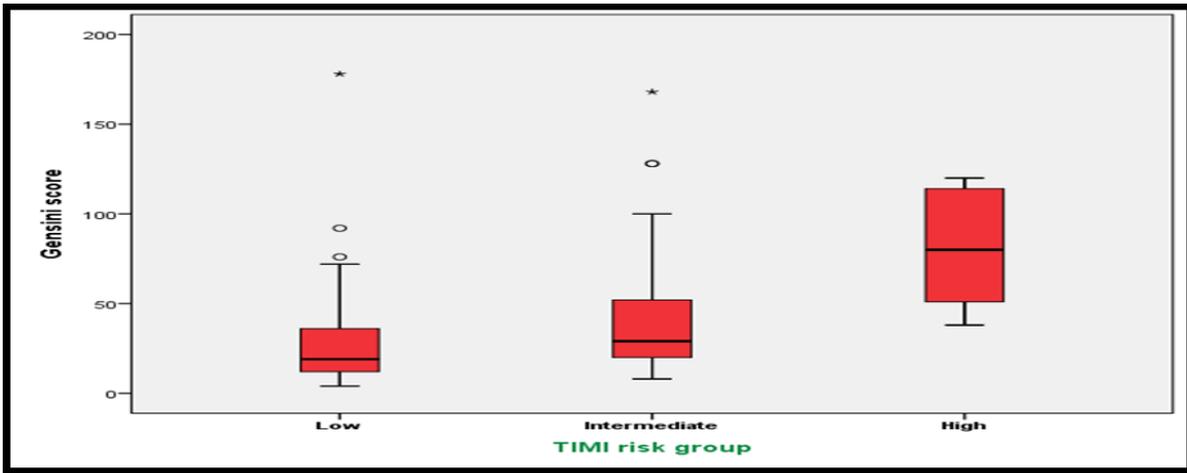


Figure (1): Comparison of TIMI risk score and Gensini score

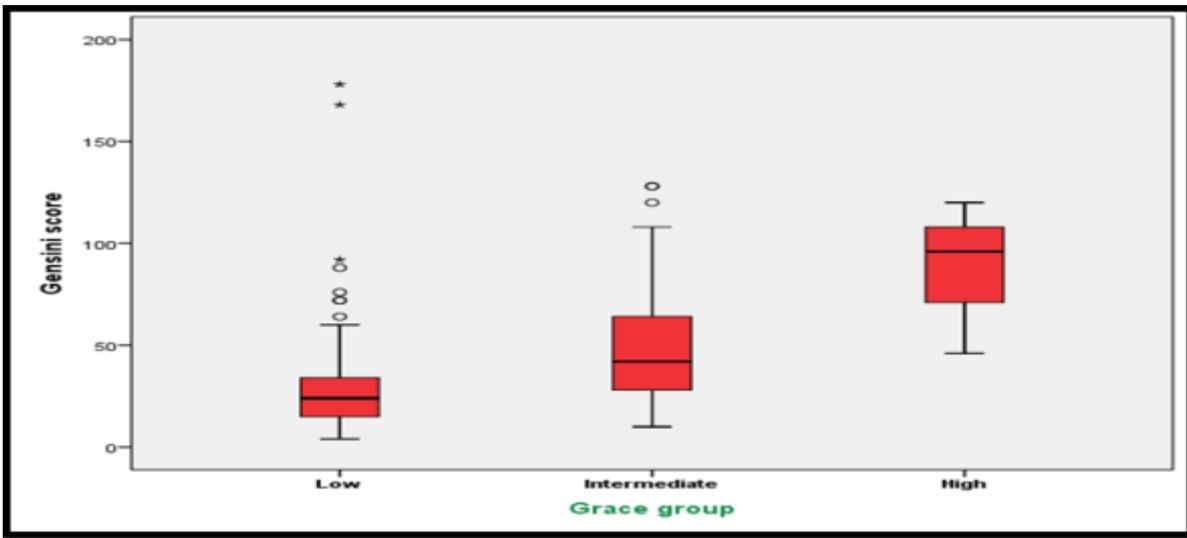


Figure (2): Comparison between the GRACE risk groups regarding Gensini score

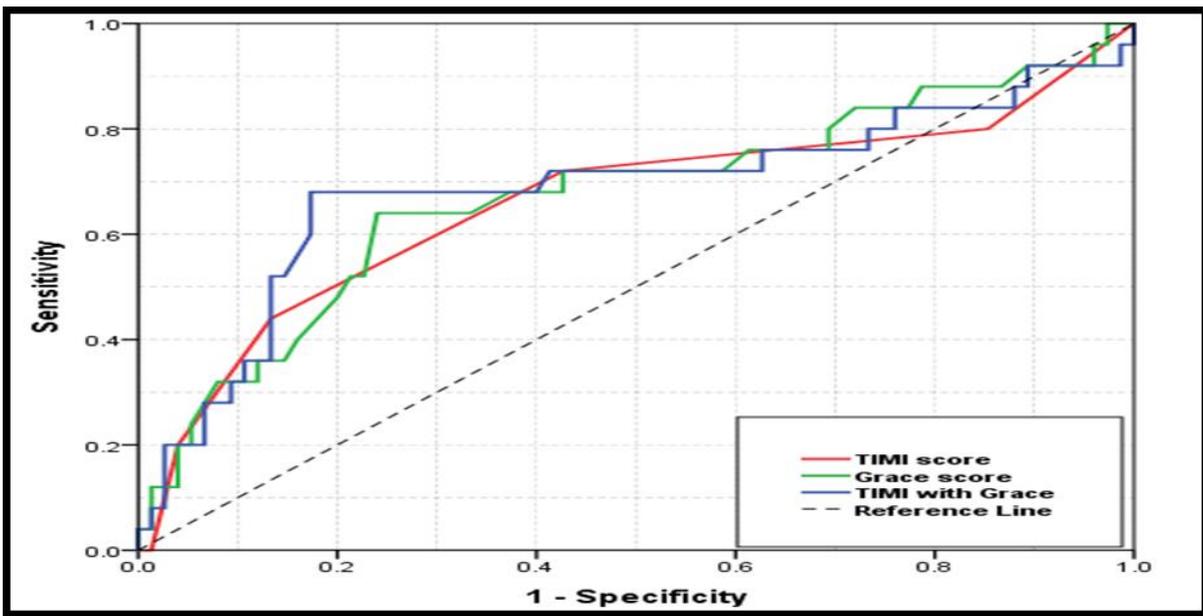


Figure (3): ROC curve analysis for different scores in predicting LM or three-vessel disease

DISCUSSION

The relationship between CAD by coronary angiography, short- and long-term events in ACS patients was established in many studies. So, we tried to find the correlations between prognostic scores and the extent of angiographic disease, and also tried to determine cutoff values of TIMI and GRACE scores that could predict high risk CAD. The target is to avoid an invasive strategy below this cutoff or, conversely, to consider a more aggressive approach for patients whose prognostic score indicates severe angiographic disease.

As regard TIMI score 50 percent of the study population had a low TIMI, forty two percent had an intermediate TIMI risk score and five percent had high TIMI risk score. We found similar pattern of distribution for GRACE risk score where seventy one percent of the study population had a low GRACE risk score, twenty six percent had an intermediate GRACE risk score and three percent had high GRACE risk score, this correlation was demonstrated by **Santos *et al.*** ⁽¹²⁾ who found that coronary lesions more than 50 % is correlated to risk scores positively (TIMI risk score $r = 0.363$ ($p < 0.0001$); hospital GRACE score $r = 0.255$ ($p < 0.0001$); and GRACE score in six months $r = 0.209$ ($p < 0.0001$)).

We used Gensini score as it is rapid and easy score for assessment of severity of CAD. We found good correlation between Gensini RS and TMI RS which was revealed in study done by **Iscanli *et al.*** ⁽¹³⁾ which enrolled 165 NSTEMI-ACS patients where they found moderate correlation between TIMI and Gensini scores, that patients at high risk according to either GRACE or TIMI, have a higher Gensini score, and more associated with LM or 3VD.

In our study we found that GRACE and TIMI have a significant association with LM or 3 vessel disease with a higher non-significant association with GRACE, where a GRACE ≥ 102 and TIMI ≥ 3 was more associated with 3 vessel disease or LM disease (AUROC 0.672 P 0.007 for GRACE and AUROC 0.659 P 0.014 for TIMI).

We assessed a combined TIMI and GRACE risk scores for prediction of 3 vessels disease or LM disease using ROC curve and we found that combined approach had better accuracy where sensitivity (68%), specificity (62.7%), positive predictive value (56.7%) and negative predictive value (88.6%) but we didn't find other studies with this combined approach to compare our results with it.

In a study by **Mahmood *et al.*** ⁽¹⁴⁾ a cohort of 406 patients with NSTEMI-ACS, showed that on admission, a TIMI score >4 and GRACE score >133 were significantly correlated with three vessel disease and left main disease, while TIMI score ≤ 4 and GRACE score ≤ 133 were correlated with non-obstructive

CAD ($p < 0.01$). However that GRACE score was more accurate depending on the angiographic data.

Khandelwal *et al.* ⁽¹⁵⁾ in their study found that the GRACE correlates moderately with modified Gensini Score ($r=0.3$), while the correlation was weak with the PURSUIT ($r=0.274$) and TIMI scores ($r=0.166$).

Barbosa *et al.* ⁽¹⁶⁾ found in patients with ACS the GENSINI score had a positive correlation but weak association with the GRACE ($p= 0.017$), ($r = 0.23$) and TIMI ($p = 0.02$), ($r = 0.27$) scores. The GRACE score failed to predict obstructive coronary disease (area under the ROC curve = 0.57; 95% CI = 0.46 0.69), and failed also to predict severe coronary disease (ROC = 0.59; 95% CI = 0.48 0.70). The TIMI score had small prediction for coronary disease (ROC = 0.65; 95% CI = 0.55 0.76) and for severe coronary disease (ROC= 0.66; 95% CI = 0.56 0.76). They deduced that a positive association between the TIMI or GRACE scores and the extension of coronary artery disease in patients with ACS is present, but not enough to be a good predictors of coronary angiography results.

CONCLUSION

In NSTEMI-ACS patients who had coronary angiography, both TIMI and GRACE risk scores have a good value in CAD prediction. However, when both compared, the GRACE score has a non-statistically significant superiority with multivessel and LM disease, and combination of both scores has a higher accuracy.

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