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Risk stratification in non-ST-elevation myocardial infarction: evaluating the predictive accuracy of various risk scores in an Indian population

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Abstract

Risk stratification is essential in managing patients with non-ST-elevation myocardial infarction (NSTEMI). While multiple risk scores exist, their validation in developing countries like India remains limited. This study compares the predictive accuracy of the PURSUIT, HEART, TIMI, GRACE 2.0, and CAMI-NSTEMI scores for major adverse cardiovascular events (MACE), including death, non-fatal myocardial infarction, emergency percutaneous coronary intervention, and coronary artery bypass grafting, in NSTEMI patients. This was a single-center prospective observational study wherein patients diagnosed with NSTEMI were enrolled. Detailed clinical histories, including symptomatology and risk factors, were recorded. Five risk scores (TIMI, GRACE 2.0, PURSUIT, HEART, and CAMI-NSTEMI scores) were computed. Outcomes were assessed for in-hospital, 14-day, six-month, and one-year MACE. A total of 1102 patients were enrolled, with a mean age of 59.6 ± 11.2 years. MACE occurred in 140 patients (12.7%), with 89 deaths (8.1%). Patients with MACE were older and more likely to smoke or have hypertension, diabetes, or stroke. Multivariate logistic regression analysis identified angina in the last 48 hours, diabetes, smoking, cardiac arrest, and fragmented QRS on electrocardiogram as independent MACE predictors. TIMI showed the highest predictive ability for in-hospital MACE, while GRACE excelled for 14-day, 6-month, and 1-year outcomes. All risk scores effectively predicted short- and intermediate-term MACE, with GRACE performing best for longer-term predictions.

Key words: acute coronary syndrome, myocardial infarction, cardiovascular risks, cardiovascular mortality.

Introduction

Acute coronary syndrome (ACS) encompasses clinical conditions ranging from ST-elevation myocardial infarction (STEMI) to non-ST-elevation myocardial infarction (NSTEMI) or unstable angina [1]. NSTEMI accounts for a significant portion of ACS cases, with wide variations in presentation and outcomes [2]. Clinical guidelines on NSTEMI advocate for risk stratification in the emergency department to identify patients at high risk for ischemic events or adverse outcomes [3]. Effective risk stratification aids in triaging patients and guiding treatment strategies, helping identify high-risk individuals and optimizing decision-making [4].

Several risk scores have been proposed for NSTEMI patients, including the Thrombolysis in Myocardial Infarction (TIMI), Global Registry of Acute Coronary Events (GRACE), GRACE 2.0, HEART, and Chinese Acute Myocardial Infarction (CAMI)-NSTEMI scores [5-9]. The TIMI score developed in a cohort of 1957 ACS patients, is a simple semi-quantitative tool (range 0-7) for predicting 14-day MACE risk [5]. However, its ability to predict long-term outcomes remains unclear. The GRACE score, derived from 26,267 patients across America, Europe, and Australia, estimates in-hospital death risk and six-month mortality [6]. Despite its robust dataset, GRACE's complexity somewhat limits its bedside utility without digital tools. A newer GRACE 2.0 score has been validated to predict outcomes up to three years post-discharge [7]. The HEART score, initially developed for acute chest pain in the emergency department, has shown better performance than TIMI and GRACE in low-risk ACS patients [8]. Meanwhile, the CAMI-NSTEMI score addresses the lack of Asian-specific risk tools, predicting in-hospital mortality for NSTEMI patients in China [9]. TIMI and GRACE scores were primarily developed using Western populations, necessitating validation in diverse cohorts to ensure their applicability across different ethnicities and healthcare settings [5,6,8,10]. Many scores exclude sicker patients from trial data, raising concerns about real-world applicability. While most countries have validated these scores, data from India remain limited. This study aims to identify prognostic factors in NSTEMI and compare the performance of risk stratification scores to validate their utility in an Indian population.

Materials and Methods

Study design

This was a single-centre, prospective observational study conducted over a two-year period in the Department of Cardiology at a tertiary care medical centre. All patients over 18 years of age presenting to the Emergency Department with chest pain suggestive of ACS were evaluated. Patients diagnosed with NSTEMI based on the Fourth Universal Definition of Myocardial

Infarction were included in the study [11]. The following patients were excluded: i) Patients with ST-segment elevation myocardial infarction (STEMI) on presentation, ii) Patients with an alternate cause for symptoms (e.g., findings suggestive of pneumonia), iii) Patients with incomplete data preventing calculation of risk scores, iv) Pregnant females, v) Patients unwilling or unable to provide informed consent or comply with follow-up after discharge, vi) Patients with coexisting conditions associated with a limited life expectancy of less than six months. A detailed clinical history was obtained for all included patients, covering symptomatology, presence of cardiovascular (CVD) risk factors, family history, and prior evidence of CVD. Blood samples were collected on admission for routine haematological and biochemical parameters, including troponin-T levels. A 12-lead electrocardiogram (ECG) and echocardiographic assessment were performed, with left ventricular ejection fraction (LVEF) estimated using the bi-plane Simpson's method. Coronary angiography and percutaneous coronary intervention (PCI) were performed based on risk assessment by the treating cardiologist. Standardized definitions of all patient-related variables and clinical diagnoses were applied.

Risk scores and outcomes

Five risk scores-TIMI, GRACE version 2.0, PURSUIT, HEART, and CAMI-NSTEMI were computed for all patients using prospectively collected data [5-9]. Follow-up data on outcomes were obtained from hospital records (outpatient clinic visits) or direct telephonic contact at 14 days, six months, and one-year post-discharge. The primary endpoint of the study was the occurrence of major adverse cardiovascular events (MACE), defined as a composite of all-cause mortality, non-fatal recurrent myocardial infarction, target-vessel revascularization, or stroke. Written informed consent was obtained from all eligible patients before study inclusion, and the study protocol was approved by the institutional review board.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean values with standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Statistical comparisons of baseline characteristics and outcomes were performed using the chi-square test for categorical variables and the Student's t-test for continuous variables. Univariate and multivariate logistic regression analyses were conducted to determine independent predictors of MACE. For each of the five risk scores, receiver operating characteristic (ROC) curves were generated to assess their predictive value for MACE at hospital discharge, 14 days, six months,

and one year. The area under the curve (AUC) or c-statistic was used as a measure of predictive accuracy. The diagnostic performance of each risk score was classified as follows: (a) Excellent: AUC 0.90; (b) Good: AUC 0.80; (c) Fair: AUC 0.70; (d) Poor: AUC < 0.70 [12]. Pairwise comparisons of the AUCs for the multiple ROC curves were performed using the method described by DeLong et al [13]. Data analysis was conducted using SPSS software version 24 (SPSS, Chicago, Illinois, USA). A P-value <0.05 was considered statistically significant.

Results

A total of 1,102 patients with NSTEMI were enrolled and included in the final analysis. The mean age of the study population was 59.6 ± 11.2 years, with a majority being male (73%). The most common presenting symptoms were angina (99.3%), dyspnoea (16.2%), diaphoresis, and palpitations. The mean duration of symptoms before presentation was 7.1 ± 11.6 days.

Risk factors for ischemic heart disease in this cohort included hypertension (34.8%), diabetes (24.5%), prior coronary artery disease (30.4%), family history of CVD (9.6%), and peripheral vascular disease (3.1%). A history of cigarette/beedi smoking was noted in 46.5% of patients, with a mean peak pack-year of 8.2 ± 11.3. The mean heart rate on presentation was 81.8 ± 12.8 beats per minute, and the average systolic blood pressure was 125.1 ± 20.1 mmHg. Most patients presented with Killip class I (89%) or class II (7.4%), while class III (1.4%) and class IV (2.2%) were less frequent. Cardiac arrest on admission was reported in 24 patients (2.2%), ventricular tachycardia/ventricular fibrillation (VT/VF) in 28 patients (2.5%), and signs of heart failure were observed in 64 patients (13.9%). The clinical and demographic characteristics of the study population are summarized in Table 1.

Coronary angiography was performed in 887 (80.5%) patients, and revascularization was conducted in 630 (57.1%) patients. Percutaneous coronary intervention (PCI) was the most common procedure, performed in 547/630 (86.8%) patients, while coronary artery bypass grafting (CABG) was done in 83/630 (13.2%) patients. Normal epicardial coronaries or non-significant coronary obstruction was observed in 51/887 (5.7%) patients, while single-vessel disease was reported in 315/887 (35.5%), double-vessel disease in 270/887 (30.4%), and triple-vessel disease in 251/887 (28.3%) patients. Left-dominant coronary circulation was present in 108/887 (12.1%) patients.

Outcomes

The primary endpoint (MACE) was reached in 140 of the 1102 subjects (12.7%), with mortality occurring in 89 (8.1%) patients. The mean follow-up duration was 447.9 ± 143.8 days. Recurrent myocardial infarction (MI) was observed in 32/140 (22.8%) patients, with anterior wall MI being the most common (18/32, 56.2%), followed by inferior wall MI (14/32, 43%). Acute/sub-acute stent thrombosis leading to target vessel revascularization (TVR) occurred in 14/140 (10%) patients, while stroke was documented in 5/140 (3.5%). Cardiogenic shock was reported in 28/140 (20.4%) patients, and ventricular tachycardia/ventricular fibrillation (VT/VF) occurred in 18/140 (12.8%), with most episodes documented within three days of admission. Sepsis followed by multiorgan dysfunction was reported in 20/140 (14.2%) patients, while acute exacerbation of chronic obstructive pulmonary disease (COPD) leading to mortality occurred in 7/140 (5%). A significant proportion of MACE events [68/140 (48.6%)] occurred during the hospital stay. Patients who experienced MACE were significantly older, had a lower body mass index (BMI), a shorter duration of symptoms, and a higher prevalence of smoking, alcohol intake, hypertension, diabetes, and stroke. Additionally, these patients had a higher heart rate, lower systolic blood pressure, and a greater frequency of cardiac arrest and VT/VF upon admission (Tables 2 and 3). Independent predictors of MACE based on univariate logistic regression analysis are shown in *Supplementary Table 1*.

Predictors of MACE

Multivariate logistic regression analysis revealed that the following were independent predictors of MACE (a) angina in the last 48 hours (OR: 5.75; 95% CI: 2.21-14.97; P<0.0001), (b) diabetes (OR: 2.24; 95% CI:1.24-4.02; P=0.007), (c) smoking (OR: 1.11; 95% CI:1.08-1.14; P<0.0001), (d) cardiac arrest on presentation (OR: 25.61; 95% CI: 4.36-150.46; P<0.0001), (e) fragmented QRS on ECG (OR = 1.02; 95% CI: 1.01-1.03; P=0.005).

Risk scores

Patients who experienced MACE had significantly higher risk scores compared to those who did not. The receiver operating characteristic (ROC) curve plots are represented in Figure 1. All risk scores performed well in predicting MACE events. However, for in-hospital MACE prediction, the TIMI risk score had the highest predictive ability, followed by the HEART and GRACE scores. A comparison between TIMI and GRACE scores for in-hospital MACE showed no significant difference in their area under the curve (AUC) values (P=0.16), indicating similar predictive

ability. For 14-day MACE prediction, the GRACE score had a higher AUC value compared to the TIMI score, but the difference was not statistically significant (P=0.26). For predicting MACE at six months, the GRACE score had the highest AUC, followed by the PURSUIT and TIMI scores, but the difference between GRACE and TIMI scores was not significant (P=0.32). At one year, the GRACE score had the highest predictive ability, followed by CAMI, PURSUIT, and TIMI scores. A significant difference was found in AUC values between GRACE and TIMI scores (P=0.002), suggesting a superior predictive ability of the GRACE score at one year. Overall, the predictive ability of the HEART and CAMI scores was lower compared to the GRACE and TIMI scores. The optimal cutoff values for risk scores in determining MACE in this study were (a) TIMI score: 3 (sensitivity: 94.3%; specificity: 86.7%), (b) GRACE 2.0 score: 143 (sensitivity: 80%; specificity: 74.5%), (c)HEART score: 5 (sensitivity: 91.5%; specificity: 57.8%), (d) PURSUIT score: 12 (sensitivity: 82.9%; specificity: 70.9%), (e) CAMI-NSTEMI score: 106 (sensitivity: 77.1%; specificity: 70.3%).

Discussion

This single-centre study among patients with NSTEMI validated the short- and intermediate-term prognostic roles of various risk scores in the Indian population. All risk scores effectively differentiated patients with and without MACE over a short follow-up period, aligning with their original purpose for short-term prognosis. Additionally, these scores demonstrated strong discriminatory ability over a one-year follow-up period, with the GRACE 2.0 score exhibiting the best predictive performance, followed by the TIMI and HEART risk scores. Similar findings were reported in a retrospective study involving 460 NSTEACS patients by Gonçalves et al. [14]. Another long-term follow-up study comparing the GRACE and TIMI scores found that the GRACE score had slightly better performance than the TIMI score in predicting three-year mortality among NSTEMI patients [15].

Most of these risk scores have been validated in various countries to account for ethnic variations, as race is associated with differential ACS risk. In the Canadian ACS II Registry [16], which enrolled 1,728 NSTEACS patients, risk stratification was performed using the TIMI-RS, PURSUIT-RS, and GRACE-RS. The study found that all three risk scores had good discrimination for in-hospital death (AUC = 0.68, 0.80, and 0.81, respectively, all $P < 0.001$) and one-year mortality (AUC = 0.69, 0.77, and 0.79, respectively, all $P < 0.0001$). The PURSUIT and GRACE scores performed significantly better than the TIMI score in predicting both in-hospital ($P = 0.036$ and 0.02, respectively) and one-year ($P = 0.006$ and 0.001, respectively) outcomes. Our study

produced similar findings, with the GRACE 2.0 and PURSUIT scores outperforming the TIMI score at the one-year follow-up.

A Portuguese registry [14] involving 460 consecutive NSTEACS patients reported a one-year MACE rate of 15.4%, with the GRACE score having the best predictive accuracy for death or MI (AUC: 0.715; 95% CI: 0.672-0.756), followed by the PURSUIT (AUC: 0.63) and TIMI (AUC: 0.585) scores. In an Asian population validation study, data from a Japanese registry involving 604 patients indicated good discriminatory ability of the HEART, TIMI, and GRACE risk scores (AUC: 0.78, 0.65, and 0.62, respectively) for MACE at one year [17]. Data from India remains limited, with only two previous studies comparing risk scores in NSTEMI [18,19]

In a small study from Bangalore involving 235 ACS patients (127 with NSTEACS), the GRACE score predicted both in-hospital mortality and angiographic severity [18]. Another study involving 213 NSTEMI patients found that the GRACE score had superior predictive ability compared to the TIMI and PURSUIT scores for both short-term and one-year follow-up [19]. However, both studies had small sample sizes and used the GRACE 1.0 score. In contrast, we used GRACE 2.0 [7], which is a more accurate tool with superior long-term predictive ability, extending up to three years. Additionally, we evaluated two newly proposed risk scores, the HEART and CAMI-NSTEMI scores, both of which demonstrated good predictive ability (AUC > 0.8) for MACE events at both short- and mid-term follow-up. However, the CAMI-NSTEMI score, originally developed for an Asian cohort to predict in-hospital mortality, did not perform as well as the TIMI or GRACE scores for in-hospital MACE events in our study.

Predictors of MACE

In a cohort of 3,822 NSTEACS patients, independent predictors for MACE at six months included age >70 years, female sex, diabetes, and anaemia. Impaired renal function was a strong independent predictor of mortality but not MACE at six months [20]. In a study involving 11,814 NSTEMI patients, MACE at one year was reported in 11.3% of patients, with independent predictors including older age, elevated creatinine, LV systolic dysfunction, higher Killip class, TIMI flow on angiogram, and major bleeding events [21]. Our study reported a similar MACE rate (12.7%), with renal dysfunction, higher Killip class, diabetes, and smoking identified as independent predictors of MACE. A study from Iran reported a one-year MACE rate of 15% among 1,219 NSTEACS patients, with independent predictors including diabetes, higher admission heart rate, and prior PCI [22]. Our study also identified similar independent predictors of mortality.

One limitation of our study is that it was conducted at a single centre. However, as our institution

is a tertiary care centre catering to a diverse population from nearby states, the cohort exhibited heterogeneity. Given India's vast ethnic diversity, there is a need for multicentre studies to validate these risk scores across various population subgroups. Additionally, our sample size, though not large, was adequate for AUC analysis and statistical comparisons. Another limitation is that our follow-up period was limited to one year, preventing an evaluation of risk score performance over longer durations.

Conclusions

All evaluated risk scores demonstrated strong discriminative and predictive accuracy for short- and mid-term MACE events and mortality among Indian NSTEMI patients. With superior discriminative ability both at short-term (14 days) and one-year follow-up, the GRACE 2.0 score outperformed other risk scores, including TIMI and PURSUIT. Future large-scale, multicentre validation studies are necessary to assess the applicability of these risk scores in the Indian population.

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Online supplementary material:
Supplementary Table 1. Univariate logistic regression analysis for independent predictors of major adverse cardiac events.

Table 1. Clinical and demographic parameters of the study group.

	NSTEMI patients (n=1102)
Age (mean ± SD) / sex (males)	59.56 ±11.21 years/804 (73%)
Locality (urban vs rural)	812 vs 289
Mean body mass index (kg/m^2)	25.14±3.58
Duration of symptoms (mean ± SD)	7.13±11.6 days
Duration of follow-up (mean ± SD)	447.9±143.8 days
Co-morbidities:	
Hypertension	384 (34.8%)
Diabetes mellitus	270 (24.5%)
Stroke	56 (5.1%)
COPD	142 (12.8%)
PVD	34 (3.1%)
Family history of coronary artery disease	106 (9.6%)
Prior history of coronary artery disease	335 (30.4%)
Smoking:	513 (46.5%)
Former smoker	265 (24%)
Current smoker	248 (22.5%)
Pack-years (mean ± SD)	8.15±11.3
Alcohol consumption	114 (10.3%)
Symptomatology:	
- Angina:	1094 (99.3%)
- CCS class III/IV	275 (25%)/78 (7.1%)
- Mean CCS class	2.2 ± 0.8
- Dyspnea	179 (16.2%)
Heart rate (per minute)	81.8±12.8
Systolic blood pressure (mmHg)	125.1±20.1
Killip Class:	
Class I	981 (89%)
Class II	81 (7.4%)
Class III	16 (1.5%)
Class IV	24 (2.2%)
Cardiac arrest on admission	24 (2.2%)
VT/VF on presentation	28 (2.5%)

CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; MACE, major adverse cardiac events; PVD, peripheral vascular disease; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2. Comparison of demographic and clinical parameters between patients with MACE and without MACE.

	MACE (n=140)	No MACE (n=962)	P-value
Age	64.46±11.09	58.84±11.05	**<0.0001**
Sex (Males)	104 [74.3%]	700 [72.8%]	0.705
Mean body mass index (kg/m^2)	23.02±3.61	25.45±3.46	**<0.0001**
Duration of symptoms (mean ± SD)	5.05±9.8	7.43±11.8	**0.023**
Co-morbidities:			
Hypertension	74 (52.8%)	310 (32.2%)	**0.0001**
Diabetes Mellitus	61 (43.5%)	209 (21.7%)	**0.0001**
Stroke	20 (14.3%)	36 (3.7%)	**0.001**
COPD	32 (22.8%)	63 (6.5%)	**0.0001**
Family history of coronary artery disease	28 (20%)	78 (8.1%)	0.34
Smoking:			
Former smoker	36	229	0.589
Current smoker	68	180	**<0.0001**
Pack-years (mean ± SD)	18.97±16.14	6.58±9.35	**0.03**
Alcohol consumption	40 (28.5%)	74 (7.6%)	**0.0001**
Symptomatology:			
- Angina:	140 (100%)	954 (99.1%)	0.35
- CCS class III/IV	56(40%)/50(35.7%)	219(22.7%)/28(2.9%)	**0.0001**
- Mean CCS class	1.05±0.21	2.00±1.12	**0.0001**
- Dyspnea	56 (40%)	123 (12.7%)	**0.0001**
Heart rate (per minute)	96.3±17.2	79.7±10.4	**0.0001**
Systolic blood pressure (mmHg)	127.4±17.3	108.9±28.9	**0.0001**
Killip Class:			
Class I	64 (13.9%)	917 (95.3%)	**<0.0001**
Class II	36 (25.7%)	45 (4.7%)	**<0.0001**
Class III	16 (11.4%)	0	**<0.0001**
Class IV	24 (17.1%)	0	**<0.0001**
Cardiac arrest on admission	20 (14.2%)	4 (0.4%)	**<0.0001**
VT/VF on presentation	24 (17.1%)	4 (0.4%)	**<0.0001**
Signs of heart failure	64 (13.9%)	40 (4.1%)	**<0.0001**

CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; MACE, major adverse cardiac events; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3. Comparison of laboratory parameters between patients with MACE and without MACE.

	MACE (n=140)	No MACE (n=962)	P-value
Hemoglobin (gm%)	12.5±2.7	13.1±2.0	**0.002**
Total leucocyte count (per mm^3)	10.7±4.2	8.8±2.7	**<0.0001**
Platelet count (*10^5/mL)	2.3±0.6	2.3±0.9	0.517
Hematocrit (%)	38.2±6.7	40.9±4.9	**<0.0001**
Random blood sugar (mg/dl)	124.1±67.5	126.1±72.1	0.75
Serum Creatinine (mg/dl)	1.7±0.9	1.1±0.3	**<0.0001**
Serum Sodium (mMol/L)	137.5±5.1	138.9±2.9	**<0.0001**
Serum Potassium (mMol/L)	4.41±0.60	4.32±0.54	0.068
Aspartate aminotransferase (U/L)	88±129.94	46.29±66.68	**<0.0001**
Alanine aminotransferase (U/L)	50.54±47.84	34.82±25.7	**<0.0001**
Troponin T (g/L)	1.13±1.63	0.46±1.3	**<0.0001**
PT-INR	1.70±0.40	1.08±0.23	**<0.0001**
Serum Triglyceride (mg/dL)	151.3±76.7	105.7±46.3	**0.001**
HDL Cholesterol (mg/dl)	36.8±6.9	37.4±8.5	0.613
LDL Cholesterol (mg/dl)	120±36.5	96.4±27.1	**<0.0001**
Heart Rate (per min)	91.4±21.8	80.1±13.7	**<0.0001**
Mean PR interval (ms)	143.6±23.1	141.1±19.8	**<0.0001**
Mean QRS duration (ms)	99.8±27.6	94.7±19.9	**0.018**
Mean QT duration (ms)	378.32±42.6	378.53±43.5	0.962
Mean QTc duration (ms)	436.4±30.5	426.6±38.7	**0.011**
ST-T changes	124/140 (88.5%)	375/962 (38.9%)	**<0.0001**
fQRS	62/140 (44.2%)	146/962 (14.6%)	**<0.0001**
RWMA	48/142(33.2%)	227/942 (24.1%)	**0.005**
Ejection fraction (%)	46.3±11.2	51.5±8.6	**<0.0001**

CK-MB, creatine kinase myocardial band; fQRS, fragmented QRS; HDL, high density lipoprotein; LDL, low density lipoprotein; PT-INR, prothrombin time-international normalised ratio; RWMA, regional wall motion abnormality.

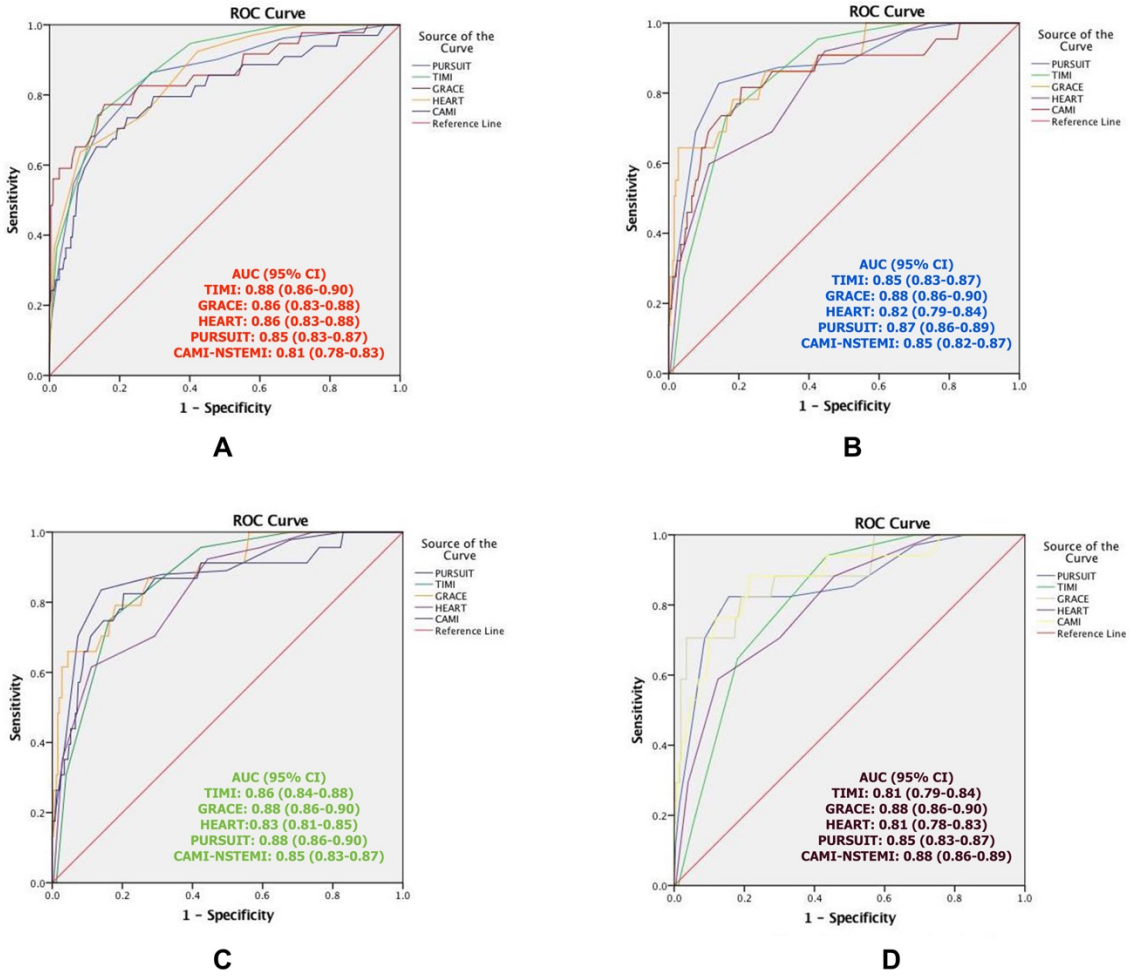

Figure 1. A) Figure showing the receiver operating characteristic (ROC) curve plot for of various risk scores to predict in-hospital MACE; B) figure showing the receiver ROC curve plot for of various risk scores to predict MACE at 14 days; C) figure showing the ROC curve plot for of various risk scores to predict MACE at six months; D) figure showing the ROC curve plot for of various risk scores to predict MACE at one year.