IMPACT OF CORONARY LESION COMPLEXITY, AS ASSESSED BY SYNTAX SCORE, ON CLINICAL PRESENTATION AND IN-HOSPITAL OUTCOMES IN PATIENTS WITH ACUTE CORONARY SYNDROME

Amr Elsayed Elhadidy, Ahmed Abd Elaziz, Ahmed Gamal Mohamed Attallah

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Abstract
Background: Acute Coronary Syndrome is one of the leading causes of mortality worldwide. Patients of ACS can present either with STEMI or NSTE-ACS. Many tools and scores were validated for risk stratification. Few studies correlated these risk scores with the anatomical complexity. **Methods:** This study was conducted on 976 participants with ACS, admitted to the critical care department, Kasr Elainy hospital, Cairo University during the period between January 2015 and December 2019. GRACE, TIMI and ACTION registry GWTG risk scores were calculated and correlated to the SYNTAX score. **Results:** There was a positive correlation between GRACE, TIMI, AR-G and the SYNTAX score in both STEMI and NSTE-ACS patients. In patients with STEMI, GRACE score (AUC: 0.774, CI: 0.652 – 0.859, P: 0.0001), AR-G (AUC: 0.79, CI: 0.670 – 0.910, P: 0.0001) and TIMI score (AUC: 0.785, CI: 0.675 – 0.896, P: 0.0001) could predict SYNAX score > 32. In NSTE-ACS patients, GRACE score (AUC: 0.831, CI: 0.694 – 0.969, P: 0.001) and AR-G score (AUC: 0.847, CI: 0.734 – 0.960, P: 0.0001) could predict SYNAX score > 32. Residual SYNTAX score was significantly higher in the MACE groups (P: 0.001). **Conclusion:** The presence of more severe coronary lesion in ACS patients would result into worse clinical presentation. More aggressive management to achieve complete revascularization should be proposed in high risk ACS patients.
Key words: Acute Coronary Syndrome, STEMI, NSTE-ACS, MACE, SYNTAX score, GRACE score.

Critical Care Medicine department, faculty of medicine Cairo University
Corresponding author: Ahmed Gamal Mohamed Attallah

Introduction

Acute coronary syndrome is a subgroup of coronary artery disease that represents a broad spectrum of symptoms and signs that result from acute myocardial ischemia. The clinical presentation of acute coronary syndrome ranges from cardiac arrest and hemodynamic instability to mild acute chest pain or pain equivalent symptoms or patients who are pain free at time of presentation. [1]

Acute coronary syndrome includes two distinct groups; patients who present with acute chest discomfort and persistent ST-segment elevation (STEMI) and patients who present with acute chest discomfort without persistent ST segment elevation (non-ST elevation acute coronary syndrome [NSTE-ACS]). [2]

Many tools were used for risk stratification of acute coronary syndrome that is important to guide proper therapeutic decision making and to predict outcomes. Many scoring systems were validated for risk assessment like Thrombolysis in Myocardial Infarction (TIMI) risk score, Global Registry of Acute Coronary Event (GRACE) score and Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get with the Guidelines (GWTG) mortality risk score. [3]

SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score was created as an angiographic tool for grading of anatomical lesion complexity and to guide the proper revascularization strategy. [4]

Some authors investigated the presence of a relationship between risk class and clinical presentation of patients of acute coronary syndrome and the anatomical complexity of coronary artery lesion as assessed by SYNTAX score. [5]

The aim of our study was to Delineate the predictors of in-hospital and 1-year MACE in patients with ACS, Correlate the clinical picture at presentation and risk scores (GRACE, TIMI, ACTION registry GWTG risk scores) with the anatomical complexity (SYNTAX score) in patients with STEMI and NSTE-ACS to Assess the prognostic value of the SYNTAX score for in-hospital and 1- year outcomes in acute coronary syndrome patients (both STEMI and NSTE-ACS).

Patients

The current study is an observational, cohort, single center study that was carried out prospectively and retrospectively. The study was conducted on 976 patients (345 prospectively and 664 retrospectively) who were admitted to the critical care department, Kasr Elainy hospital, Cairo university with acute coronary syndrome who had been subjected to diagnostic coronary angiography during their hospital stay. This study covered the period from January 2015 to December 2019.

Inclusion criteria: Patients aged 18 years or older who presented with acute coronary syndrome that includes 2 categories of patients: Patients presented with ST-segment elevation myocardial infarction (380 patients) that includes the patients who presented with acute chest pain and persistent (>20 minutes) elevation of the J point at least two contiguous leads with elevation ≥ 2.5mm in men < 40 years, ≥ 2mm in men ≥ 40 years, or ≥ 1.5mm in women in leads V2–V3 and/or ≥ 1mm in the other leads {in the absence of left ventricular hypertrophy or left bundle branch block} or ST-segment depression in leads V1–V3 with positive terminal T wave with elevation of the cardiac troponin at least one value above the 99th percentile upper reference limit. Patients presented with Non ST-segment elevation acute coronary syndrome (596 patients) who's ECG may show transient ST-segment elevation, transient or persistent ST-segment depression, inverted, flattened or pseudonormalized T waves or normal ECG.

Exclusion criteria: Patients with previous coronary artery bypass graft operation, patients who were subjected to conservative medical management without performing coronary angiography and patients known to have severe valvular regurgitation/stenosis or severe impairment of cardiac systolic function (EF<30%).

Methodology

All the patients were subjected to the following:

Full medical history with special emphasis on: Demographic data including age and sex. Risk factors for coronary artery disease and comorbidities including: diabetes mellitus, hypertension, dyslipidemia, obesity, metabolic syndrome, sedentary lifestyle, family history of coronary artery disease, chronic kidney disease, peripheral vascular disease and chronic inflammatory diseases (rheumatoid arthritis or systemic lupus), personal history of coronary artery disease or coronary intervention, medication history including: antiplatelet, antidiabetic, antihypertensive, lipid lowering drugs and substance abuse and analysis of the complaint either typical chest pain or equivalent symptoms as dyspnea, chest discomfort and upper abdominal pain.

Physical examination on admission that includes: Hemodynamics including blood pressure and heart rate, systemic examination with emphasis on cardiac and chest examination to prove/rule out signs of heart failure and mechanical complications in cases of myocardial infarction and determination of Killip class according to physical examination

Twelve lead Electrocardiogram: With standard calibration of 10mm/mV to be done at admission, 20 minutes after admission, In case of urgent coronary intervention it was done before and after intervention and daily. In other cases to be repeated every 6 hours in the first day then daily or as indicated.

Laboratory investigations including: Complete blood count, prothrombin time, prothrombin concentration and INR, serum creatinine on admission and repeated 48 and 72 hours after coronary intervention to assess the incidence of contrast induced nephropathy that is defined as 25% increase in serum creatinine from baseline or 0.5 mg/dL rise in absolute serum creatinine within 48 to 72 hours after administration of intravenous contrast. CK, CK-MB and troponin on admission, 6 hours and 12 hours after and when indicated.

Global Registry of Acute Coronary Events (GRACE) score on admission: GRACE score is calculated on admission for all patients that include the following variables: age, heart rate, systolic blood pressure, serum creatinine, Killip class, presence of cardiac arrest on admission or not, elevation in cardiac enzymes and ST-segment deviation.

Thrombolysis in Myocardial Infarction (TIMI) risk score calculation on admission: TIMI score calculated for all cases on admission.

Echocardiography: Echocardiography done to all cases to assess the ventricular diameter, presence of regional wall motion abnormalities, assesses the systolic function and any mechanical complication of myocardial infarction.

Coronary angiography with or without percutaneous coronary intervention: All patients were subjected to coronary angiography. The procedure was done under clinical, electrocardiographic and hemodynamic monitoring. The procedure was done mostly through right femoral artery and was done through right radial artery or left femoral artery in a minority of cases using modified Seldinger technique under complete aseptic conditions. Variety of diagnostic and guiding catheters and guide wires were used. Balloon and stent size selection were primarily based on visual assessment of vessel size and lesion length.

The following data were obtained: Assessment of anatomical complexity of the coronary artery disease by calculating the SYNTAX score, residual SYNTAX score is calculated in cases where PCI

was performed and thrombolysis in Myocardial Infarction (TIMI) flow grading before and after the procedure.

Clinical end points and follow-up: All clinical events were reviewed during hospital stay and 1-year after discharge. Follow up data were obtained through outpatient clinic visits, hospital re-admission or through phone calls. ***Clinical follow up for all patients during hospital stay, major Adverse Cardiac and Cerebrovascular Events (MACCE) during hospital stay and 1 year after, stroke:*** clinical and or radiological evidence of CVS, ***contrast induced acute kidney injury*** and ***mortality*** either in hospital or within 12 months from discharge.

Statistical analysis: Data was collected and coded prior to analysis using the professional statistical Package for Social Science (SPSS 23). Data were summarized using ranges, mean, standard deviation (SD) and percentiles for quantitative numerical variables or frequency and percentages for qualitative categorical values. Statistical significance for quantitative variables were analyzed and comparison between groups was done using independent sample t-test and one way analysis of variance (ANOVA) for parametric data while Mann Whitney test and Kruskal Wallis test were used for non-parametric data. Chi square test and Fischer exact test were used to test the statistical significance for the qualitative data. The relationship between the studied parameters was assayed by correlations. Pearson correlation coefficient was applied to get the association between different quantitative variables. The cut-off points was used as (< 0.3) for weak correlation, (0.3 - 0.7) for moderate correlation, and (> 0.7) for strong correlation.

Results

Our study was conducted as an observational, prospective and retrospective study on 976 patients admitted to the critical care department, Cairo University hospital with acute coronary syndrome during the period between January 2015 and December 2019. The patients were classified into 2 groups: **STEMI group:** Patients admitted with STEMI. This group includes 380 patients. **NSTE-ACS group:** Patients admitted with NSTE-ACS that includes 596 patients.

STEMI Group*:* This group includes 380 patients and will be divided into 2 groups according to the occurrence of MACCE and/or mortality either during the hospital stay or during the 1-year follow up period as follows: **Group I:** Included **234** patients who survived without occurrence of MACCE. **Group II:** Included **146** patients where mortality and/or MACCE occurred.

GRACE score: Mean score for the STEMI group was 122.6±34.4 with significant difference between the 2 groups (108.2± 25.1 in group I vs 145.7± 34.8 in group II) with p value 0.0001.

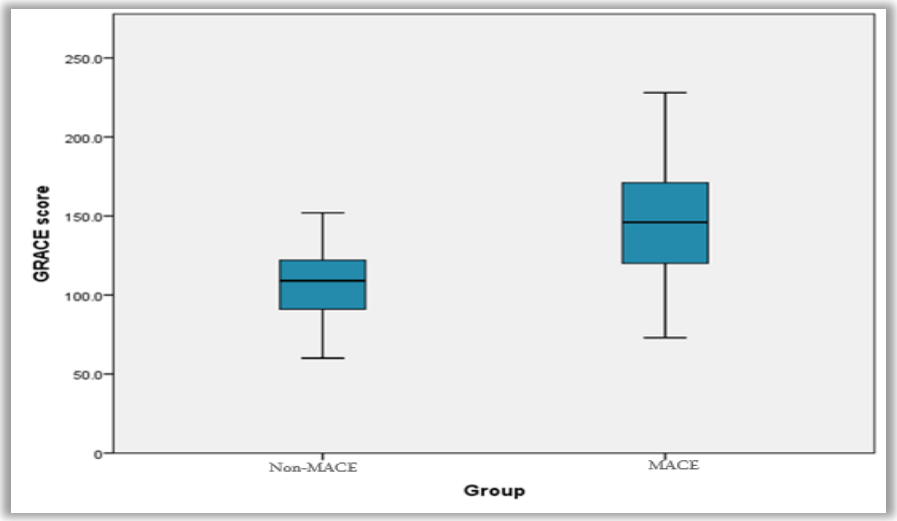

Figure 1: Box plot showing the difference in GRACE score between STEMI groups

TIMI score for STEMI: Mean TIMI score for the STEMI group was 4.3±2.6. It was significantly higher in group II 6.2 ± 2.7 vs 3.1± 1.7 in group I with p value 0.0001

ACTION Registry risk score: Mean score for the STEMI patients was 38.5±10.3 with statistically significant difference between the 2 groups (45.6 ± 11.7 in group II vs 34.1 ± 6 in group I) with p value 0.0001.

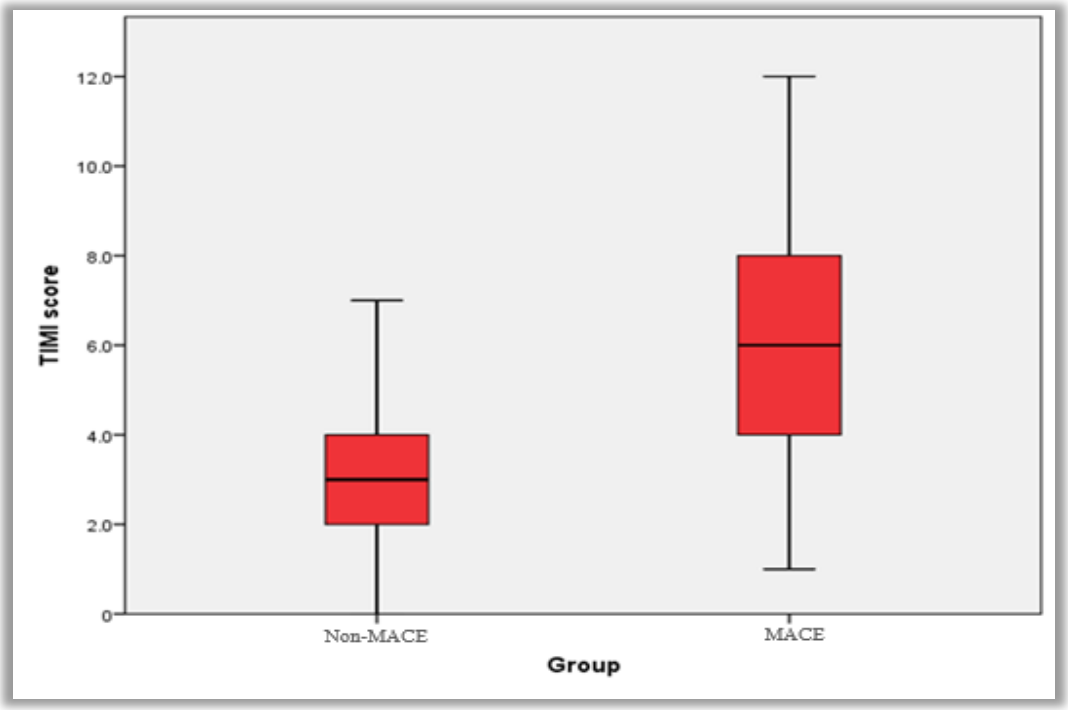

Figure 2: Box plot showing the difference in TIMI score between study groups

HASBLED score: Mean HASBLED score for the STEMI group was 1.5±0.7 and it was significantly higher in group II (1.8±0.8) versus (1.4±0.6) in group I with p value 0.003.

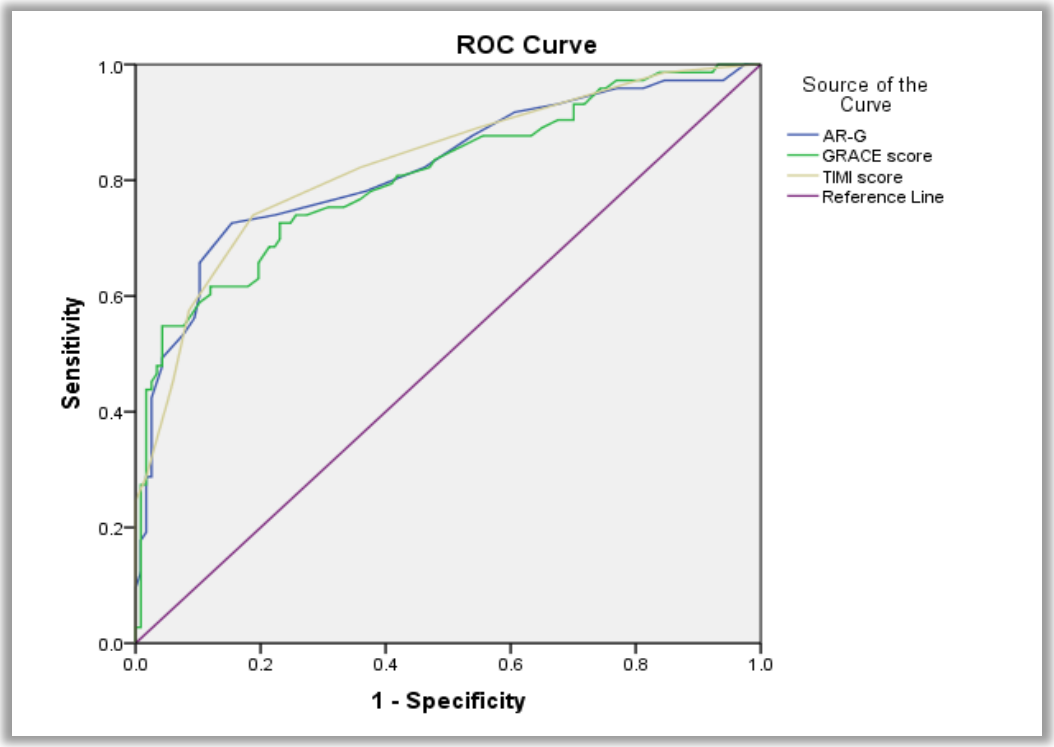

Figure 3: ROC curve showing cutoff value of GRACE score, AR-GWTG score and TIMI score in STEMI patients for prediction of occurrence of MACE

TIMI flow pre and post procedure: There was a statistically significant difference between groups in regarding TIMI flow pre and post procedure with p value 0.012 and 0.02

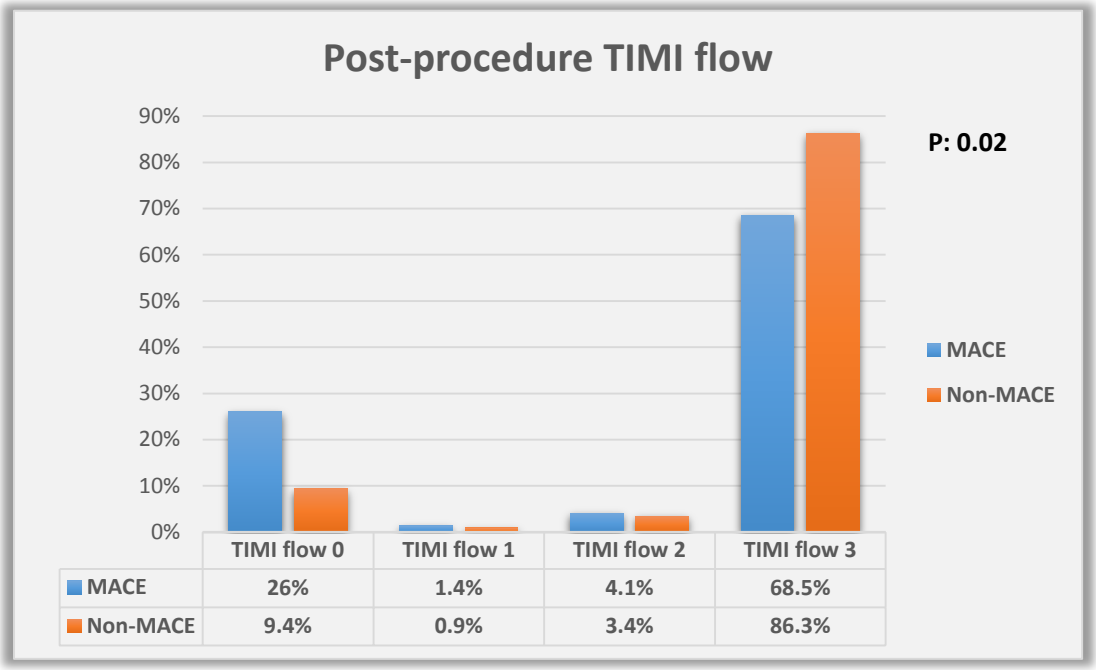

Figure 4: Post-procedure TIMI flow grades among the groups of STEMI patients

Table 1: Clinical presentation, risk scores, MACE and procedure complications in different SYNTAX categories in STEMI patients

		SYNATX score			P value
		Low (≤22)	Moderate (23-32)	High (≥33)	
Number of patients		271 (71.5%)	75 (19.5%)	34 (8.9%)	
Killip Class	**I**	228 (83.8%)	46 (62.2%)	10 (29.4%)	**0.0001**
	II	15 (5.3%)	9 (13.5%)	8 (23.5%)	
	III	11 (4.6%)	5 (5.4%)	2 (5.9%)	
	IV	17 (6.9%)	15 (18.9%)	14 (41.2%)	
AR-G score		35.8±8.0	42.2±10.9	49.6±13.5	**0.0001**
GRACE score		114.2±29.2	134.4±34.5	154.9±39.4	**0.0001**
TIMI score		3.6±2.2	5.2±2.7	7.1±3.2	**0.0001**
Non-MACE		194 (82.9%)	33 (14.5%)	7 (2.6%)	**0.0001**
MACE		78 (53.4%)	41 (27.4%)	27 (19.2%)	
Procedure complications		13 (60%)	3 (33.3%)	2 (10%)	0.79
CIN		19 (56.3%)	8 (25%)	6 (18.8%)	0.25

NSTE-ACS Group*:* This group included 596 patients and will be divided into 2 groups according to the occurrence of MACCE and/or mortality either during the hospital stay or during the 1-year follow up period as follows: **Group I:** Included **410** patients who survived without occurrence of MACCE. **Group II:** Included **186** patients where mortality and/or MACCE occurred. Among the NSTE-ACS **165** patients presented with NSTEMI (negative cardiac enzymes) while **431** patients presented with unstable angina with a statistically significant difference between the 2 groups (patients of NSTEMI had higher incidence of in-hospital and post-discharge complications.

Table 2: Distribution of NSTE-ACS patients according to cardiac biomarkers

	Total		Group I		Group II		P value
	Count	%	Count	%	Count	%	
NSTEMI	165	27.8%	92	22.5%	73	39.8%	**0.008**
Unstable angina	431	72.2%	319	77.6%	112	60.2	

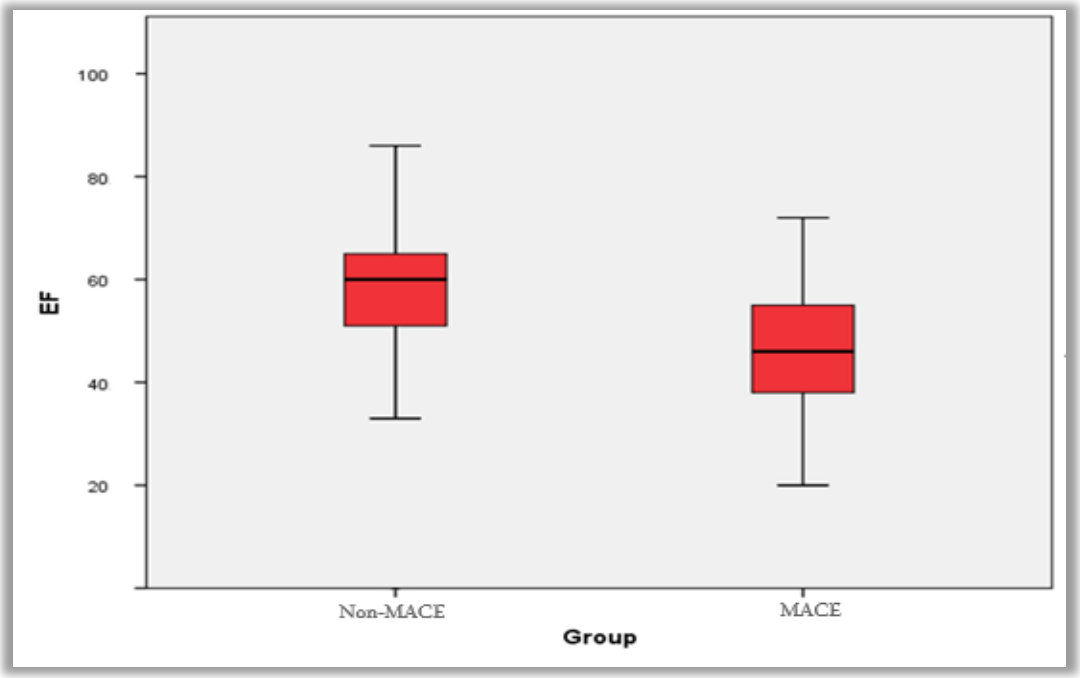

Figure 5: Box plot showing EF distribution in NSTE-ACS patients

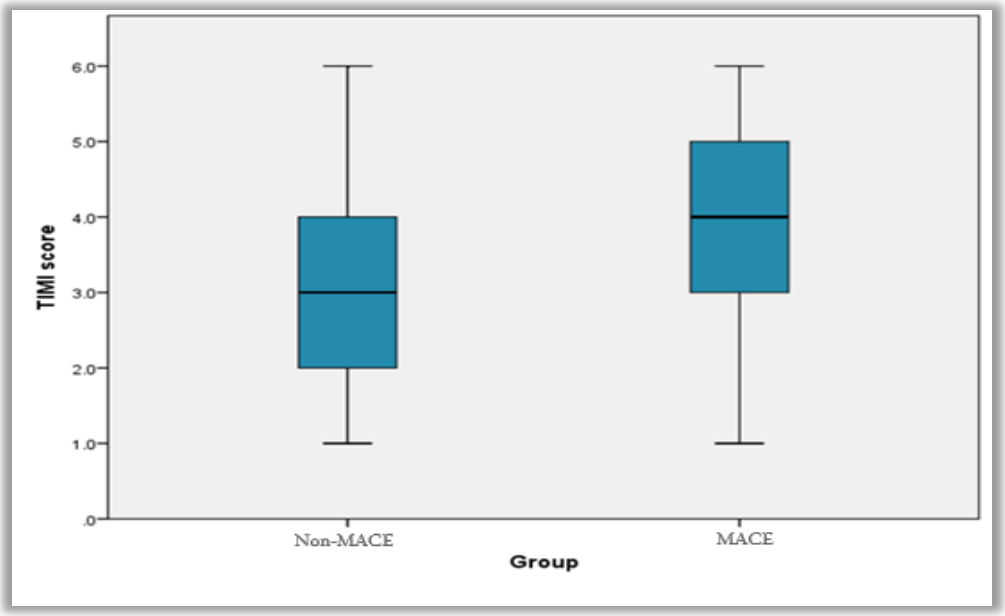

Figure 6: Box plot showing the difference in TIMI score for UA/NSTEMI between study groups of NSTE-ACS patients

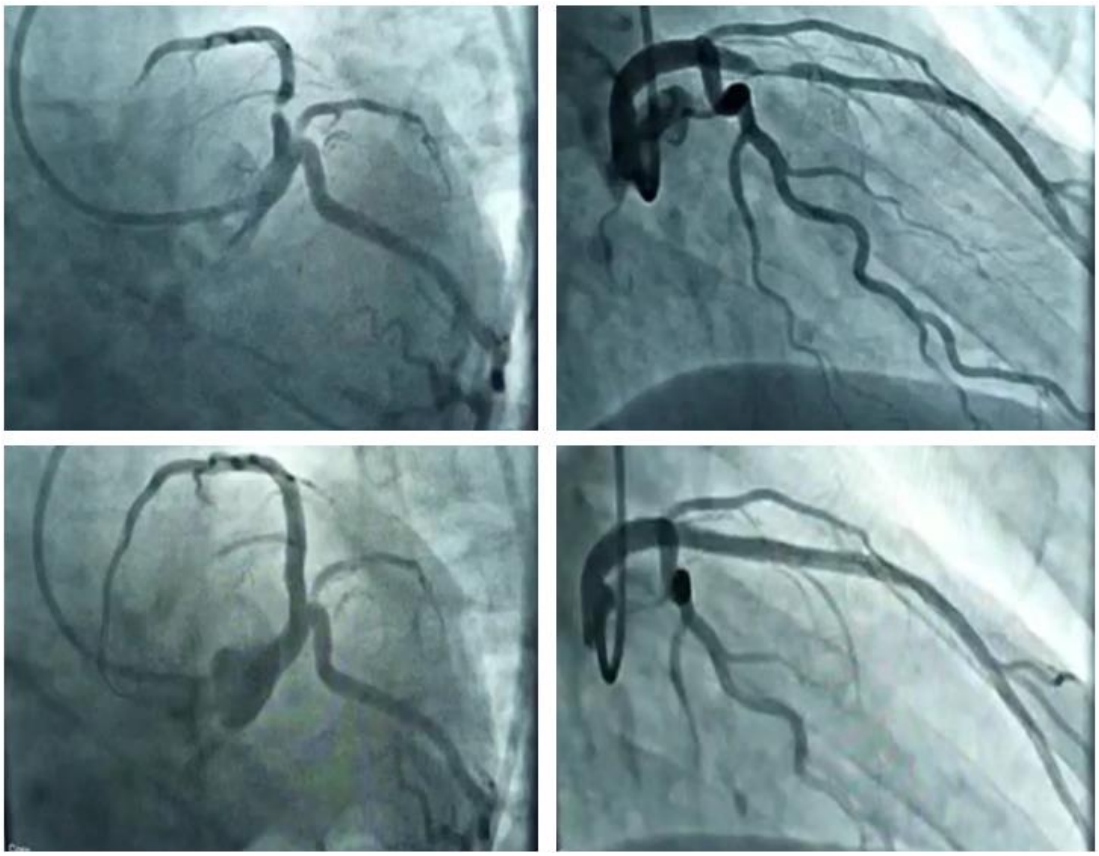

Figure 7: Coronary angiography of a patient with NSTE-ACS before and after revascularization

Lesion diameter and length Average lesion diameter was 3 mm with no statistically significant difference between the 2 groups. However, the lesion length showed statistically significant difference between the 2 groups (long lesion were more prevalent in group II with p value 0.0001).

Table 8: Lesion length and diameter among NSTE-ACS groups

		Group I		Group II		P value
		Count/ mean ± SD	%/ range	Count/ mean ± SD	%/ range	
Lesion diameter (mm)		3.1±0.4	2-4	3.0±0.4	2-4	0.13
Lesion length	**<20 mm**	240	58.5%	44	23.7%	0.0001
	>20 mm	170	41.5%	142	76.3%	

TIMI flow pre and post procedure: There was a statistically significant difference between groups in regarding TIMI flow pre and post procedure with p value 0.0001.

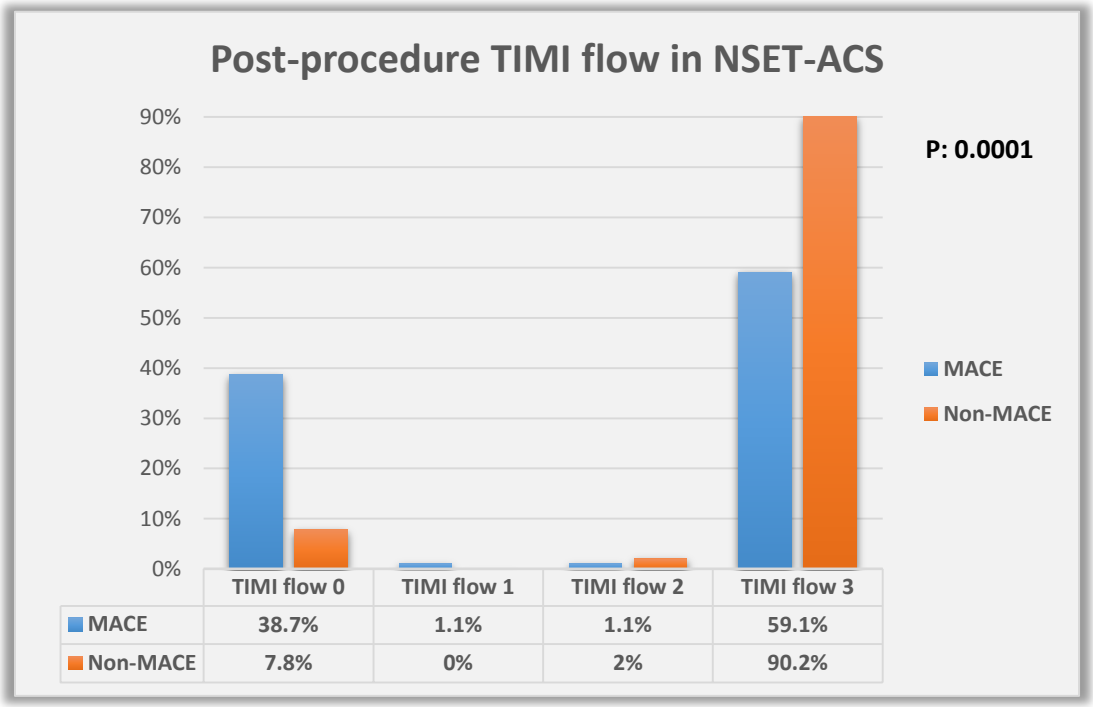

Figure 9: Post-procedure TIMI flow grades among the groups of NSTE-ACS patients

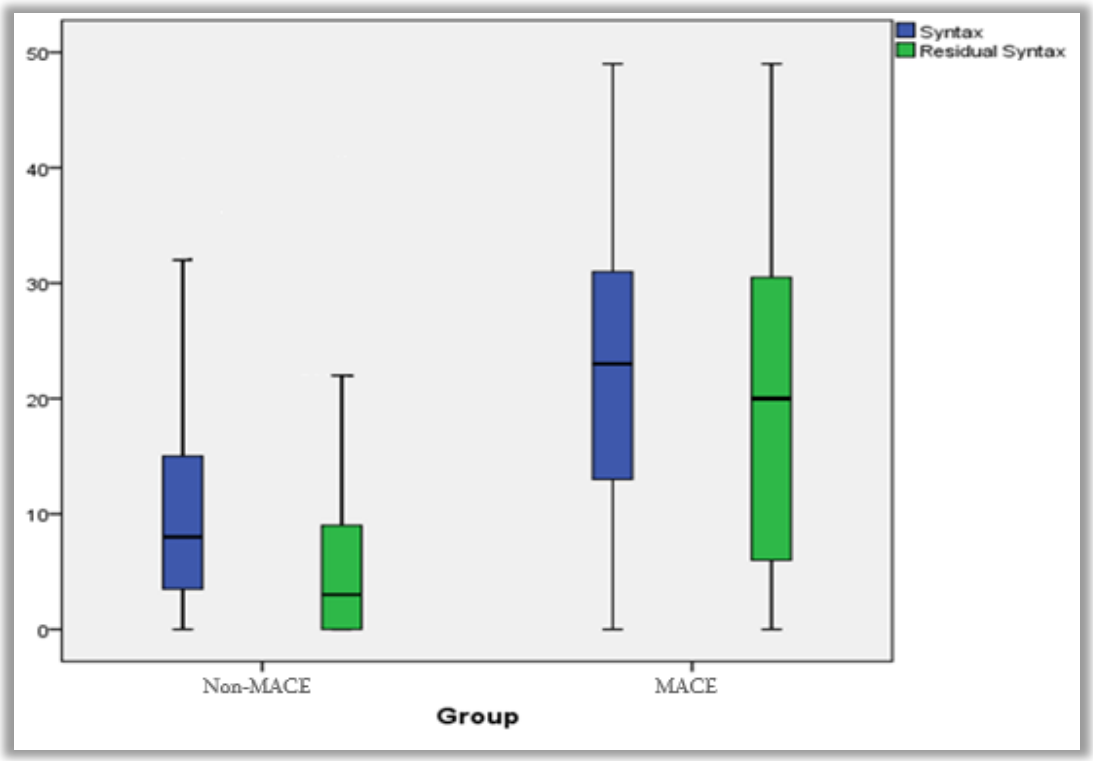

Figure 10: Box plot showing SYNTAX and residual SYNTAX scores distribution among NSTE-ACS groups

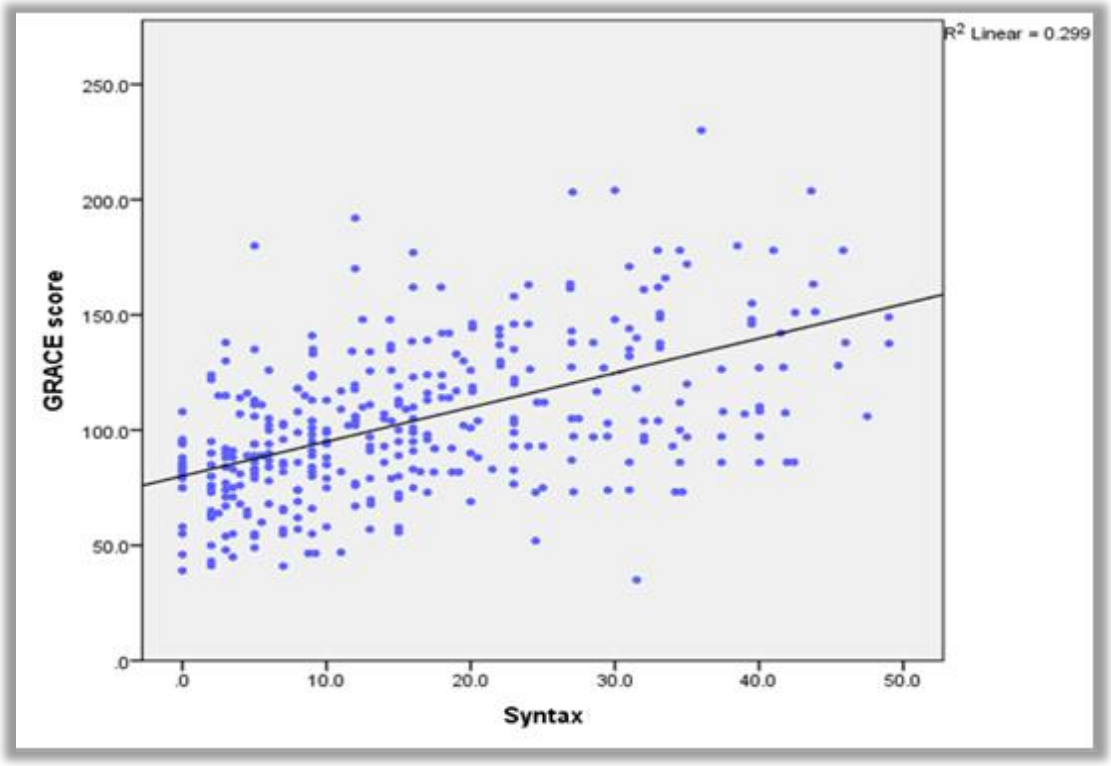

Figure 11: Scatter plot showing correlation between SYNTAX score and GRACE score in NSTE-ACS patients

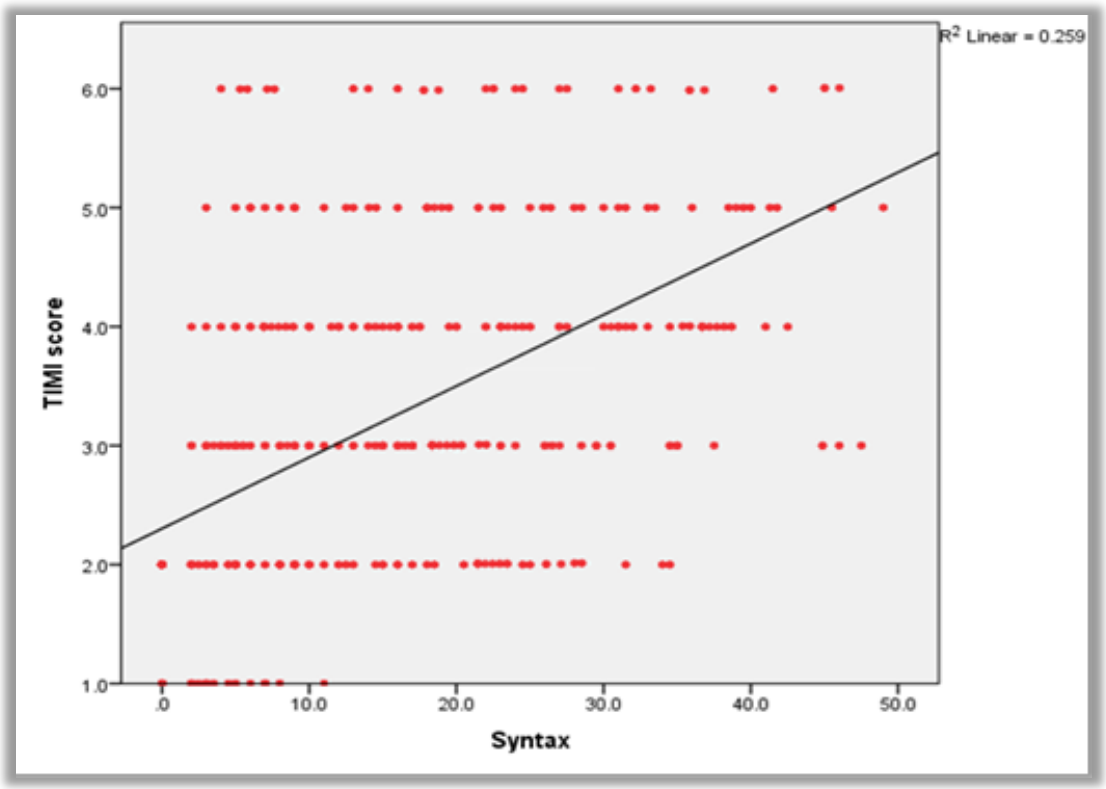

Figure 12: Scatter plot showing correlation between SYNTAX score and TIMI score in NSTE-ACS patients

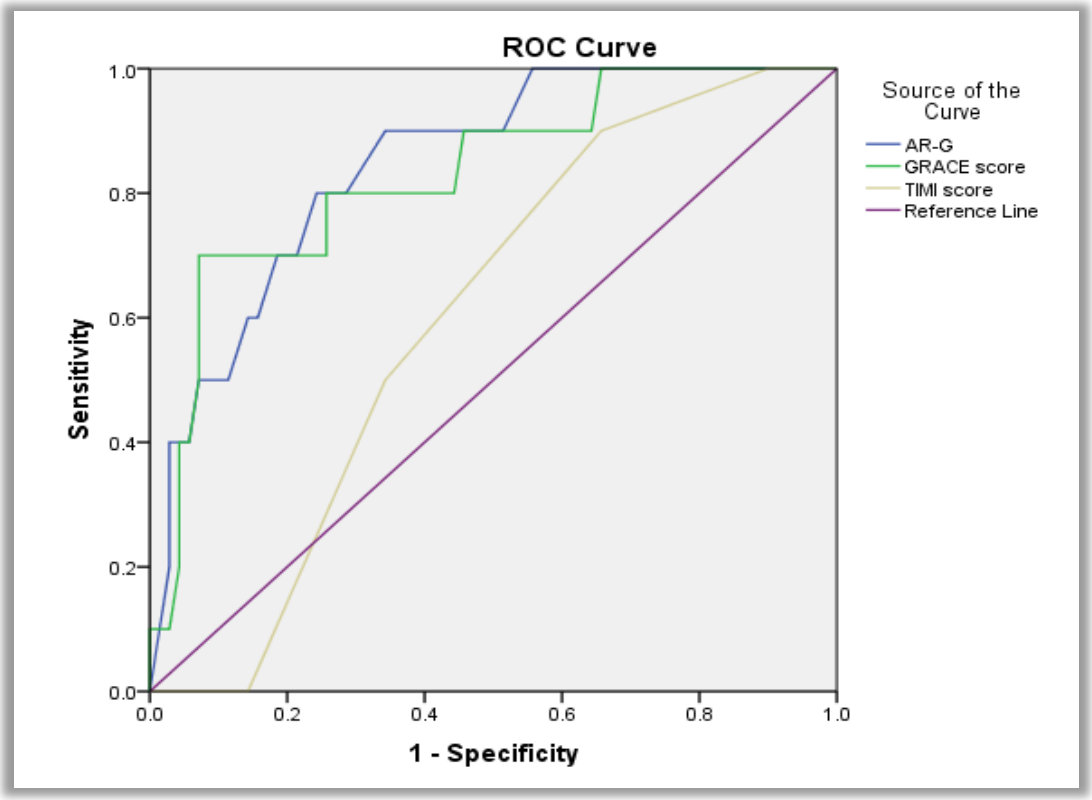

Figure 13: ROC curve showing cutoff value of GRACE score, AR-GWTG score and TIMI score for STEMI for prediction of SYNTAX score more than 32 in NSTE-ACS patients

Table 9: Clinical presentation, risk scores, MACE and procedure complications in different SYNTAX categories in NSTE-ACS patients

		SYNATX score			P value
		Low (≤22)	Moderate (23-32)	High (≥33)	
Number of patients		456 (76.5%)	92 (15.4%)	48 (8.1%)	
Killip Class	**I**	381 (83.3%)	45 (50%)	4 (8.3%)	**0.0001**
	II	45 (9.6%)	27 (28.3%)	20 (41.7%)	
	III	22 (4.8%)	17 (19.6%)	17 (33.3%)	
	IV	8 (1.8%)	2 (2.2%)	8 (16.7%)	
AR-G score		30.7±7.8	36.5±7.6	46.5±12	**0.0001**
GRACE score		93.9±25.7	118.6±31	137±35.9	**0.0001**
TIMI score		2.9±1.3	4±1	4±1.1	**0.0001**
Non-MACE		366 (89.3%)	34 (8.3%)	10 (2.4%)	**0.0001**
MACE		90 (48.4%)	58 (31.2%)	38 (20.4%)	
Procedure complications		22 (84.6%)	2 (7.7%)	2 (7.7%)	0.075
CIN		10 (38.5%)	10 (38.5%)	6 (23%)	**0.002**

Discussion

The aim of our study was to correlate the severity of coronary lesions with clinical presentation and risk scores in acute coronary syndrome patients and to delineate clinical, laboratory, echocardiographic and angiographic predictors of MACE in different groups of acute coronary syndrome.

Our study was conducted on 976 patients presented to Critical Care Department, Cairo University Hospitals with acute coronary syndrome (380 patients presented with STEMI and 596 patients presented with non ST segment elevation ACS).

Our study demonstrated a significant relationship between advanced age and occurrence of MACE. Also, diabetes mellitus and history of peripheral arterial disease were more associated with the occurrence of MACE.

In concordance with our study ***Vernon et al.***, [6] revealed significant relationship between advanced age and in-hospital MACE in patients of STEMI

using multivariate analysis {P: 0.001}. Also, ***Tsukui et al.***, [7] revealed higher incidence of MACE in elderly patients (>65 years old) who presented with STEMI by univariate Cox hazard analysis {P: 0.023}. In agreement with our study ***Akashi et al***. [8] stated higher incidence of MACE in diabetic patients after STEMI {P: 0.02}. Our results also go with the results of ***Attar et al***. [9] who demonstrated the significant higher incidence of 1-year MACE following STEMI in patients with peripheral arterial disease.

Our study revealed lower ejection fraction in the MACE group {42.6% vs 53.5% in the non-MACE group, P: 0.001}. Also, we found that LV end systolic diameter and LV end diastolic diameter were significantly higher in the MACE group.

Our study revealed significant relationship between higher GRACE, TIMI, HASBLED, and ACTION registry mortality model and risk scores and the development of in-hospital and 1-year MACE in patients of STEMI.

In concordance with our study, ***Martha et al.*** [10] stated that TIMI risk score for STEMI was a good predictor of in-hospital mortality in patients of STEMI. Also, ***Brkovic et al.*** [11] showed the significant predictive value of TIMI risk score for STEMI in predicting development of MACE in the first 30 days following acute STEMI.

In agreement with our study, ***Parco et al.*** [12] reported the significant predictive value of ACTION registry GWTG mortality model and risk score for in-hospital mortality in STEMI patients. Also, they reported that ACTION risk model {c-index: 0.84, 95% CI 0.80 to 0.89} was superior to GRACE score {c-index: 0.83, 95% CI: 0.79 to 0.88} in prediction of in-hospital mortality, bleeding, AKI and stroke following acute STEMI.

Our study revealed significant relationship between initial TIMI flow (pre-procedure) and the development of MACE. Also, TIMI flow pos-procedure had a significant impact on the development of MACE.

Also, ***Brener et al.*** [13] revealed that at 1 year, patients with initial TIMI grade 3 flow had lower rates of all-cause mortality than the patients with initial TIMI flow 0-2 {2.7% vs 4.3%, p = 0.02} and cardiac mortality {1.3% vs 2.9%, p = 0.04}.

Our study revealed significant relationship between SYNTAX score and development of MACE in STEMI patients. Also, residual SYNTAX score significantly correlated with the occurrence of MACE.

Few studies discussed the correlation between the risk scores and the anatomical complexity in patients of STEMI. Our study revealed a positive correlation between GRACE score and severity of coronary artery disease (SYNTAX score) in patients of STEMI.

Our results go with the results published by ***Putra et al.*** [14] that revealed a positive correlation between GRACE score and SYNTAX score in STEMI patients. GRACE score consistently increased from low to high SYNTAX score groups (101.8 ± 28.5 vs. 110.5 ± 27.5 vs. 119.5± 32.3; p: 0.03). Also, ***Ali et al.*** [15] found a positive correlation between both GRACE and TIMI scores for STEMI and the SYNTAX score. However, this relationship was not significant according to their results

Our study demonstrated a significant relationship between advanced age and occurrence of MACE. Also, diabetes mellitus and chronic renal failure were more associated with the occurrence of MACE.

These results go with the results of ***EPICOR and EPICOR Asia registries*** that delineated increased risk of 2-year mortality in cases of NSTE-ACS with increasing age {HR: 1.55, 95% CI: 1.43-1.66}and high blood glucose {HR: 1.26,95% CI:1.12 – 1.42}. Also, ***Lansky et al.*** [16] stated that advanced age and insulin treated diabetes mellitus were independent predictors of 1 year death and myocardial infarction after ACS on multivariate regression analysis. Also, they stated that renal insufficiency was a predictor of composite ischemia at 30 days {OR: 1.63, 95% CI: 1.31 - 2.03, P: <0.01} and at 1 year following acute coronary syndrome {OR: 1.38, 95% CI: 1.14 – 1.68, P: <0.01. In the same line, ***Okkonen et al.*** [17] stated that diabetes and advanced age were independent predictors for MACE following first acute coronary syndrome.

According to EPICOR and EPICOR Asia registries male sex was an independent predictor of 2-years mortality but our revealed prevalence of male sex in the MACE group but this difference didn't reach a statistical significance.

Our study revealed a relationship between development of MACE and lower ejection fraction. This is in line with the results of ***EPICOR and EPICOR Asia*** results. They stated that low ejection fraction is an independent factor of 2-year mortality in NSTE-ACS {HR: 1.89, 95% CI: 1.50 – 2.38} for LVEF < 40% and {HR: 2.28, 95% CI: 1.69 – 3.08} for LVEF < 30%. Similarly, ***Mukherjee et al.*** [18] stated that lower LVEF was significantly associated with 1-year mortality or hospitalization for heart failure and increased risk of 1-year mortality or heart failure in participants with LVEF < 40% {HR 3.59; 95 % CI 2.05, 6.27, P<0.001}.

The validity of GRACE risk score and TIMI risk score for NSTE-ACS to predict composite endpoints has been demonstrated in different studies. ***D'Ascenzo et al.*** [19] performed meta-analysis of 40 derivation studies on 216,552 patients and 42 validation studies on 31.625 patients on GRACE score, TIMI risk score and other risk scores for ACS.

Our study also showed significant relationship between ACTION registry GWTG risk model for mortality and the development of MACE. Some authors validated the AR-G risk score for in-hospital mortality as ***Raposeiras-Roubin et al.*** [20] who stated that AR-G risk score demonstrated good discrimination for in-hospital mortality (AUC: 0.90) with optimal calibration. Also, ***Parco et al.*** [12] stated that AR-G risk score showed good discrimination of risk for in-hospital and it was superior to GRACE score in NSTEMI patients. Both studies discussed the value of AR-G risk score in discrimination of in-hospital mortality only.

Our results revealed a statistically significant relationship between post-procedure TIMI flow and the development of MACE. These results go with those published by ***Karwowski et al.*** [21] that showed the important significance of final TIMI flow on 1-year mortality in NSTEMI patients (15.6% in TIMI 0/1, 18% in TIMI 2 ,8.5% in TIMI 3, P: 0.0028) with no statistically significant differences in the outcomes in final TIMI 0/1 when compared to TIMI 2 flow as only final TIMI 3 flow had a significant impact on survival.

Our study revealed a positive correlation between the risk scores (GRACE, TIMI risk score for NSTE-ACS and AR-G risk score) and the SYNTAX score.

In concordance with our results, ***Hammami et al.*** [45] showed a significant positive correlation between the GRACE and SYNTAX scores ($r=0.23$, $p<0.001$) as well as between TIMI and SYNTAX. However, according to their results GRACE and TIMI risk scores predict obstructive CAD moderately well for GRACE score and for TIMI score but not severe disease

Conclusion

In patients with STEMI and NSTE-ACS the anatomical complexity expressed by SYNTAX score was correlated to GRACE, TIMI and ACTION registry GWTG risk scores. In other words, worse clinical presentation and higher risk scores could predict complex coronary lesions in both patients of STEMI and NSTE-ACS. Higher residual anatomical complexity after PCI was associated with worse outcomes. Aggressive management and complete revascularization are recommended in high-risk ACS patients. This mandates better triaging plans for anticipated potential in-hospital complications.

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