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RISK PREDICTION AND PROGNOSIS IN PATIENTS PRESENTING WITH ACS: THE GRACE, CADILLAC AND KILLIP CLASS AND TIMI RISK INDEX COMPARISON.

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Abstract:

Background: Cardiovascular disease remains the most common cause of death and disability in developed countries (1). According to a World Health Organization report published in 2012, around 7.4 million deaths occurred from CHD globally, accounting for 42% of cardiovascular-related deaths and 13% of worldwide death (2). A reliable method of risk assessment for major adverse cardiac events (MACE) during the treatment of acute coronary syndrome (ACS) is needed due to differences in clinical appearance and mortality in patients with this condition to Planning early treatment, discharge, and rehabilitation for ASC patients, conducting research following ACS, and accelerate the final treatment decision all benefit from the application of risk stratification (3,4)

Aim: To determine the predictive accuracies of the GRACE risk score, CADILLAC, TIMI risk index and Killip class for patients that been diagnosis as Acute Coronary Syndrome. And find out which of them is the most accurate between them

Methods: This single-center retrospective study involved 88 patients with acute coronary syndrome (ACS) who was admitted in King Faisal Medical Complex in Taif, Makkah, in the period from May 2019 to November 2021. The GRACE, TIMI, and Killip class scores were compared for their predictive ability.

Results: A total of 88 patients [65 men (73.9%) and 23 women (26.1%), with the mean age (±standard deviation, SD) of 60.3±12.9 years] were enrolled in this study. There were 59 NSTEMI/UA and 29 STEMI patients in our study. There were significant differences regarding patient age ($p<0.001$), TRI ($p<0.001$), CADILLAC score ($p<0.001$) and GRACE score ($p<0.001$) in all patients between the low-, intermediate-, and high-risk groups. The area under the ROC curves for TRI was 0.954 (95% CI: 0.901-1.000, $p=0.001$) in the prediction of the severity of CAD (GRS >140) in patients with ACS. And ROC curves for CADILLAC was 0.859 (95% CI: 0.767-950, $p=0.001$) in the prediction of the severity of CAD (GRS >140) in patients with ACS.

Conclusions: *Our study is significant since it is the first in the field of literature to compare GRS, TRI and CADILLAC and to investigate how they relate to GRS were evaluated in the same patient population. In this study, in this research, we believe that information regarding patient short- and long-term mortality as well as information about the severity and extent of CAD may be obtained from the calculated of GRS or TRI and CADILLAC of patients who are admitted to the emergency department with ACS.*

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INTRODCTION:

Cardiovascular disease remains the most common cause of death and disability in developed countries (1). According to a World Health Organization report published in 2012, around 7.4 million deaths occurred from CHD globally, accounting for 42% of cardiovascular-related deaths and 13% of worldwide death (2). A reliable method of risk assessment for major adverse cardiac events (MACE) during the treatment of acute coronary syndrome (ACS) is needed due to differences in clinical appearance and mortality in patients with this condition to Planning early treatment, discharge, and rehabilitation for ASC patients, conducting research following ACS, and accelerate the final treatment decision all benefit from the application of risk stratification (3,4). Thrombolysis in Myocardial Infarction (TIMI) risk scores and Global Registry of Acute Coronary Events (GRACE) have been generally utilized for prognosis predicting in patients with ACS (5-8). The TIMI risk score was derived from clinical trial databases, although it has been approved in a community-based populations (9). The GRACE registry, a global registry of acute coronary syndrome (ACS) patients from 94 hospitals in 14 nations, created two models to assess the danger of both in-hospital and half year mortality among all patients with an ACS The in-hospital model was based upon information from 11,389 patients with either an STEMI or a non-ST elevation ACS (10). Compering to both these score the Killip classification arranges patients with an acute myocardial infarction (MI) based upon the presence or absence of simple physical examination findings that suggest LV dysfunction (11). The higher the Killip class on presentation, the greater the subsequent mortality. The higher the Killip class on presentation, the greater the risk for mortality (12-13-14). The CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) is a different risk score that was created from a group of patients with ST segment elevation MI (STEMI) who underwent initial PCI. The CADILLAC risk score may be also useful for risk stratification However, whether these risk predicting models are associated with clinical outcomes after acute MI in current real-world practice is Unclear (15). The TIMI score, however, was developed based on clinical research involving carefully chosen patient populations with low comorbidity rates, so it may not always accurately reflect clinical practice. And The GRACE score was found to be a better predictor of clinical outcome than the TIMI score in several international investigations that compared the two scores (16-17). For testing populations of hundreds of thousands of patients, the GRACE risk score and TIMI risk score were applied to predict early and late mortality. In patients with NSTE-ACS and patients with STEMI, the TIMI risk index (TRI) has recently been modified and is now able to predict mortality, is simpler to measure, and can perform scoring with less parameters (age, blood pressure, heart rate, etc.). Numerous research has indicated that this indicator is beneficial and useful (9-18). According to our theory, the TIMI risk index might predict a composite MACE in patients with ACS as accurately as the KILLIP class and GRACE scores.

Table 1 *Abbreviations: ACS – acute coronary syndrome; NSTEMI – non ST elevation myocardial infarction; UA – unstable angina; STEMI – ST elevation myocardial infarction; SD – standard deviation; MI – myocardial infarction;

									ACS
			ACS		STEMI		NSTEMI		UA
		Mean	Count	Mean	Count	Mean	Count	Mean	Count
	Age	60	88	59	29	61	33	61	26
	male		65		23		25		17
	female		23		6		8		9
sex									
	MORE THEN 3 RISK FACTOR		21		2		11		8
	NONE		16		3		8		5
Medical history	DM		47		14		19		14
	HTN		56		17		20		19
	prior MI		22		5		7		10
	prior Angina		2		0		1		1
	CHF		4		0		3		1
	DLP:		3		0		1		2
	smoking		9		4		5		0
	Anterior MI		0		0		0		0
ECG	ST Elevation		29		28		0		1
	ST depression		15		1		14		0
	ABBB		2		0		0		2
	none		42		0		19		23
Killip classification	killip 1		81		27		29		25
	killip 2		7		2		4		1
	killip 3		0		0		0		0
	killip 4		0		0		0		0
	Pulse	79		75		82		80	
	Systolic Blood pressure	141		135		145		141	
	Echo.LV.EF	54		52		53		58	
	Peak troponin	761		1749		457		35	
	Glucose	206		213		204		200	
	wbc	10		12		9		9	
	Creatinine	1.0		1.1		.9		1.0	

AP – angina pectoris; CHF – congestive heart failure; AVB III – atrioventricular block grade III; ABBB – acute bundle branch block; SBP – systolic blood pressure; LVEF – left ventricular ejection fraction.
†KILLIP – classification of the severity of heart failure by Thomas Killip: class I – no heart failure; class II - heart failure, diagnostic criteria include rales, S3 gallop, and venous hypertension; class III - pulmonary edema; class IV – cardiogenic shock.

METHODS:

Study population:

88 patients with signs and symptoms consistent with ACS who were admitted to King Faisal Medical complex between May 2019 and November 2021 were included in this single-center retrospective analysis. There were 65 men and 23 women, with the mean age (±standard deviation, SD) of 60.3±12.9 years (table 1). Acute chest pain or its equivalent, an increase in cardiac troponin above the upper reference limit, new significant ST- segment-T wave (ST-T) changes on an electrocardiogram (ECG), and/or images demonstrating the loss of viable myocardium or regional contractile abnormality were the signs and symptoms that were consistent with ACS. Clinical information was taken into account, including risk factors and prior medical history.

The following were the exclusion criteria: unwillingness to consent to invasive treatment, intracranial mass or aneurysm, active or recent internal bleeding, history of bleeding after non-steroid anti-inflammatory drugs, and known bleeding diathesis. Cardiogenic shock at admission, non-cardiac conditions that might prevent adherence to the protocol or call for stopping the treatment with thienopyridines, intolerance to or allergy to acetylsalicylates or clopidogrel, a history of hypersensitivity to iodinated contrast media, and coexisting conditions with a short life expectancy at 30-day follow-up. Patients have received acetylsalicylates and clopidogrel loading doses in addition to anticoagulant treatment. Each patient received thorough information about the intervention process before signing a written consent.

Study protocol:

First, the patients were categorized into three risk groups based on each score including the GRS and TRI and CADILLAC. low (GRS <109, n=62)-, intermediate (GRS 109-140, n=17)-, and high (GRS >140, n=9)- risk groups based on the GRS. And to Low [Group 1 (TRI <17, n=30)], Moderate [Group 2 (TRI 17-26, n=34)], and High [Group 3 (TRI >26 n=24)] risk groups based on the TRI. And to low risk (CADILLAC <2, n=78), intermediate risk (CADILLAC 2 – 4, n=6) and high risk (CADILLAC >4, n=4) risk groups based on the CADILLAC. risk groups were defined as patients having values in the third, second, and first tertials. The GRS, TRI and CADILLAC were calculated on admission using specified variables.

Calculation of the GRACE risk score and the TIMI risk index

For each patient, GRS (for death in hospital GRS) was calculated by using specific variables (age, heart rate, SBP, creatinine, Killip class, cardiac arrest at admission, elevated cardiac markers, and ST-segment deviation) collected at admission. The formula "heart rate X (age 10)2SBP" was used to get the TRI for each patient.

Statistical analysis:

All statistical analyses were conducted using the SPSS software (version 21.0, SPSS, Chicago, IL, USA). Qualitative factors were expressed as percentages (%) whereas quantitative data were expressed as the mean value and standard deviation. The normal distribution was tested using the Kolmogorov-Smirnov test. A comparison of parametric values between the groups was performed using one-way ANOVA and Tukey test for post hoc analysis for normal distribution. Categorical variables were compared by the likelihood ratio chi-square test. Pearson correlation analysis was used for determining the association between GRS, TRI, and Killip classification. A p value <0.05 was considered statistically significant. The receiver operating characteristics (ROC) curve was used to test the predictive accuracy of risk scores regarding the severity of CAD. A significant prediction occurred when the area under the ROC curve was statistically different from 0.5.

RESULTS:

A total of 88 patients [65 men (73.9%) and 23 women (26.1%), with the mean age (±standard deviation, SD) of 60.3±12.9 years] were enrolled in this study. There were 59 NSTEMI/UA and 29 STEMI patients in our study. Table 1 shows the characteristics of all patients.

There were significant differences regarding patient age (p<0.001), TRI (p<0.001), CADILLAC score (p<0.001) and GRACE score (p<0.001) in all patients between the low-, intermediate-, and high-risk groups. (Table 2). The means of age (p<0.001) and admission level of creatinine (p=0.068) and the level of peak troponin (p=0.360) were significantly higher in the high-risk patients compared to the low-risk patients compering to ejection fraction (p=0.083) and rate of pulse (0.072) were significantly higher in the intermediate-risk patients.

Table 2 **The baseline characteristics and laboratory findings of patients with low, intermediate, and high GRS.**

The baseline characteristics and laboratory findings of patients with low, intermediate, and high GRS

		GRACE. Class					
		'low' (0 to 108)		intermediate (109 to 140)		'high' (≥141)	P value
		Mean ± Standard Deviation	Count	Mean ± Standard Deviation	Count	Mean ± Standard Deviation	Count	
	Age	54±9		73±7[a]		80±4[a,b]		<0.001
	Pulse	79±16		81±11		76±11		0.072
	Systolic Blood pressure	142±30		142±26		126±10		0.370
	Creatinine	0.9±0.3		1.0±0.5		1.4±0.9[a]		0.068
	Peak troponin	551±1225		1230±2076		1372±3065		0.360
	WBC	10±4		10±4		9±4		0.523
	Glucose	195±97		232±129		227±128		0.258
	Echo LV EF	54±11		55±14		49±16		0.083
Killip. Class	Killip class 1		58		16		7	0.247
	Killip class 2		4		1		2	
	Killip class 3		0		0		0	
	Killip class 4		0		0		0	
Gender	male		49		10		6	0.213
	female		13		7		3	
Medical History	None		12		2		2	
	DM		33		9		5	0.991
	HTN		37		12		7	0.460
	prior MI		16		5		1	0.570
	prior Angina		2		0		0	0.651
	CHF		2		1		1	0.545
	DLP:		3		0		0	0.521
	smoking		8		1		0	0.395
	Anterior MI							
	GRACE score	83±17		122±10[a]		153±7[a,b]		<0.001
	TRI	17±6		31±6[a]		39±7[a,b]		<0.001
	CADILLAC score	0.48±1.13		2.24±1.39[a]		3.33±2.00[a]		<0.001
ACS	STEMI		19		5		5	0.582
	NSTEMI		23		7		3	
	UA		20		5		1	

a P<0.05 between the low and high GRS groups,
b P<0.05 between the low and intermediate GRS groups,
c P<0.05 between the intermediate and high GRS groups,
ACS - acute coronary syndrome; BP - blood pressure; bpm - beats per minute; BUN - blood urea nitrogen
; Echo LV EF – echocardiography left ventricular ejection fraction; GRS - Grace risk score; WBC – white blood cell; NSTEMI/UA-ACS - non-ST elevated acute coronary syndrome / unstable angina
; STEMI - ST elevation myocardial infarction; TRI - TIMI risk index one-way ANOVA and chi-square test;
CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications)

There were significant differences regarding mean age (p<0.001), and TRI (p<0.001) in all patients between groups according to TRI (table 3). Age was significantly higher in-patient group 3 compared to patient groups 2 and 3 (p<0.001), and pulse (p=0.373), creatinine (p=0.109), glucose (p=0.289) and GRACE risk score (p=0.191) were significantly higher in patient group 3 compared to patient group 1. There were statistically significant differences between the GRACE risk score and TRI in the study groups (p<0.001) but there were no statistically significant differences between the KILLIP and CADILLAC score classification and TRI in the study group (p=0.452) and (p=0.0218).

Table 3 **The baseline characteristics and laboratory findings of patient groups according to**

The baseline characteristics and laboratory findings of patient groups according to TRI

Variable		TIMI risk group						
		low [Group 1 (TRI <17)]		moderate [Group 2 (TRI 17-26)]		High [Group 3 (TRI >26)		
		Mean ± Standard Deviation	Count	Mean ± Standard Deviation	Count	Mean ± Standard Deviation	Count	P valu
Age		49±8		60±8[a]		75±8[a,b]		<0.001
Pulse		73±18		81±13		84±10[a]		0.373
Systolic Blood pressure		145±40		140±17		135±24		0.396
Creatinine		1.0±0.2		.9±0.3		1.1±0.7		0.109
Peak troponin		695±1325		926±2042		605±1486		0.415
Wbc		11±4		9±4		10±4		0.420
Glucose		184±87		187±95		259±129[a]		0.289
Echo.LV.EF		55±11		53±12		54±15		0.079
Killip class	Killip class 1		29		31		21	0.452
	Killip class 2		1		3		3	
	Killip class 3		0		0		0	
	Killip class 4		0		0		0	
Gender	male		26		25		14	0.062
	female		4		9		10	
Medical History	None		7		6		3	
	DM		12		16		19	0.010
	HTN		15		22		19	0.085
	prior MI		7		8		7	0.858
	prior Angina		1		1			0.678
	CHF		1		1		2	0.578
	DLP:		1		1		1	0.968
	smoking		5		4		0	0.124
	Anterior MI							0.353
GRACE score		74±14		97±21[a]		129±21[a,b]		0.191
TMI		12±3		21±3[a]		35±6[a,b]		<0.001
CADILLAC score		0.33±1.06		0.82±1.31		2.50±1.79[a,b]		0.0218
ACS	STEMI		14		10		5	
	NSTEMI		9		13		11	
	UA		7		11		8	

a P<0.05 between groups 1 and 3
b P<0.05 between groups 1 and 2
c P<0.05 between groups 2 and 3
ACS - acute coronary syndrome; BP - blood pressure; bpm - beats per minute; BUN - blood urea nitrogen ; Echo LV EF – echocardiography left ventricular ejection fraction; GRS - Grace risk score; WBC – white blood cell; NSTEMI/UA-ACS - non-ST elevated acute coronary syndrome / unstable angina ; STEMI - ST elevation myocardial infarction; TRI - TIMI risk index one-way ANOVA and chi-square test; CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications)

Table 4 The baseline characteristics and laboratory findings of patients with low, intermediate, and high CADILLAC.

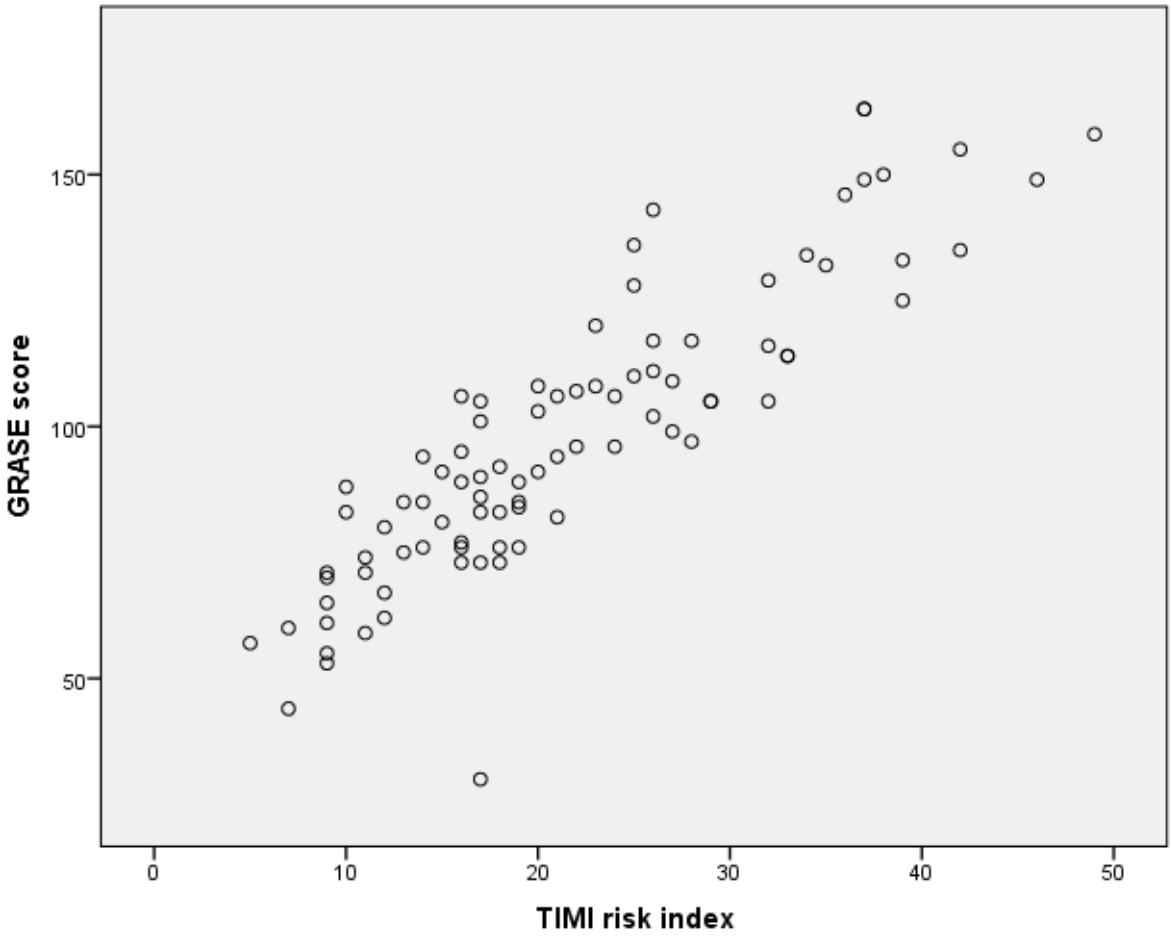
The baseline characteristics and laboratory findings of patients with low, intermediate, and high CADILLAC

		low risk		intermediate risk		high risk		
		Mean± Standard Deviation	Count	Mean± Standard Deviation	Count	Mean± Standard Deviation	Count	P value
Age		60±13		55±13		75±6		0.081
Pulse		79±15		80±13		80±6		0.506
Systolic Blood pressure		142±30		135±17		125±10		0.462
Creatinine		1.0±0.4		1.2±0.4		1.3±0.6		0.192
Peak troponin		835±1765		322±432		8±4		0.360
Wbc		10±4		14±5[a]		12±5		0.347
Glucose		201±105		214±91		277±159		0.250
Echo.LV.EF		57±9[b,c]		29±4		27±6		<0.001
Killip class	killip 1		75		5		1	<0.001
	killip 2		3		1		3	
	killip 3		0		0		0	
	killip 4		0		0		0	
Gendar	Female		22		0		1	0.673
	Male		56		6		3	
Medicalhistory	None		14		2		0	
	Smocking		4		0		0	
DM			43		0		4	0.005
HTN			49		3		4	0.248
MI			20		1		1	0.887
Angina			1		1		0	0.049
CHF			2		1		1	0.037
Dyslipidemia			3		0		0	0.819
Smoking			9		0		0	0.526
Anterior MI			0		0		0	
GRACE score		96±27		96±21		147±23[a,b]		0.666
TRI		21±10		19±8		36±2[a,b]		<0.001
CADILLAC score		0.64±0.94		4.00±0.00[a]		6.00±0.00[a]		<0.001
ACS Type	NSTEMI		29		3		1	0.365
	STEMI		25		1		3	
	UA		24		2		0	

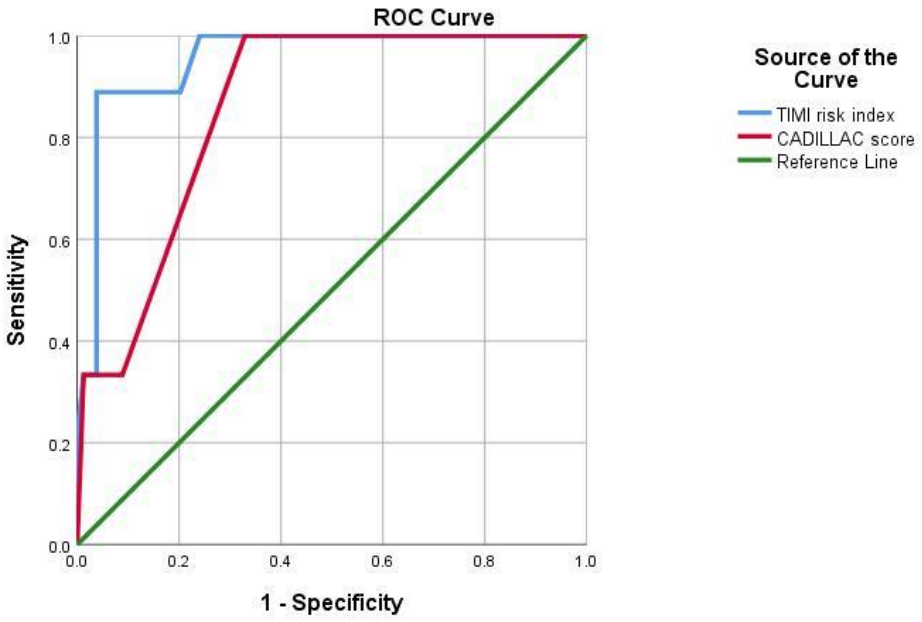
a P<0.05 between the low and high GRS groups,
b P<0.05 between the low and intermediate GRS groups,
c P<0.05 between the intermediate and high GRS groups,
ACS - acute coronary syndrome; BP - blood pressure; bpm - beats per minute; BUN - blood urea nitrogen ; Echo LV EF – echocardiography left ventricular ejection fraction; GRS - Grace risk score; WBC – white blood cell; NSTEMI/UA-ACS - non-ST elevated acute coronary syndrome / unstable angina ; STEMI - ST elevation myocardial infarction; TRI - TIMI risk index one-way ANOVA and chi-square test; CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications)

There were significant differences regarding mean of echo LV EF (p<0.001), Killip classification (p<0.001), TRI (p<0.001) and CADILLAC score (p<0.001) in all patients between groups according to CADILLAC (table 4).

In the correlation analysis, there were significant positive correlations between GRS and TRI (r=0.884, p<0.001) and between CADILLAC and TRI (r=0.549, p<0.001), and between GRS and CADILLAC (r=0.598, p<0.001), but there were no significant correlations between TRI and KILLIP classification (r=0.542, p=0.066) and between GRS and KILLIP classification (r=0.180, p=0.144). The area under the ROC curves for TRI was 0.954 (95% CI: 0.901-1.000, p=0.001) in the prediction of the severity of CAD (GRS >140) in patients with ACS. And ROC curves for CADILLAC was 0.859 (95% CI: 0.767-950, p=0.001) in the prediction of the severity of CAD (GRS >140) in patients with ACS. (Figure 1-2)



the relationship between GRACE risk score and TIMI risk index in Patients with acute coronary (figure 1)



Receiver operating characteristic (ROC) curves for CADILLAC score and TIMI risk index in prediction of CAD severity (GRS >140) in patients with ACS. (Figure 2)

DISCUSSION:

Two significant findings from our investigation were attained. First off, one of the quantitative indices of the degree and severity of CAD, TRI and GRS, showed a statistically significant positive correlation in patients with ACS. Second, there was no correlation between KILLIP and TRI or GRS. Because TRI is not associated with KILLIP and its parameters are in GRS. We believe that factors other age, heart rate, and Systolic blood presser can accurately predict the presence and severity of CAD. Additionally, in comparison to other studies that indicate differences in glucose level during admission and WBC (19-20), our study found substantial variations in creatinine level at admission and patient age between the GRACE risk groups.

The TIMI risk score, which has been confirmed to be useful and beneficial in numerous studies with sizable patient populations, is unquestionably one of the main scoring systems used in risk stratification in patients with ACS. Additionally, numerous studies have demonstrated a connection between the TIMI risk score and the severity of CAD (5-21-22).

As has been showing in numerous studies that CADILLAC and GRS In a contemporary cohort of acute MI patients receiving primary PCI, that the CADILLAC and GRS were both predictive for short- and long-term mortality and MACE rates, indicating the relevance of these scores in ordinary clinical practice in the present day (23).

When predicting the degree and severity of the CAD in individuals with ACS, the TRI is significantly more related to GRS than CADILLAC and Killip. Simple and low-cost techniques are used by the GRS, TRI, and CADILLAC to assess patients with ACS. High GRS and TRI may also be helpful for identifying people at high risk and selecting the best plans for treatment.

Study limitations:

Our research has some limitations. First of all, the study population was collected from a single center and was based on a retrospective study of a relatively small number of patients. Second, the method of measuring SBP, which is one of the GRS and TRI parameters, was by arterial blood pressure. This method is non-invasive, and the evaluation of interobserver variability is important for accurate and clear results. However, because our research was retrospective, this evaluation was not possible.

CONCLUSION:

Our study is significant since it is the first in the field of literature to compare GRS, TRI and CADILLAC and to investigate how they relate to GRS were evaluated in the same patient population. In this study, in this research, we believe that information regarding patient short- and long-term mortality as

well as information about the severity and extent of CAD may be obtained from the calculated of GRS or TRI and CADILLAC of patients who are admitted to the emergency department with ACS.

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