Comparison of the GRACE risk score and the TIMI risk index in predicting the extent and severity of coronary artery disease in patients with acute coronary syndrome

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Abstract

Objective: The prognostic value of the Global Registry of Acute Coronary Events (GRACE) risk score (GRS) and the Thrombolysis In Myocardial Infarction (TIMI) risk index (TRI) has been reported in coronary artery disease (CAD) patients. We aimed to evaluate the relationship between the GRS, TRI, and severity of CAD evaluated by SYNTAX score (SS) in patients with acute coronary syndrome (ACS).

Methods: Patients with ACS who were admitted to the coronary care unit of our institution were retrospectively evaluated in this study. A total of 287 patients with ACS [154 non-ST elevated ACS (NSTE-ACS), 133 ST elevated myocardial infarction (STEMI)] were included in the study. The GRS and TRI were calculated on admission using specified variables. The severity of CAD was evaluated using the SS. The patients were divided into low (GRS<109)-, intermediate (GRS 109-140)-, and high (GRS>140)-risk groups and group 1 (TRI<17), group 2 (TRI 17-26), and group 3 (TRI>26) according to GRS and TRI scores. A Pearson correlation analysis was used for the relation between GRS, TRI, and SS.

Results: Patients with a history of coronary artery bypass surgery, those who had missing data for calculating the GRS and TRI, and those whose systolic blood pressure (SBP) was more than 180 mm Hg or whose diastolic blood pressure (DBP) was more than 110 mm Hg were excluded from the study. Were excluded from the study. There were significant differences in mean age ($p<0.001$), heart rate ($p<0.001$), SS ($p<0.001$), TRI ($p<0.001$), rate of NSTE-ACS ($p<0.001$), and STEMI ($p<0.001$) in all patients between the risk groups. There was a positive significant correlation between the GRS and the SS ($r=0.427$, $p<0.001$), but there were no significant correlation between the TRI and SS ($r=0.121$, $p=0.135$). The area under the ROC curve value for GRS was 0.65 (95% CI: 0.56-0.74, $p=0.001$) in the prediction of severity of CAD.

Conclusion: The GRS is more associated with SS than TRI in predicting the severity of CAD in patients with ACS.

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Keywords: acute coronary syndrome, GRACE risk score, SYNTAX score, TIMI risk index

Introduction

Acute coronary syndrome (ACS) is a significant cause of morbidity and mortality in patients with coronary heart disease in developed countries (1). ACS includes non-ST elevated ACS (NSTE-ACS) and ST elevated myocardial infarction (STEMI). Recently, one of the major issues cardiologists have addressed is risk stratification in patients with ACS, in order to identify the severity and complexity of coronary artery disease (CAD). For this purpose, a large number of scoring systems and laboratory parameters have been used in clinical practice. The SYNTAX score (SS) is one of the scoring systems for determining the extent and severity of CAD (2). Although these scoring systems have many advantages, they require an invasive method, such as coronary angiography, to perform the scoring. Therefore, those interested in cardiovascular medicine still need an easily accessible, cost-effective, and noninvasive method to carry out risk stratification by determining the extent and severity of CAD in ACS patients.

In order to identify high-risk patients with ACS, various risk classification systems and scoring systems are quite frequently used (3-8). The prediction of early and late mortality with the GRACE risk score and TIMI risk score has been used for testing populations of hundreds of thousands of patients. Recently, the TIMI risk index (TRI) has been improved and is able to predict mortality, is easier to assess, and can perform scoring with fewer parameters (age, blood pressure, and heart rate,

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etc.) in patients with NSTE-ACS and patients with STEMI. This index has been shown in many studies to be useful and helpful (9, 10). However, although a number of studies have investigated the relationship between GRS, TRI, and CAD (11, 12), none has addressed the association between GRS, TRI, and the severity of CAD assessed by SS in patients with ACS. Thus, the aim of the current study was to investigate whether high GRS and TRI are associated with the extent and severity of CAD in patients with ACS.

Methods

Study design

Patients with ACS who were admitted to the coronary care unit of our Çanakkale Onsekiz Mart University Faculty of Medicine between April 2012 and August 2013 were retrospectively evaluated in this study.

Study population

Patients with ACS, defined as NSTE-ACS and STEMI. Patients with a history of coronary artery bypass surgery, those who had missing data for calculating the GRS and TRI, and those whose systolic blood pressure (SBP) was more than 180 mm Hg or whose diastolic blood pressure (DBP) was more than 110 mm Hg were excluded from the study. Therefore, a total of 287 patients diagnosed with ACS (154 NSTE-ACS and 133 STEMI) were included in the analysis. The study protocol was approved by the local Ethics Committee of Çanakkale Onsekiz Mart University Faculty of Medicine hospital.

Study protocol

First, the patients were divided into low (GRS <109, n=90)-, intermediate (GRS 109-140, n=104)-, and high (GRS >140, n=93)-risk groups based on the GRS. Second, the study population was divided into tertiles based on TRI values. High [Group 1 (TRI >26, n=94)], moderate [Group 2 (TRI 17-26, n=97)], and low [Group 3 (TRI <17, n=96)] groups were defined as patients having values in the third, second, and first tertiles. The GRS and TRI were calculated on admission using specified variables.

Study variables

The diagnosis of ACS was based on the criteria of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/Word Heart Federation Task definition (13). NSTE-ACS was diagnosed according to the following criteria: typical chest pain and/or electrocardiographic changes without new ST elevation indicating myocardial ischemia with negative or elevated cardiac enzymes. Typical chest pain was evaluated as follows: more than 20 minutes in duration, new-onset angina, and an increase in its frequency and duration or severity. The diagnosis of STEMI was based on typical chest pain and new ST-segment elevation at the J point in ≥2 contiguous leads (≥0.2 mV in V1 through V3 and ≥0.1 mV in other leads). (According to the new definition; the J point is used to determine the magnitude of the ST-segment shift. New, or presumed new, J point elevation 0.1mV is required in all leads other than V2 and V3.) Demographic information, cardiovascular history, and risk factors [i.e., smoking, hypertension (HT), and diabetes mellitus (DM)] were obtained from the patients' medical records. Patients who had been treated with antihypertensive drugs or those whose baseline blood pressure exceeded 140/90 mm Hg were diagnosed with HT (14). Patients with DM were defined as being prediagnosed and/or being antidiabetic medications or newly diagnosed if fasting plasma glucose was ≥126 mg/dL or blood glucose was ≥200 mg/dL at any time (15).

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 TRI of patients was calculated by the formula "heart rate X $(age \div 10)^2 \div SBP$."

Analysis of blood samples and echocardiography

CBCs and biochemical values were retrospectively evaluated from blood samples obtained by antecubital vein puncture upon admission to the emergency department. The hemogram parameters and other biochemical measurements were determined using standard biochemical techniques with the Beckman Coulter LH 780 (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland) device in the hematology laboratory of our institution. Simpson's method was used to assess left ventricular ejection fraction (LVEF), as recommended by the American Society of Echocardiography (16), by using a machine (Vivid 7®, GE Vingmed Ultrasound A/S, Horten, Norway) with a 3.5-MHz transducer for all patients.

Coronary angiography and SYNTAX score

All patients underwent a coronary angiography by using a machine (GE Healthcare Innova 2100, New Jersey, USA) by the femoral approach using the standard Judkins technique. Iopromide as a contrast agent (Ultravist-370, Bayer Schering Pharma, Germany) and a 6 F diagnostic catheter were used in all subjects. The extent and severity of CAD were assessed by the SS (17). All angiographic variables pertinent to the SS calculation were computed by 2 of 3 experienced cardiologists who were blinded to the current study on the angiograms. In the case of disagreement, an opinion was obtained from the third cardiologist, and the final decision was made by consensus. Occluded infarct-related arteries in patients with AMI were scored as occlusions of less than 3 months in duration. Each coronary lesion with a diameter stenosis of at least 50%, in vessels of at least 1.5 mm, had to be scored. The latest online updated version was used for the calculation of the SYNTAX score (http:// www.SYNTAXscore.com).

Statistical analysis

All statistical studies were carried out with the SPSS program (version 17.0, SPSS, Chicago, IL, USA). Quantitative vari-

Table 1. The characteristics of all patients

Parameters	All patients n=287
Age, years	61.9±12.7
Heart rate, bpm	75±15
Creatinine, mg/dL	0.84±0.21
Blood urea nitrogen, mg/dL	11.9±3.6
Systolic blood pressure, mm Hg	138±26
Diastolic blood pressure, mm Hg	87±16
Body mass index, kg/m^2	25.4±5.4
Ejection fraction, %	48±9
Female, % (n)	74.9 (215)
Smoking, % (n)	31.7 (91)
GRS	124.3±35.2
TRI	22.5±10.4
SYNTAX score	13.4±7.9
Diabetes mellitus, % (n)	40.1 (115)
Hypertension, % (n)	45.3 (130)
Type of ACS, % (n)	
Non-ST elevated ACS	53.7 (154)
ST elevated ACS	46.3 (133)
Culprit lesion, % (n)	
Left anterior descending	45.3 (130)
Circumflex	24.4 (70)
Right coronary artery	30.3 (87)
Glucose, mg/dL	157±78
Low-density lipoprotein, mg/dL	123±36
High-density lipoprotein, mg/dL	42.5±14.2
Triglyceride, mg/dL	140±59
Hemoglobin, g/dL	13.3±1.9
Neutrophil, 10^3/mm^3	8.4±3.9
Lymphocyte, 10^3/mm^3	3.9±3.3
Neutrophil-lymphocyte ratio	3.2±2.3
High-sensitivity troponin-T, ng/L	592±1086

ACS - acute coronary syndrome; bpm - beat per minute; GRS - Grace risk score; TRI - TIMI risk index

ables were expressed as the mean value±standard deviation, and qualitative variables were expressed as percentages (%). The Kolmogorov-Smirnov test was used for normal distribution. 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 SS. 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.

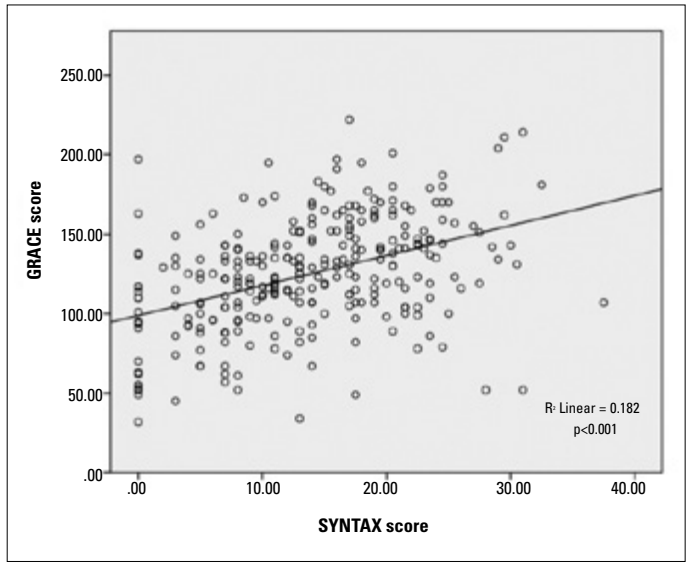

Figure 1. The relationship between GRACE risk score and SYNTAX score in patients with acute coronary
Pearson correlation analysis

Results

A total of 287 patients [215 females (74.9%), mean age 61.9±12.7 years] were enrolled in this study. There were 154 NSTE-ACS and 133 STEMI patients in our study. Table 1 shows the characteristics of all patients.

There were significant differences regarding mean age (p<0.001), heart rate (p<0.001), SS (p<0.001), TRI (p<0.001), rate of NSTE-ACS (p<0.001), and STEMI (p<0.001) in all patients between the low-, intermediate-, and high-risk groups (Table 2). The rates of females (p=0.021) and admission level of glucose (p=0.044) were significantly higher and the level of hemoglobin (p=0.028) and the rate of circumflex lesion (p=0.001) were significantly lower in the high-risk patients compared to the low-risk patients. The neutrophil-to-lymphocyte ratio (NLR) (p=0.016) was significantly higher in the high-risk patients compared to the intermediate-risk patients (Table 2).

There were significant differences regarding mean age (p<0.001), heart rate (p<0.001), rate of females (p<0.001), and GRS (p<0.001) in all patients between groups according to TRI (Table 3). SBP and DBP were significantly higher in patient group 1 compared to patient groups 2 and 3 (p<0.001), and triglycerides were significantly higher in patient group 1 compared to patient group 3 (p=0.039). There were no statistically significant differences between the SS and TRI in the study groups (p=0.686) (Table 3).

In the correlation analysis, there were significant positive correlations between GRS and SS (r=0.423, p<0.001) and between GRS and TRI (r=0.756, p<0.001), but there were no significant correlations between TRI and SS (r=0.121, p=0.135). The

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

Variable	Low GRS (n=90)	Intermediate GRS (n=104)	High GRS (n=93)	*P*
Age, years	52±10[a,b]	63±10[b,c]	70±10[a,c]	<0.001
Heart rate, bpm	70±13[a,b]	76±14[b]	80±16[a]	<0.001
Creatinine, mg/dL	0.8±0.2	0.9±0.2	0.8±0.2	0.166
BUN, mg/dL	12±3.7	11.8±3.7	11.8±3.4	0.928
Systolic BP, mm Hg	141±26	137±26	135±25	0.358
Diastolic BP, mm Hg	90±16	87±16	86±16	0.248
Body mass index, kg/m^2	25.5±5.5	25.3±5.4	25.4±5.3	0.968
Left ventricle EF, %	46.7±8.9	47.5±10.5	49.6±9.6	0.127
Female, % (n)	15.6 (14)[a]	26 (27)	33.3 (31)[a]	0.021
Smoking, % (n)	27.8 (25)	32.7 (34)	34.4 (32)	0.606
GRS	84.4±19.8[a,b]	124.3±8.8[b,c]	162.8±18.5[a,c]	<0.001
TRI	14.1±5.9[a,b]	22.8±8.1[b,c]	30.3±10.1[a,c]	<0.001
SYNTAX score	9.9±8.3[a,b]	12.6±6.9[b,c]	17.9±6.7[a,c]	<0.001
Diabetes mellitus, % (n)	31.1 (28)	40.4 (42)	48.4 (45)	0.058
Hypertension, % (n)	52.2 (47)	44.2 (46)	39.8 (37)	0.231
Type of ACS, % (n)				0.001
NSTE-ACS	80 (72)[a,c]	52.9 (55)[b,c]	29 (27)[a,c]	
STE-ACS	20 (18)[a,c]	47.1 (49)[b,c]	71 (66)[a,c]	
Culprit lesion, % (n)				
LAD	37.8 (34)	49 (51)	48.4 (45)	0.223
Cx	40 (36)[a]	23.1 (24)	17.2 (16)[a]	0.001
RCA	25.6 (23)	30.8 (32)	34.4 (32)	0.425
Glucose, mg/dL	145±77[a]	153±73	172±81[a]	0.044
LDL, mg/dL	128.1±33.3	123.1±37.7	118.4±36.4	0.190
HDL, mg/dL	40.3±12.1	43±12.4	44±17.5	0.199
Triglyceride, mg/dL	151.4±70.4	135.6±54.2	133.8±52.1	0.086
Hemoglobin, g/dL	13.7±1.8[a]	13.4±2.1	12.9±1.8[a]	0.028
Neutrophil, 10^3/mm^3	8.3±3.9	8.2±3.6	8.8±4.3	0.507
Lymphocyte, 10^3/mm^3	4.1±3.6	4±3.2	3.6±3.2	0.557
NLR	3±2.4	2.8±1.8[c]	3.7±2.7[c]	0.016
hs-TnT, ng/L	625±1099	488±893	676±1259	0.451

[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; Cx - circumflex; EF - ejection fraction; GRS - Grace risk score; HDL - high-density lipoprotein; Hs-TnT - high-sensitivity troponin-T; LAD - left anterior descending; LDL - low-density lipoprotein; NLR - neutrophil-lymphocyte ratio; NSTE-ACS - non-ST elevated acute coronary syndrome; RCA - right coronary artery; STEMI - ST elevation myocardial infarction; TRI - TIMI risk index
one-way ANOVA and chi-square test

relationship between GRS and SS in patients with ACS is shown in Figure 1. The area under the ROC curves for GRS was 0.65 (95% CI: 0.56-0.74, p=0.001) in the prediction of the severity of CAD (SS >22) in patients with ACS (Fig. 2).

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

Variable	Group 1 (n=96)	Group 2 (n=97)	Group 3 (n=94)	*P*
Age, years	50±9[a,b]	63±8[b,c]	73±10[a,c]	<0.001
Heart rate, bpm	68±12[a,b]	74±12[b,c]	85±16[a,c]	<0.001
Creatinine, mg/dL	0.8±0.2	0.8±0.2	0.9±0.2	0.189
BUN, mg/dL	11.5±3.7	12.2±3.8	11.8±3.2	0.367
Systolic BP, mm Hg	145±25[a]	138±26	130±24[a]	<0.001
Diastolic BP, mm Hg	93±15[a,b]	87±16[b]	83±15[a]	<0.001
Body mass index, kg/m^2	25.6±5.5	24.9±5.3	25.8±5.3	0.451
Left ventricle EF, %	47.3±9.9	47.7±9	48.9±10.3	0.508
Female, % (n)	12.5 (12)[a,b]	25.8 (25)[b,c]	37.2 (35)[a,c]	<0.001
Smoking, % (n)	30.2 (29)	34 (33)	30.9 (29)	0.831
GRS	98.6±34.5[a,b]	123.4±22.1[b,c]	151.3±26[a,c]	<0.001
TRI	11.8±3.2[a,b]	21.3±2.7[b,c]	34.7±6.9[a,c]	<0.001
SYNTAX score	13.1±9	13.2±7.3	14±7.5[a,c]	0.686
Diabetes mellitus, % (n)	32.3 (31)	41.2 (40)	46.8 (44)	0.119
Hypertension, % (n)	54.2 (52)[a]	49.5 (48)[c]	31.9 (30)[a,c]	0.005
Type of ACS, % (n)				0.804
NSTE-ACS	51 (49)	55.7 (54)	54.3 (51)	
STE-ACS	49 (47)	44.3 (43)	45.7 (43)	
Culprit lesion, % (n)				
LAD	41.7 (40)	46.4 (45)	47.9 (45)	0.667
Cx	32.3 (31)	22.7 (22)	24.5 (23)	0.275
RCA	27.1 (26)	35.1 (34)	28.7 (27)	0.445
Glucose, mg/dL	145±70	159±77	166±85	0.171
LDL, mg/dL	126.9±35.1	124.9±39.2	117.5±33.2	0.170
HDL, mg/dL	40±9.8	43.5±15.7	43.9±16.1	0.120
Triglyceride, mg/dL	148.6±66.7[a]	143.4±61.3	127.5±47[a]	0.039
Hemoglobin, g/dL	13.9±1.7[a]	13.5±1.9[c]	12.6±1.9[a,c]	<0.001
Neutrophil, 10^3/mm^3	9.2±4.3	8.1±3.7	7.9±3.7	0.05
Lymphocyte, 10^3/mm^3	4±3.2	4.2±3.8	3.5±3	0.315
NLR	3.2±2.3	2.8±2	3.5±2.6	0.194
hs-TnT, ng/L	759±1231	543±983	471±1017	0.163

[a]; *P*<0.05 between groups 1 and 3, [c]; *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; Cx - circumflex; EF - ejection fraction; GRS - Grace risk score; HDL - high-density lipoprotein; hs-TnT - high-sensitivity troponin-T; LAD - left anterior descending; LDL - low-density lipoprotein; NLR - neutrophil-lymphocyte ratio; NSTE-ACS - non-ST elevated acute coronary syndrome; RCA - right coronary artery; STEMI - ST elevation myocardial infarction; TRI - TIMI risk index
one-way ANOVA and chi-square test

Discussion

In our study, two important results were obtained. Firstly, in patients with ACS, there was a significant positive correlation between GRS and SS, one of the quantitative indicators of the extent and severity of CAD. Secondly, TRI was not correlated

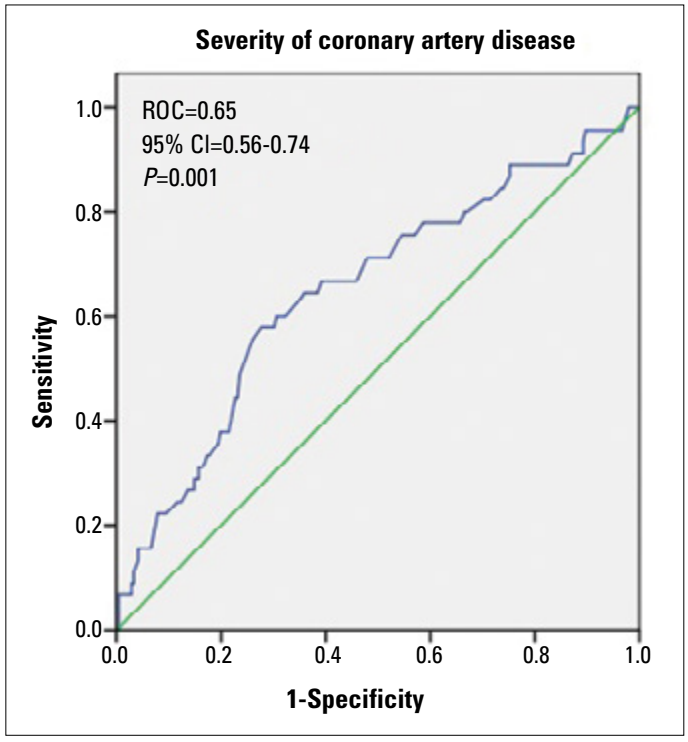

Figure 2. Receiver operating characteristic (ROC) curves for GRACE risk score in the prediction of CAD severity (SYNTAX score >22) in patients with acute coronary syndrome

with SS. Because the parameters in TRI are in GRS and because TRI is not correlated with SS, we think that parameters other than age, heart rate, and SBP predict the extent and severity of CAD. In addition, in our study, significant differences in admission glucose levels and NLR between the GRACE risk groups were confirmed by the results of recently conducted studies (18, 19) in large patient groups.

Because GRACE score has been shown to be a predictor of major adverse cardiac events in patients with ACS (20), it is frequently used in clinical practice. GRS includes a variety of clinical, laboratory, and electrocardiographic parameters. Because angiographic findings are not included in these parameters, scoring systems that predict the prognosis and also the prevalence and severity of CAD, such as SS, have begun to be used in the clinic to contribute to risk stratification (2).

Undoubtedly, one of the important scoring systems used in risk stratification in patients with ACS is the TIMI risk score, since it has been shown to be useful and helpful in many studies with large patient populations. Also, the relationship between the TIMI risk score and the severity of CAD has been shown in several studies. For example, the TIMI score was compared with the results of coronary angiography in 683 patients with NSTE-ACS. In each increased risk category, 3-vessel disease or left main coronary disease was shown to be more frequent (12). In another study, the PRISM-PLUS study, in 1491 patients with ACS, it was shown that there were more severe coronary lesions and left main coronary lesions in patients with high TIMI risk scores compared to those with low TIMI risk scores (21). These results were confirmed in the retrospective study of Ben Salem et al. (22). Also, in another study, the relationship between GRS, TIMI risk score, and Gensini score was investigated in patients with NSTE-ACS, and a positive significant correlation was observed between GRS and Gensini score, but it has been shown that this significance was not sufficient for GRS to predict obstructive CAD (23).

As a result of these studies conducted with the GRACE and TIMI risk score, SBP, heart rate, and age were found to be three major important parameters predicting mortality. Therefore, Morrow et al. (24) showed that TRI, an index consisting of these three parameters, can be used in the risk assessment of patients with ACS. In another study, Truong et al. (25) showed that TRI predicts long-term mortality and heart failure in patients with STEMI. Ilkhanoff et al. (26) and Bradshaw et al. (10) showed that TRI predicts short- and long-term mortality in patients with ACS (NSTE-ACS and STEMI).

Our study is important, because it is the first study in the literature in which GRS and TRI and their relationship with SS were evaluated in the same patient population. In this study, we think that with the help of the calculated GRS of patients who are admitted to the emergency department with ACS, information about the short-and long-term mortality of patients and information about the severity and extent of CAD may be obtained.

Study limitations

Our study has some limitations. Firstly, this was a retrospective study based on a relatively small number of patients, and the study population was from a single center. Secondly, 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, this evaluation could not be done in our study, since our study was retrospective. Third, because there was a predominance of female patients in our study, the results may not be applicable to a group with a male predominance. Fourth, 109 and 140 values were used for the risk classification of GRS in all patients (STE-ACS and NSTE-ACS). This condition might not be applicable for STEMI patients.

Conclusion

The GRS is associated more with SS than TRI in predicting the extent and severity of the CAD in patients with ACS. The GRS is using simple and inexpensive methods for evaluating patients with ACS. In addition, high GRS may be helpful in identifying high-risk patients and determining appropriate treatment strategies.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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