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Göğüs Ağrısı İle Acil Servise Başvuran Akut Koroner Sendrom Şüphesi Olan Yaşlı Hastaların Değerlendirilmesinde Risk Skorlamalarının Geçerliliği Ve Güvenilirliği

Determınatıon Of The Validity And Reliability Of Chest Pain Risk Stratification Scores In Elderly Patients With Suspected Acute Coronary Syndrome In The Emergency Department

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ÖZ

GİRİŞ ve AMAÇ: *Göğüs ağrısı ile acil servise başvuran akut koroner sendrom (AKS) düşülerek takip edilen 65 yaş üzeri hastalarda 6 haftalık major kardiyak olay (MACE) görülme oranlarını ön görmede GRACE, TIMI, HEART skorlarının güvenli olup olmadığının araştırılmasıdır.*

YÖNTEM ve GEREÇLER: *Bu tek merkezli prospektif gözlemsel çalışmaya 6 aylık dönemde 3. basamak eğitim araştırma hastanesi acil servisine göğüs ağrısı ile başvuran akut koroner sendrom düşünülen 65 yaş üzeri hastalar dahil edildi. Tüm hastalar için GRACE, TIMI, HEART skorları hesaplandı. İlk başvurudan itibaren 6 hafta içinde hastalardaki MACE gelişimi değerlendirildi.*

BULGULAR: *Çalışmaya 181 hasta dahil edildi. Araştırmada yer alan hastaların ortalama yaşı 73.9 ve % 61.9'u erkekti. Hastaların 22'sinde (% 12.2) altı haftalık takip sonucunda MACE tespit edildi. HEART skoru ≤ 3 olan 15 hastanın 1'inde (%6.6), TIMI skoru ≤ 2 olan 53 hastanın 6'sında (%11.3) ve GRACE skoru <110 olan 46 hastanın 4'ünde (%8.7) MACE geliştiği bulunmuştur. Risk skorlarının ROC analizinde eğri altında kalan alan; HEART: 0.59 (%95 GA: 0.435-0.684), TIMI: 0.505 (%95 GA: 0.386 - 0.624), GRACE: 0.603 (%95 GA: 0.479 - 0.727) olarak bulunmuştur.*

TARTIŞMA ve SONUÇ: *HEART, TIMI ve GRACE skorlarının akut koroner sendrom düşündüren göğüs ağrısı şikayeti olan ileri yaş hastalarda 6 hafta içerisindeki MACE tahmininde etkinlikleri genel popülasyonla karşılaştırıldığında daha düşük seviyede olduğu görülmektedir.*

Anahtar Kelimeler: *Risk skor, HEART, TIMI, GRACE, Göğüs ağrısı, Acil servis*

ABSTRACT

INTRODUCTION: *This study aimed to investigate whether GRACE, TIMI, and HEART scores were reliable in predicting the major cardiac events (MACE) for six weeks of duration in patients older than 65 years, who were followed-up with the suspicion of acute coronary syndrome (ACS).*

METHODS: *This single-center prospective observational study included patients over the age of 65 years who had presented to the emergency department (ED) of a tertiary hospital with acute chest pain. The development of MACE that had occurred within 6 weeks following the ED admission was evaluated*

RESULTS: *A total of 181 patients were included in the study. The mean age of the patients was 73.9 years, and 61.9% were male. During six weeks of follow-up, MACE developed in 22 (12%) patients. MACE was observed in one (6.6%) of 15 patients with a HEART score of ≤ 3 points, in 6 (11.3%) of 53 patients with a TIMI score of ≤ 2 points, and in 4 (8.7%) of 46 patients with a GRACE score of <110 points. In the ROC analysis of the risk scores, the area under the curve (AUC) was found to be 0.59 (95% CI = 0.435-0.684) for HEART, 0.505 (95% CI = 0.386 - 0.624) for TIMI, and 0.603 (95% CI = 0.479-0.727) for GRACE.*

DISCUSSION AND CONCLUSION: *The HEART, TIMI, and GRACE risk scores were lower in the MACE prediction over a six weeks period in patients over 65 years of age who had presented with chest pain suspected of acute coronary syndrome compared to the general population.*

Keywords: *Risk score, HEART, TIMI, GRACE, chest pain, emergency department*

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INTRODUCTION

Today, the human population is getting older, and a significant proportion of cardiovascular diseases are seen in individuals over 65 years of age(1). The cause of death in 85% of elderly patients is coronary artery disease, which increases with aging (2).

Although chest pain is one of the most common causes of admission to the emergency department (ED), previous studies have shown that 2-4% of patients with acute myocardial infarction can be discharged mistakenly (3). Therefore, some classification methods are needed to establish the diagnosis in patients presenting with chest pain, to provide appropriate treatment options and to determine their prognosis. According to the 2014 American Heart Association/American College of Cardiology Non-ST elevation ACS (AHA/ACC NSTE-ACS) guidelines4, the patients presenting with NSTE-ACS who have refractory angina or hemodynamic or electrical instability require coronary angiography and percutaneous coronary intervention to provide coronary reperfusion. However, additional strategies are needed if these signs/symptoms are absent. Thus, chest pain risk stratification scores such as the Thrombolysis in Myocardial Infarction (TIMI) score, the troponin (HEART) score, and the Global Registry of Acute Coronary Events (GRACE) score, as well as medical history, ECG, advanced age, and traditional risk factors are commonly used in the decision making in the management of these patients5. However, no consensus has been established on which classification would be more reliable6. In order for risk classification to be advantageous in the evaluation of patients in the emergency department, it should be easy to use, to use the information at the time of admission, and to initially provide an accurate prediction for the clinical course of the patient7.

Accuracy rates of scoring systems in MACE prediction have been previously evaluated in many studies. However, these studies cover the whole patient population. Age is an independent predictor for MACE development. Due to the presence of many chronic diseases, various atherosclerotic vascular structural changes, difficulties in expressing chest pain, and additional comorbidities, it is not clearly defined whether the accuracy rate of these scoring systems is affected in patients with advanced age8, 9.

To the best of our knowledge, there is no study investigating the reliability of the risk scoring systems in patients over 65 years of age. The aim of this study was to determine whether the risk scores of GRACE, TIMI, and HEART are reliable in predicting the 6-weeks of the major adverse cardiac events (MACE) in patients over 65 years of age presenting with chest pain and followed up with the suspicion of acute coronary syndrome (ACS).

MATERIALS AND METHODS

Study design

This single-center prospective observational study included patients over 65 years of age who had presented with chest pain and had a suspicion of acute coronary syndrome for a period of six weeks in the ED of the tertiary education and research hospital, which receives approximately 250,000 admissions to ED per year. The study was approved by the Local Ethics Committee of Kocaeli University, Faculty of Medicine, Kocaeli, Turkey (KU GOKAEK 2017/5.29/ Project No: 2017/94). The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and the current guideline on effective clinical procedures. All patients were informed before participation in the study and written informed consent was obtained from all participants.

Study Setting and Population

Consistent with the definition of the American Heart Association (AHA), the patients with suspected ACS who had presented to the ED with chest pain without ST elevation on ECG, who were older than 65 years of age and had no history of trauma were included in the study. Patients with the diagnosis of ST-elevation myocardial infarction (STEMI), those who had a non-cardiac diagnosis (such as pneumonia, pneumothorax) to explain chest pain, a history of trauma or malignancy, left

or right bundle branch block and those under 65 years of age were excluded from the study.

Protocol

The initial evaluation of the patients was performed by the resident fellows of emergency medicine department having at least two years of clinical experience. The vital signs of each patient were recorded. All patients underwent a 12-channel ECG within the first 10 minutes of admission. The patients who had a suspicion of ACS were taken to the observation room and re-evaluated by the emergency medicine specialist (EMS) in the observation room. The patient's medical history, cardiovascular risk factors, medications used, vital signs, ECGs, thorough medical anamnesis and data needed for the scoring systems were filled out in detail. At least two follow-up ECGs were recorded, and cardiac enzymes were measured at 3-hour intervals. Troponin I was used as the cardiac enzyme.

The times of entrance and discharge from the ED were noted together with the laboratory results, consultation information and whether the patients had undergone percutaneous coronary interventional procedures or not. The diagnosis and management of patients with non-ST elevation ACS was performed according to the AHA / ACC 2014 NSTEMI guidelines4 protocols. While the TIMI score was calculated at the bedside, the HEART and the GRACE scores were calculated after laboratory results were obtained. All patients were followed-up for MACE development (acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, and cardiovascular death) within 6 weeks of initial admission. The patients were called for questioning MACE 6 weeks after discharge.

Statistical analysis

The data of the study were analyzed using the SPSS version 21.0 (SPSS Inc. Chicago, USA) statistical software for Windows. By using the Flauhalt method, the expected sensitivity was assumed as 99%, and the minimum lower reliability limit was assumed as 95%, so that the required study sample was calculated as 181 subjects. The sociodemographic and clinical features of the patients were presented as mean ± standard deviation, median & interquartile range (IQR) and 95% confidence interval and percentages (%). The Student's T-test or Mann Whitney U test was used to compare the groups in terms of continuous variables, and the Chi-square test was used for discrete variables. The sensitivity, specificity, negative predictive values (NPV) and negative likelihood ratios (LR–) of the risk scores were calculated within the 95% confidence interval (CI).

Outcome Measurement

The primary outcome measurement was the presence of a fatal or non-fatal acute myocardial infarction and revascularization occurring within six weeks of admission to the ED.

RESULTS

A total of 191 patients were evaluated for enrollment during the study period. Three patients were excluded from the study due to the unavailability of their medical files and seven patients did not sign the informed consent form. The flow chart of the patients evaluated and analyzed to be included in the study has been presented in Figure 1.

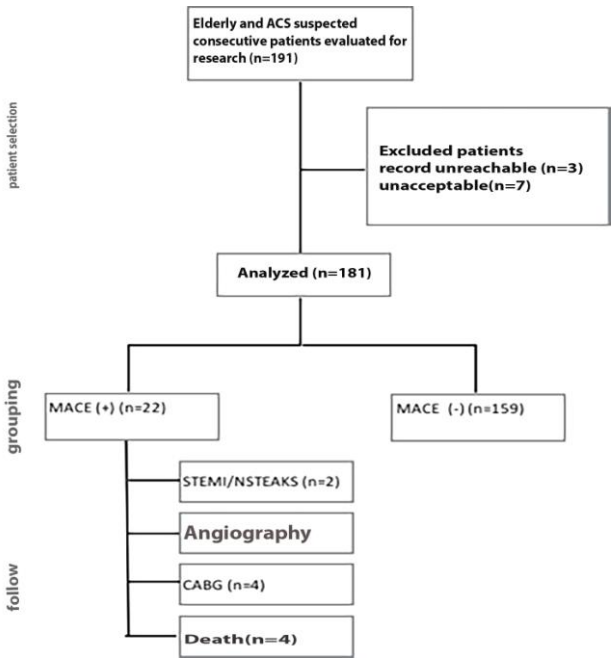

Figure 1. A flowchart of patients with and without MACE (Major Adverse Cardiac Event) during the 6-week follow-up period

Baseline Characteristics

The mean age of the patients in the study was 73.9 years (95% CI = 72.8-74.9 years). 112 (61.9%) of our patients were male. The initial demographic data, cardiac risk factors and vital findings on admission of the patients with and without MACE at the end of 6-weeks have been summarized in Table 1. The mean systolic blood pressures were lower in patients with MACE than in patients without (p = 0.036, mean difference = 13.3 (0.89-25.7). The other risk factors and vital signs were similar between the two groups.

Table 1. Demographic Characteristics

	All patients n=181	**MACE (+) n= 22**	**MACE (-) n= 159**	***p* value**
Characteristics				
Male gender, n (%)	112 (61.9)	16 (72.7)	96 (60.4)	0.351
Age, years, mean (95% CI)	73.9 (72.8-74.9)	72.6 (69.7 – 75.6)	74.1 (72.9-75.3)	0.385
Cardiac Risk Factors n, (%)				
ACS History	131 (72.4)	15 (68.2)	116 (73.0)	0.639
Smoking	86 (47.5)	11 (50)	75 (47.2)	0.803
Family History of CAD	84 (46.4)	11 (50)	73 (45.9)	0.719
Hypertension	151 (83.4)	20 (90.9)	131 (82.4)	0.539
Diabetes Mellitus	72 (39.8)	6 (27.3)	66 (41.5)	0.249
Hypercholestrolemia	71 (39.2)	10 (45.5)	61 (38.4)	0.523
Obesity (BMI>30kg/m^2)	1 (0.6)	0	1 (4.5)	-
Heart Failure	67 (37)	9 (40.9)	58 (36.5)	0.428
CKD	28 (15.5)	6 (27.3)	22 (13.8)	0.102
COPD	16 (8.8)	4 (18.2)	12 (7.5)	0.111
Vital Signs				
Heart rate, bpm, mean (±SD)	84.2 (20.7)	90.1 (26.4)	83.4 (19.7)	0.153
SPB, mmHg, mean (±SD)	138.9 (27.9)	127.3 (26.2)	140.6 (27.8)	0.036
Body temperature, °C mean (±SD)	36.3 (0.7)	36.1 (0.4)	36.3 (0.7)	0.100
SPO_2, %, mean (±SD)	93.8 (5.9)	94.7 (4.8)	93.8 (6.1)	0.639
Respiratory Rate, mean (±SD)	25.4 (5.6)	25.4 (5.6)	25.2 (5.6)	0.903

n: number, CI: Confidence Interval, ACS: Acute coronary syndrome, CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, SBP: Sistolic blood pressure, SD: Standart deviation, SPO2: Pulmonary oxygen saturation, MACE: Major Adverse Cardiac Event

The Primary Outcome

MACE was determined in 22 (12.2%) of the patients during 6 weeks of the follow-up period. While 4 (18.2%) of these patients died, 2 (9%) of them had STEMI. While PCI was performed on 12 (54.5%) patients, 4 (18.2%) patients underwent PCI after CABG. The mean HEART, TIMI and GRACE scores of the patients who developed the primary outcome have been summarized in Table 2.

There was no statistically significant difference between patients with and without MACE in terms of the mean HEART, GRACE and TIMI risk scores (Fig. 2).

Table 2. The mean HEART, TIMI, and GRACE scores of the patients with and without MACE

	All patients n=181	**MACE (+) n= 22**	**MACE (-) n= 159**	***p* value**	**mdf**	**95% CI**
HEART, mean (95% CI)	5.9 (5.6-6.1)	6.2 (5.4-6.9)	5.8 (5.5-6.1)	0.37	-0.37	-1.19 − 0.45
TIMI, mean (95% CI)	3.2 (3.1-3.4)	3.3 (2.8-3.9)	3.2 (3.0-3.4)	0.77	-0.09	-0.68 − 0.51
GRACE, mean (95% CI)	125.9 (121.9-129.9)	135.2 (122.7-147.8)	124.7 (120.5-128.9)	0.09	-10.55	- 22.5 – 1.65

MACE: Major Adverse Cardiac Event (Acute myocardial infarction, percutaneous coronary intervention, mortality, coronary artery bypass grafting), CI: Confidence interval, mdf: mean difference

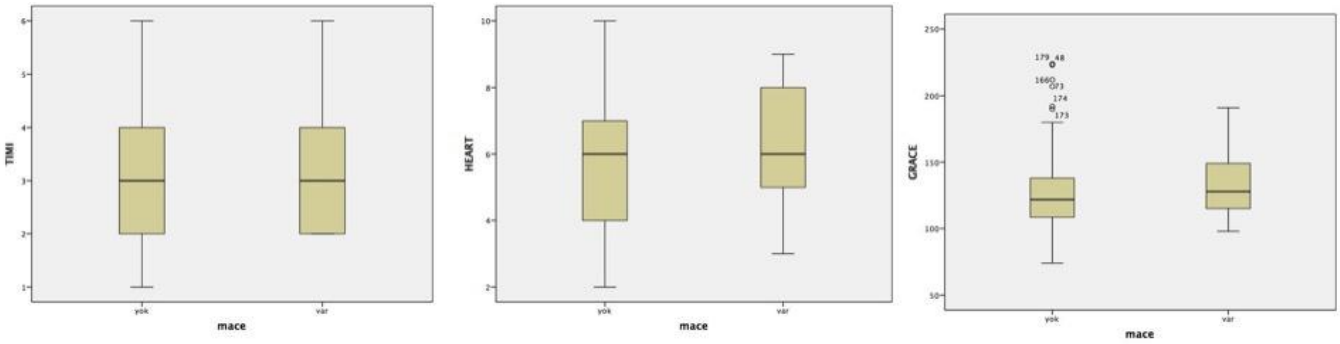

Figure 2. Comparison of HEART, GRACE and TIMI risk scores of MACE (+) and MACE (-) patients

Performance of Risk Scores

The ROC curve showing the MACE estimation of the HEART, TIMI and GRACE risk scores within six weeks has been displayed in Figure 3. The GRACE risk score was found to have the largest area under the curve (AUC = 0.603, 95% CI = 0.479-0.727). The area under the curve for the TIMI score was 0.505 (95% CI = 0.386-0.624), and 0.559 (95% CI = 0.435-0.684) for the HEART score.

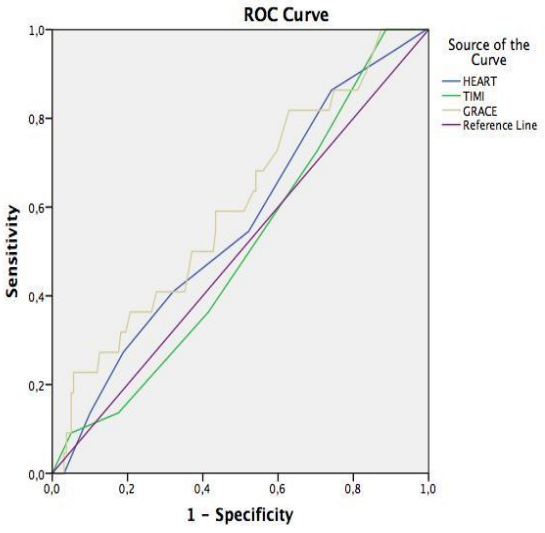

Figure 3. Receiver operating characteristic (ROC) curve showing the MACE estimation of HEART, TIMI and GRACE risk scores within 6 weeks AUC: Area Under Curve, for HEART (AUC=0.59, 95% CI=0.435-0.684), for TIMI (AUC=0.505, 95% CI=0.386 - 0.624), and for GRACE (AUC=0.603, 95% CI=0.479 - 0.727)

Table 3 shows the comparison of the HEART, TIMI and GRACE risk scores in terms of efficiency and reliability. When the 'low risk' scores are assumed to have missed the 5% of the patients who will develop MACE and have 95% sensitivity, MACE was observed in one (% 6.6) of 15 patients with a HEART score of ≤3 points, in 6 (11.3%) of 53 patients with a TIMI score of ≤2 points, and in 4 (8.7%) of 46 patients with a GRACE score <110 points. When we compared the performance of HEART, TIMI and GRACE risk scores in predicting MACE within 6 weeks following admission with chest pain, although all scoring systems had low performance compared to the general population, the HEART score was found to have the highest sensitivity and the highest negative predictive value in elderly patients who had presented with chest pain (95.5% and 93.3%, respectively).

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio values of HEART, TIMI and GRACE risk scores

	MACE n, (%)	Sensitivity %	Specificity %	PPV %	NPV %	LR +	LR -
HEART ≤ 3	1/15 (6.6)	95.5	8.8	12.7	93.3	1.05	0.5
TIMI ≤ 2	6/53 (11.3)	72.7	29.6	12.5	88.7	1.03	0.9
GRACE ≤ 110	4/46 (8.7)	81.8	26.4	13.3	91.3	1.11	0.7

PPV: Positive Predictive Value, NPV: Negative Predictive Value, +LR: Positive Likelihood Ratio, -LR: Negative Likelihood Ratio

When the troponin results were compared in MACE (+) and MACE (-) patients, which is an important diagnostic tool in the management of patients with acute coronary syndrome, there was no significant difference between the groups in terms of the initial troponin results. The median troponin value in the MACE (+) group was 0.014 (0.10) ng/ml, and it was 0.010 (0.05) ng/ml in the MACE (-) group (p = 0.683). However, in patients who were followed-up in the ED and in whom second troponin measurement was made, the median troponin value was 0.090 (1.6) ng/ml in the MACE (+) group, and it was 0.012 (0.13) ng/ml in the MACE (-) group (p = 0.016).

DISCUSSION

This study has compared the performances of the HEART, TIMI and GRACE risk scoring systems in MACE estimation in patients over 65 years of age. Although the HEART risk score had higher sensitivity and negative predictive value compared to other scoring systems in elderly patients presenting with chest pain, all three scoring systems were found to have lower performance in MACE prediction compared to the general population.

The risk classification systems to be used in the evaluation of patients presenting to the emergency department with chest pain is expected to have high sensitivity in predicting the development of MACE, as well as to identify low-risk patients and to reduce unnecessary follow-up and medical practices10. In a multinational validation study, MACE development was found to be 1.7% in patients with a HEART score of 0-3 points, and it was concluded that the HEART risk scoring system in identifying low-risk patients was useful and low risk patients could be safely discharged11. Similarly, in the three studies performed by Sakamoto6, Backus11, and Poldervaart12, the patients with low HEART score (0-3 points) developed MACE at a rate of 2% in the follow-up period.

In the study conducted by Sakamoto6 on 604 patients, the HEART score of ≤3 points had a sensitivity of 99%, a specificity of 24%, and an NPV of 98% in the 30-day MACE estimation. A TIMI risk score of ≤1 point had a sensitivity of 87%, a specificity of 37.5%, and an NPV of 83.9%. The sensitivity of having a GRACE score of less than 110 points was 60%, the specificity was 54.5%, and the NPV was 71%. According to our results, having a HEART score of ≤ 3 points was found to have the highest sensitivity and the highest negative predictive value in MACE estimation (95.5% and 93.3%, respectively). However, 6.6%

of the patients with a HEART score of ≤3 points developed MACE within six weeks of admission in our study population. This rate is higher than those reported in previous publications in the literature, which was probably due to primarily the fact that previous studies included patients from all age groups, but in our study only patients over 65 years of age were enrolled. Although our patients had cardiovascular risk factors similar to that of the general population, they may have had additional comorbidities, which may have led to the development of MACE due to their advanced age. In the light of all these results, we think that risk scoring systems used in predicting MACE development are limited in terms of decision making during safe discharge, because they have lower sensitivity in elderly patients compared to the general population. In two studies by Hess and Six, 12% and 12.9% of the patients who had presented to the emergency department with chest pain and discharged, had developed MACE at the end of the 30-days or 6-weeks of follow-up period respectively10, 13. Consistently, the mean HEART, TIMI and GRACE risk scores of MACE-positive patients were 6.74, 3.22, and 125.7, respectively, whereas MACE-negative subjects had 4.85, 2.34, and 108.4 points, respectively, and all three scores were statistically significantly higher in the MACE-positive group in Sakamoto's study. Similar to other publications in the literature, MACE developed in 12.2% of our patient population at the end of the 6-weeks of follow-up in our study. However, there was no statistically significant difference in the mean HEART, GRACE and TIMI risk scores between patients with and without MACE. Similarly, we believe that the main reason for this result was because our study group consisted of elderly patients, since the age variable is an independent predictive factor in the development of MACE and that patients had additional comorbidities.

In the study of Backus, patients with TIMI of <1 point had constituted 34% of the study population, and only 2.8% had developed MACE, while only 2.9% of the patients with a GRACE score of <60 points had developed MACE11. In the study of Sakamoto, MACE developed in 12 (33%) of 334 patients who were considered as 'low-risk' according to the GRACE score, and MACE developed in 14 (3.2%) of 439 patients with a low risk TIMI risk score6. In our study, as in the HEART score, the patients with low TIMI and GRACE risk scores were found to experience MACE at a higher rate than that in other studies in the literature. Besides, MACE was observed in 6 (%11.3) of 53 patients having a TIMI score of ≤2 points, and in 4 (8.7%) of 46 patients with a GRACE score of <110 points. As with the HEART score, the patients with low-risk TIMI and GRACE scores also experienced higher MACE rates in the older population according to studies evaluating the general population.

In a study comparing HEART, TIMI and GRACE scores, the area under the curve was 0.86 (95% CI = 0.84-0.88) in the HEART classification, 0.80 (95% CI = 0.78-0.83) in the TIMI score, and 0.73 (95% CI = 0.70-0.76) in the GRACE score, and the HEART score was found to be the strongest in predicting MACE development12. In another study, the GRACE and TIMI risk scores were compared and AUC was found to be 0.79 (95% CI = 0.74–0.83) for the TIMI score, and it was 0.83 (95% CI = 0.79I0.87) for the GRACE score; hence, the researchers concluded that GRACE score was superior in MACE estimation14. In our study, we determined the AUC as 0.603 (95% CI = 0.479-0.727) for the GRACE score, and it was a greater value than the other scoring systems. However, the AUC in all three scoring systems was found to be lower than in previous studies.

Limitations:

We included 3 scoring methods in our study, but there are other scoring systems used in the evaluation of chest pain. Perhaps another scoring method we did not consider in our study may be more favorable for elderly patients and provide more significant results. If the number of patients included in the study were higher, we could have obtained more statistically significant results. In addition, since the autopsy results were not clearly defined in patients who died and considered as MACE development, it is possible that these patients died due to reasons other than MACE.

Conclusion

In the evaluation of elderly patients who had presented to the emergency department with chest pain, the HEART, TIMI, and GRACE scores were found to have inadequate performance in MACE prediction. More reliable risk scoring systems are needed in the evaluation of such patients.

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