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Original Contribution

Inaccuracy of Thrombolysis in Myocardial Infarction and Global Registry in Acute Coronary Events scores in predicting outcome in ED patients with potential ischemic chest pain☆,☆☆

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ABSTRACT

Purpose: The Thrombolysis in Myocardial Infarction (TIMI) and the Global Registry in Acute Coronary Events (GRACE) scores were largely evaluated and validated in stratifying risk of cardiovascular events in patients with chest pain and acute coronary syndrome. Our objective was to compare these 2 scores in predicting outcome in emergency department (ED) patients with undifferentiated chest pain.

Materials and methods: This was a prospective cohort study including patients presenting to 4 EDs with chest pain with nondiagnostic or normal ECG. For all included patients (n = 3125), TIMI and GRACE scores were calculated. Follow-up was conducted at 30-day and 1-year post-ED index admission to identify major adverse events. Main outcome included all cause mortality, acute coronary syndrome, and coronary non-ED planned revascularization. Prognostic performance of the scores was assessed by the receiver operating characteristic (ROC) curves.

Results: We reported 285 (9.1%) major adverse events at 30 days and 436 (13.9%) at 1 year. In patients with low TIMI (≤2) and GRACE (<109) scores, a significant proportion had major adverse events at 30 days (5% and 7.5%, respectively) and 1 year (7.9% and 12.9%, respectively). Area under ROC curve at 30 days was 0.66 (95% confidence interval [CI], 0.62-0.71) vs 0.57 (95% CI, 0.53-0.62), respectively, for TIMI and GRACE scores. At 1 year, the area under ROC was 0.67 (95% CI, 0.62-0.71) and 0.65 (95% CI, 0.60-0.70), respectively, for TIMI and GRACE scores.

Conclusions: The TIMI and GRACE scores are not valid in short- and long-term risk stratification in our chest pain patients.

1. Introduction

Chest pain is one of the most common diagnostic and prognostic challenges in patients presenting to emergency department (ED). To start the appropriate treatment and decide early discharge of patients with low risk, accurate and rapid stratification of patients with chest pain is required. Many scoring models have been developed for that purpose, but most of them have been tested in patients with confirmed acute coronary syndrome (ACS) [1-6]. Yet, risk stratification models need to be used in patients with suspected rather than in established ACS. In chest pain population, the 2 most commonly validated scores are the Thrombolysis In Myocardial Infarction (TIMI) and the Global Registry in Acute Coronary Events (GRACE) scores. Both scores were widely evaluated and validated in several independent ED populations, but, apart from some exceptions [7,8], these validations were not performed in populations different from those included in the original studies [9-15]. Overall, evidence suggest that, in patients with defined ACS as in those with suspected chest pain, the TIMI and GRACE scores had good accuracy in stratifying risk with a slight superiority of the GRACE score [6,9]. Only few studies found that GRACE and TIMI scores are of little prognostic value [11,16,17]. Accordingly, estimation of the prognostic accuracy of the 2 scores derived from different practice settings is needed before their use in a particular clinical setting.

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Our objectives in this study are to evaluate and compare the 30-day and 1-year prognostic performance of the TIMI and GRACE scores in Tunisian patients with suspected ACS.

2. Patients and methods

2.1. Participants

This is a prospective cohort study of patients presenting with acute chest pain at ED from 4 Tunisian hospitals: Fattouma Bourguiba University Hospital, Monastir; Sahloul University Hospital, Sousse; Farhat Hached University Hospital, Sousse; and Tahar Sfar University Hospital, Mahdia. Patients were screened and included from June 2009 to June 2012.All the participating hospitals are tertiary care centers receiving approximately between 70 000 and 110 000 of ED visits each year; 3 among these EDs used an observation unit. Patients were enrolled into the study if they were an adult aged older than 30 years who is presenting with nontraumatic acute chest pain as primary complaint and who had a normal or nondiagnostic electrocardiogram (ECG). Patients were excluded if they had an obvious noncardiac cause, greater than 1-mm ST deviation or greater than 3-mm T-wave inversion, admission to the ED more than 12 hours after their most significant episodes of chest pain, and if they did not consent to be included in this study or if they were lost to follow-up. This study was approved by the ethical committee of each participating center.

After obtaining written informed consent in each patient, study investigators prospectively collected data about demographics, cardiovascular risk factors, and clinical findings using uniform data collection work sheet. The etiologic approach included serial ECGs; cardiac biomarkers; and, as needed, exercise testing or coronary computed tomography scan angiography. The diagnosis of ACS was established by an ED senior physician and a cardiologist at the time of ED presentation. Any discrepancy is clarified by one of the investigators and resolved by consensus. The TIMI and GRACE risk scores were separately calculated to insure blinding of data collection.

These scores are not used routinely at the participating centers for ED risk stratification. In patients without a troponin result, the value was assumed to be negative in TIMI score calculation. For GRACE score calculation, a score of zero was assigned if creatinine was not obtained to most closely reflect clinical practice. The investigators reviewed 10% of the case report forms randomly selected for quality assessment of data ($\kappa = 0.96$).

2.2. Study outcomes

Patients with an established diagnosis of ACS were admitted to the coronary care unit, whereas the others were admitted to the hospital ward or discharged from the ED according to the emergency physician decision. A follow-up study was performed at 30-day and 1-year post-ED index admission by telephone contact and reviewing hospital records. Relevant clinical outcomes included death from any cause, ACS, or revascularization procedure not arranged from the ED.

2.3. Statistical analysis

All continuous data are presented as either the median with the interquartile range or the mean with SD, according to the distribution of the data. The categorical data are presented as the percentage frequency of occurrence. The discriminatory abilities of the 2 scores for 30-day and 1-year cardiovascular events were measured by C statistics. The areas under the receiver operating characteristic curve for the 2 scores were compared by methods of Hanley and McNeil. A P value $<.05$ was considered a level of statistical significance. Data were analyzed using SPSS version 20 (SPSS Inc, Chicago, IL).

3. Results

Overall, 3415 patients were enrolled in this study of whom 290 (8.5%) patients were lost to follow-up. From the remaining included group (n = 3125), data were available in 2817 cases for complete GRACE score and 2940 for complete TIMI score. Baseline characteristics of the study population are shown in Table 1. Mean age was 57.7 years with male predominance (58%). History of coronary artery disease and smoking were the most prevalent cardiovascular risk factors (20.5% and 16.5%, respectively). Median time from pain onset to ED presentation was 145 minutes (95% confidence interval [CI], 80-210). Baseline ECG was normal in most cases (75%). There were 2052 (65.7%) patients discharged home from the ED, 692 (22.1%) admitted to coronary care unit, and 381 (12.2%) admitted to the ward. Fig. 1 shows patients distribution according to the TIMI and GRACE scores. Most of our patients had a TIMI score less than or equal to 2 (67%) and GRACE score less than or equal to 109 (75%). Within 30 days after ED admission, cardiovascular events were reported in 285 (9.1%) patients. During this period, 33 patients died, and 244 patients were diagnosed as ACS, and 8 underwent coronary revascularization. Within 1 year, cardiovascular events were observed in 436 (13.9%) patients. Of these, 41 patients died, and 370 patients were diagnosed as ACS, and 25 underwent urgent revascularization. The distribution of major cardiovascular events in the different risk groups for each risk score at 30 days and 1 year is shown in Fig. 2. The proportion of major events increases when the 2 scores increased. The ability of the TIMI and GRACE scores to predict outcome in the study cohort is shown in Fig. 3; the area under receiver operating characteristic curve was 0.66 (95% CI, 0.62-0.71) vs 0.57 (95% CI, 0.53-0.62) at 30 days and 0.67 (95% CI, 0.62-0.71) vs 0.65 (95% CI, 0.60-0.70), at 1 year, respectively, for TIMI and GRACE scores. Table 2 shows sensitivity, specificity, and positive and negative predictive values of both scores using the cutoff values usually accepted. A significant proportion of patients with low TIMI (≤ 2) and GRACE (<109) risk scores had major events at 30 days (5% and 7.5%, respectively) and after 1 year (7.9% and 12.9%, respectively).

4. Discussion

In this study, we compared the TIMI and GRACE scores in predicting short- and long-term risk of major cardiovascular events in a large

Table 1
Baseline characteristics of the population

Variables	Patients
	n = 3125
Age, mean (SD)	57.7 (13.7)
Sex ratio (M/F)	1.4
Medical history n (%)	
Hypertension	349 (11.2)
Diabetes mellitus	132 (4.2)
Coronary artery disease	640 (20.5)
Heart failure	69 (2.2)
Smoking	517 (16.5)
Data at chest pain unit admission	
Heart rate, mean, beats per minute	81 (16)
Systolic blood pressure, mm Hg (SD)	140 (27)
Diastolic blood pressure, mm Hg (SD)	81.2 (39)
Troponin, pg/mL, median [IQR][a]	0.11 [0.07-0.19]
Normal ECG n (%)	2351 (75)
Patients issue n (%)	
Discharged home from the ED[b]	2052 (65.7)
Coronary care unit admission	692 (22.1)
Admitted to the ward	381 (12.2)
TIMI risk score, mean (SD)	1.86 (1)
GRACE risk score, mean (SD)[c]	88.3 (32)

Abbreviations: M, male; F, female.
[a] Troponin result was not available in 185 patients.
[b] Creatinine result was not available in 308 patients.
[c] Mean length of stay in the ED was 4.5 (1.1) hours.

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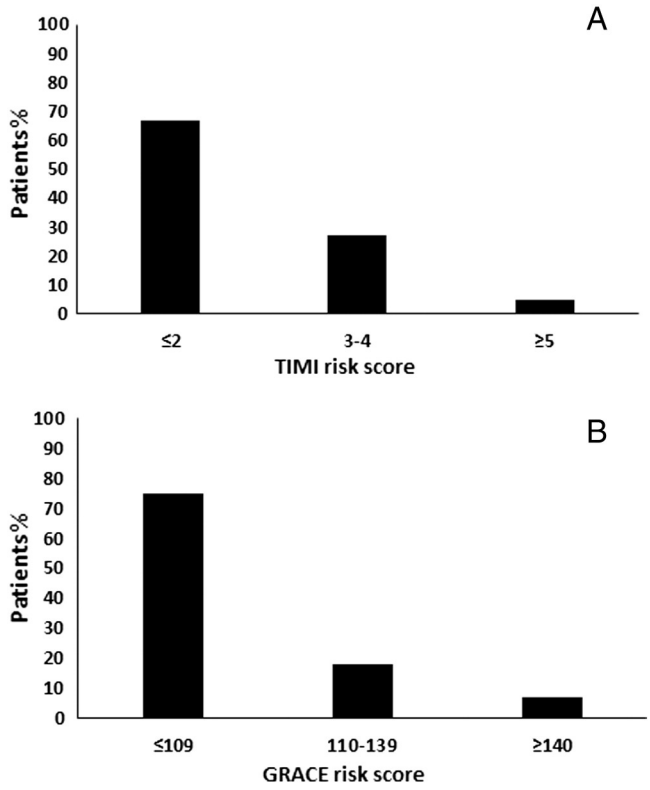

Fig. 1. Patients distribution according to TIMI (A) and GRACE (B) risk scores.

contemporary cohort of Tunisian patients admitted to the ED for suspected ACS. Our results demonstrated that both scores had low prognostic value and may not serve as an effective risk stratification tool for ED patients with chest pain.

It is well known that patients admitted to the ED with chest pain are at risk for several life-threatening conditions in particular, ACS. In these patients, emergency physicians need to make early and accurate diagnosis of ACS and identify those with an acceptable low risk of cardiovascular events to be suitable for discharge from the ED. Although many prognostic stratification models have been developed in this issue, the

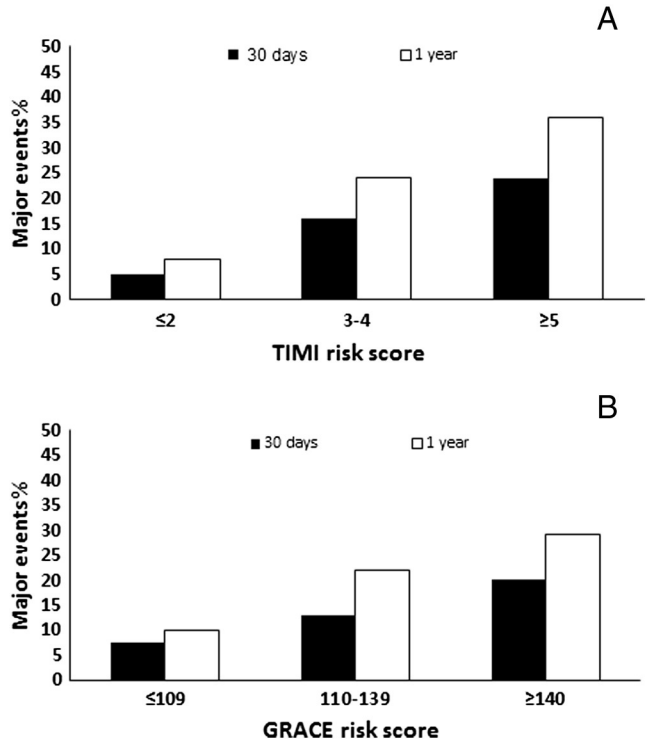

Fig. 2. Rate of major events according to TIMI (A) and GRACE (B) risk scores.

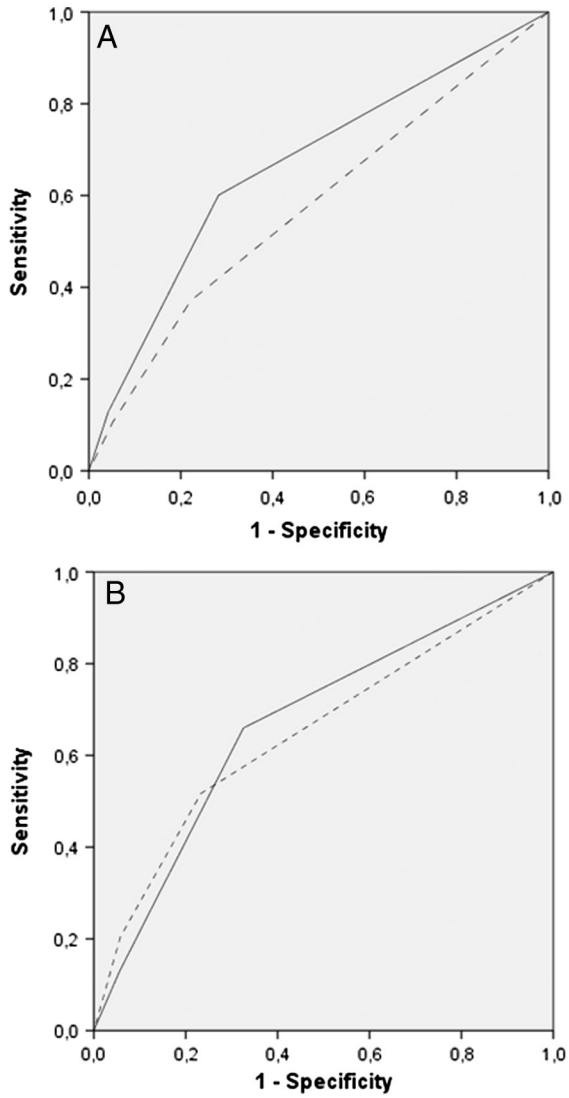

Fig. 3. Receiver operating characteristic curves for TIMI (—) and GRACE (—) risk scores in predicting major events at 30 days (A) and 1 year (B). Area under curve for TIMI score, 0.66 and 0.67, respectively, at 30 days and 1 year. Area under curve for GRACE score, 0.57 and 0.65, respectively, at 30 days and 1 year.

Table 2
Prognostic performance of TIMI and GRACE risk scores using their currently used cutoffs[a]

	At 30 d	At 1 y
Sensitivity, % [95% CI]		
TIMI risk score	60 [54-66]	65 [58-72]
GRACE risk score	37 [30-44]	52 [44-60]
Specificity, % [95% CI]		
TIMI risk score	73 [71-75]	69 [67-71]
GRACE risk score	78 [76-80]	77 [75-79]
Negative predictive value, % [95% CI]		
TIMI risk score	96 [95-97]	97 [96-98]
GRACE risk score	93 [92-94]	95 [94-96]
Positive predictive value, % [95% CI]		
TIMI risk score	14 [12-16]	12 [10-14]
GRACE risk score	14 [11-17]	15 [12-18]

[a] The cutoff is 3 for TIMI score and 109 for GRACE score.

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best one to be used is still unknown. In addition, validation of available scores was rarely performed in populations with different ethnic backgrounds, and, therefore, none is universally accepted [7]. To date, there are only limited data on the comparative accuracy of these risk scores despite substantial differences in their complexity, derivation cohorts, and predicted end points [18,19]. Among available scores, the TIMI and GRACE scores were the most extensively externally validated, but their comparative performance has not been studied in a Tunisian population. This is the first study comparing TIMI and GRACE scores in a large sample of Tunisian patients with acute chest pain. Our study indicates that these scores should not be used to guide clinical decision making in our population. The area under curve for both scores showed that neither score accurately discriminated between those who will and who will not have major adverse cardiovascular event. At any cut point, both scores were insufficiently sensitive to allow safe exclusion of ACS based upon the initial value. Our findings challenged the results of many previous studies conducted in United States, Europe, and China showing that TIMI and GRACE scores accurately predict short- and long-term prognosis [7,9-15]. Many of these studies demonstrated that both scores effectively stratified the cardiovascular risk of patients with chest pain but did not perform a comparison between them. In the few comparison studies available, GRACE score was often shown slightly better [16-19]. In 1 study, Lyon et al [9] showed that the TIMI and GRACE risk scores had similar discrimination value for adverse outcomes in patients with chest pain. However, most previous findings concluded that the prognostic predictive value of both scores was not enough to support clinical decision making, as more than 3% of low risk patients had major cardiovascular events, a risk that is unacceptable to clinicians [20-22]. Goodacre et al [17] found that the GRACE and TIMI scores are little better than age alone as predictors of MACE adverse events in patients with suspected ACS. These controversial results may reflect clinical characteristics of the different populations included but may also be explained by methodological differences. In fact, many studies related to TIMI and GRACE score validation consist of data derived from randomized clinical trials, whereas others came from observational registries, which may undermine the reproducibility of their results [23]. The difference in management strategies and medical facilities could also explain our findings.

5. Limitation

There are a number of limitations to the present study. First, consecutive patients were not enrolled in this study with regard to the difficulties in including all patients with chest pain in the setting of ED. Second, the absence of a perfect criterion standard for ACS could limit the validity of our study. However, diagnoses on admission and at follow-up in our study were independently adjudicated by an emergency physician and a cardiologist in adherence to the current standardized guidelines. Third, the fact that missing variables at ED admission were considered normal would have underestimated the discriminatory accuracy of the risk score. However, complete case analysis was available for up to 90% of our patients when calculating GRACE score and 94% for TIMI score. In addition, in some similar studies, it was demonstrated that accuracy of risk scores was not significantly different in both complete and incomplete data set groups [17]. Fourth, at 1 year after index admission, only 9.5% of patients were lost to follow-up. Despite their similar risk scores on presentation compared with patients with follow-up data, we could not rule out any potential bias. Finally, whether our results could be extrapolated to patients with an established diagnosis of ACS is a question that requires a specific study.

To summarize, this study did not validate the TIMI and GRACE scores for short- and long-term risk stratification in a Tunisian ED population with chest pain. We therefore do not recommend their use in our clinical practice. There are other potentially useful risk scores available that perhaps need to be assessed in the future [2,14,24].

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