Correlation of Risk Scores with Coronary Anatomy in Non-ST-elevation Acute Coronary Syndrome

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Abstract

Background: The literature lacks studies regarding the correlation between risk scores and coronary anatomy in acute coronary syndrome (ACS).

Objective: Correlate risk scores with the severity of the coronary lesion in ACS with non-ST elevation.

Methods: A total of 582 patients were analyzed between July 2004 and October 2006. The correlation between TIMI risk score and GRACE (hospital and six months) scores was performed for patients with coronary lesion ≥ 50%, using Spearman's non-parametric method. Multiple regression logistics was used to determine the predictive ability of the scores to discriminate who will have a coronary lesion ≥ 50%.

Results: Most subjects were male (319 [54.8%]), mean age of 59.9 (± 10.6) years. A positive correlation was observed between risk scores and coronary lesion ≥ 50% (TIMI r = 0.363 [p < 0.0001]; hospital GRACE r = 0.255 [p < 0.0001]; GRACE at six months r = 0.209 [p < 0.0001]). The area under the ROC curve for each score to discriminate who will have a coronary lesion ≥ 50% was: TIMI = 0.704 [CI 95% 0.656-0.752; p <0.0001]; hospital GRACE = 0.623 [CI 95% 0.573-0.673; p < 0.0001]; GRACE at six months= 0.562 [CI 95% 0.510-0.613; p = 0.0255]. Comparing the areas under the ROC curve, it was found: TIMI versus hospital GRACE: p = 0.01; TIMI versus GRACE at six months: p < 0.0001; hospital GRACE versus GRACE at six months: p = 0.0461.

Conclusion: Risk scores correlate with the severity of coronary lesions, and the TIMI risk score showed the best predictive ability (Arq Bras Cardiol. 2013;100(6):511-517).

Keywords: Risk Factors; Coronary Vessels / anatomy & histology; Acute Coronary Syndrome; Prognosis.

Introduction

Ischemic heart disease is a leading cause of death worldwide. According to data from the *Heart Disease and Stroke Statistics*[1] approximately 2,300 North Americans die of cardiovascular disease each day, with acute coronary syndrome (ACS) being responsible for the largest number.

Patients presenting with non-ST elevation ACS (acute myocardial infarction non-ST-elevation or unstable angina) are at risk for adverse events such as death or recurrent infarction. The risk scores were created and are recommended by national[2] and international[3] guidelines to identify patients with a higher probability for the occurrence of adverse events, with a recommendation for more intensive treatment and early coronary angiography in this population.

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The TIMI[4] risk score has proven its validity in predicting death and ischemic events in patients with non-ST elevation ACS. It is comprised of seven independent variables related to the occurrence of death, (re)infarction or urgent myocardial revascularization (MR) due to recurrent ischemia within 14 days from its calculation, with the advantage of being easily calculable and reproducible in the real world.

The GRACE[5,6] (Global Registry of Acute Coronary Events) risk scores, which were developed based on the GRACE registry database, aim to provide a simple and applicable risk score for all forms of ACS (with or without ST elevation). The clinical outcomes were all-cause mortality in the hospital or within 180 days, respectively, for the hospital GRACE risk score and GRACE risk score for six months.

Despite good performance in discriminating which patients are most likely to experience an adverse event, the literature lacks studies that demonstrate the correlation between the scores and the magnitude of coronary lesions found by coronary angiography.

The objective of this research is to evaluate the correlation between TIMI risk score, hospital GRACE score and GRACE score at six months with the severity of coronary lesions found by coronary angiography during hospitalization in patients with non-ST elevation ACS.

Methods

Study Population

A prospective analysis of 582 consecutive patients with the clinical diagnosis of non-ST elevation ACS admitted from July 1, 2004 to October 31, 2006 was performed; the patients had undergone coronary angiography during hospitalization, after presenting to the emergency room of a tertiary cardiology center. Patients were eligible if they were age 18 years or older and had symptoms consistent with acute coronary ischemia within the last 48 hours. We excluded those with unstable secondary angina, those with confounding electrocardiography (ECG) changes on admission (pacemaker rhythm, atrial fibrillation, and bundle branch blocks), patients with suspected evolving infarction or those who had had previous coronary artery bypass surgery. During hospitalization, patients were followed up by medical visits in the emergency room, on the coronary care unit or on the ward and, after being discharged, they were contacted within 14 and 180 days by telephone to verify the presence of any specific outcomes pertinent to each score. The TIMI risk score and GRACE (hospital and six months) scores were applied to the population to determine their risk of adverse events.

The local research ethics committee approved the study protocol, and all patients signed an informed consent form.

Coronary Angiography

To analyze the correlation between risk scores and coronary anatomy, lesions were considered if ≥ 50% in the left main coronary artery, anterior descending coronary artery (or its diagonal branches), circumflex artery (or in its marginal branches) and right coronary artery.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows version 13.0 (SPSS Institute, Chicago, Illinois).

Continuous variables are reported as mean ± standard deviations and categorical variables as simple or relative frequencies.

To evaluate the correlation between the severity of coronary lesions and TIMI risk score, GRACE hospital and 6 months scores, we used the Spearman nonparametric method[7].

The predictive ability of risk scores to discriminate who will have a coronary lesion ≥ 50% was determined initially by univariate analysis using the nonparametric Mann-Whitney test[7]. Following the identification of significant differences in scores between the groups with and without coronary lesion ≥ 50%, the predictive power of the scores was evaluated using the C statistic (area under the ROC curve)[8]. Subsequently, the C statistic of the risk scores were compared using the formula $z = \frac{(ASC_{escore1} - ASC_{escore2})}{\sqrt{EP_1^2 - EP_2^2 - 2rEP_1EP_2}}$

where *r* is the correlation coefficient between the areas[9].

Results

Exploratory data analysis

One thousand and twenty seven (1,027) patients were admitted with non-ST elevation ACS in the study period. Of these, 734 underwent coronary angiography, excluding from analysis those with previous surgical MR. Therefore, 582 patients were included in the study population. The data in Table 1 includes the baseline characteristics of the study population.

There were 319 men (54.8%) and the mean age was 59.8 years (± 10.6). The most frequent risk factor for coronary arterial disease was systemic arterial hypertension, followed by dyslipidemia. Upon admission, 179 patients (30.8%) had non-ST elevation acute myocardial infarction, 383 patients (65.8%) had unstable angina class III B and 20 patients (3.4%) had unstable angina class III C[10].

The patients were medicated with beta-blockers (92.4%), acetylsalicylic acid (98.1%), intravenous nitroglycerin (94.3%), antithrombins (89.8%), thienopyridines (90.5%), angiotensin converting enzyme inhibitors (86.4%) and statins (93.5%). Percutaneous coronary intervention (PCI) was performed in 199 patients (34.2%) and surgical MR in 104 patients (17.9%). The procedure for myocardial revascularization (surgery or PCI) was performed during the initial hospitalization in 263 patients (45.2%).

During hospitalization, 12 patients died (2.1%), which corresponded to the hospital GRACE risk score, 54 (9.3%) experienced the compound event of the TIMI risk score within 14 days (death, [re]infarction or urgent MR due to recurrent ischemia) and 24 (4.1%) died within six months, corresponding to the GRACE risk score event within six months.

For each patient, TIMI risk score, hospital GRACE risk score and GRACE risk score for six months was calculated. Table 2 shows the absolute and relative frequencies of the main findings of coronary angiography in 571 patients who had complete data.

A positive correlation was observed between the risk scores and coronary lesions ≥ 50% (TIMI risk score r = 0.363 [p <0.0001]; hospital GRACE score r = 0.255 [p <0.0001]; and GRACE score in six months r = 0.209 [p < 0.0001]).

When comparing the mean score of each risk score with the presence or absence of coronary lesion, it is observed that in all risk stratification models the mean score was significantly higher in patients with at least one coronary lesion ≥ 50% (Table 3).

In multiple logistic regression analysis, represented by the C statistic (area under the *ROC* curve), the predictive ability of risk scores to discriminate who will have a coronary lesion ≥ 50% (C statistic: TIMI risk score = 0.704, confidence interval [CI] 95% from 0.656 to 0.752,p < 0.0001; hospital GRACE score = 0.623, CI 95% 0.573 to 0.673, p < 0.0001; GRACE score in six months = 0.562, CI 95% 0.510 – 0.613, p = 0.0255) was determined - (Chart 1).

Comparing the areas under the ROC curve, we have: TIMI versus hospital GRACE score: p = 0.0111; TIMI versus GRACE score in six months: p < 0, 0001; hospital GRACE score versus GRACE score in six months: p = 0.0461.

Table 1 - Baseline characteristics of the study population

Characteristics	Study population (n = 582)
Demographic and Clinical	
Age in years (mean ± SD)	59.8 (± 10.6)
Male, n (%)	319 (54.8)
Typical pain, n (%)	569 (97.8)
Smoker, n (%)	143 (24.6)
Diabetes Mellitus, n (%)	174 (29.9)
Hypertension, n (%)	449 (77.1)
Dyslipidemia, n (%)	345 (59.3)
Family history of premature coronary arterial disease, n (%)	216 (37.1)
Previous acute coronary syndrome (unstable angina and/or infarction), n (%)	298 (51.2)
Peripheral arterial disease, n (%)	29 (5.0)
Previous cerebral vascular accident, n (%)	30 (5.2)
Previous coronary arterial disease ≥ 50%, n (%)	228 (39.2)
Previous procedures of myocardial revascularization (by surgery and/or angioplasty), n (%)	164 (28.1)
Previous Medications	
Beta-blocker, n (%)	313 (53.8)
Aspirin, n (%)	389 (66.8)
Statin, n (%)	217 (37.3)
angiotensin converting enzyme inhibitor, n (%)	321 (55.2)
Physical Examination	
Heart rate (bpm) (mean ± SD)	75.2 (± 13.3)
Systolic arterial pressure (mmHg) (mean ± SD)	141.00 (± 26.9)
Diastolic arterial pressure (mmHg) (mean ± SD)	86.4 (± 15.02)
Electrocardiography	
Depression of ST segment ≥ 0.5 mm in at least one derivation, except for *aVR*, n (%)	145 (24.9)
Laboratory	
Hematocrit (%) (mean ± SD)	41.0 (±4.5)
Hemoglobin (g/dl) (mean ± SD)	14.0 (±1.5)
Glucose (mg/dl) (mean ± SD)	123.8 (±63.62)
Leukocytes ($\times 10^3/mm^3$) (mean ± SD)	8.12 (± 2.75)
Creatinine (mg/dl) (mean ± SD)	1.08 (± 0.48)
Elevation cardiac troponin I, n (%)	193 (33.2)

SD: standard deviation.

Discussion

Due to the heterogeneous nature of the population of patients with non-ST elevation ACS, there is wide variation in terms of risk for the occurrence of death or recurrent ischemic events[4,11-15]. From the deepest knowledge of the physiopathology of this syndrome, one moves toward refinement and, therefore, better performance in prognostic evaluation. To perform risk stratification, one has current independent prognostic variables and models of risk stratification. The main focus of this strategy is to evaluate the probability of occurrence of adverse events, particularly death or (re)infarction, analyzing data from the clinical history, physical examination, ECG and markers of myocardial necrosis.

In determining clinical outcomes, the non-uniformity among the currently available risk scores is considered an important factor, since for some models mortality from all causes is analyzed[5,6] while others include death, myocardial infarction ([re]infarction) or urgent MR due to recurrent ischemia[4].

The importance of risk stratification becomes evident in the initial evaluation of the patient in the emergency ward, both for discharging patients safely and for immediate admission of those who are at high risk and require immediate medical care. Among medical strategies, one must choose between the incorporation of more intensive measures, such as the administration of drugs that carry a higher risk of bleeding, or early invasive strategy.

Table 2 - Results of coronary angiography of 571 patients with complete data

Description	Number of Patients (%)
Left main coronary artery	21 (3.7)
Impairment of AD only*	72 (12.6)
Impairment of CX only*	13 (2.3)
Impairment of RC only*	44 (7.7)
Two-arterial*	150 (26.3)
Three-arterial*	88 (15.4)
Stent lesion	34 (6.0)
Thrombus	24 (4.2)
Calcification	101 (17.7)
Ulceration	18 (3.2)
Intracoronary collateral circulation	71(12.4)
Intercoronary collateral circulation	128 (22.4)
Ejection fraction (mean ± standard deviation)†	57.6 (13.8)
Access right femoral artery	568 (99.5)
Access right radial artery	3 (0.5)

**There were considered simple and relative frequencies of the lesions ≥ 50% in larger coronary artery or its main branches. The ejection fraction could be quantified in 519 patients (90.9%). AD: Anterior descending; CX: circumflex; RC: right coronary.*

Table 3 - Comparison of the mean value of each risk score and the presence of at least one coronary lesion ≥ 50%

Risk Score	Absence of Coronary lesion ≥ 50%	Presence of at least one Coronary lesion ≥ 50%	p
TIMI (mean ± SD)	2.48 (±1.22)	3.47 (±1.37)	< 0.0001
Hospital GRACE (mean ± SD)	92.32 (± 23.25)	105.68 (± 28.10)	< 0.0001
GRACE within 6 months (mean ± SD)	87.83 (± 21.93)	93.36 (± 26.50)	0.0255

There were considered the lesions ≥ 50% in larger coronary artery or in their main branches. SD: standard deviation.

Coronary angiography in patients at highest risk objectively determines those who are likely to have MR procedures (PCI or surgery). Nevertheless, risk stratification, using independent variables or models of risk stratification, does not have the ability to assess the severity of coronary anatomy. To that end, little has been published in the literature regarding the correlation between risk scores and the extent or severity of coronary artery disease.

Many independent variables with poor prognosis are correlated with severe coronary arterial obstruction. Among the clinical variables, elderly patients with coronary artery disease have more severe lesions compared to younger patients and experience more frequent complications [16]. Diabetes mellitus is considered to be the highest risk factor for cardiovascular morbidity and mortality[17], leading to a three to five-fold higher chance of developing coronary artery disease[18].

Likewise, the type of previous MR procedure is a marker of the severity of coronary artery disease. In patients undergoing previous PCI, the underlying coronary artery disease is often less marked. Those with previous MR surgery often have left ventricular dysfunction or multivessel disease. Consequently, patients with PCI have a more favorable prognosis[19].

Suspected ACS, with marked symmetric inversion of T-waves on the precordial leads, suggests acute ischemia, particularly due to critical nature of stenosis of the anterior descending coronary artery[20].

Additionally, lesions involving a larger number of vessels are present in patients with positive troponin tests compared to those with negative troponin tests[21].

It is believed that estimating the possible severity of coronary lesions before performing coronary angiography may contribute to more satisfactory therapeutic decisions[22]. For instance, in those with a high probability of having coronary lesions likely to require MR surgery, one may choose not to administer thienopyridines before performing cinecoronariography.

Garcia et al[22] evaluated the correlation between TIMI risk score and the severity of coronary artery disease in 688 patients with non-ST elevation ACS undergoing coronary angiography. They excluded patients who had previous MR surgery or recent PCI. The authors concluded that for every increase in the risk category, there is an increase not only in the percentage of adverse events, but also the likelihood that patients will have

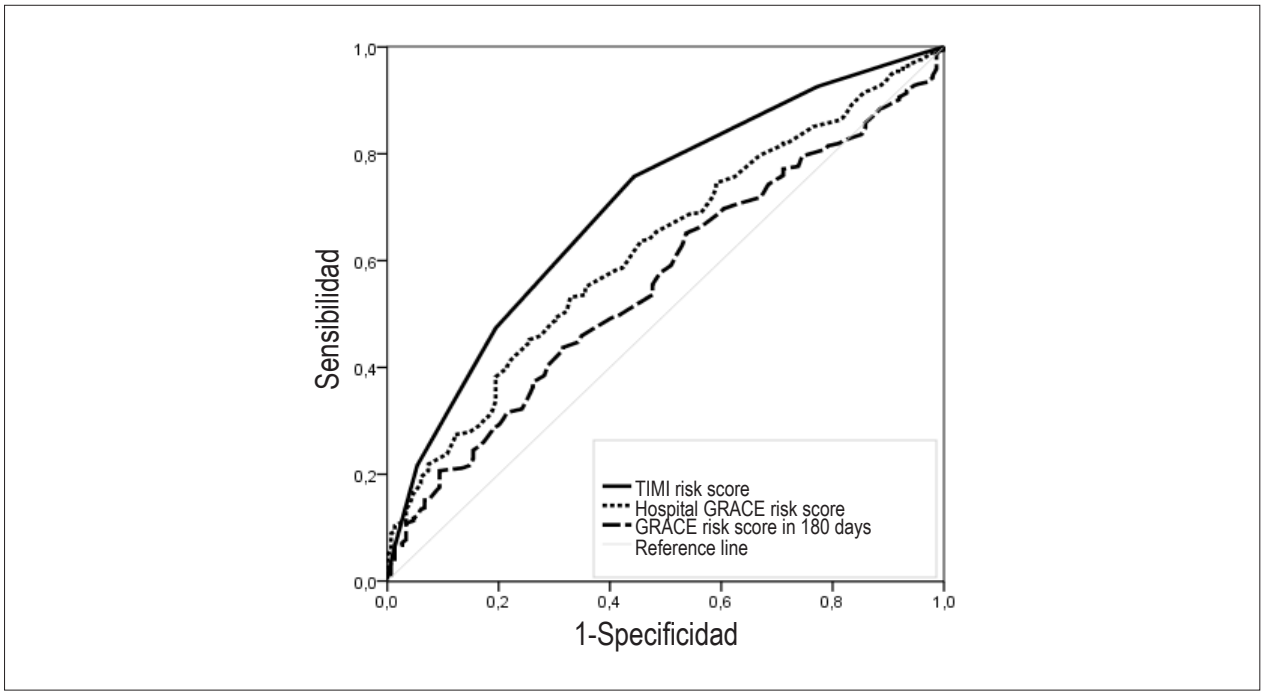

Chart 1 - *Area under the ROC curve of the TIMI, hospital GRACE and GRACE in six months risk scores to discriminate who will have a coronary lesion ≥ 50%.*

disease involving three vessels or injury to the left main coronary artery. Unlike our work, the data from this study were limited by the retrospective analysis, which evaluated only the TIMI risk score.

Likewise, to explore the physiopathological basis of TIMI risk score variables, Mega et al[23] analyzed the relationship between this model of risk stratification and coronary anatomy in 1,491 patients diagnosed with non-ST elevation ACS, who were included in the clinical trial PRISM-PLUS[24]. Patients with risk scores 5 - 7 (high risk) frequently presented with serious stenosis and multiarterial disease, compared to those with risk scores of 0 to 2 (low risk). Likelihood of injury in the left main coronary artery, presence of intracoronary thrombus and reduced flow in the culprit artery were progressively higher with increasing risk scores. Previous history of coronary artery disease, advanced age, and ST-segment deviation were variables of the TIMI risk score that showed the most significant association with the severity of coronary artery lesions. Moreover, elevated biomarkers of myocardial necrosis, ST-segment deviation and previous use of aspirin were significantly correlated with intracoronary thrombus and/or reduction of the blood flow in the culprit coronary artery. The data from this study partly explain the particular benefit of antithrombotics in patients at highest risk.

Recently, Ben Salem et al[25] evaluated the extent and severity of coronary artery lesions in a retrospective analysis of 239 patients with non-ST elevation ACS. The authors classified patients into TIMI risk scores of low, intermediate and high risk and compared the angiographic findings among the three groups. It was observed that patients with risk scores of 0-2 had significantly more normal coronary angiography or insignificant coronary artery disease, compared with a score of 5-7 (36.3% *versus* 13%, $p < 0.001$). On the other hand, disease involving three vessels or lesions of the left main coronary artery were found more frequently among the high risk patients. The authors concluded that higher TIMI risk scores correlated with more severe arterial disease.

In our study we evaluated a population of 582 patients with non-ST elevation ACS, with characteristics very representative of the real world. Aiming to analyze the correlation between the risk scores currently recommended by the guidelines and the presence of more severe coronary artery lesions, this is the first study that assessed three risk stratification models simultaneously in the same population.

In the three risk scores analyzed, the mean score was significantly higher in patients with more severe coronary artery lesions, thereby validating the ability of the models to discriminate those with more important coronary artery disease. With this result, we decided to perform a multiple logistic regression analysis to assess the independent ability of each risk score to predict the presence or absence of coronary lesions ≥ 50%.

In calculating the C statistic (area under the *ROC* curve) it can be seen that the TIMI risk score shows the best performance. This was demonstrated by comparing the areas under the *ROC* curve of the three models. The TIMI risk score showed the greatest ability to discriminate those likely to have a coronary lesion ≥ 50%, predicting more accurately than the GRACE scores. The hospital GRACE score, in turn, was more accurate than the GRACE risk score in six months.

Limitations

This study has limitations. The results apply only to patients with non-ST elevation ACS who were referred for angiography and cannot be applied, therefore, to all

patients with ACS. The study population was from a single center, and it is possible that the results not could be applied to the real world of other centers.

Conclusion

The TIMI, hospital GRACE and GRACE in six months risk scores correlate with the severity of coronary lesions found by coronary angiography. The TIMI risk score showed better predictive ability to discriminate who is most likely to have a coronary lesion ≥ 50%.

Author contributions

Conception and design of the research: Santos ES, Aguiar Filho LF, Fonseca DM, Xavier RM, Pereira MP, Minuzzo L, Londero JH; Analysis and interpretation of the data: Santos ES, Aguiar Filho LF, Fonseca DM, Xavier RM, Londero JH; Acquisition of data: Santos ES, Pereira MP, Minuzzo L; Statistical analysis: Santos ES, Souza R; Writing of the manuscript: Santos ES, Aguiar Filho LF, Fonseca DM, Xavier RM, Londero JH; Critical revision of the manuscript for intellectual content: Santos ES, Minuzzo L, Timerman A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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