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The GRACE score is not a good predictor of angiographic complexity in acute coronary syndrome

O escore GRACE não é um bom preditor da complexidade angiográfica na síndrome coronária aguda

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ABSTRACT – Background: Although much is known about the prognostic value of the GRACE risk score, there are few studies investigating how it relates with the angiographic complexity of coronary artery disease. For this reason, in this study, we aimed to assess the predictive capacity of the GRACE score in acute coronary syndrome in respect to the angiographic complexity based on the SYNTAX score. **Methods:** A cross-sectional study of patients with acute coronary syndrome undergoing coronary angiography during hospitalization, with at least one $\geq 50\%$ stenotic lesion in vessels $\geq 1.5\text{mm}$ in diameter. Complex coronary artery disease was defined as SYNTAX ≥ 23 . **Results:** This study investigated 183 patients. A positive correlation was observed between the GRACE and the SYNTAX scores ($p=0.005$), however the association was weak ($r=0.20$). The GRACE score showed discriminatory capacity between patients with and without complex coronary artery disease, however the relevance was low, with an area under the ROC curve of 0.59 (95%CI: 0.51-0.67; $p=0.042$). **Conclusion:** The GRACE risk score is not a sufficiently accurate predictor of angiographic complexity in acute coronary syndrome.

Keywords: Acute coronary syndrome; Coronary angiography; Propensity score; Comparative study

RESUMO – Introdução: Embora o valor prognóstico do escore de risco GRACE seja extensamente conhecido, é limitado o número de estudos que avaliaram a relação entre este e a complexidade angiográfica da doença arterial coronariana. Por esse motivo, no presente estudo, objetivou-se avaliar a capacidade preditora do escore GRACE na síndrome coronária aguda em relação à complexidade angiográfica estratificada, de acordo com o escore SYNTAX. **Métodos:** Estudo transversal, no qual foram incluídos pacientes com síndrome coronária aguda submetidos à coronariografia durante a internação, com pelo menos uma estenose $\geq 50\%$ em vasos de diâmetro $\geq 1,5\text{mm}$. Doença arterial coronariana complexa foi definida como SYNTAX ≥ 23 . **Resultados:** Foram estudados 183 pacientes. Observou-se correlação positiva entre o GRACE e o SYNTAX ($p=0,005$), porém essa associação foi fraca ($r=0,20$). O GRACE apresentou capacidade discriminatória entre pacientes com ou sem doença arterial coronariana complexa, mas de pequena relevância, com área sob a curva COR de 0,59 (IC95% 0,51-0,67; $p=0,042$). **Conclusão:** O escore de risco GRACE não é um preditor suficientemente acurado da complexidade angiográfica na síndrome coronária aguda.

Descritores: Síndrome coronariana aguda; Angiografia coronária; Pontuação de propensão; Estudo comparativo

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BACKGROUND

Risk stratification in acute coronary syndrome (ACS) is essential to estimate patient prognosis and help in therapeutic decision-making. Multiple classification systems have been developed to identify patients at high risk for ACS. These scores assess the risk of death or non-fatal adverse events, and include clinical and electrocardiographic parameters, in addition to cardiovascular biomarkers.¹ The two most commonly used scores are the Global Registry in Acute Coronary Events (GRACE)² and the Thrombolysis in Myocardial Infarction (TIMI),^{3,4} both extensively validated and recommended in ACS guidelines.^{5,6} Although the TIMI is simpler to apply, the GRACE

score has superior discriminatory capacity and encompasses all forms of ACS in the same model.⁷

Both the GRACE and TIMI scores have only clinical variables and are not intended to identify the complexity of coronary artery disease (CAD). This is the purpose of the SYnergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery (SYNTAX) score, calculated by 11 angiographic variables that consider the location and characteristics of each lesion.^{8,9} However, despite its countless advantages, the SYNTAX requires an invasive procedure to be calculated. An accessible, low-cost method, which can indirectly estimate the complexity of CAD before a coronary angiography is performed, may have a major role in therapeutic decision-making, allowing for early identification of patients who could benefit from more aggressive strategies.

Although much is known about the prognostic value of the GRACE risk score,¹⁰ there are few studies investigating how it relates with the angiographic complexity of CAD as quantitatively measured.¹¹⁻¹⁵

The purpose of this study was to investigate the predictive capacity of the GRACE score in respect to the angiographic complexity of CAD in ACS, stratified as per the SYNTAX score.

METHODS

Sample selection

A cross-sectional study of patients with ACS undergoing coronary angiography between January and December, 2016, in the cath lab of *Hospital Nossa Senhora da Conceição*, in the city of Tubarão (SC), with at least one $\geq 50\%$ stenotic lesion in vessels ≥ 1.5 mm in diameter.

In 2016, 1,131 coronary angiographies were performed in the institution in patients with ACS. Considering the expected frequency of 83.6% for $\geq 50\%$ stenosis,¹⁶ the minimum sample size calculated was 178 patients, with 95%CI and sample error of 5%. To make sure the sample size was enough to ensure good accuracy, in the second analysis, assuming an area under the Receiver Operating Characteristic (ROC) curve of 0.65, 144 patients (103 without complex disease and 41 with complex disease) would be required to provide a statistical power of 80% and reject the null hypothesis of an area of 0.50, with an alpha of 0.05. Patients of the study were obtained by random sampling of the population described above. We excluded patients with prior coronary artery bypass graft (CABG) or data found inconclusive for calculation of the scores at issue.

Study protocols

Data regarding diagnosis, comorbidities and therapies applied were obtained from the subjects' electronic medical records. The glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula,¹⁷ and the Killip classification¹⁸ was determined for all patients, for calculation of the GRACE score.

Patients with ACS included those with ST-segment-elevation myocardial infarction (STEMI), non-ST-segment-

elevation myocardial infarction (NSTEMI), and unstable angina (UA). The criteria for diagnosing ACS followed the currently applicable definitions.¹⁹ Obstructive CAD was defined as $\geq 70\%$ stenosis in any of the epicardial coronary arteries or their main branches, or $\geq 50\%$ stenosis in the left main coronary artery (LMCA).²⁰

The GRACE score was calculated retrospectively, using the online platform for the score,²¹ with clinical data from the time of admission. Patients were stratified into high, intermediate and low risk, using the originally proposed cutoff points.²² This score considers eight variables: age, systolic blood pressure, heart rate, plasma creatinine, Killip classification, ST-segment elevation, increased myocardial necrosis biomarkers, and cardiorespiratory arrest at admission. The final score can vary from zero to 372.²

The SYNTAX was calculated independently from the GRACE by two interventional cardiologists using the algorithm available on the website for the score.²³ It was designed as an angiographic tool to determine the complexity of lesions, and has played a major role for selecting the ideal revascularization approach in CAD patients.²⁴ The calculation of the score considers only $\geq 50\%$ coronary stenosis in vessels ≥ 1.5 mm in diameter. In the original study, high SYNTAX scores (≥ 33) identified patients in which CABG resulted in better outcomes when compared with patients undergoing percutaneous coronary intervention (PCI).²⁵ However, in the 5-year follow-up, CABG was identified as superior for patients with score ≥ 23 .⁹ For this reason, in this study, complex CAD was defined as SYNTAX ≥ 23 .

Data analysis

We used the software EpiData (EpiData Association, Odense, Denmark), version 3.1, for data tabulation, and the Statistical Package for Social Science (SPSS, IBM Corp, New York, USA), version 23.0, and MedCalc (MedCalc Software bvba, Oostende, Belgium), version 14.8.1, for statistical analysis. Numerical variables with normal distribution were presented as mean $\pm$ standard deviation (SD), and those with non-normal distribution, as median and interquartile ranges (IQR). Categorical variables were described as absolute numbers and percentages. To check for normality of data distribution, we used the Shapiro-Wilk test.

To compare the SYNTAX scores between the groups stratified as per the GRACE tertiles, we used the Kruskal-Wallis test. To assess the correlation between the scores, we used Spearman's correlation test. As a general rule, we adopted the following classification for the correlation coefficient (r): $r=0$, if no correlation; $0 < r < 0.2$, if very weak correlation; $0.2 \leq r < 0.4$, if weak correlation; $0.4 \leq r < 0.6$, if moderate correlation; $0.6 \leq r < 0.8$, if strong correlation; $r \geq 0.8$, if very strong correlation.²⁶ The Chi-square test was used to compare the complex CAD rates in GRACE tertiles. The predictive accuracy of the GRACE in respect to the presence of complex CAD was estimated by analysis of the ROC curve. To interpret the AUROC, we considered the following values: AUROC=0.5 as absent discrimination; $0.5 < \text{AUROC} < 0.7$ as

low-relevance discrimination; $0.7 \leq \text{AU ROC} < 0.8$ as acceptable discrimination; $0.8 \leq \text{AU ROC} < 0.9$ as excellent discrimination; $\text{AU ROC} \geq 0.9$ as nearly perfect discrimination.²⁷ All analyses with $p < 0.05$ were considered statistically significant.

The study was approved by the Research Ethics Committee of *Universidade do Sul de Santa Catarina* under opinion number 2.274.684 and CAAE 62170416.4.0000.5369, and was authorized by the hospital in which the study was conducted.

RESULTS

We enrolled 239 patients in this study. Of these, 45 were excluded due to prior CABG and 11 due to insufficient data for calculation of the GRACE score. Therefore, 183 patients were investigated, of which 61.7% were male, with a mean age of 65.7 ± 10.4 years. The ACS-related diagnosis was STEMI in 54 patients (29.5%), NSTEMI in 60 patients (32.8%), and UA in 69 patients (37.7%). The median GRACE score was 115 (IQR 94-138), while the median SYNTAX score was 18.5 (IQR 8-28.5). All other characteristics are summarized in table 1.

Table 1. Characteristics of the sample

Variables	
Age, years	65.7±10.4
Male sex	113 (61.7)
Hypertension	130 (71.0)
Dyslipidemia	45 (24.6)
Diabetes mellitus	51 (27.9)
Current smoking	36 (19.7)
COPD	23 (12.6)
Peripheral vascular disease	4 (2.2)
GFR (mL/min/1.73m ²)	78.2 (58.1-97.5)
Heart rate, bpm	74 (63-85)
Systolic blood pressure, mmHg	130 (120-150)
Diastolic blood pressure, mmHg	80 (70-87)
STEMI	54 (29.5)
NSTEMI	60 (32.8)
Unstable angina	69 (37.7)
Killip 1-2	174 (95.1)
Killip 3-4	9 (4.9)
GRACE score	115 (94-138)
Angiographic analysis	
Single vessel	81 (44.3)
Two-vessel	47 (25.7)
Three-vessel	46 (25.1)
Left main coronary artery	2 (1.1)
Complex CAD	71 (38.8)
SYNTAX score	18.5 (8-28.5)
Treatment	
Percutaneous coronary intervention	130 (71)
CABG	37 (20.2)
Medical treatment	16 (8.7)

Results expressed as n (%), mean±standard deviation, median (interquartile range). COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; CAD: coronary artery disease; CABG: coronary artery bypass grafting.

Figure 1 illustrates Spearman's correlation coefficient, which pointed to a low correlation between the GRACE and the SYNTAX ($r=0.20$; $p=0.005$). Based on stratification by the GRACE, 88 patients were considered low-risk (48.1%), 66 medium-risk (36.1%) and 29 high-risk (15.8%). The median SYNTAX in the first GRACE tertile was 15 (IQR=7-24.9), 20.7 (IQR=9-34) in the second tertile, and 19 (IQR=11.7-28) in the third tertile ($p=0.098$) (Figure 2).

The prevalence of complex CAD was 38.8% and there was no significant difference between the three GRACE tertiles (40.8%, 43.7% and 15.5%, respectively; $p=0.209$). The GRACE showed discriminatory capacity between patients with and without complex CAD, however of low relevance, with AUROC=0.59 (95%CI 0.51-0.67; $p=0.042$) (Figure 3). The best cutoff points for prediction of complex CAD by the GRACE are presented in table 2.

Figure 1. Dispersion graph of GRACE and SYNTAX score numerical values.

Figure 2. Distribution of patients by SYNTAX score among the GRACE score tertiles.

Figure 3. Receiver Operating Characteristic (ROC curve) of GRACE to detect complex coronary artery disease.

Table 2. Better cutoff points of GRACE score in prediction of complex coronary artery disease

GRACE	Sensitivity (%)	Specificity (%)
>89	91.5	29.5
>101	74.6	41.1
>127	42.2	67.9

DISCUSSION

The earlier recognition of patients with complex CAD could allow for timely identification of potential candidates for CABG. This enables, for instance, a safer determination of the ideal moment to initiate a second antiplatelet agent, reducing the risk of periprocedural bleeding and the need for blood transfusion.²⁸ The severity of CAD can be classified in different ways. The most commonly used is segregation by LMCA involvement and the number of vessels occluded. In a large part of the studies looking into the relation between the GRACE score and the severity of CAD, LMCA involvement or three-vessel disease are taken as the definition of severe CAD.^{12,14,29} However, this is not the most appropriate definition, since it does not differentiate coronary complexity.

In this study, to determine the severity of the atherosclerotic burden, we used the SYNTAX score, which is a quantitative angiographic score. The SYNTAX is widely accepted as a marker of CAD complexity³⁰ and has an important role in determining the best revascularization procedure to be used.²⁴ Also, its prognostic value has been demonstrated,

and patients in higher tertiles of the score have significantly more adverse cardiovascular events.³¹

The GRACE was developed to stratify the risk of adverse cardiovascular events in patients with ACS, and is frequently used in clinical practice for this purpose.¹ This study investigated how the GRACE performs as a predictor of angiographic complexity of coronary artery disease, stratified by the SYNTAX score. Since the mere existence of an association is not enough to ensure accuracy,³² this study also looked at the discriminatory capacity of the GRACE regarding complex and non-complex disease.

The results of this study suggest that the GRACE is not a good predictor of complexity of coronary artery disease in patients with ACS. First, the weak correlation ($r=0.20$) with the SYNTAX demonstrates that the linear dependence between the two scores is poor. Second, there was no statistically significant difference between the median SYNTAX scores in the different GRACE tertiles. Third, the GRACE AUROC, although statistically significant, reveals low-relevance accuracy (AU ROC=0.59) when discriminating patients with complex DAC.

Bekler et al.,¹⁵ when assessing how accurately the GRACE can predict CAD severity in patients with ACS, reported a correlation coefficient of $r=0.43$ ($p<0.001$) and AUROC of 0.65 (95%CI 0.56-0.74; $p=0.001$) for SYNTAX scores ≥ 23 . Although the authors concluded that there is an association between the scores, it is important to emphasize that the AUROC value reported points to low diagnostic accuracy and, therefore, low clinical relevance. Although the relation between the extension and prognosis of CAD has been known for decades,³³ the results of this study suggest that the angiographic complexity of the disease is only one of the multiple determinants of severity of its clinical outcomes.

It is important to note some limitations of this study. Since this was a retrospective study, its results can be considered hypothesis generators. The inter- and intraobserver agreement and variability for both interventional cardiologists regarding the SYNTAX classification cannot be determined due to practicability issues. Also, this study was conducted in a single center and involved a small number of patients with ACS in its different spectra.

CONCLUSION

The GRACE risk score is not a sufficiently accurate predictor of angiographic complexity evaluated by the SYNTAX score in patients with acute coronary syndrome.

SOURCE OF FINANCING

None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

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