Validation of the Grace Risk Score to Predict In-Hospital and 6-Month Post-Discharge Mortality in Patients with Acute Coronary Syndrome

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Abstract

**Background:** The wide range of clinical presentations of acute coronary syndrome (ACS) makes it indispensible to use tools for risk stratification and for appropriate risks management; thus, the use of prognosis scores is recommended in the immediate clinical decision-making.

**Objective:** To validate the Global Registry of Acute Coronary Events (GRACE) score as a predictor of in-hospital and 6-month post-discharge mortality in a population diagnosed with ACS.

**Methods:** This is a prospective cohort study of consecutive patients diagnosed with ACS between May and December 2018. GRACE scores were calculated, as well as their predictive value for in-hospital and 6-month post-discharge mortality. The validity of the model was assessed by two techniques: discriminative power using the area under the receiver operating characteristic curve (AUC) and goodness-of-fit, using the Hosmer-Lemeshow (HL) test, at the 5% level of significance.

**Results:** A total of 160 patients were included, mean age 64 (±10.9) years; of which 60% were men. The risk model showed to have satisfactory ability to predict both in-hospital mortality, with an area under the curve (AUC) of 0.76 (95% confidence interval [CI], 0.57-0.95; p = 0.014), and 6-month post-discharge mortality, with AUC of 0.78 (95%CI, 0.62-0.94), p = 0.002. The HL test indicated good-fit for both models of the GRACE score.

**Conclusion:** In this study, the GRACE risk score for predicting mortality was appropriately validated in patients with ACS, with good discriminative power and goodness-of-fit. The results suggest that the GRACE score is appropriate for clinical use in our setting.

**Keywords:** Acute Coronary Syndrome; Mortality; Prognosis.

Introduction

Cardiovascular disease is the leading cause of mortality in Brazil and worldwide, and ischemic heart disease accounts for a large portion of this concerning scenario.1 Among its forms of presentation, acute coronary syndrome (ACS) has a wide range of severity.2 However, the use of validated mathematical models of clinical prediction is essential and recommended in national and international guidelines for the management of patients with ACS.3,4

With this stratification, high-risk patients may receive more aggressive antiplatelet and antithrombotic therapy and early invasive intervention, whereas lower-risk patients may receive less aggressive treatments.3,5

Based on the Global Registry of Acute Coronary Events (GRACE) report, the GRACE score was designed with 8 variables analyzed on patient’s admission,6 5 semi-quantitative ones (age range, heart rate, systolic blood pressure, plasma creatinine, and Killip class) and 3
mortality or myocardial infarction so as to facilitate the stratification of patients with ACS. Based on the GRACE score, patients were classified into low (<1%), intermediate (1 to 3%), and high risk (>3%) for in-hospital mortality. For the 6-month post-discharge prognosis, patients were divided into those with low (<3%), intermediate (3 to 8%), and high mortality risk (>8%).

Clinical outcomes

The primary outcome was defined as in-hospital and 6-month post-discharge mortality. With regard to secondary outcomes, the accuracy of the GRACE score was assessed in the different presentations of ACS.

Statistical analysis

Categorical data were presented as frequencies (percentages), and continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR). The Kolmogorov-Smirnov test was used to verify distribution. The level of significance was set at p < 0.05 for all analyses. The discriminative power of the score with regard to in-hospital and 6-month post-discharge was assessed using the C statistics. The area under the receiver operating characteristic curve (AUC) represented the accuracy of the GRACE score in distinguishing survivors from non-survivors. Along with this analysis, cutoff values were identified to define the best prognostic sensitivity and specificity, with their 95% confidence intervals (CI). Goodness-of-fit for the scores was assessed by the Hosmer-Lemeshow test and by the dispersion graph between predicted mortality at each risk decile and the observed mortality. The analysis was performed using the SPSS 20.0, Minitab 16 and MedCalc, version 19.1 software.

Results

Sample characteristics

The sample consisted of 160 patients. Two patients (1.25%) were lost to follow-up, due to absence of outpatient follow-up and telephone contact failure. Demographic and clinical characteristics with regard to the prevalence of cardiovascular risk factors and initial presentation are presented in Table 1.
**Primary outcome**

In-hospital mortality was 5.1% (8 deaths). Six hospital deaths were caused by cardiogenic shock, and 2 by infectious complications with septic shock. The Hosmer-Lemeshow test for the in-hospital GRACE score yielded a $c^2$ of 7.14 ($p = 0.522$) and an AUC of 0.76 (95% confidence interval (CI), 0.57-0.95). Six-month post-discharge mortality was 7% (11 deaths). Among the patients who died after hospital discharge, 2 had sudden death, and 1 had a new episode of MI. The results for the 6-month post-discharge GRACE score showed $c^2$ of 4.53 ($p = 0.81$) and AUC of 0.78 (95%CI, 0.62-0.94). Therefore, both predictions exhibited a good-fit (Figure 1).

According to the ROC curve, the best cutoff value for the in-hospital GRACE score was 179, with sensitivity of 50% and specificity of 98%. Conversely, the best cutoff value for the 6-month post-discharge GRACE score was 119.5, with sensitivity of 72.7% and specificity of 81.6% (Table 2).

**Secondary outcome**

The accuracy of the GRACE score in the different forms presentations of ACS was also tested. There was no outcome UA to be analyzed.

With regard to the non-ST segment elevation myocardial infarction (NSTEMI), mortality rate was 5.3%, all of which occurred during hospitalization. The in-hospital GRACE score had a $c^2$ of 5.96 ($p = 0.425$) and an AUC of 0.64. The cutoff value was 121.5, with sensitivity of 66.7% and specificity of 74.1%. Conversely, the GRACE score 6 months after discharge had a $c^2$ of 5.6 ($p = 0.102$) and an AUC of 0.59. The cutoff value was 98.5, with sensitivity of 66.7% and specificity of 63% (Figure 2 and Table 3).

In the ST segment elevation myocardial infarction (STEMI), which had a mortality rate of 11.9%, the in-hospital GRACE score had $c^2$ of 8.8 ($p = 0.359$) and an AUC of 0.78. The cutoff value was 179, with sensitivity of 80% and specificity of 91.9%. Conversely, the GRACE score 6 months after discharge, when cumulative mortality was 19%, had a $c^2$ of 7.99 ($p = 0.435$) and an AUC of 0.77. The cutoff value was 135, with sensitivity of 62.5% and specificity of 88.2% (Figure 2 and Table 3).

The hospital mortality rates for patients with predicted low, intermediate, and high risk according to the in-hospital GRACE score were 2.8% (2 deaths), 2% (1 death), and 13.9% (5 deaths) respectively. Conversely, for patients with predicted low, intermediate, and high risk according to the 6-month post-discharge GRACE score was 3% (3 deaths), 0% (0 death) and 22% (8 deaths), respectively (Figure 3 and Table 4).

**Discussion**

The use of score risk for stratification and prognostic is recommended in the clinical practice by the national and international guidelines on NSTEMI and STEMI.\(^3\)\(^5\) The GRACE score includes quantitative and qualitative variables and has greater discriminative accuracy than other prognostic tools, such as the TIMI risk.\(^3\)

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**Table 1 – Sample characteristics**

| Variables                      | Distribution |
|--------------------------------|--------------|
| Sample                         | 160          |
| Age (years)                    | 64 (10.9)    |
| Male gender                    | 96 (60%)     |
| BMI (kg/m\(^2\))               | 28.2 (5.1)   |
| Treatment on SUS               | 142 (88.8%)  |
| Diabetes                       | 112 (70%)    |
| Hypertension                   | 121 (75.6%)  |
| Sedentary                      | 66 (41.25%)  |
| Smoking                        | 50 (31.25%)  |
| Systolic blood pressure (mm Hg)| 138 (29.1)   |
| Heart rate (bpm)               | 78.7 (20.7)  |
| Killip class > 1               | 16 (10%)     |
| ST-segment depression          | 43 (26.9%)   |
| Creatinine (mg/L)              | 1.07 (0.94-1.25) |
| Positive HS troponin           | 100 (62.5%)  |
| ACS                            | 60 (37.5%)   |
| UA                             | 58 (36.25)   |
| NSTEMI                         | 42 (26.25%)  |
| STEMI                          |              |
| GRACE score - Intra-hospital   | 111.5 (94.3-139.5) |
| GRACE score - 6 months after discharge | 95.5 (80.5-117) |

Creatinine and GRACE scores were expressed in median and interquartile range. The remaining (continuous) variables were expressed as mean (SD).

BMI: body mass index; SUS: Brazilian Unified Health System (Sistema Único de Saúde); HS: high sensitivity; ACS: acute coronary syndrome; UA: unstable angina; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; and GRACE: Global Registry of Acute Coronary Events.
In our validation study, the GRACE score showed a satisfactory discriminative power. The AUC was 0.76 for the in-hospital GRACE score and 0.78 for the 6-month post-discharge GRACE score. In the classical study of Eagle et al. with 17,142 patients, this score had a discriminative value of 0.81 in patients with ACS.

With regard to the secondary outcome, the subgroup of patients with STEMI showed an in-hospital AUC of 0.78. Two Brazilian studies were conducted with patients with STEMI, one by Correia et al., who reported an AUC of 0.867 in a sample of 152 patients, and another by Sola et al., who shown an AUC of 0.803 in a cohort of 169 individuals from Salvador, state of Bahia. In these national studies, it was not possible to compare 6-month post-discharge outcomes, because they were not assessed.

International studies, such as that conducted by Bargos et al. with an Argentinian cohort, found results similar to those of our study for the in-hospital GRACE score, with an AUC of 0.76. Furthermore, a similar AUC (0.6) for in-hospital mortality was observed in patients with NSTEMI.

The Spanish study by Abu-Ass et al. validated the 6-month post-discharge GRACE score with an AUC of 0.861.

In our setting, in-hospital mortality was 5.1%. However, it was 2.8%, 2% and 13.9% for patients with predicted low, moderate, and high mortality risk, respectively. In the Spanish study with 6997 participants conducted by Cordero et al., mortality rate was 5.33% and 0%, 0.6% and 9.6%, respectively. Even with a smaller

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**Table 2 – Predictive accuracy of in-hospital and 6-month post-discharge GRACE scores**

|                          | Area (AUC)     | Specificity | Sensitivity | p-value |
|--------------------------|----------------|-------------|-------------|---------|
| In-hospital GRACE score  | 0.76 (0.57-0.95) | 98%         | 50%         | 0.014   |
| 6-month post-discharge GRACE score | 0.78 (0.62-0.94) | 81.6%       | 72.7%       | 0.002   |

AUC: area under the receiver operating characteristic curve.
In our sample, our study found values similar to those obtained in the Spanish study.

The limitation of our study is the fact that there was no exploratory analysis either of the factors related to mortality in our sample or of the impact of the prescribed pharmacological and interventional treatments.

It is the first Brazilian study that showed the validity of the GRACE score beyond in-hospital prognosis.
Table 3 – Predictive accuracy of in-hospital and 6-month post-discharge GRACE scores in NSTEMI and STEMI subgroups

| Area                     | Sensitivity (%) | Specificity (%) | p-value |
|--------------------------|-----------------|-----------------|---------|
| In-hospital              |                 |                 |         |
| NSTEMI                   | 0.64 (0.29-0.98)| 66.7            | 74.1    | 0.432   |
| STEMI                    | 0.78 (0.49-1)   | 80              | 91.9    | 0.043   |
| 6-month post-discharge    |                 |                 |         |
| NSTEMI                   | 0.59 (0.25-0.93)| 66.7            | 63      | 0.592   |
| STEMI                    | 0.77 (0.57-0.98)| 62.5            | 88.2    | 0.018   |

Area under the receiver operating characteristic curve for in-hospital and 6-month post-discharge GRACE scores in the NSTEMI and STEMI subgroups, with sensitivity and specificity for their cutoff values.

NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

Figure 3 – Comparison of mortality rates according to risk stratification by in-hospital and 6-month post-discharge GRACE scores.

Conclusion

The GRACE score was validated to predict in-hospital and 6-month post-discharge mortality in our setting in a non-selected sample of patients with ACS. The discriminative power of the score was found to be satisfactory, ratifying recent guidelines that recommend using the GRACE score in risk stratification and selection of intensive early treatment strategies, as well as in the watchful post-discharge follow-up.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.
Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade Meridional – IMED under the protocol number 2.531.453. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Table 4 – Number of deaths according to risk classification

| Death                      | Risk          |
|---------------------------|--------------|
|                           | Low          | Intermediate | High               |
| In-hospital               | 2 (2.8%)     | 1 (2%)       | 5 (13.9%)          |
| 6-month post-discharge     | 3 (5%)       | 0 (0%)       | 8 (22.8%)          |

Author contributions

Conception and design of the research: Neves VB, Roman MF, Boclin KSL. Acquisition of data: Neves VB, Roman MF, Vendruscolo T, Heineck G, Mattos CAS, Mattos EI, Bin LCP. Statistical analysis: Neves VB, Roman MF. Writing of the manuscript: Neves VB, Roman MF, Roman RM. Conception and design of the research: Neves VB, Roman MF, Boclin KSL.

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