

## Sesgo en la estratificación del síndrome coronario agudo al calcular el grace-score con 1ª, 2ª o troponina Δ

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Como citar: Teherán AA, González G, Martínez V, Hernández JC, Caicedo A, Montoya N, Villamil L., Núñez DN. Sesgo en la estratificación del síndrome coronario agudo al calcular el grace-score con 1ª, 2ª o troponina Δ. Revisión de literatura. Revista Cuarzo 2018;24 (2) 20-26.

Recibido: 3 de agosto de 2018  
Aceptado: 23 de noviembre de 2018  
Publicado: 30 de diciembre de 2018

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### Resumen

**Introducción:** el síndrome coronario agudo (SCA) es la primera causa de mortalidad en Colombia. Una estratificación de riesgo errónea, en la sala de emergencias (ER), afecta las intervenciones realizadas y la tasa de eventos adversos cardiovasculares puede ser mayor. El objetivo de esta investigación fue medir la diferencia en el puntaje GRACE y la estratificación del riesgo coronario, utilizando los resultados de las troponinas medidas secuencialmente durante la atención inicial.

**Metodología:** con un diseño descriptivo retrospectivo, se evaluaron los registros clínicos de pacientes tratados por dolor precordial de probabilidad intermedia para SCA, sin indicación de manejo invasivo inmediato, atendidos en la sala de emergencias de una clínica del tercer nivel de Bogotá, durante el año 2017. Se determinó la diferencia entre la puntuación GRACE calculada con la primera troponina (GRACE-1), la segunda troponina (GRACE-2) o la troponina delta (GRACE-delta) [prueba T pareada], y la proporción de pacientes poco estratificados se midió al usar la primera troponina [X2, puntaje Z].

**Resultados:** se identificaron 44 pacientes en un período de 6 meses. La mayoría hombres con edad mediana de 73 años. El promedio (DE) de los puntajes GRACE-1, GRACE-2 y GRACE-delta, fue de 114.14 (30.73), 115.55 (30.14) y 111.11 (28.79), respectivamente; al comparar GRACE-delta con GRACE-1 y GRACE-2 se identificaron diferencias significativas ( $p < 0.05$ ). Se identificó un error en la estratificación del riesgo coronario en 10/44 pacientes (22.7%) y 9/44 (20.4%) presentaron sobreestratificación.

**Conclusión:** la estratificación del riesgo coronario con la primera troponina, a diferencia de la troponina delta (ítem no aclarado en las guías), evidenció una sobreestratificación en al menos 20% de los pacientes, estableciendo la necesidad de procedimientos más invasivos y posiblemente hospitalización más prolongada permanecer.

**Palabras clave:** Troponina, Síndrome Coronario Agudo, GRACE score.

## Grace score bias in acute coronary syndrome due to use 1th, 2th or troponin Δ.

### Abstract

**Background:** Acute coronary syndrome (ACS) is the first cause of mortality in Colombia. An erroneous risk stratification, in the emergency room (ER), affects the interventions performed and the rate of major cardiovascular adverse events. We measured the difference in GRACE score and stratification of coronary risk, by using the results of troponins measured sequentially during initial care.

**Methods:** With a retrospective descriptive design, clinical records of patients treated for precordial pain of  $\geq$  intermediate probability for ACS were evaluated, without indication of immediate invasive management, attended in the ER of a clinic of the third level of Bogotá, during 2017. De-

terminated the difference between the GRACE score calculated with the first (GRACE-1), second (GRACE-2) or troponin delta (GRACE-delta) [paired T-test], and the proportion of poorly stratified patients was measured when using the first troponin [X2, Z-score].

**Results:** 44 patients in a period of 6 months were identified. The majority men, older adults, middle age 73 years. The average (SD) of scores GRACE-1, GRACE-2 and GRACE-delta, was 114.14 (30.73), 115.55 (30.14) and 111.11 (28.79), respectively; when comparing GRACE-delta with GRACE-1 and GRACE-2 significant differences were identified ( $p < 0.05$ ). Error in the stratification of coronary risk was identified in 10/44 patients (22.7%), and 9/44 (20.4%) presented over-stratification.

**Conclusion:** The stratification of coronary risk using the first troponin, unlike the troponin delta (item not clarified in the guidelines), evidenced an over-stratification in at least 20% of the patients, establishing the need for more invasive procedures and possibly longer hospital stay.

**Keywords:** Troponin, Acute Coronary Syndrome, GRACE score.

## Background

It is estimated that in North America more than 15 million people suffer from coronary heart disease (CHD) and every 42 seconds a diagnosis of acute myocardial infarction (AMI) is made. Coronary diseases affects both men and women and in all age groups, but it is clear that, before age 50, it is more frequent in men and when it reaches 50 years, the incidence and prevalence is equalized by sex (1). The approach in the emergency room (ER) to patients with precordial pain of intermediate or high probability for an acute coronary syndrome (ACS) includes, in addition to medical management, the stratification of coronary risk, applying the GRACE or TIMI scales, validated for this purpose and accepted in the American and European guidelines for management of acute myocardial infarction without ST elevation / Unstable Angina (NSTEMI / UA) (2,3).

In ER, the GRACE scale offers some advantages over the TIMI scale, including an easy execution without requiring additional information on previous coronary risk, including data on the use of antiplatelet agents, occlusive involvement of the coronary arteries and factors of cardiovascular risk (4,5); in addition, in some investigations and in a general way (not in subgroups), the GRACE scale has shown better operative capacities and correlation with the SYNTAX score and major cardiovascular adverse events (6-8).

The GRACE scale was proposed since 2002 and within the components required to calculate the score is the result of troponin (positive or negative), it should be mentioned that at the time the scale was designed and validated, it was not established a control with a second troponin to measure the troponin  $\Delta$ , that is to say the dynamic changes between them (Troponin 2 / Troponin 1), given the possibility of a false positive due to clinical conditions that raise serum levels of troponin, among them the processes infectious, the exacerbation of a chronic obstructive pulmonary disease, chronic kidney disease, cardiac arrhythmias, among other clinical conditions; this was a consideration that began to emerge from 2009 onwards and was established as a standard for the interpretation of biomarkers in the latest guide for the management of NSTEMI / UA (3,9-11).

Given the changes in the interpretation of myocardial biomarkers (troponins), in the context of the approach to the patient with suspected ACS treated in the ER, we consider that it is possible that the GRACE score obtained with the first troponin is biased, given the clinical conditions mentioned, which can raise troponin levels; the above can result in an erroneous stratification of coronary risk and expose the patient to unnecessary hospital procedures and costs.

## Methods.

### Subjects and settings.

A retrospective descriptive research was done, using clinical register of patients admitted consecutively to the ER and evaluated by a Cardiologist in Occidente Clinic (OC), Bogotá - Colombia, between January-June/2017. Patients with two sequential troponins results and a chest pain with intermediate probability to CAD were included; patients that required a pre-surgical assessment were not included. Exclusion criteria were a diagnosis at admission of 1. STEMI type I, 2. STEMI o N-STEMI type II, IV, V. Finally, patients included were that with any of the follows conditions: 1. Unstable Angina/N-STEMI type I, 2. N-STEMI type II and 3. Chest pain of intermediate probability, with any feature related to coronary disease (typical, atypical or non-cardiac); patients with atypical or non-cardiac chest pain should have at least one of the following acute manifestations of cardiovascular disease: palpitations, dyspnea, cardiac syncope or cardiac arrhythmia (Figure 1). In a pilot study we determine that GRACE score of 20 patients has a standard deviation of 22 points; to establish a difference of 13 points in a paired T-test (13 points contributed by a positive troponin), a confidence of 99% and a power of 90%, it was calculated a sample size of 25 patients (Minitab® Version 18).

To execute this research, we require data contained in clinical registers and, into database designed to store variables; a consecutive number, which started from the first to the last patient included, replaced the identification number. Based on the foregoing and the provisions of Resolution 008439/1993 of Colombia, this research was classified without risk and was executed after the approval of the research committee of OC.

## Database and variables.

Data collected were stored in an Excel® archive. The variables required to calculate GRACE score were included: age (years old), heart rate, systolic blood pressure (mmHg), seric creatinin (mg/dL), Killip Kimbal classification (KK), heart attack, ST deviation and positive/negative cardiac biomarker cardiac at admission. In addition, sex, Charlson's Comorbidity Score (CCS), main symptom at admission, time between the onset of symptoms and first attention at ER, initial (first troponin) and control (second troponin) troponin concentrations results, estimated Glomerular Filtration Rate (eGFR), seric potassium concentration, Left Ventricular Ejection Fraction (LVEF) and the three-main diagnosis established for Internal Medicine or Cardiology Services (12-14). To calculate GRACE, Killip Kimbal, CCS y eGFR we used the available calculators on MdCalc®.

High sensitivity T troponin (hs-cTnT), with a cut-point  $\geq 0.014$  to identify as positive, was applied in CDO; those patients with a troponin  $\Delta > 20\%$  or  $< 20\%$  (second troponin divided first troponin) was identified such as positive (15, 16). Using the cut-points established to identify patients with troponins positive results (first, second or  $\Delta$ ), we calculate three GRACE scores: GRACE-1 (first troponin), GRACE-2 (second troponin) and GRACE-delta (troponin  $\Delta$ ).

The rest of the variables included were used to evaluate possible interactions or relationships that influenced the GRACE score or coronary risk stratification.

## Outcomes.

The primary outcome was the difference between the GRACE-1 and GRACE-2 compared to GRACE-delta, and the secondary outcome was the proportion of patients with a biased stratification when using first troponin.

## Statistical analysis.

Statistical packages Minitab® Version 18 y EPIDAT® Version 4.2 were used to perform analysis. A descriptive analysis was done, presenting numeric data in means (SD) and categoric data in proportions; Shapiro Wilks test was used to determine normality. Paired t-test (one tail) was used to compare continuous variables and Chi square (X<sup>2</sup>) or Z-score, to compare qualitative variables or proportions, respectively; Spearman coefficient (Rho) was used to determine correlation grade among continuous variables; a p-value  $< 0.05$  was establish as significant.

## Results

### General characteristics.

From January to June 2017, 147 evaluations by the Cardiology Service in the ER and other areas were carried out; after excluding pre-surgical assessments and patients who did not meet

the eligibility criteria, 44 patients were identified, consecutively attended who fulfilled the definitive inclusion criteria; the majority males (31/44, 70.4%) and older adults. The most frequent cardinal symptoms were atypical chest pain (18/44, 40.9%) and typical chest pain (16/44, 36.4%), followed by arrhythmias, dyspnea, palpitations, syncope with cardiac risk and non-cardiac chest pain. The median (25th percentile - 75th percentile) time between onset of symptoms and initial attention in the ER was 19.5 hours (3.25-48) and the median Charlson Comorbidity score was 4 (3-6).

### Comparison of GRACE scores.

Table 1 shows the distribution of the components that make up the GRACE score and identified that, when compared to the initial troponin result, when evaluating the troponin delta, the proportion of patients with a positive myocardial biomarker definition decreased 25% and 31.8% in relation to the results of troponin 1 and 2, respectively (p:  $< 0.05$ , Table 1). Among the components that are part of the GRACE it should be noted that, on average, most patients had high systolic pressure, category I in the KK classification and although the creatinine level did not show very high concentrations, the 25th percentile presented eTFG below 60 (48.9 mL / min / 1.73 m<sup>2</sup>).

Table 1. Parameters of GRACE Score.

Variables	N: 44 patients
Age <sup>a</sup>	73.5 (61-83)
Heart rate <sup>a</sup>	80 (70-88)
Systolic blood pressure <sup>b</sup>	148.6 (35.6)
Creatinine <sup>a</sup>	0.98 (0.76-1.39)
ST segment deviation on EKG <sup>c</sup>	8 (18.2)
Abnormal troponins <sup>c</sup>	
Troponin 1	33 (75)*
Troponin 2	36 (81.8)**
Troponin $\Delta$	22 (50)
Killip class (signs/symptoms) <sup>c</sup>	
I	40 (90.9)
II	3 (6.8)
III	1 (2.3)

a: median (25th percentile - 75th percentile), b: mean (standard deviation), c: count (proportion). Z-score: p-value\* 0.015, p-value\*\* 0.002

When the GRACE scores calculated with the interpretations of the troponins were lower, in most cases they corresponded to that calculated with the interpretation of the troponin delta or the first troponin result. The average (SD) of the GRACE-1 score was 114.14 (30.73) and GRACE-2 115.55 (30.14), with a difference of -1.40 points (CI 90% -2.59 - -0.21) when comparing both, identifying that, the GRACE- 2 had a higher value than the

first (one-tail p-value: 0.026; paired T-test). The average (SD) of the GRACE-delta score [111.11 (28.79)] was lower than GRACE-1 (difference: -3.02, CI 90% -5.19 - -0.84) and GRACE-2 (difference: -4.43, CI90%: - 6.01 - -2.85)

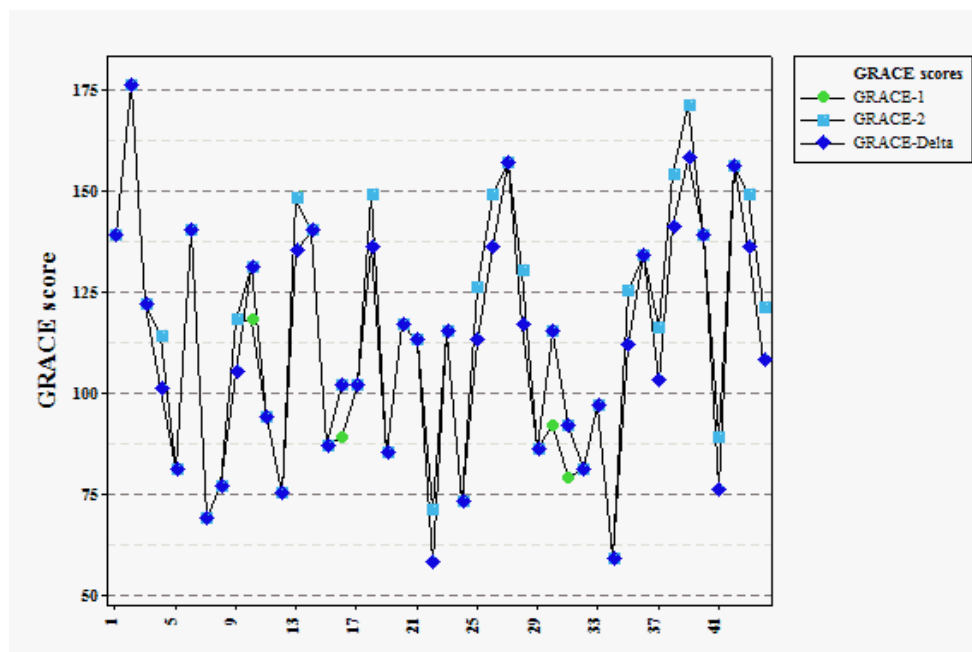
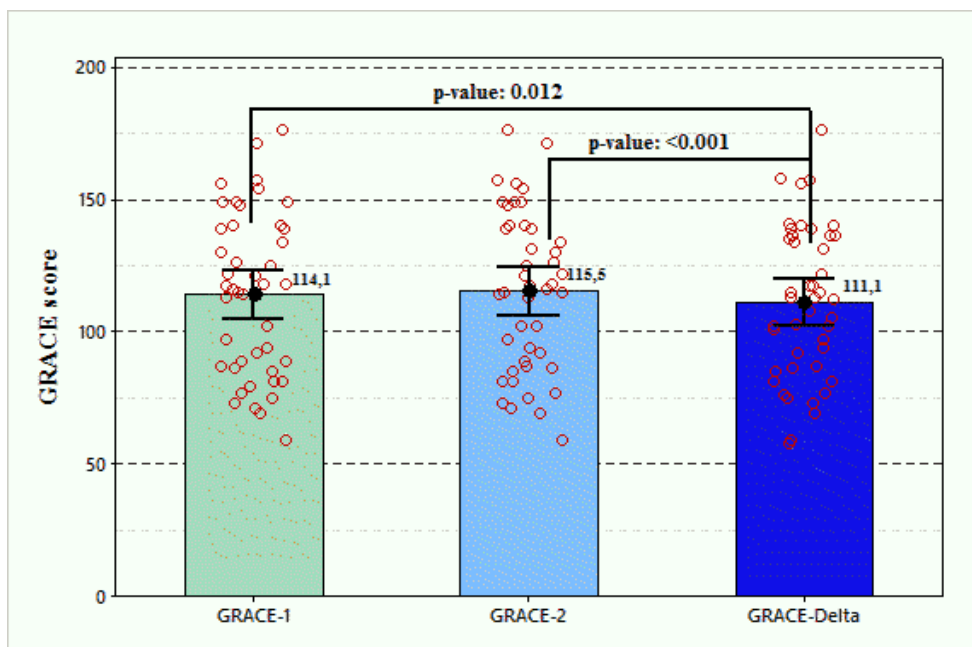


Figure 2a, 2b. Average differences between Grace delta score, Grace 1 and Grace 2.

Comparison of GRACE scores calculated with troponin 1 (GRACE-1), troponin 2 (GRACE-2) and troponin  $\Delta$  (GRACE-  $\Delta$ ); in both figures the GRACE calculated with troponin 1 is represented with the light green color, the one calculated with troponin 2 with light blue color and the one calculated with the delta of troponin with dark blue. The figure on the top shows the three GRACE scores calculated, consecutively to each patient. In the

figure below shows the confidence intervals of the mean of each calculated GRACE score. Finally, when comparing the stratifications of coronary risk established with the GRACE-1, GRACE-2 and GRACE-  $\Delta$  scores, it was found that 22.7% (10/44) had bias in the stratification and in the majority it was secondary to over-Stratification of coronary risk (9/44, 20.4%) (Figure 2a, 2b.).

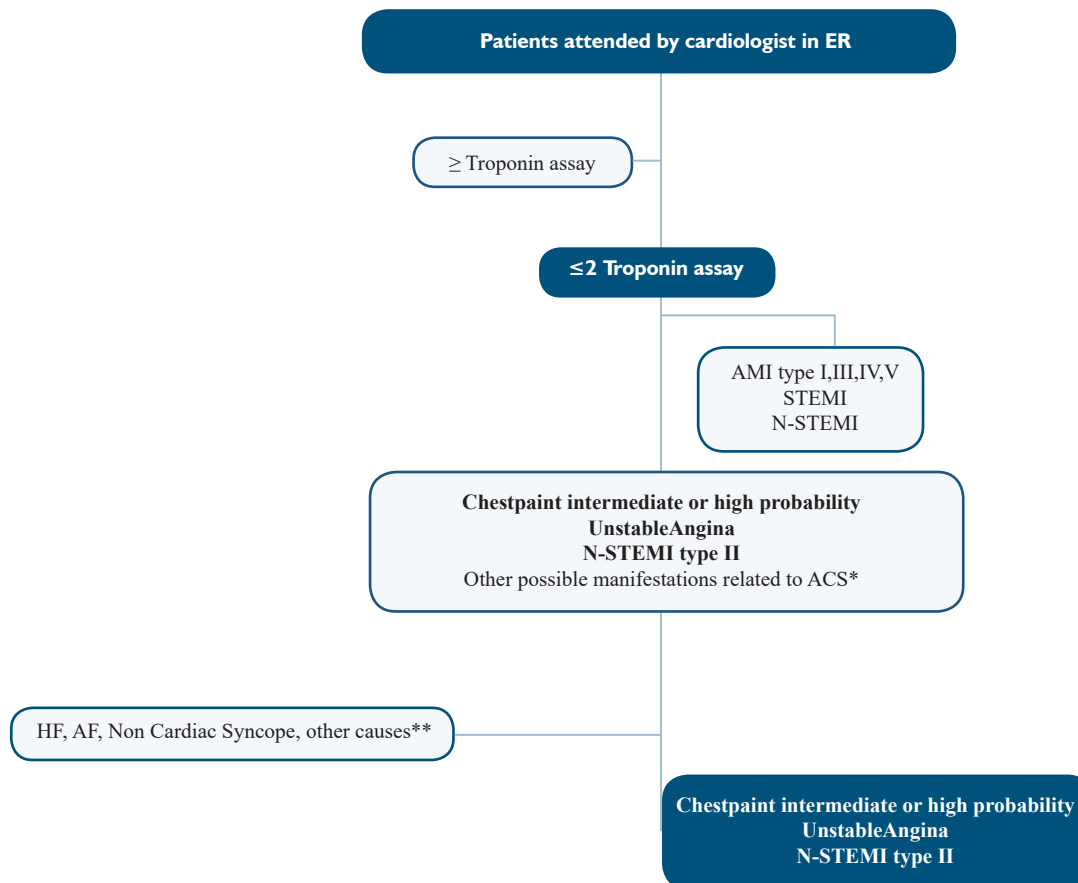


Figure 1. Participants selection flowchart.

### Characteristics related to the GRACE score.

When evaluating the relationship between the three calculated GRACE scores (GRACE 1, GRACE 2, GRACE delta) and other characteristics or variables that are not part of the scale, a relationship was identified with the Charlson score (GRACE delta: Rho 0.614, p : 0.000; GRACE 1: Rho 0.628, p: 0.000; GRACE 2: Rho 0.614, p: 0.000); no relationship was identified with the time of evolution of symptoms (delta GRACE: Rho: -0.222, p: 0.147, GRACE 1: Rho: -0.104, p: 0.503, GRACE 2: Rho: -0.151, p: 0.328), with eTFG (GRACE delta: Rho: -0.262, p: 0.086; GRACE 1: Rho: -0.282, p: 0.064; GRACE 2: Rho: -0.273, p: 0.073), potassium (GRACE delta: Rho: 0.170, p: 0.294; GRACE 1: Rho: 0.148, p: 0.363; GRACE 2: Rho: 0.124, p: 0.445), or LVEF (GRACE delta: Rho: 0.037, p: 0.812, GRACE 1: Rho: 0.046, p: 0.770; GRACE 2: Rho: 0.041, p: 0.792).

### Discussion

The present investigation allowed identifying differences in the stratification of coronary risk, when using the results of the troponins requested sequentially, in comparison with the delta of troponins.

The private institution where this research was carried out serves between 11,000-14,000 monthly emergencies and after trauma as the main reason for consultation (60%), cardiovascular emergencies are the next priority of care (15-22%); administrative agreements, geographic location, the demographic condition of the area of influence and availability of cardiovascular care resources, including the Coronary Care Unit and Hemodynamics, create the required scenario to meet the demand of patients with coronary-type cardiovascular conditions.

Troponins are the myocardial biomarker gold standard, given their specificity for this tissue, in comparison with other biomarkers previously implemented (17-19). Therefore, due to its ability to predict relevant outcomes in patients with ACS, it was possible to integrate them, along with other predictor variables, into scales that predicted MACEs (20-24); among them, the TIMI and GRACE score have demonstrated the best operational capabilities and calibration, and have been adopted by the American and European Societies of Cardiology as a diagnostic and prognostic standard in the context of the SCA (2,3,25,26). The GRACE score presents the following operative advantages over the TIMI score since it only requires data from the physical examination, the patient's clinical condition (vital signs) and the result of basic paraclinical tests (electrocardiogram, troponin and creatinine); With this information obtained in an easy and



routine way, the GRACE score maintains and, in some studies, it surpasses the operative capacities to discriminate patients with ACS or STEMI / N-STEMI in the SE, also it is very useful to predict MACEs and mortality to the 30 days or 6 months after the event (22-24).

Despite the utilities of the risk scales, specifically the GRACE score, there is a natural bias underlying them: the imbalance with respect to the change in the interpretation of myocardial biomarkers, a relatively new variation, not contemplated during the design and validation of the scale (6). We identified differences when calculating the GRACE score and in the stratification of coronary risk, when using the results of the individual troponins and the troponin delta. It should be noted that the selected clinical records only included patients requiring the application of the GRACE score, excluding patients who, with or without the GRACE score, required invasive therapy (thrombolysis or PCI) or with clinical diagnoses with a high probability of bias (false positive), for example, acute heart or kidney failure, among others.

Therefore, we consider that we were able to exclude most of the clinical conditions that influenced the difference between the individual troponins and the delta. Both the initial and recent studies, which have implemented high sensitivity troponins, established the usefulness of the troponin delta and are consistent with the stratification bias when using the individual troponin results, and have also demonstrated its usefulness as a predictor of MACEs (9,10,16,27-29).

Although decision making in the context of the SCA from the interpretation of the troponin delta was integrated into the guidelines and management standards, it has not been coupled in the coronary risk scores used in the SE, including the HEART score, which modified the old interpretation of positive or negative biomarker, made a level of positivity, but maintaining the first troponin as the biomarker required to assess the risk (30,31).

We identified a correlation between the Charlson score and the calculated GRACE scores, mainly GRACE-1 and GRACE-2; a multivariate regression (analysis not shown) that included as a predictor the Charlson score to predict the GRACE scores, showed that the influence of the Charlson score ranged between 3.43-9.37 GRACE points (coefficient  $\beta$ ), predominantly for the GRACE-1 and GRACE scores -2; This could be due to the collinearity between some variables or categories found in the GRACE and Charlson score, including age and the presence of chronic kidney disease.

The retrospective nature of the research could be a limitation, given the possibility of selecting clinical histories with influential results, this was avoided by including consecutive records that met the eligibility criteria; another limitation was the lack of evaluation of the time between taking the first and second troponins, which could affect the results. Finally, although we included patients with evolution times, between the onset of symptoms and prolonged first troponin, a condition that would exclude the need

for 4444the second troponin, no correlation was found between this variable and the calculated GRACE scores.

This investigation showed that, when comparing the stratification of the coronary risk, using the troponin delta in relation to the initial troponin (item not clarified in the guidelines), a bias could be found in the stratification of the patients, locating at least one of the every five in categories that required more invasive procedures and possibly longer hospital stay.

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