

## ORIGINAL ARTICLE

## Correlation Between the Complexity of Coronary Lesions and High-Sensitivity Troponin Levels in Patients with Acute Coronary Syndrome

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### Abstract

**Background:** Cardiovascular diseases are the leading cause of death in Brazil. Biochemical markers have diagnostic and prognostic importance in acute coronary syndromes (ACSs), with troponin as the preferred biomarker. Studies have already demonstrated a positive relationship between increased levels of high-sensitivity troponin (hsTn) and prognosis. However, few studies have correlated hsTn levels with the complexity of coronary lesions.

**Objectives:** To compare hsTn levels with the complexity of coronary lesions according to the SYNTAX score, and to correlate the levels of this biomarker with the TIMI and GRACE scores in patients with ACS.

**Methods:** Retrospective, cross-sectional study with 174 patients with ACS. The correlation between variables was assessed by the nonparametric Spearman's rank correlation, and statistical analysis was performed by the SPSS program, with a significance level of 5%.

**Results:** Mean age was 63 years, and most patients were women (52.9%), hypertensive, non-diabetic and non-smokers. Nineteen percent of the patients had STEMI, 43.1% NSTEMI, and 36.8% unstable angina. Most were in Killip 1 (82.8%). Median hsTn was 67 pg/mL. Median risk scores were 3, 121 and 3 in the TIMI, GRACE and SYNTAX scores, respectively. There was a correlation of hsTn with SYNTAX ( $p < 0.001$ ,  $r = 0.440$ ), TIMI ( $p < 0.001$ ,  $r = 0.267$ ) and GRACE ( $p = 0.001$ ,  $r = 0.261$ ) scores.

**Conclusion:** A positive linear correlation was found of hsTn levels with the complexity of coronary lesions, and with the TIMI and GRACE clinical scores. (International Journal of Cardiovascular Sciences. 2018;31(3):218-225)

**Keywords:** Acute Coronary Syndrome; Troponin; Cardiovascular Diseases / Mortality; Myocardial Infarction; Hospitalization / Economy.

### Introduction

Cardiovascular diseases (CVDs) are the main cause of death in Brazil, generating high costs of hospitalizations every year.<sup>1</sup> According to the World Health Organization, there were 214.2 deaths per 100,000 inhabitants from CVDs in Brazil in 2012, with higher prevalence among men.<sup>2</sup>

Acute myocardial infarction (AMI) is one of the main causes of death and disability worldwide.<sup>3</sup> According to

the third international definition of AMI, published in 2012, AMI occurs when there is evidence of myocardial necrosis in a clinical context of acute myocardial ischemia.

The importance of biochemical markers in both diagnosis and prognosis of acute coronary syndromes (ACSs) has been well documented.<sup>4</sup> Cardiac troponin has been considered the best biomarker for AMI diagnosis since 2000, when a redefinition of myocardial infarction was published.<sup>5</sup> High-sensitivity troponin (hsTn) assay, as compared with the first generations of troponin assays,

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shows higher analytical sensitivity enabling precise quantification of low troponin concentrations. Therefore, hsTn can exclude AMI earlier than other less sensitive, conventional markers. However, its indiscriminate use may lead to false positive results while contributing with few additional cases of ischemia.<sup>6</sup>

Prognostic evaluation of ACSs includes clinical, laboratory and anatomical criteria. One of the anatomical criteria is the SYNTAX score, which has been established to evaluate the complexity of coronary lesions diagnosed by coronary angiography. SYNTAX score is a comprehensive angiographic rating system derived from anatomical features and coronary lesion.<sup>7</sup>

Several studies have consistently demonstrated a positive relationship between increased hsTn and the prognosis of patients with ACSs.<sup>8</sup> Nevertheless, few studies have evaluated the relationship between hsTn and the complexity of angiographic coronary lesions.<sup>9</sup>

In light of this, the aim of the present study was to correlate hsTn levels with the complexity of coronary lesions according to the SYNTAX score in patients admitted for ACSs. Considering the prognostic value of this biomarker, we will also compare this hsTn levels with previously validated risk scores, the GRACE and TIMI scores.

## Methods

This was a retrospective, cross-sectional, analytical study using convenience sampling, and collection of secondary data from medical records. From January to June 2013, 211 patients with suspicion of ACS (AMI and unstable angina) were admitted to the emergency department of Maria Aparecida Pedrossian University Hospital. Among these patients, 174 had the diagnostic confirmed and underwent coronary angiography during hospitalization, and hence considered eligible for the study.

The myocardial necrosis markers and respective reference values used in this institution are: hsTn > 14 pg/mL and CKMB (mass) > 3.8 ng/mL in women and 6.7 ng/mL in men. Patients' highest troponin levels were considered for the analysis of correlation between troponin and lesion complexity. For the diagnosis of unstable angina, we considered: pain or discomfort in the chest, epigastrium, mandible, shoulder, back or upper limbs, with onset at rest, and of early or progressive onset.<sup>10</sup>

Anatomical complexity of coronary lesions was classified by the SYNTAX score, using a validated calculator available at <http://www.syntaxscore.com>. The score evaluates the number, localization, extension and morphology of lesions. Patients with scores lower than 22 were considered at low risk, patients with scores from 23 to 32 were considered at moderate risk, and those with scores higher than 32 were considered at high risk. All tests were revised and the score rated by the same experienced hemodynamic technician.

TIMI and GRACE clinical scores were used for risk stratification of the included patients. GRACE score was calculated using the electronic calculator available at [http://www.outcomes-umassmed.org/GRACE/acs\\_risk/acs\\_risk\\_content.html](http://www.outcomes-umassmed.org/GRACE/acs_risk/acs_risk_content.html). Patients with a score lower than 109 were considered at low risk; patients with a score between 109 and 140 were considered at intermediate risk, and those with scores higher than 140 were considered at high cardiovascular risk.

Patients were considered diabetic if they met one of the following criteria, according to the Brazilian Diabetes Society Guidelines:<sup>11</sup> previous diagnosis of the disease and use of glucose-lowering agents; patients without a previous diagnosis of the disease with fasting glucose levels equal to or greater than 126 mg/dL, plasma glucose level after a 75 g glucose load equal to or greater than 200 mg/dL, casual glucose level equal to or greater than 200 mg/dL associated with classical symptoms (polyuria, polydipsia, unexplained weight loss), or glycated hemoglobin levels higher than 6.5%.<sup>11</sup> Patients who reported smoking a cigarette in the year prior to the study, and those who had quit smoking less than 30 days were considered smokers.

Inclusion criteria were: patients older than 18 years with a confirmed diagnosis of ACS according to the Third Universal Definition of Myocardial Infarction.<sup>3</sup> Patients who had not undergone a coronary angiography during hospitalization were excluded from the study.

The study was approved by the research ethics committee of the Federal University of Mato Grosso do Sul (approval number 51783415.1.0000.0021).

## Statistical analysis

Linear correlations of hsTn levels with TIMI, GRACE and SYNTAX scores were assessed by the nonparametric Spearman correlation coefficient, since the data did not pass the Shapiro-Wilk test for normality. The other results were described using descriptive statistics or in tables

and graphics. Quantitative variables were expressed as median and interquartile range, and categorical variables as relative and absolute frequency. Statistical analyses were performed using the SPSS software version 24.0, and statistical significance was set at 5%.<sup>12</sup>

### Limitations

- Small number of patients;
- Some of the medical records data were missing, which made the exact calculation of the GRACE and TIMI prognostic score impossible; data of family history were also missing in 35.6% of the medical records. Most medical records did not contain patients' body weight or time of symptom onset, which were required for TIMI calculation in patients with ST-segment elevation myocardial infarction (STEMI). No patient was rated because of missing body weight, since, from our experience, for most patients, body weight must have been greater than 67 kg. However, all patients were rated for 'time of symptom onset', since due to a failure in the city's control system, most patients have been suffering pain for more than 4 hours when admitted to the service. For this reason, some patients may have received a score higher than they actually had, since some characteristics may have not been properly rated.
- Patients with previous myocardial revascularization were not included in the analysis using the SYNTAX score, since this instrument does not consider the history of bypass.
- Lack of standardization in the time of blood collection for troponin measurement, as well as lack of some measurements due to structural and operational problems of the service. This limitation may have influenced the detection of the peak concentration of this biomarker.

### Results

Patients' age varied from 37 to 92 years, and most patients were women, hypertensive, non-diabetic and non-smokers. Only 20.7% (n = 36) of patients had a positive history of CAD. Forty percent of the patients used acetylsalicylic acid (ASA) at the moment of the event, and most of them reported episodes of severe angina, without ST-segment depression in electrocardiography. Electrocardiographic changes other than ST-segment elevation or depression were not considered for analyses.

Of the 174 patients evaluated, 19.0% (n = 33) had the diagnosis of STEMI, 43.1% (n = 75) had non ST-segment

elevation myocardial infarction (non-STEMI), and 36.8% (n = 64) had unstable angina. Most patients were in Killip class I at admission. These results and the distribution of patients by history of diseases and Killip classification are described in Table 1.

Results of quantitative clinical variables (vital data, biochemical and risk parameters) are described in Table 2. Median hsTn was 67 pg/mL.

There was a significant moderate, positive linear correlation between hsTn levels and SYNTAX score ( $p < 0.001$ ,  $r = 0.440$ ) (Figure 1). In addition, a significant but weak positive linear correlation was found of hsTn levels with TIMI score ( $p < 0.001$ ,  $r = 0.267$ ), and GRACE score ( $p = 0.001$ ,  $r = 0.261$ ) (Figures 2 and 3, respectively).

### Discussion

The relationship between altered hsTn and the prognosis of ACS patients has been consistently demonstrated in previous studies. However, few studies have correlated hsTn levels with the complexity of coronary lesions in patients undergoing coronary angiography.<sup>9</sup> Similarly, few studies comparing troponin levels with well-established clinical prognostic scores, such as TIMI and GRACE, have been found in the literature.

Our results indicate that there is a significant, positive moderate linear correlation of hsTn levels with the complexity of coronary lesions evaluated by the SYNTAX scoring system. These findings may be explained by the fact that zero point has been assigned to many patients (n = 65/174), and many patients have not been rated because of the history of myocardial revascularization in SYNTAX score. In contrast, although patients with STEMI were the minority (33/174), they showed higher severity, and consequently higher hsTn levels (mean 3.073 pg/dL). However, we also included patients with unstable angina, who did not show increased hsTn levels, which may have caused a decrease in the mean value. For these reasons, despite positive, the importance of this correlation may be questioned.

In the study by Altun et al.,<sup>9</sup> involving 287 patients, a linear correlation of hsTn levels with the complexity of coronary lesions measured by the SYNTAX score was also reported, but with lower statistical power ( $r = 0.327$ ) compared with our study ( $r = 0.440$ ). The authors established a cut-off point for hsTn, above which the severity of coronary lesions was higher (high SYNTAX scores). This is a relevant conclusion, considering the

**Table 1 - Age, history of diseases and Killip classification in patients diagnosed with acute coronary syndrome, who underwent cardiac catheterization**

Variable	Median (IQR) or % (n)
Age (years)	63.5 (16.5)
Sex	
Female	52.9 (92)
Male	47.1 (82)
SAH	
No	11.5 (20)
Yes	88.5 (154)
Diabetes Mellitus	
No	60.3 (105)
Yes	39.7 (69)
STEMI	
No	81.0 (141)
Yes	19.0 (33)
Non-STEMI	
No	56.3 (98)
Yes	43.1 (75)
Missing information	0.6 (1)
Unstable angina	
No	62.6 (109)
Yes	36.8 (64)
Missing information	0.6 (1)
Smoking	
No	66.7 (116)
Yes	25.3 (44)
Missing information	8.0 (14)
Family history	
No	43.7 (76)
Yes	20.7 (36)
Missing information	35.6 (62)
ASA	
No	47.1 (82)
Yes	42.5 (74)
Missing information	10.3 (18)

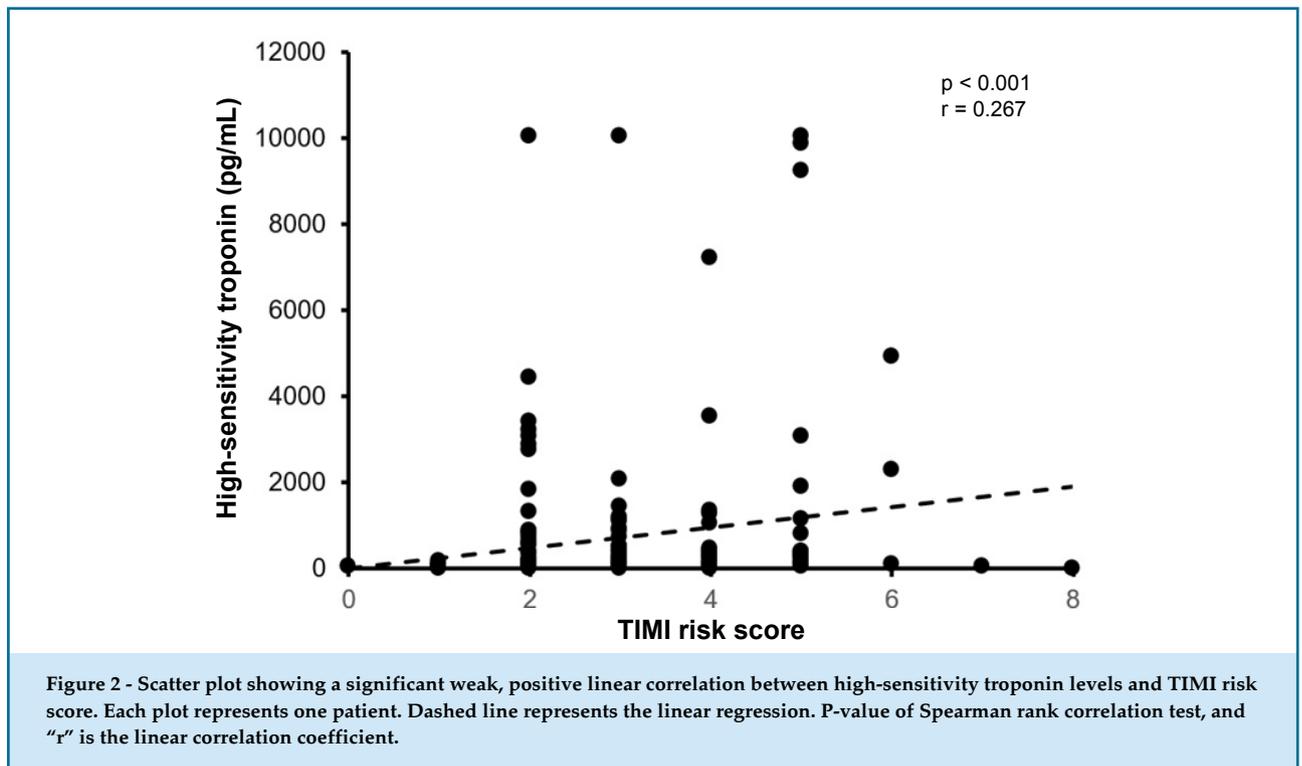
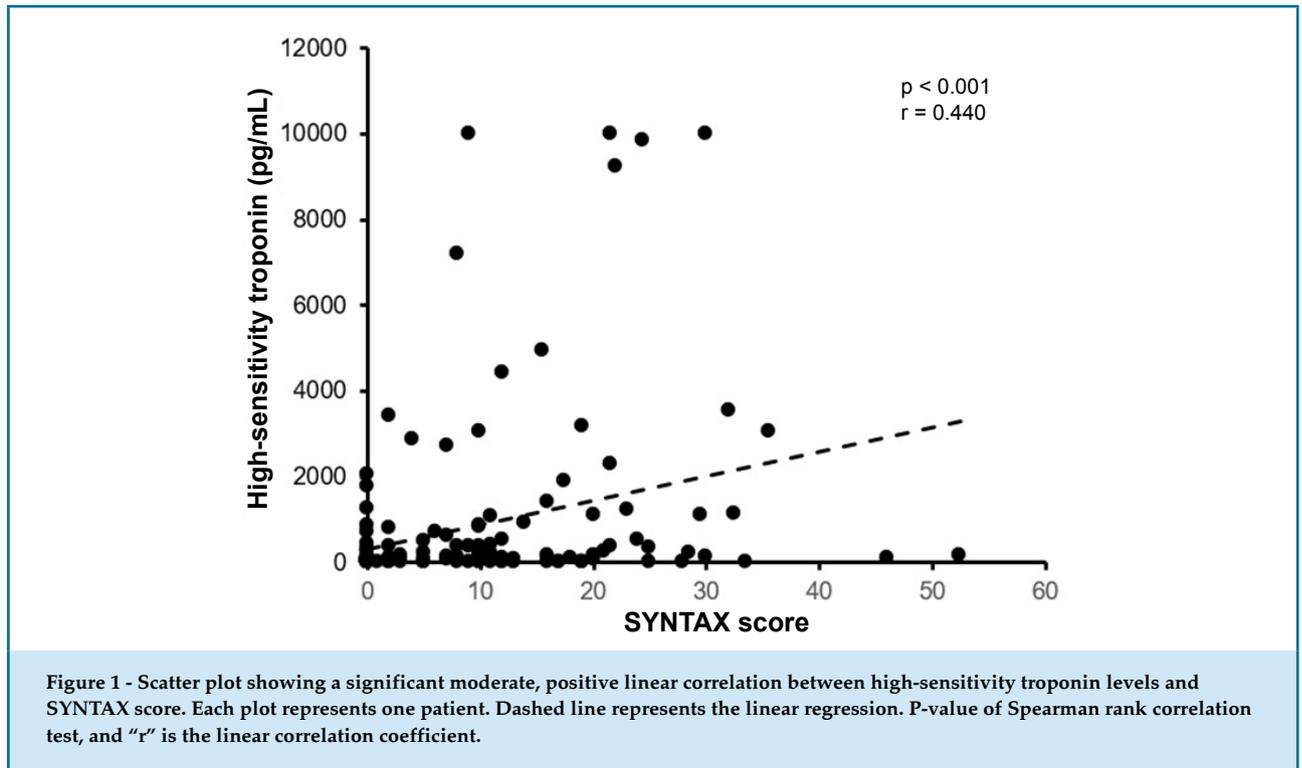
Severe angina	
No	19.0 (33)
Yes	78.2 (136)
Missing information	2.9 (5)
ST depression	
No	86.8 (151)
Yes	6.9 (12)
Missing information	6.3 (11)
Killip	
1	82.8 (144)
2	15.5 (27)
3	1.7 (3)

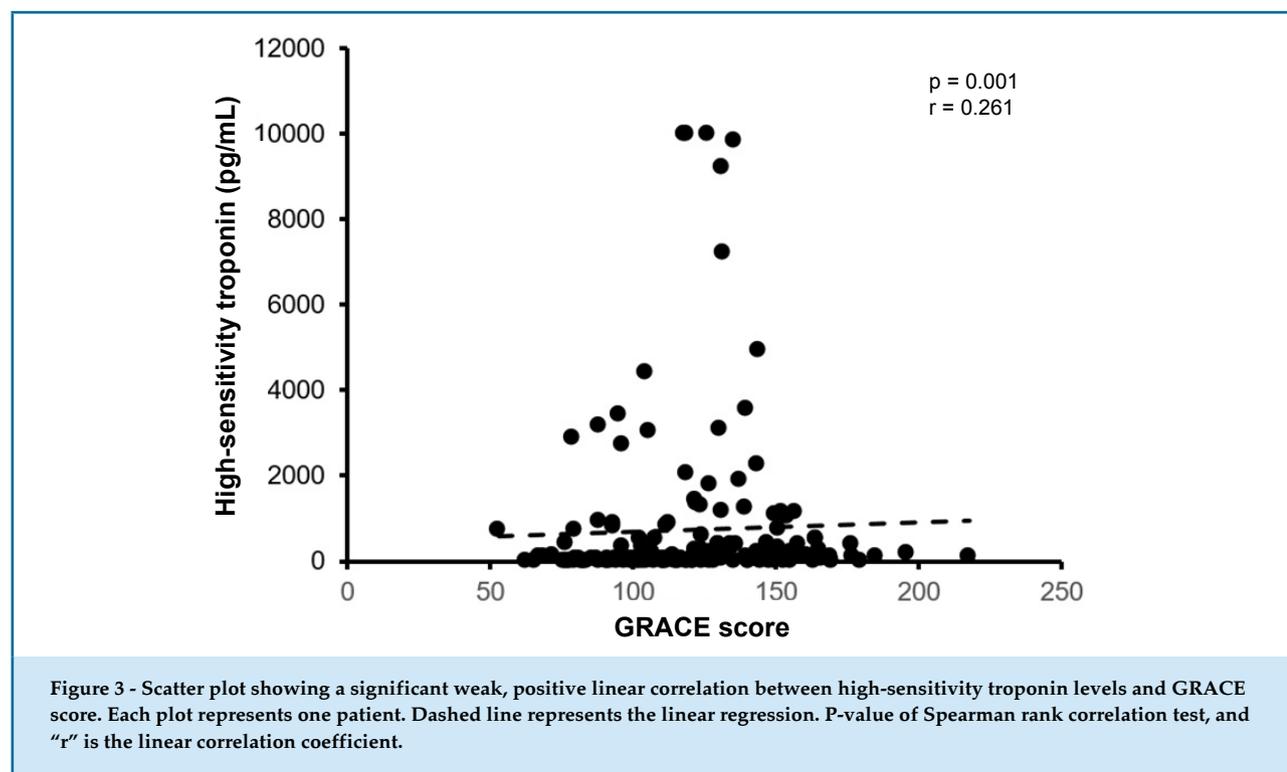
*IQR: Interquartile range; SAH: systemic arterial hypertension; ASA: acetylsalicylic acid; STEMI: ST-segment elevation myocardial infarction; ST: ST-segment.*

**Table 2 - Results of quantitative clinical variables (vital data, biochemical and risk parameters) in patients with acute coronary syndrome, who underwent cardiac catheterization**

Variable	Median (IQR)
Heart rate (bpm)	80 (21)
SBP (mmHg)	130 (33)
Ejection fraction (%)	59 (21)
Total cholesterol (mg/dL)	181 (72)
Non-HDL cholesterol (mg/dL)	133 (68)
HDL (mg/dL)	43 (18)
LDL (mg/dL)	106 (68)
Triglycerides (mg/dL)	127 (86)
Troponin (pg/mL)	67 (38)
Creatinine (mg/dL)	1 (1)
CRP	7 (16)
Killip (points)	1 (0)
TIMI (points)	3 (2)
GRACE (points)	121 (43)
SYNTAX (points)	3 (12)

*IQR: Interquartile range; SBP: systolic blood pressure; CRP: C-reactive protein; HDL: high density lipoprotein; LDL: low density lipoprotein.*





high sensitivity of the troponin used in our study, and the possibility of increased hsTn levels in conditions other than ACSs, such as sepsis, stroke, among others.

Although previous studies on the subject have compared troponin levels with the severity of coronary lesions, neither hsTn nor the SYNTAX score for evaluation of the severity of these lesions was used in these studies. One example was the Brazilian study by Faria RC.<sup>13</sup> The author compared the levels of troponin I with the severity of coronary lesions, which was measured by characteristics of the lesions in cardiac catheterization or changes in coronary circulation. In this study, although the author found no statistically significant correlation between increased troponin I levels and lesion severity or coronary circulation, the protein levels were correlated with a higher number of obstructive lesions and the presence of thrombus.<sup>13</sup>

In addition, in our study, hsTn levels were correlated with GRACE and TIMI clinical prognostic scores. The linear correlation between these parameters, despite weak, suggests a worse prognosis of patients with higher levels of this biomarker.

Median GRACE and TIMI scores (121 and 3, respectively) found in our population indicated an intermediate risk in these patients, whose hsTn levels

were 4 times the upper limit of normal range (cut-off point: 14 pg/dL).

In a similar study by Biener et al.,<sup>14</sup> rising and falling changes of hsTn at admission were correlated with GRACE risk score, aiming to evaluate whether these changes would improve the prognostic performance of the score. The authors suggested that a GRACE score  $\geq 140$  points and hsTn admission values above the 99th percentile are reliable indicators of adverse cardiovascular events in hospitalized patients with suspicious of ACS. Nevertheless, neither rising nor falling hsTn kinetic changes seemed to add prognostic information.<sup>14</sup>

Although we did not evaluate the presence of kinetic changes or the possibility of future cardiovascular events, we found slightly increased hsTn levels associated with intermediate GRACE score values. The linear relationship, despite weak, may also suggest a worse prognosis in these patients.

With respect to TIMI score, we also found some studies that directly compared it with troponin. Gomes et al.,<sup>15</sup> for example, evaluated the relative contribution of hsTn to the final risk classification of patients with ACS without ST-segment elevation, previously evaluated by the TIMI score, and found that hsTn contributed to their

reclassification to a higher risk. O'Donoghue et al.,<sup>16</sup> after evaluating several biomarkers, concluded that troponin T was associated with higher TIMI scores. Although the authors did not use hsTn in their study, these data corroborate our findings.

Therefore, there is a correlation between hsTn and the complexity of lesions quantified by the anatomical SYNTAX score in ACS patients, and a correlation of this biomarker with the prognostic clinical scores GRACE and TIMI. Thus, despite the limitations in blood collection for troponin measurements, and late admission of patients to the emergency department, troponin was shown to be a biomarker capable of predicting intermediate levels of risk score and higher complexity of coronary lesions, indicating a worse prognosis. Additional studies, including larger samples and the follow-up of future cardiovascular events, are needed to better evaluate and, if possible, to identify the cut-off point for hsTn, indicative of a worse prognosis.

Although it was not the aim of the present study, LDL-cholesterol levels were not very increased, as the study population was classified as intermediate risk. Even with borderline cholesterol levels, patients had acute coronary event, which highlights the importance of other associated risk factors.

In addition, although this parameter was not measured in the whole sample due to insufficient data, increased c-reactive protein levels were found in our population (reference value < 5 mg/dL in our institution). This indicates a higher inflammation status, which has been well correlated with increased risk for acute coronary events.

## Conclusion

The present study found a significant moderate positive linear correlation between hsTn levels and

the complexity of coronary lesions evaluated by the SYNTAX score. Besides, a weak correlation was found between this biomarker and the TIMI and GRACE clinical prognostic scores.

## Author contributions

Conception and design of the research: Cardoso MR, Silva Junior DG. Acquisition of data: Cardoso MR, Ribeiro EA, Rocha Neto AM. Analysis and interpretation of the data: Cardoso MR, Silva Junior DG, Ribeiro EA, Rocha Neto AM. Statistical analysis: Cardoso MR, Silva Junior DG. Writing of the manuscript: Cardoso MR. Critical revision of the manuscript for intellectual content: Silva Junior DG.

## Potential Conflict of Interest

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

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## Study Association

This article is part of the thesis of completion of course work (Residence in Cardiology) submitted by Monique Rodrigues Cardoso, from Universidade Federal de Mato Grosso do Sul.

## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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