

# Elevated High-Sensitivity Troponin I in the Stabilized Phase after an Acute Coronary Syndrome Predicts All-Cause and Cardiovascular Mortality in a Highly Admixed Population: A 7-Year Cohort

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## Abstract

**Background:** High-sensitivity cardiac troponin I (hs-cTnI) has played an important role in the risk stratification of patients during the in-hospital phase of acute coronary syndrome (ACS), but few studies have determined its role as a long-term prognostic marker in the outpatient setting.

**Objective:** To investigate the association between levels of hs-cTnI measured in the subacute phase after an ACS event and long-term prognosis in a highly admixed population.

**Methods:** We measured levels of hs-cTnI in 525 patients 25 to 90 days after admission for an ACS event; these patients were then divided into tertiles according to hs-cTnI levels and followed for up to 7 years. We compared all-cause and cardiovascular mortality using Cox proportional hazards models and adopting a significance level of 5%.

**Results:** After a median follow-up of 51 months, patients in the highest tertile had a greater hazard ratio (HR) for all-cause mortality after adjustment for age, sex, known cardiovascular risk factors, medication use, and demographic factors (HR: 3.84, 95% CI: 1.92-8.12). These findings persisted after further adjustment for estimated glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup> and left ventricular ejection fraction < 0.40 (HR: 6.53, 95% CI: 2.12-20.14). Cardiovascular mortality was significantly higher in the highest tertile after adjustment for age and sex (HR: 5.65, 95% CI: 1.94-16.47) and both in the first (HR: 4.90, 95% CI: 1.35-17.82) and second models of multivariate adjustment (HR: 5.89, 95% CI: 1.08-32.27).

**Conclusions:** Elevated hs-cTnI levels measured in the stabilized phase after an ACS event are independent predictors of all-cause and cardiovascular mortality in a highly admixed population. (Arq Bras Cardiol. 2018; [online].ahead print, PP0-0)

**Keywords:** Coronary Artery Disease / mortality; Troponin I; Prognosis; Metabolic Syndrome; Biological Variation, Population; Risk Factors.

## Introduction

Acute coronary syndrome (ACS) is a major driver of mortality and the leading cause of years of life lost worldwide.<sup>1</sup> In recent decades, several therapeutic interventions have been proven beneficial in the treatment of ACS, and structured strategies for early diagnosis and appropriate treatment have been recommended by several cardiology societies.<sup>2-5</sup> Because of the progress made in therapeutics for ACS, a heterogeneous group of survivors from this condition has received long-term follow-up from medical services. The prognosis of patients in the stabilized phase after ACS varies widely;<sup>6</sup> validation of easily obtainable, low-cost prognostic markers may enhance long-term risk stratification in this population.

Several studies showed cardiac troponins (cTns) to be more sensitive and specific for diagnosing myocardial infarction, and to have greater correlation with higher mortality than the previous reference standard, creatine kinase isoenzyme MB (CK-MB).<sup>7-11</sup> Over the past two decades, new assays have been developed which conferred greater sensitivity to the diagnosis of myocardial infarction; these high-sensitivity cardiac troponins (hs-cTns) showed greater accuracy in discriminating patients at higher risk for death, even in those who had undetectable first-generation cTn levels.<sup>12</sup> More recently, the use of hs-cTnT as a prognostic marker in the subacute phase after an ACS episode has been studied in an European cohort of white patients.<sup>13</sup> These findings have not been replicated in more heterogeneous populations in the developing world. In this single-center observational cohort, we aimed to study the association of elevated levels of hs-cTnI with long-term all-cause and cardiovascular mortality in a highly admixed population in Brazil.

## Methods

The Strategy of Registry of Acute Coronary Syndrome (ERICO) study design has been described in detail elsewhere.<sup>14,15</sup> In brief, ERICO is a prospective cohort

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study of ACS patients enrolled between February 2009 and December 2013 at a community hospital in Sao Paulo, Brazil. All patients with suspected acute coronary syndrome in the emergency department were screened for participation in the study. ERICO participants must fulfill diagnostic criteria for ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA); the criteria used to define acute coronary syndromes were:<sup>14</sup>

1) Myocardial infarction (MI): presence of symptoms consistent with cardiac ischemia within 24 hours of hospital presentation, and troponin I levels above the 99th percentile with a test-specific coefficient of variation < 10%.

1a) STEMI: presence of criteria for MI plus one of the following: persistent ST segment elevation  $\geq 1$  mm in two contiguous electrocardiographic leads, or the presence of a new or presumably new left bundle branch block.

1b) NSTEMI: presence of criteria for MI, but not STEMI.

2) UA: symptoms consistent with cardiac ischemia 24 hours prior to hospital admission, absence of MI criteria, and at least one of the following: history of coronary heart disease; positive coronary disease stratification test (invasive or noninvasive); transient ST segment changes  $\geq 0.5$  mm in two contiguous leads, new T-wave inversion  $\geq 1$  mm, and/or pseudonormalization of previously inverted T-waves; troponin I  $\geq 0.4$  ng/ml; or diagnostic concordance of two independent physicians.

During the in-hospital phase, all subjects were treated at the discretion of the hospital staff with standard procedures, without influence from the study. The study protocol was approved by the Institutional Review Board addressing research in human participants. All participants provided written informed consent for the study.

Participants were interviewed during admission to the hospital and provided data regarding sociodemographic factors, medical history, and main cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia, smoking, physical inactivity, cocaine use, menopause, and familial and personal history of coronary heart disease). Three physicians were responsible for reviewing patient information and for validating ACS cases. According to the study protocol, a blood sample was drawn for laboratory tests (troponin I, MB-creatinine kinase, serum glucose, total cholesterol, HDL and LDL-cholesterol, triglycerides and total blood cell count).

At approximately 30 days after the event, participants were invited to undergo a new on-site evaluation by a physician to update data on cardiovascular risk stratification, current medication use, and additional clinical data. New blood samples were also collected. At six months after the index event and annually thereafter, all participants were contacted by phone to update information about their vital status, cardiovascular history, medications and symptoms.

All participants enrolled in the ERICO study who had blood samples collected 25 to 90 days after an ACS episode were included in this analysis. The lower limit of this interval was chosen to avoid confounding by the expected elevated circulating cTn levels in the first few days after an ACS episode; the upper limit of 90 days allows comparison with previous studies,<sup>13,16</sup> although there is currently no widely accepted definition of subacute phase after ACS in the literature.

High-sensitivity cardiac troponin I was measured in all patients at presentation and in the subacute phase after the event. The assay used to measure hs-cTnI was the Advia Centaur TnI-Ultra Assay (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA), with the 99th percentile reference value of 0.04 mcg/L in healthy subjects and coefficient of variance lower than 10% at this range. Subjects were classified into three subgroups according to hs-cTnI tertiles in the subacute phase after the index ACS event.

In this study, our endpoints were all-cause mortality and cardiovascular mortality. We searched official death records on a regular basis for information about all participants if (1) we received information that they had died or (2) we could not contact them at the time. Municipal and state health offices searched their files to obtain death certificates and returned the results of this search to the ERICO research team. Two medical doctors reviewed these data and classified the cause of death for deceased participants according to the information from the death certificates. Participants were defined to have died from a cardiovascular cause (cardiovascular mortality) if we identified a cause of death classified in Chapter IX of the 10th version of the International Classification of Diseases (ICD-10), entitled "Diseases of the circulatory system", or if we identified a cause of death classified with the ICD-10 code R57.0 "Cardiogenic shock".

### Statistical analysis

The statistical analyses were performed with R for Mac version 3.5.0. Categorical variables are presented as proportions and compared using the chi-square test. To test the assumption of normality in the distribution of continuous variables, we used the Shapiro-Wilk test. Continuous variables with normal distribution are presented as means (standard deviations) and compared using one-way ANOVA. Continuous variables with non-normal distribution are presented as medians (interquartile intervals) and compared using the Kruskal-Wallis test. Cumulative survival probabilities across the tertiles are presented as Kaplan-Meier curves and compared using the log-rank test.

We built Cox proportional hazard models for all-cause mortality and cardiovascular mortality, and presented them as crude, age-sex adjusted, and two multivariate models. Model 1 was adjusted for age, sex, ACS subtype, traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking history, and body mass index), and medication use at the first follow-up visit (aspirin, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and statins). Model 2 was additionally adjusted for estimated glomerular filtration rate (GFR) < 60 ml/min/1.73 m<sup>2</sup> and left ventricular ejection fraction < 0.40, two variables associated with worse prognosis in previous studies.<sup>13,17</sup> All tests were two-sided, and p value < 0.05 was considered significant.

### Results

From February 2009 to December 2013, 1085 patients were enrolled in the ERICO study. Blood samples were collected at the emergency room and between 25 and 90 days after the initial event from 525 of these participants, who were included

in the present study (median second collection interval: 39 days after the index event; interquartile range: 33-50 days). The initial diagnosis was STEMI in 144 (27.4%) patients, NSTEMI in 230 (43.8%), and UA in 151 (28.8%). The mean age was 61.6 years and 60.2% were men. The main cardiovascular risk factors found in this population were hypertension (75.5%), current or previous smoking (66.9%), and sedentary lifestyle (69.9%). Cutoff values for hs-cTnI among the tertiles were: < 0.012, 0.013-0.023 and > 0.023 mcg/L. Most hs-cTnI samples collected from patients in the subacute phase after ACS were below the 99th percentile of the method (83.8%). Patients were followed for a median of 51 months; baseline characteristics of the study according to hs-cTnI tertiles are shown in Table 1. Individuals in the highest tertile were more likely to be male, have STEMI or NSTEMI diagnoses at the index event, and chronic kidney disease and sedentary lifestyle at baseline.

From the data collected after patient admission, lower glomerular filtration rate (calculated according to CKD-Epi) and lower ejection fraction estimated in echocardiography were strongly correlated with persistently elevated levels of hs-cTnI ( $p < 0.001$ ).

Figure 1 shows the Kaplan-Meier curves for cumulative survival according to each hs-cTnI tertile during follow-up. We found significantly lower survival rates in individuals in the highest tertile ( $p < 0.001$ ). Analyses evaluating cardiovascular mortality as the main outcome showed similar findings (Figure 2).

Table 2 shows the results of the Cox regression analyses. Participants in the third tertile of troponin, using the first tertile as the reference, presented a hazard ratio (HR) of 4.14 (95% Confidence Interval [95% CI]: 2.19-7.86) for all-cause mortality after adjustment for age and sex; this effect persisted in multivariate adjustment models 1 (HR: 3.84, 95% CI: 1.92- 8.12) and 2 (HR: 6.53, 95% CI: 2.12-20.14). For cardiovascular mortality, there were significant differences between the first and the third tertiles after adjustment for age and sex (HR: 5.65, 95% CI: 1.94-16.47), and both multivariate adjustment models 1 (HR: 4.90, 95% CI: 1.35-17.82) and 2 (HR: 5.89, 95% CI: 1.08-32.27).

## Discussion

In this cohort of patients with hs-cTnI levels measured 25 to 90 days after an ACS event, participants had sociodemographic characteristics and cardiovascular comorbidities similar to that of large international registries, like the Global Registry of Acute Coronary Events (GRACE).<sup>18</sup> As in this registry, our cohort had a predominantly male population with a high prevalence of hypertension; other cardiovascular risk factors, such as heart failure and smoking history, were more prevalent in our study. The most frequent ACS type in our study was NSTEMI (41.5% of participants), which is also consistent with the current trend in the incidence of MI,<sup>19</sup> although contrasting with the smaller frequency of NSTEMI in the GRACE cohort (26% of participants).<sup>18</sup>

Medication use on the first follow-up visit was similar to the treatment received on discharge by participants in the Brazilian Registry on Acute Coronary Syndromes (BRACE) study, which included hospitals of all regions of Brazil.<sup>20</sup> When we evaluated

the percentage of patients receiving each therapeutic group, we found clear similarities between our study and BRACE for the use of aspirin (83.6% vs 86.0%, respectively), clopidogrel (53.0% vs 50.1%), betablockers (64.2% vs 69.8%), ACE inhibitors/angiotensin receptor blockers (68.3% vs 70.6%) and statins (76.4% vs 82.7%). These data also show that adherence to guideline-recommended therapies was still not optimal by the time of enrollment of these participants.

Most patients in our study (83.8%) had hs-cTnI levels below the 99th percentile during the subacute phase after an ACS event; nevertheless, even at this range, those in the highest tertile had a greater hazard ratio for all-cause and cardiovascular mortality compared to the first tertile. Elevated levels of hs-cTnI at 25 to 90 days post-ACS remained an independent risk factor for all-cause and cardiovascular mortality after adjustment for multiple confounders.

The mechanisms by which some patients present persistent elevations in cardiac troponin levels are not well established. Previous experimental studies demonstrated the incidence of chronic myocardial injury after induced mechanical coronary obstruction in rats;<sup>21</sup> accelerated apoptosis due to chronic myocardial dysfunction has also been shown in patients with heart failure.<sup>22</sup> Other speculated mechanisms include normal myocyte turnover, cellular release of proteolytic degradation products, higher myocyte cell wall permeability, and the formation of blebs in the cellular walls with the presence of these proteins.<sup>23</sup>

The association between higher levels of cardiac troponins and worse outcomes in out- of-hospital settings has been reported by previous studies. In 2007, Eggers et al.<sup>16</sup> analyzed a cohort of patients with earlier-generation cardiac troponin I (cTnI) measured at 6 weeks, 3 and 6 months after an ACS event. Throughout this study, the subgroup of patients with permanently elevated levels of cTnI ( $\geq 0.01$ ) had a greater probability of death during follow-up than patients with transiently elevated or negative cTnI.<sup>16</sup>

In 2012, two studies addressed the prognostic role of high-sensitivity cardiac troponin T (hs-cTnT) in the stabilized phase after a cardiac event. Ang et al.<sup>13</sup> followed 326 patients for a median of 30 months, after measurement of hs-cTnT 7 weeks post-ACS; after adjustment for age, ACS subtype, hypertension, type 2 diabetes, smoking, anemia, BNP, estimated GFR, and echocardiographic findings, hs-cTnT remained a strong predictor of death and AMI during follow-up.<sup>1</sup> Koenig et al.<sup>24</sup> studied 1050 patients for a median of 8.1 years after an ACS event or CABG, with hs-cTnT levels measured approximately 43 days after the event; patients in the highest quartile were at increased risk for new cardiac events throughout the observation period. One study published in 2014 also addressed the prognostic role of hs-cTnI after an ACS episode. White et al.<sup>25</sup> followed 7,836 patients who had suffered an ACS event; after a median of 6 years follow-up, patients in the highest tertile were at increased risk for CAD death and MI. Compared to our study population, these studies followed patients with similar ages and estimated GFR, but with lower baseline frequency of hypertension, diabetes, and dyslipidemia.

**Table 1 – Baseline characteristics of the study population according to 25–90 day troponin tertile**

Characteristic	1 <sup>st</sup> tertile	2 <sup>nd</sup> tertile	3 <sup>rd</sup> tertile	p-value
Number of participants	179	171	175	
25–90 day troponin range	< 0.012	0.012–0.023	> 0.023	
<b>ACS subtype (%)</b>				
UA	80 (44.9)	47 (27.5)	24 (13.7)	
NSTEMI	67 (37.4)	77 (45.0)	86 (49.1)	< 0.001
STEMI	32 (17.9)	47 (27.5)	65 (37.1)	
Age* (years)	60 (51-68)	63 (55-70)	61 (53-73)	0.05
Male gender (%)	95 (53.1)	102 (59.6)	119 (68.0)	0.02
Previous history of CHD (%)	49 (29.2)	39 (23.8)	40 (25.2)	0.51
Family history of CHD (%)	52 (36.4)	43 (31.4)	50 (38.46)	0.46
Hypertension (%)	136 (78.2)	127 (75.1)	126 (73.3)	0.56
Diabetes (%)	61 (35.7)	61 (37.2)	67 (39.6)	0.75
Dyslipidemia (%)	87 (54.4)	85 (55.6)	75 (48.4)	0.40
Heart failure (%)	27 (16.2)	36 (22.4)	39 (23.8)	0.19
Chronic kidney disease (%)	5 (3.1)	6 (4.1)	15 (10.3)	0.02
Previous stroke (%)	17 (9.9)	15 (9.1)	21 (12.1)	0.91
Sedentary lifestyle (%)	117 (68.8)	106 (63.5)	127 (77.4)	0.02
<b>Smoking status (%)</b>				
Current	44 (25.6)	48 (28.7)	58 (33.9)	
Past	68 (39.5)	64 (38.3)	69 (40.4)	0.31
Never	60 (34.9)	55 (32.9)	44 (25.7)	
Body mass index*	27.1 (24.5-30.4)	26.6 (24.2-29.4)	26.0 (23.5-29.4)	0.05
Total cholesterol* (mg/dL)	174 (145-205)	169 (139-207)	174 (141-205)	
LDL cholesterol* (mg/dL)	101 (79-133)	103 (79-136)	109 (80-135)	
HDL cholesterol* (mg/dL)	37 (31-44)	36 (31-44)	36 (30-44)	0.65
Triglycerides* (mg/dL)	131 (100–190)	141 (97–192)	130 (97–181)	
Hemoglobin* (g/dL)	14.3 (13.4-15.2)	14.1 (13.1-15.2)	14.2 (12.9-15.4)	0.84
Troponin levels on admission† (mcg/L)	1.88 (0.09–9.20)	7.03 (1.16–41.97)	16.82 (3.05–44.16)	0.32
Estimated GFR-CKD-Epi* (ml/min/1.73 m <sup>2</sup> )	83 (67-95)	79 (62-92)	71 (48-94)	<0.001
LVEF < 0.40 (%)	4 (3.5)	8 (6.6)	28 (21.9)	<0.001
<b>Medication at 1<sup>st</sup> follow-up (%)</b>				
Aspirin	155 (87.6)	143 (83.6)	134 (79.3)	0.12
Clopidogrel	92 (52.0)	100 (58.5)	82 (48.5)	0.17
Beta blocker	117 (66.1)	119 (69.6)	96 (56.8)	0.04
Statin	137 (77.4)	135 (78.9)	123 (72.8)	0.38
ACE inhibitor	120 (67.8)	108 (63.2)	94 (55.6)	0.06
Angiotensin receptor blocker	10 (5.6)	15 (8.8)	6 (3.6)	0.12

\* Median (Interquartile interval).

Outside the scope of ACS, several studies have also found an association between elevated cTn levels and risk of death. In patients with stable coronary heart disease, a greater risk for cardiovascular mortality and incidence of heart failure has been found in those with higher levels of hs-cTnT<sup>26-28</sup> and hs-cTnI.<sup>29</sup> Elevated circulating hs-cTnT was also shown

to be independently associated with higher mortality in outpatients with stable heart failure,<sup>30,31</sup> and in patients with aortic stenosis.<sup>32</sup> Even in the general population, de Lemos et al.<sup>33</sup> found an association between high levels of hs-cTnT and poorer survival in a population-based cohort of 3546 individuals. These results suggest that persistently

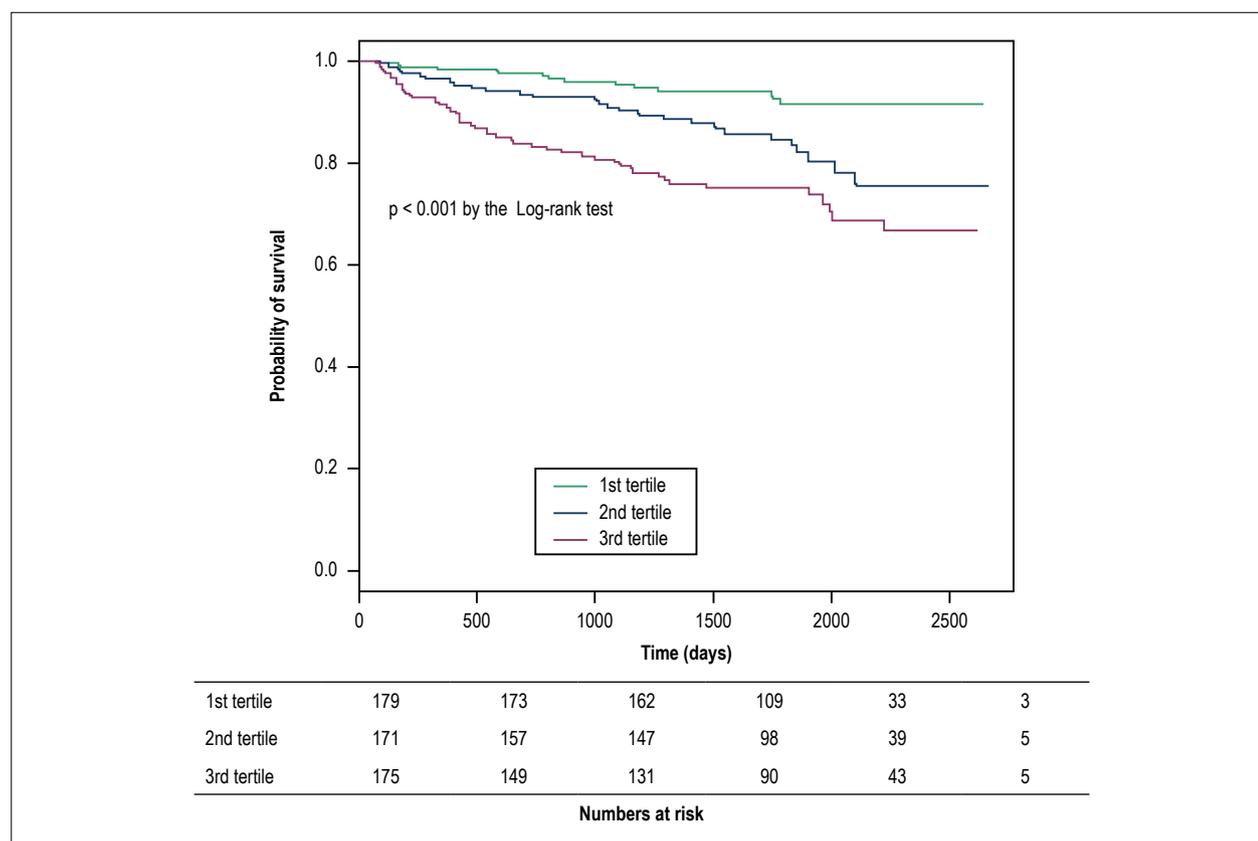


Figure 1 – Kaplan-Meier curve for all-cause mortality according to hs-cTnI tertile measured 25 to 90 days after acute coronary syndrome.

elevated levels of circulating cardiac troponins are general markers of higher risk for death in different populations, independently of age and comorbidities.

Some aspects of our study should be highlighted. First, it was conducted at a community-based hospital with no in-house cardiology staff; this type of medical care is received by many ACS patients in Brazil, but few prognostic studies have been published in this setting. Second, our sample size and long-term follow-up make this one of the largest studies with prognostic biomarkers in ACS patients in Brazil. In addition, because we searched for the death records of all patients who could not be contacted during follow-up, our analysis of all-cause mortality was not significantly affected by selection bias.

This study has some limitations. As in all single-center studies, outcomes in both groups could have been influenced by local practices. Since coronary interventions were not performed on-site, data regarding type of revascularization (if any) were not accessible for most patients and could not be accounted for in our Cox model. We also did not have data about the proportion of patients presenting with STEMI who received reperfusion therapy. Additionally, adherence to guideline recommended therapies for ACS was suboptimal in our cohort. Lastly, even though we used standardized assays to measure all troponin levels in the subacute phase of ACS,

these were not the same assays used on admission of these patients to the hospital; this precluded further analyses of evolutive trends in hs-cTnI levels through time. Despite these limitations, our findings could demonstrate an association between elevated levels of hs-cTnI and worse outcomes in this highly admixed population.

## Conclusions

Elevated levels of hs-cTnI in the stabilized phase after an ACS event are associated with higher all-cause and cardiovascular mortality that is independent from comorbidities, renal function and left ventricular ejection fraction. These findings may potentially enhance risk stratification of post-ACS patients in the ambulatory setting.

## Author contributions

Conception and design of the research: Castro LT, Bittencourt MS, Lotufo PA, Bensenor IM; acquisition of data: Castro LT, Santos IS, Goulart AC, Lotufo PA, Bensenor IM; analysis and interpretation of the data: Castro LT, Santos IS, Goulart AC, Pereira AC, Staniak HL, Bittencourt MS, Bensenor IM; statistical analysis: Castro LT, Santos IS, Goulart AC, Bittencourt MS, Bensenor IM; writing of the manuscript: Castro LT, critical

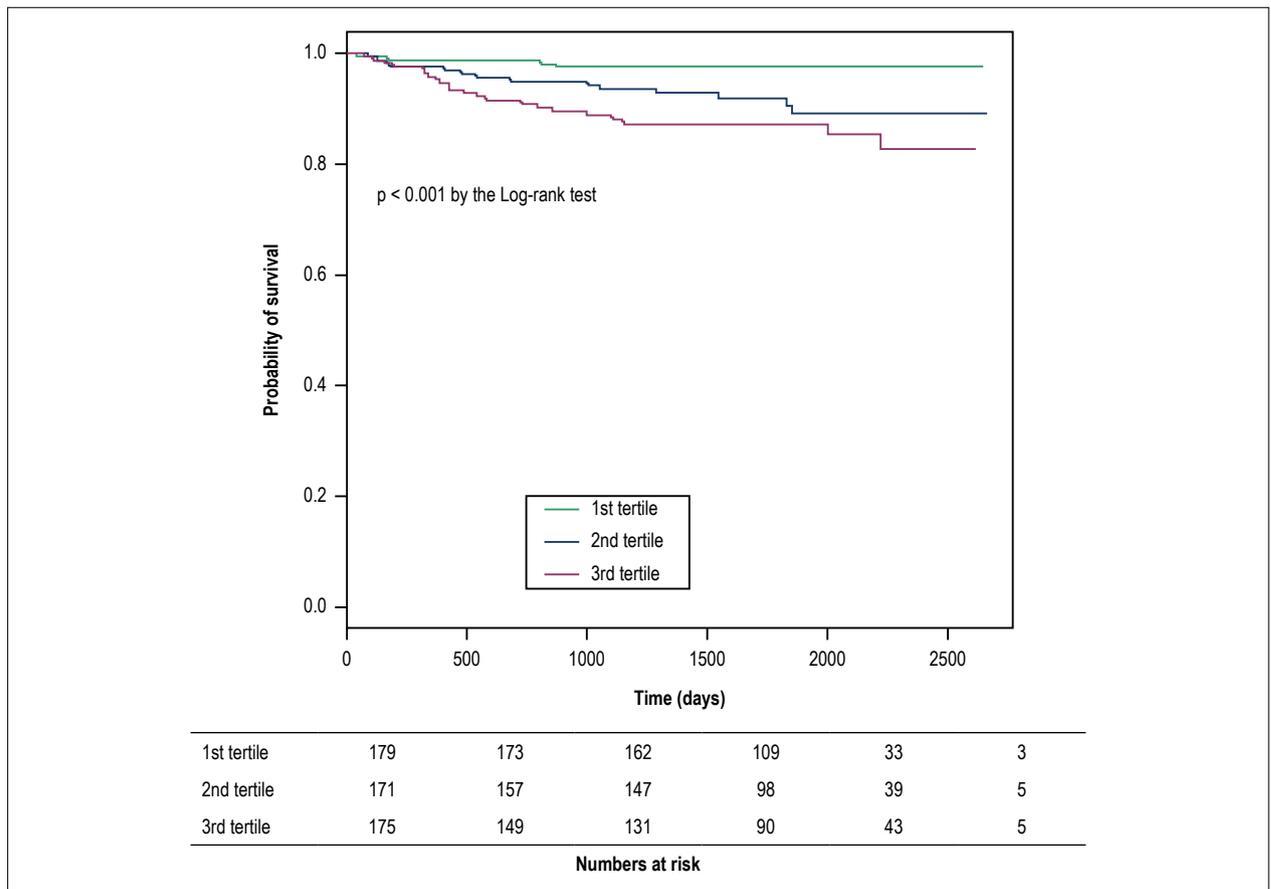


Figure 2 – Kaplan-Meier curve for cardiovascular mortality according to hs-cTnI tertile measured 25 to 90 days after acute coronary syndrome.

Table 2 – Hazard ratios and respective 95% confidence intervals on crude and age-sex adjusted models, and two multivariate adjusted models of Cox regression analysis

	Crude	Age-sex adjusted	Multivariate adjusted (Model 1)	Multivariate adjusted (Model 2)
<b>All-cause mortality</b>				
1 <sup>st</sup> tertile	(reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2 <sup>nd</sup> tertile	2.44 (1.23-4.81)	2.02 (1.02-4.01)	1.86 (0.86-4.05)	2.33 (0.74-7.33)
3 <sup>rd</sup> tertile	4.20 (2.22-7.94)	4.14 (2.19-7.86)	3.84 (1.92-8.12)	6.53 (2.12-20.14)
<b>Cardiovascular mortality</b>				
1 <sup>st</sup> tertile	(reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2 <sup>nd</sup> tertile	3.77 (1.24-11.47)	2.90 (0.95-8.90)	2.66 (0.72-9.84)	1.30 (0.21-8.00)
3 <sup>rd</sup> tertile	6.05 (2.08-17.57)	5.65 (1.94-16.47)	4.90 (1.35-17.82)	5.89 (1.08-32.27)

Model 1: Adjusted for age, sex, ACS subtype, hypertension, diabetes, dyslipidemia, smoking history, body mass index, and medication use at first follow-up (25–90 days after ACS). Model 2: Model 1 with addition of estimated GFR <math>< 60\text{ ml/min/1.73 m}^2</math> and LVEF <math>< 0.40</math>.

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#### Potential Conflict of Interest

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

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#### Study Association

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### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário da USP under the protocol number

866/08. 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.

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