High-sensitivity cardiac troponin I predict death and hospitalization at 1 year in patients assisting for a suspected acute cardiovascular condition: prospective cohort in a middle-income country

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Abstract:
Introduction and Objectives: High sensitivity cardiac troponin (Hs-cTn) are specific biomarkers of myocardial injury. Besides diagnostic purposes, its use has been recommended for risk stratification. Most studies have evaluated the role of Hs-cTn T in prognosis estimation but there are few studies evaluating the performance of Hs-cTn I.
Methods: We prospectively included patients assisting with a suspected acute cardiovascular condition. All patients have a Hs-cTn I measurement. Telephone-based interviews were performed at 3, 6, and 12 months. Medical chart review, telephonic follow-up, and national statistical system were used for event adjudication. A multivariable analysis, Kaplan Meier curves, and Cox proportional-hazards regression model were performed.
Results: We include 555 patients. Mean age was 63 years and 56.8% were male. The most frequent diagnosis after hospitalization were acute coronary syndromes (29.7%) and non-specific chest pain (28.6%). Hs-cTn I was > 99th percentile in 44.5% of cases. At 1 year the primary outcome occurred more frequently in Hs-cTn I > 99th percentile group (HR 1.99, 95% CI 1.5 – 2.64; p< 0.001 (Figure 1). We found a linear relationship between primary outcome and the first Hs-cTn I concentration (Figure 2). In multivariable analysis, Hs-cTn I > 99th was independently associated with the primary outcome (OR 2.25, 95% CI 1.27 – 3.98; p = 0.05).
Conclusions: Beyond diagnosis use, Hs-cTn I has a relevant role in risk stratification of patients with suspected acute cardiovascular conditions. The first Hs-cTnI value obtained in the emergency room has an independent association with primary outcome at 1 year.

Keywords: cardiac troponin, prognosis, risk stratification, cardiovascular disease.

Introduction

Cardiovascular diseases (CVD) are still the main cause of mortality among non-communicable diseases in the world(1). Hence, strategies to improve diagnosis,

treatment, and prognosis prediction in CVD are of utmost importance. Cardiac troponins are part of the myocardial contractile apparatus and are sensitive biomarkers of myocardial injury(2). High-sensitivity cardiac troponin (Hs-cTn) has become the preferred biomarker for the diagnosis of acute myocardial infarction and the 2020 European Society of Cardiology Guidelines for the management of acute coronary syndromes (ACS) recommends its use for diagnosis and also for prognosis estimation(3).

Besides diagnostic utility, Hs-cTn has a role in risk estimation in cardiovascular diseases. Studies have shown a direct relation between troponin values and mortality (4). Increased Hs-cTn values can be detected in conditions other than ACS and its prognostic value has been demonstrated in patients with heart failure, pulmonary embolism, and atrial fibrillation(5). In acute heart failure, higher Hs-cTn I was associated with worsened in-hospital outcomes (length of stay and worsening of heart failure during the hospitalization)(6). Elevated Hs-cTn T predicted adverse 30-days outcomes in a population of normotensive pulmonary embolism and helped to reclassify the risk in 50% of cases(7).

Despite similar accuracy between Hs-cTn I and Hs-cTn T for diagnostic purposes, observational studies suggest greater prognostic accuracy of Hs-cTn T in acute coronary syndromes(8,9) and cardiovascular risk stratification in the general population(10). Most studies have evaluated the prognostic role of T troponin(11) and less is known about the performance of Hs-cTn I for risk prediction in patients with cardiovascular diseases beyond 30 days of adjudicated outcomes(12). In this study, we prospectively evaluated the role of Hs-cTn I in predicting all-cause dead and readmission at 1 year in a population of patients assisting to the emergency department for a suspected acute cardiovascular condition.

Methods

Study design and population

We prospectively included patients admitted to the Hospital Universitario San Vicente Fundación, a tertiary care center in Medellín (Colombia). From June 2019 to October 2019, a total of 555 consecutive patients presenting to the emergency department with symptoms suggestive of an acute cardiovascular condition were enrolled. Several conditions were entered in the study including, but not limited to, chest pain, acute coronary syndromes, heart failure, pulmonary embolism, and arrhythmias. The study was approved by the hospital ethics committee and all included patients provided informed consent.

Patients who attended the emergency department with a suspected acute cardiovascular condition and in whom Hs-cTn measurement was deemed pertinent were selected. Individuals with at least one Hs-cTn value measurement performed upon admission to the institution were included. Treatment of patients was left at the discretion of the attending physician. Exclusion criteria were: 1) age < 18 years; 2) individuals with hospitalization of more than 24 hours in another center previous to study entrance; 3) main reason for hospitalization different from an acute cardiovascular

condition, 4) first Hs-cTn sample taken > 24 hours after patient admission, 5) incomplete data at admission.

Demographic, clinical, and laboratory variables were prospectively collected. Echocardiography and invasive coronary angiography data were obtained when these tests were performed. Acute myocardial infarction was defined according to the Fourth universal definition of myocardial infarction(13). Pulmonary embolism was confirmed by pulmonary artery computed tomography angiography or pulmonary ventilation/perfusion scan. All arrhythmias required an electrocardiographic trace for diagnosis.

Laboratory analysis

During the study only Hs-cTn I assays were used. Hs-cTn was defined as an assay capable of detecting troponin values in at least 50% of a healthy population (14). From June to August 2019, Hs-cTnI Abbot ARCHITECT assay was employed. This assay has a limit of detection of 1.2 ng/L, a coefficient of variance of 4.7 ng/L, and a 99th percentile of 26 ng/L. From September to October 2019, Hs-cTnI Siemens Atellica was implemented. This assay has a limit of detection of 1.6 ng/L, a coefficient of variance of 2.5 ng/L, and a 99th percentile of 45 ng/L. The use of two different assays during the development of the study was due to a change in the platform system in the hospital and it was beyond the control of researchers. Abnormal hs-cTn concentration was defined as values exceeding the 99th percentile of a normal reference population.

Follow up and clinical endpoints

The primary endpoint of the study was a composite of all-cause death and re-hospitalization at 1 year of follow-up. Other outcomes like in-hospital mortality, coronary care/intensive care unit admission, and complications rates were assessed. Hospitalization was defined as hospital stay for more than 48 hours. Telephone-based interviews were performed at 3, 6, and 12 months. Telephone follow-up and medical chart review when available were used for endpoint adjudication. Survival state was also obtained consulting the registry of the national statistical system.

Statistical analysis

Sample size calculation was performed based on the primary endpoint of the study. According to previous studies, based on a primary-outcome event rate of 19% at 30 days in patients with Hs-cTn values > 99th percentile and an event rate of 0.6% in patients with values < 99th percentile(15), we estimated that 268 patients would be required to have 80% power to find differences between groups. With this in mind, we use a consecutive sampling of all patients fulfilling inclusion criteria during study admission time. At the end of the study, 555 patients were included in the analysis.

Continuous variables were presented as mean and standard deviation or median and interquartile range. Categorical variables were expressed as percentages. Differences between groups were evaluated using the *t*-test or the Mann–Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical

variables. Patients were analyzed in two groups based on Hs-cTn I concentrations categorized as values above or under the 99th percentile.

Kaplan Meier curves were used to construct cumulative survival curves based on Hs-cTn I values dichotomization (<99th percentile vs ≥ 99th percentile). The Log-rank test was implemented to compare survival curves. Hazard ratios and 95% confidence intervals were estimated with the Cox proportional hazards model. A multivariable analysis controlling for other covariates was used to evaluate the association of Hs-cTn with the primary outcome.

Results

Study population

Between June 2019, and October 2019, 902 patients were screened. The most frequent cause of exclusion from the study was inpatient admission for a cause different from cardiovascular disease and Hs-cTn I measurement > 24 hours since admission. Finally, 555 patients were eligible and were included in the study (Figure 1).

Baseline characteristics

Median (interquartile range, IQR) age was 63 years (53 – 74). 56.7% of patients were male and the most frequent comorbidities were hypertension (65.2%), dyslipidemia (36.7%), and coronary artery disease (28.2%). Patients with Hs-cTn I ≥ 99th percentile have a higher proportion of chronic kidney disease (19.1% vs 10.5% for those with Hs-cTn I < 99th percentile), diabetes (29.3% vs 20.5%), and smoking (44.9% vs 32.8%). The most common reasons for Hs-cTnI requests were chest pain (62%) and suspected acute myocardial infarction (15.2%). Table 1.

In-hospital course

Coronary angiography was performed in 198 patients (35.7%) during hospitalization. A higher proportion of patients with Hs-cTn I ≥ 99th percentile have coronary care unit/intensive care unit admission (71,2% vs 26.3%), underwent coronary revascularization (36.4% vs 10%), and have a greater percentage of complications. Higher in-hospital mortality rates and worse left ventricle ejection fraction were also documented in this group. The most common diagnosis at discharge were acute coronary syndromes and non-specific chest pain. Table 2.

Troponin levels

Hs-cTn I Abbott ARCHITECT was employed in 464 patients (83.6%) while Siemens Atellica was used in the remaining 91 patients (16.4%). All patients had at least one Hs-cTn I sample, and a second sample was obtained in 140 patients (25.2% of the cohort). Hs-cTn I concentrations were above 99th percentile in 247 patients (44.5%). Median values of Hs-cTn I are reported in Table 2.

Troponin concentration and primary endpoint

Primary endpoint (all-cause death or rehospitalization at 12 months) occurred in 51.9% of our cohort, 41.5% in Hs-cTn I < 99th percentile group and 64.5% in Hs-cTn I ≥ 99th percentile group (hazard ratio 1.99, confidence interval, 1.5 to 2.64, p < 0.001). Figure 1. Median time to death or rehospitalization in the overall cohort was 379 days; 435 days for Hs-cTn < 99th percentile and 292 days for Hs-cTn > 99th percentile.

All-cause death at 12 months was 13%, 8.41% in Hs-cTn I < 99th percentile group, and 18.8% in Hs-cTn I ≥ 99th percentile group. A stepwise increase in the proportion of patients reaching the primary endpoint was documented with increasing Hs-cTn concentrations (Figure 2).

In a multivariable analysis, after adjusting for other covariates (age, oxygen saturation, hemoglobin values, left ventricle ejection fraction, and tricuspid regurgitation velocity), the first sample of Hs-cTn I had a significant association with the primary outcome (odds ratio 2.25, 95% confidence interval 1.27 – 3.98; p = 0.05). Table 4.

Discussion

In this pragmatic study, we found that the first sample of Hs-cTn I obtained in the emergency department can be used to predict the risk of death or re-hospitalization at 12 months in patients assisting for a suspected acute cardiovascular condition. We also found a stepwise increase in the proportion of patients reaching the primary endpoint with increasing Hs-cTn I concentrations.

Despite similar behavior of Hs-cTn I and Hs-cTn T for diagnostic purposes(3), the role of Hs-cTn I for risk stratification has been called into question by several studies showing superiority of Hs-cTn T for prognosis estimation(8–10). In a prospective study, Haaf et al(9) evaluated in patients presenting with acute chest pain the prognostic accuracy of three different Hs-cTn assays. The authors found hs-cTn T outperformed 72 months mortality prediction compared with hs-cTn I assays.

Nevertheless, our study showed after multivariable adjustment that Hs-cTn I concentrations > 99th percentile at presentation were associated with a significant increase in the risk of the primary outcome at 1-year (OR 2.25 [CI 1.27 – 3.98]; p = 0.05). Our findings are consistent with other reports. In the study of Kaura et al(4), a threefold increase in overall mortality was documented at 3-years in patients with elevated troponins during hospital care.

In our study, the first sample of Hs-cTn I have a significant association with the primary outcome. Although for diagnosis purposes serial Hs-cTn have been advocated to improve accuracy (especially in suspected acute coronary syndrome), this seems not to be the case for prognosis estimation. Haaf et al describe that troponin changes did not

further improve prognosis accuracy of Hs-cTn(9). The little change between first and peak Hs-cTn I concentrations in our study (Table 3) could explain these findings.

Although we and other authors found a directly proportional relationship between Hs-cTnI concentrations and probability of occurrence of the primary outcome(9,11) this has not been described in all studies. Kaura et al(4) reported in a large retrospective cohort of the United Kingdom, an inverted U-shape of Hs-cTn with all-cause mortality in inpatients with acute coronary syndromes. The superior proportion of patients with higher Hs-cTn concentrations undergoing invasive management was suggested as the possible explanation.

Mortality rates are superior in our cohort compared with studies that only include a population with acute chest pain. In studies of patients with suspected acute coronary syndrome, Chapman et al(12) report 1-year death rate of 8.2% in Hs-cTn I > 99th percentile group (vs 18.8% in our study). The proportion of patients in this study with Hs-cTn I > 99th percentile was 18.7% (vs 44.5% in our cohort). Moreover, higher mortality has been described at 1 year in patients with elevated troponin when non-acute coronary syndrome condition is compared with acute coronary syndromes (OR 1.389; 95% CI, 1.298-1.487)(16). Some studies have excluded ST segment elevation, cardiac arrest at admission, and low expectation survival(12,16). All these features could a priori select a lower risk population.

We have a high number of events for the primary endpoint at 1 year. Most outcomes in our cohort were explained by high rehospitalization rates. The great number of events in our cohort could have several reasons: 1) The population where the study was developed (all patients were from a tertiary care center). 2) Inclusion of diverse acute cardiovascular conditions, and not only acute chest pain, could increase the basal risk of the patients. 3) Finally, flaws in ambulatory treatment of patients in Colombia could have contributed to a greater number of events in the follow-up.

There are several strengths in our study. First, we have a prospective cohort study with “hard” clinical endpoints and 1-year follow-up. Second, our investigation is a pragmatic study that included diverse acute cardiovascular conditions assisting the emergency department. Third, national statistical system was used to assess life status, therefore death could be known in all patients.

Study limitations

Our study has some limitations that should be acknowledged. First, the prospective follow-up was made by phone calls. Although telephonic follow-up is not optimal to evaluate clinical endpoints, the objective events selected for the primary outcome make improbable wrong event adjudication. Secondly, we routinely did not obtain serial troponin testing, thus is uncertain whether a change in Hs-cTn I values could improve risk estimation. Thirdly, most of our findings are explained by Abbot ARCHITECT Hs-cTn I due to its greater representation in the study. Fourthly, we were unable to have telephone contact in 117 cases (21%) for re-hospitalization endpoint adjudication. Fifthly, we could not establish the cause of death and the frequency of cardiovascular mortality.

Conclusions

Among patients with suspected acute cardiovascular conditions assisting to the emergency department, Hs-cTn I obtained at presentation predicts in an independent manner 1-year occurrence of death or rehospitalization. This prognosis ability should be used to improve the care and follow-up of patients at higher risk.

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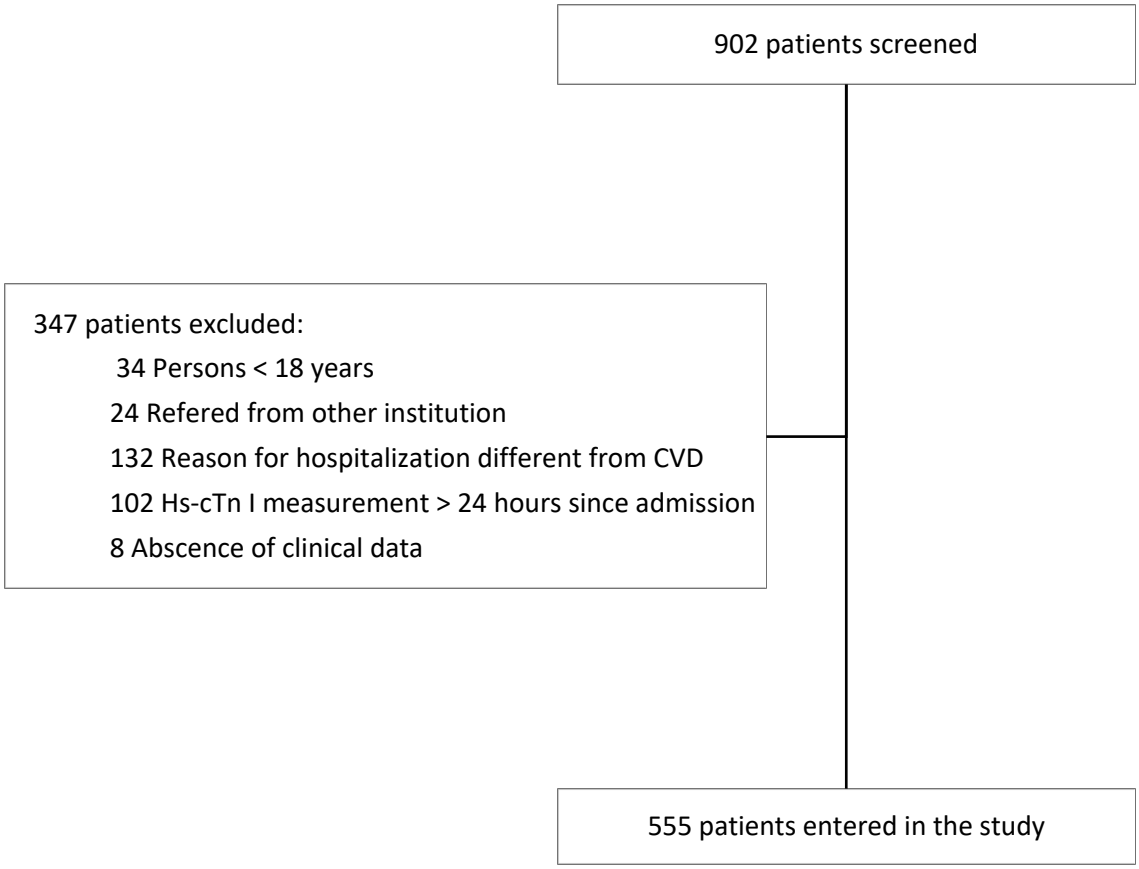
Figure 1. Screening profile



CVD, cardiovascular disease. Hs-cTn, high sensitivity cardiac troponin

Table 1. Baseline characteristics

Variable	Total 555 (100%)	Hs-cTn I < 99th percentile n = 308 (55.5%)	Hs-cTn I ≥ 99th percentile n = 247 (44.5%)
Male	315 (56.8%)	175 (56.7%)	140 (56.7%)
Age (years)	63 (53 – 74)	60 (49 – 71)	66 (57 – 75)
Risk factors			
Hypertension	360 (65.2%)	197 (64.0%)	163 (66.0%)
Dyslipidemia	203 (36.7%)	110 (35.7%)	93 (37.7%)
Diabetes	135 (24.4%)	63 (20.4%)	72 (29.1%)
Chronic kidney disease +	79 (14.3%)	32 (10.4%)	47 (19.0%)
Smoking*	210 (38.1%)	100 (32.5%)	110 (44.5%)
Previous cardiovascular disease			
Coronary artery disease	156 (28.1%)	92 (29.9%)	64 (26%)
Previous heart failure	102 (18.4%)	50 (16.2%)	52 (21.0%)
Atrial fibrilation	33 (5.9%)	20 (6.5%)	13 (5.2%)
Systolic blood pressure, mm Hg	130 (117 – 150)	130 (120 - 150)	130 (110 – 150)
Diastolic blood pressure, mm Hg	80 (70 – 90)	80 (70 – 89)	80 (68 – 90)
Heart rate, beats/min	80 (70 – 90)	80 (70 – 89)	82 (75 – 96)
Creatinine (mg/dL)	0.97 (0.81 – 1.26)	0.93 (0.8 – 1.1)	1.04 (0.83 – 1.55)
Main reason for Hs-cTn I request			
Chest pain	343 (61.8%)	232 (75.3%)	111 (45.0%)
Acute coronay syndrome	84 (15.1%)	14 (4.5%)	70 (28.3%)
Pulmonary embolism	11 (2%)	6 (2%)	5 (2%)
Decompensated heart failure	32 (5.8%)	9 (2.9%)	23 (9.3%)
Arrhythmia	31 (5.6%)	15 (4.9%)	16 (6.5%)
Stroke	13 (2.3%)	5 (1.6%)	8 (3.2%)
Other	41 (7.3%)	28 (9.0%)	13 (5.2%)

Data are mean (SD), n (%), or median (IQR), unless otherwise stated.

+ Chronic kidney disease was defined as eGFR < 60 mL/min.
* Smoking indicates prior or current smoking.

Table 2. In-Hospital course

Variable	Total 555 (100%)	Hs-cTn I < 99th percentile n = 308 (55.5%)	Hs-cTn I ≥ 99th percentile n = 247 (44.5%)
Echocardiography			
LVEF (n= 371)	0.52 (0.36 – 0.59)	0.57 (0.4 – 0.61)	0.47 (0.34 – 0.58)
TRV (cm/seg) (n= 283)	266 (243 – 293)	269 (246 – 286)	266 (243 – 297)
Coronary angiography	198 (35.7%)	56 (18.2%)	142 (57.5)
Significant CAD disease *	146 (73.7%)	41 (73.2%)	105 (73.9%)
Coronary revascularization	121 (21.8%)	31 (10%)	90 (36.4%)
PCI	96 (79.3%)	24 (77.4%)	72 (80%)
CABG	22 (18.2%)	7 (22.6%)	15 (16.6%)
Hybrid revascularization	3 (2.48%)	0	3 (3.3%)
CCU/ICU admission	257 (46%)	81 (26.3%)	176 (71.2%)
Complications			
Shock +	47 (8.5%)	14 (4.5%)	33 (13.4%)
Atrial fibrillation	27 (4.8%)	12 (3.9%)	15 (6.0%)
In-hospital mortality	31 (5.6%)	6 (1.9%)	25 (10.1%)
Diagnosis at discharge			
Acute coronary syndrome	163 (29.4%)	29 (9.4%)	134 (54.2%)
NSTEMI	95 (58.3%)	16 (55.2%)	79 (59.0%)
STEMI	68 (41.7%)	13 (44.8%)	55 (41.0%)
Non-specific chest pain	158 (28.5%)	143 (46.4%)	15 (6.0%)
Pulmonary embolism	12 (2.1%)	4 (1.3%)	8 (3.2%)
Decompensated heart failure	49 (8.8%)	20 (6.5%)	29 (11.7%)
Arrhythmia	38 (6.8%)	19 (6.2%)	19 (7.7%)
Stroke	10 (1.8%)	3 (1%)	7 (2.8%)
Pericarditis	6 (1.0%)	5 (1.6%)	1 (0.4%)
Other	116 (21%)	84 (27.2%)	32 (13%)

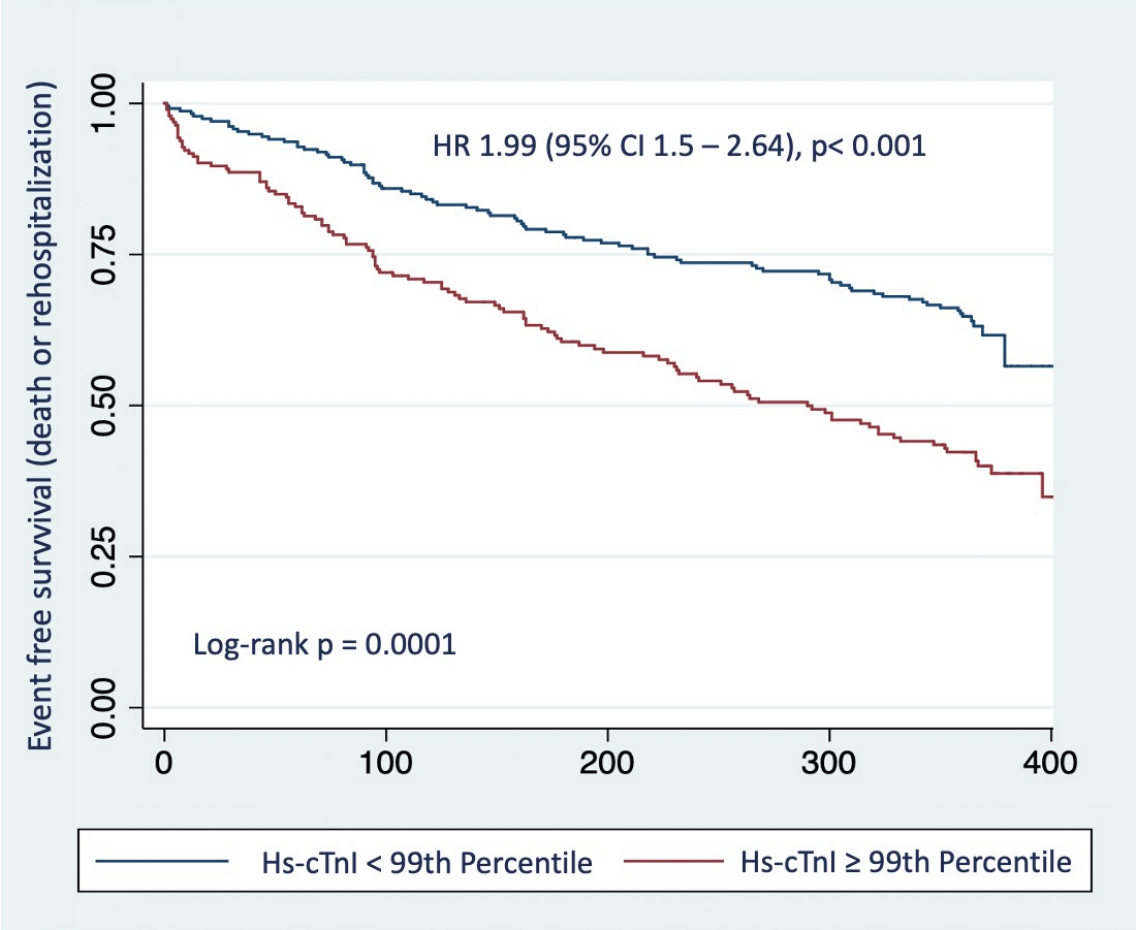
CAD, coronary artery disease. LVEF, Left ventricle ejection fraction. TRV, tricuspid regurgitation velocity. CCU, coronary care unit. ICU, intensive care unit. PCI, percutaneous coronary intervention. CABG, coronary artery bypass graft.
* Significant CAD was defined by invasive coronary angiography as > 50% stenosis of the left main stem or >70% stenosis in a major coronary vessel.
+ Shock was defined as hypotension requiring inotropes or vasopressors

Table 3. High sensitivity cardiac troponin values

Variable	Hs-cTn I < 99th percentile n = 308 (55.5%)		Hs-cTn I ≥ 99th percentile n = 247 (44.5%)	
	Abbott n = 256 (83.1%)	Siemens n = 52 (16.9%)	Abbott n = 208 (84.2%)	Siemens n = 39 (15.8%)
First value (n=555)	5 (2 – 10)	9.6 (3.5 - 20.3)	286 (62 – 2762)	527 (150 – 2584)
Second value (n=140)	10 (3 – 38.5)	9.6 (5.9 – 20.5)	309 (53 – 3300)	122 (71 – 7562)
Third value (n=15)	124 (10 – 176)	-	49 (32 – 203)	-
Peak value (n=555)	5 (2 – 10)	9.5 (3.6 – 20.4)	376 (76 – 4016)	527 (159 – 2584)

* Data are median (IQR). All values are expressed in ng/L

Figure 1. Kaplan-Meier curves for event free survival



Kaplan-Meier curves show the probability of primary endpoint which was a composite of all cause death and rehospitalization at 12 months

Figure 2. Troponin concentration and primary outcome for Abbott ARCHITECT

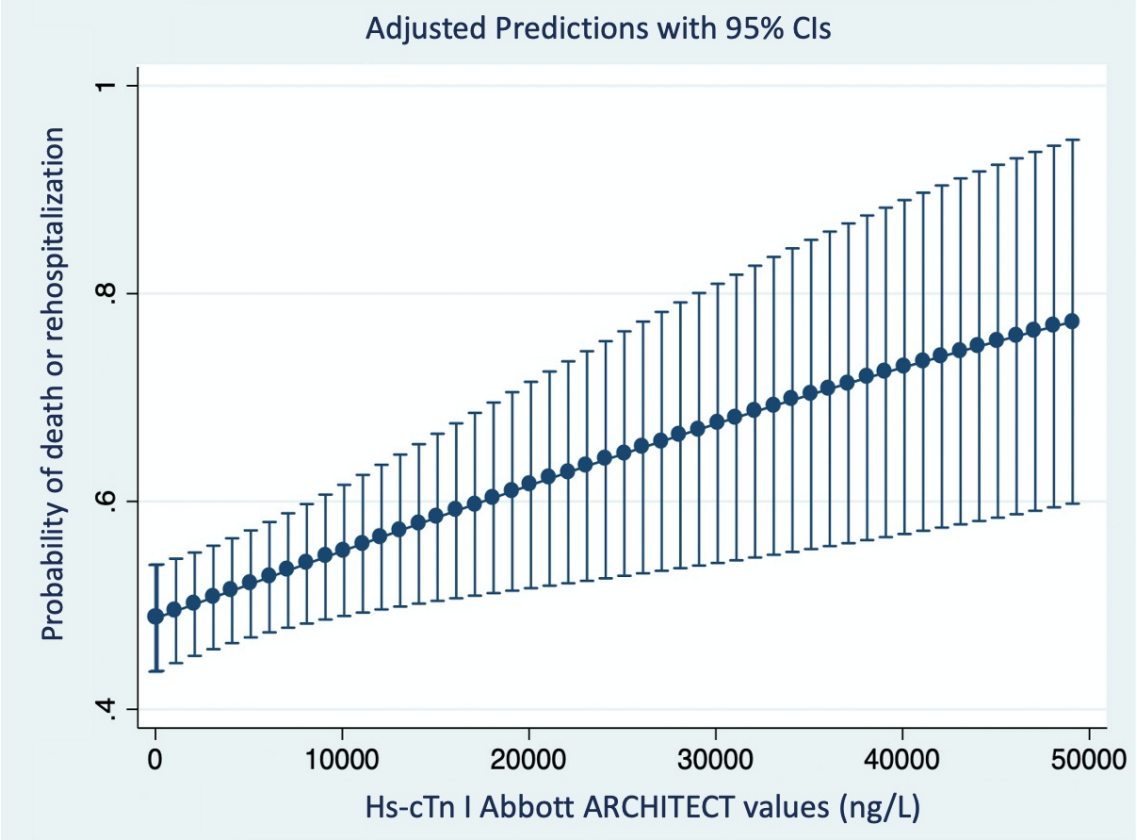


Table 4. Multivariable analysis (death or rehospitalization at 12 months)

Variable	Odds ratio	95% Confidence interval	P value
Hs-cTn I ≥ 99th percentile	2.25	(1.27 – 3.98)	0.05
Age	0.98	(0.96 – 1.00)	0.182
Oxygen saturation at admission	0.97	(0.91 – 1.02)	0.309
Hemoglobin level	0.92	(0.81 – 1.04)	0.204
Left ventricle ejection fraction	0.98	(0.96 – 1.004)	0.142
Tricuspid regurgitation velocity	1.00	(0.98 – 1.03)	0.555