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Coronavirus disease-2019 and heart: assessment of troponin and cardiovascular comorbidities as prognostic markers in patients hospitalized with coronavirus disease-2019 in a tertiary center in Brazil

Henrique Trombini Pinesi[1*], Fernando Rabioglio Giugni[1], Bruna Romanelli Scarpa Matuck[1], Fabio Grusnpun Pitta[1], Cibele Larrosa Garzillo[1], Eduardo Gomes Lima[1], Roberto Kalil Filho[1], Carlos Vicente Serrano Junior[1], On behalf of the HCFMUSP COVID-19 Study Group[†]

SUMMARY

OBJECTIVE: Our study aimed to evaluate the correlation of cardiac troponin T levels with comorbidities and in-hospital outcomes in patients with coronavirus disease-2019 in Brazil.

METHODS: Data from a cohort of 3,596 patients who were admitted with suspected coronavirus disease-2019 in a Brazilian tertiary center, between March and August 2020, were reviewed. A total of 2,441 (68%) patients had cardiac troponin T determined in the first 72 h of admission and were stratified into two groups: elevated cardiac troponin T (cardiac troponin T >0.014 ng/mL) and normal cardiac troponin T. Associations between troponin, comorbidities, biomarkers, and outcomes were assessed. Regression models were built to assess the association of several variables with in-hospital mortality.

RESULTS: A total of 2,441 patients were embraced, of which 924 (38%) had normal cardiac troponin T and 1,517 (62%) had elevated cardiac troponin T. Patients with elevated cardiac troponin T were older and had more comorbidities, such as cardiovascular disease, hypertension, diabetes, arrhythmia, renal dysfunction, liver disease, stroke, cancer, and dementia. Patients with abnormal cardiac troponin T also had more altered laboratory parameters on admission (i.e., leukocytes, C-reactive protein, D-dimer, and B-type natriuretic peptide), as well as more need for intensive care unit, vasoactive drugs, mechanical ventilation, dialysis, and blood transfusion. All-cause mortality was markedly higher among patients with increased cardiac troponin T (42 vs. 16%, P<0.001). Multiple regression analysis demonstrated that in-hospital mortality was not independently associated with troponin elevation.

CONCLUSION: This study showed that cardiac troponin T elevation at admission was common and associated with several comorbidities, biomarkers, and clinical outcomes in patients hospitalized with coronavirus disease-2019, but it was not an independent marker of in-hospital mortality.

KEYWORDS: COVID-19. Troponin. Cardiovascular disease. Myocardial ischemia.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a global pandemic with diverse clinical severity, ranging from asymptomatic disease to fatal cases. On risk stratification, cardiac troponin (cTn) has proved to be a useful tool, along with many other biomarkers and comorbidities, especially those related to the cardiovascular (CV) system[1-3]. Elevated serum cTn reflects myocardial injury, which may occur in COVID-19 due to a myriad of mechanisms[4,5]. Systemic events, such as generalized inflammation, hemodynamic instability, hypoxemia, and pulmonary embolism, are likely involved in the majority of cases. Local mechanisms, such as myocardial

[1]Universidade de São Paulo, Instituto do Coracao, Faculdade de Medicina – São Paulo (SP), Brazil.
*Corresponding author: htpinesi@hotmail.com
[†]Members of the HCFMUSP COVID-19 Study Group: Eloisa Bonfa, Edivaldo M. Utiyama, Aluisio C. Segurado, Beatriz Perondi, Anna Miethke-Morais, Amanda C. Montal, Leila Harima, Solange R.G.Fusco, Marjorie F. Silva, Marcelo C. Rocha, Izabel Marcilio, Izabel Cristina Rios, Fabiane Yumi Ogihara Kawano, Maria Amélia de Jesus, Ésper G. Kallas, Carolina Carmo, Clarice Tanaka, Heraldo P. Souza, Julio F. M. Marchini, Carlos Carvalho, Juliana C. Ferreira, Anna S.S. Levin, Maura S. Oliveira, Thaís Guimarães, Carolina S. Lázari, Alberto José da Silva Duarte, Ester Sabino, Marcello M.C. Magri, Tarcisio P. Barros Filho, Maria Cristina Peres Braido Francisco, and Silvia Figueiredo Costa.
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infarction, stress cardiomyopathy, and myocarditis, have also been described but they occur less frequently. Elevated cTn in COVID-19 patients has been previously associated with older age, higher prevalence of CV comorbidities, higher serum biomarkers, and worse outcomes, including higher rates of mechanical ventilation requirement, acute kidney injury, and in-hospital mortality[1-3,6-8]. Meta-analyses showed that cTn is an accurate prognostic tool to predict critical outcomes and mortality in COVID-19[9,10]. Dynamic changes in serial cTn measures are also associated with higher mortality[11]. Combining cTn with natriuretic peptides further improves risk prediction[12].

Most studies on COVID-19 risk assessment were conducted among Asian, European, and North American populations. Brazil, along with other South American Countries, was severely affected by the pandemic, with more than 20 million cases and more than 500,000 deaths by the end of August 2021[13]. In Brazil, a multicentric study evaluated a high CV risk population and found cTn to be an independent predictor of in-hospital mortality[7]. The patients included in this study had elevated cardiac biomarkers, abnormalities in electrocardiogram or echocardiogram, or clinically relevant cardiac manifestations. So far, however, there are no studies on cTn prognostic value in a more varied population hospitalized with COVID-19 in Brazil, including lower CV risk patients. These patients are less prone to having direct cardiac impairment by COVID-19 on admission, and the impact of cTn elevation needs better understanding.

We conducted a retrospective observational study that assessed the correlation of cTn elevation at admission with CV comorbidities, biomarkers, and in-hospital outcomes in patients hospitalized with suspected COVID-19.

METHODS

Study design and participants

We analyzed data from all patients (≥14 years) with suspected COVID-19 who were admitted for at least 24 h to Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP) between March 30 and August 31, 2020. Patients with nosocomial COVID-19 infection were excluded. HCFMUSP is a tertiary teaching hospital in São Paulo, Brazil, which is dedicated to treating high-complexity cases, and it comprises eight specialized institutes accounting for approximately 2,200 beds and 20,000 healthcare personnel. Between March and August 2020, the HCFMUSP designated 900 beds for COVID-19 patients, including 300 ICU beds[14].

Suspected cases of COVID-19 were defined according to the evaluation of the attending physicians. Confirmed COVID-19 was defined as a positive reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 on Abbott m200RT (Abbott Laboratories, Chicago, IL, USA) established at the Central Laboratory Division of HCFMUSP on swab, collected from nasopharyngeal and/or oropharyngeal samples, at admission with a minimum of 3 days of symptoms and, if negative, repeated after 48 h[15]; or a positive test by chemiluminescent immunoassays on Liaison XL analyzer (DiaSorin S.p.A., Saluggia, Italy) to detect serum antibodies against SARS-CoV-2, performed for highly suspect cases with at least two RT-PCR negative samples after 7 days of the onset of symptoms or in subjects with high clinical suspicion for whom an RT-PCR test was not available up to the 10th day of symptom onset[16]. Likely COVID-19 cases were defined as clinical and lung computer tomography (CT) signs highly suggestive of COVID-19 with negative RT-PCR tests and lack of serum antibody confirmation. Non-likely COVID-19 cases were defined as suspected COVID-19 with no RT-PCR or serum antibody confirmation who were later reviewed by an infectious diseases' specialist team as having a more plausible alternative diagnosis.

This study was approved by Hospital das Clinicas' Ethics Review Board under the registry number CAAE: 32037020.6.0000.0068. No informed consent was necessary because we acquired all data retrospectively. In this description, we sought to conform to the STROBE guidelines[17].

Data collection

Data from routine hospitalized clinical care were extracted from patients' electronic health records and organized into standardized forms in the RedCap system by trained extractors. We retrospectively collected information from all patients, including demographic data, clinical characteristics, laboratory parameters, and outcomes. Patients were stratified into two groups according to cardiac troponin T (cTnT) levels: elevated (cTnT>0.014 ng/mL, the upper normal limit) and normal.

Statistical analysis

Descriptive statistics include frequency analysis (percentages) for categorical variables and mean±standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Comparisons were determined by the t-test or Mann-Whitney U test for continuous variables, as appropriate, and by the χ^2 test or Fisher's exact test for categorical variables. The level of statistical significance was set at 0.05 (two-tailed). Regression models were constructed using the stepwise backward method to consider the risk of fatal outcome as the dependent variable

to demonstrate the effects of cTnT elevation and CV comorbidities. Statistical analyses were carried out using IBM SPSS Statistics for Windows v. 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

We screened 3,596 eligible patients with a suspected diagnosis of COVID-19, of whom 2,441 patients (68%) had cTnT determined in the first 72 h of admission and were included in this study (mean admission troponin interval of 20.2±11.5 h). Of them, 2,042 patients (83.7%) were classified as confirmed cases of COVID-19, 215 patients (8.8%) as likely COVID-19 cases, and 184 patients (7.5%) as non-likely COVID-19 cases. The study flowchart is shown in Figure 1.

Included patients had a mean age of 59±17 years and 1,342 (55%) were males. Notably, 971 (38%) patients had normal admission cTnT and 1,517 (62%) had elevated cTnT (cTnT>0.014 ng/mL). The baseline clinical characteristics are described in Table 1. Patients with an elevated cTnT were more likely to be older (67±16 years vs. 52±15 years, p<0.001) and to have a history of CV disease, hypertension, diabetes, arrhythmia, kidney dysfunction, liver disease, stroke, alcohol drinking, cancer, dementia, and hypothyroidism.

The baseline laboratory parameters are described in Table 2. Patients with abnormal cTnT were more likely to have significantly (p<0.001) worse laboratory parameters at admission (i.e., leukocytes, C-reactive protein, D-dimer, and BNP).

Clinical outcomes during the hospitalization are reported in Figure 2. Patients with elevated cTnT had more need for ICU, vasoactive agents, mechanical ventilation, dialysis, and blood transfusion. All-cause mortality was markedly higher among patients with increased cTnT than those with normal levels (42.66 vs. 16.3%, p<0.001). To better understand the relationship between troponin levels at admission and mortality, patients were stratified into three subgroups: normal, up to three times, and above three times the upper limit of normal (Figure 3). Higher levels of cTnT were associated with higher mortality (p<0.001).

Multiple regression analysis (Table 3) demonstrated that in-hospital mortality was independently associated with hypertension (p<0.004), dialytic kidney dysfunction (p<0.001), age>70 years (p=0.003), and absence of obesity (p=0.021). Elevated troponin did not meet statistical significance for independent association with mortality on the regression analysis.

DISCUSSION

This study demonstrated that elevated cTnT is frequently observed and correlates with multiple comorbidities, biomarkers, and adverse outcomes, including in-hospital mortality, in patients hospitalized with COVID-19. Yet, elevated cTnT was not independently associated with in-hospital mortality after multivariable analysis.

Myocardial injury was more frequent in our report than that previously reported in China or in the United States[2,3,18-20]. Guimaraes et al.[7] selected a high-risk population in Brazil and found that a total of 54.2% of patients presented troponin elevation[7]. Among our patients, 62% had elevated cTnT. Similar to other reports, in our study, patients with myocardial injury

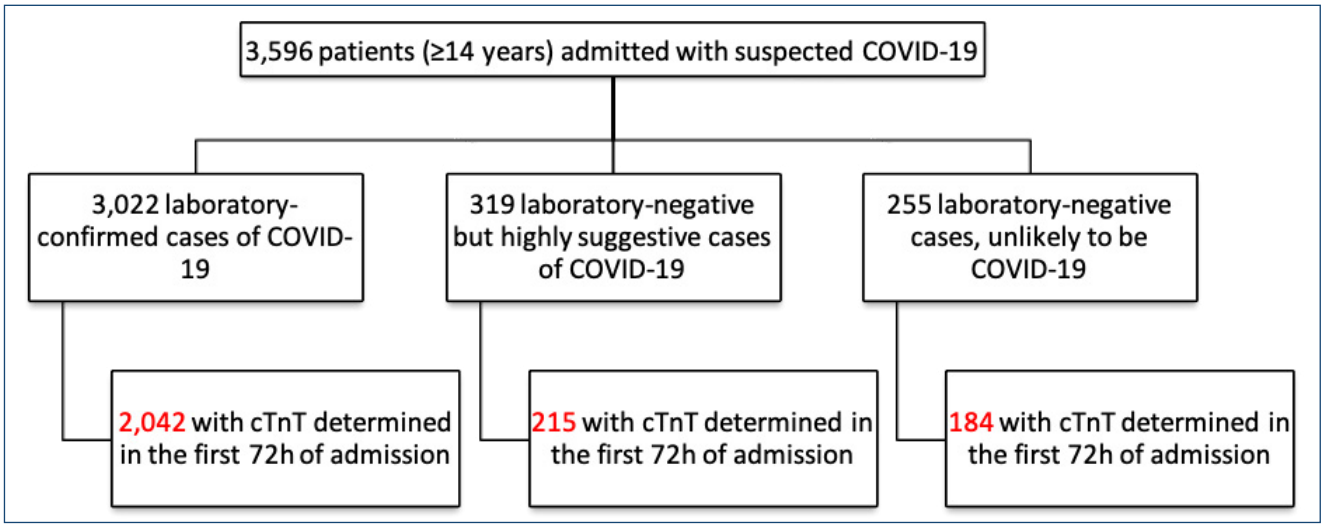

Figure 1. Flowchart showing the distribution of consecutive patients (≥14 years) admitted for at least 24 h as inpatients to Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo with suspected coronavirus disease-2019, between March and August 2020.

tended to be older and have a history of CV diseases or CV comorbidities such as hypertension, diabetes, smoking, and kidney dysfunction[2,3,19].

Our results are also in accordance with respect to the association between cTnT elevation and poor outcomes previously demonstrated[2,3,19]. Lala et al.[19] stratified troponin levels into

Table 1. Population baseline characteristics.

	Normal troponin	Elevated troponin	p-value
Age (mean±SD)	52.2±15.4	63.6±15.8	<0.001
Male (n, %)	458 (49.6)	884 (58,3)	<0.001
BMI (mean±SD)	31.5±11.9	29±12	<0.001
Race (n, %)			
White	541 (60.7)	976 (66)	0.005
Black	61 (6.8)	114 (7.7)	
Mixed race	282 (31.6)	369 (24.9)	
Asian	8 (0.9)	20 (1.4)	
Time (days) between symptom onset and hospital admission (mean±SD)	8.7±4.9	8.8±6.9	0.689
Cardiovascular disease (n, %)	81 (8.8)	427 (28.2)	<0.001
Hypertension (n, %)	430 (46.5)	1029 (67.9)	<0.001
Arrhythmia (n, %)	22 (3.4)	110 (9.2)	<0.001
Obesity (n, %)	163 (17.6)	163 (10.7)	<0.001
Diabetes (n, %)	279 (30.3)	660 (43.5)	<0.001
Dyslipidemia (n, %)	56 (20.3)	93 (22.8)	0.436
Smoker (n, %)	57 (6.2)	126 (8.3)	0.052
Former smoker (n, %)	191 (20.7)	326 (21.6)	0.613
Alcoholism (n, %)	32 (8.9)	72 (13.3)	0.043
CPOD (n, %)	44 (4.8)	128 (8.5)	<0.001
Asthma (n, %)	46 (5)	53 (3.5)	0.072
Chronic kidney disease (n, %)	21 (2.3)	184 (12.2)	<0.001
Dialysis (n, %)	4 (0.4)	78 (5.1)	<0.001
Liver disease (n, %)	14 (1.5)	54 (3.6)	0.003
Stroke (n, %)	30 (3.2)	151 (10)	<0.001
Epilepsy (n, %)	15 (6)	23 (6.4)	0.812
Dementia (n, %)	9 (1)	55 (3.6)	<0.001
Rheumatologic disease (n, %)	31 (3.4)	35 (2.3)	0.122
Hematologic disease (n, %)	38 (6.7)	92 (8.2)	0.276
Peripheral artery disease (n, %)	16 (2.6)	81 (7.1)	<0.001
Solid organ transplant (n, %)	13 (5.3)	67 (17)	<0.001
Cancer (n, %)	42 (5.2)	129 (9.2)	<0.001
Hematologic cancer (n, %)	14 (2.2)	39 (3.4)	0.167
Previous thrombotic event (n, %)	20 (7.9)	39 (10.9)	0.228
HIV (n, %)	20 (2.2)	11 (0.7)	0.002
Hypothyroidism (n, %)	58 (20.1)	124 (28.6)	0.011

BMI: body mass index; COPD: chronic obstructive pulmonary disease. The t-test was used to compare numeric variables between groups, and the chi-square test was used to compare qualitative variables between groups.

Table 2. Laboratory characteristics at admission.

Biomarkers (mean±SD or median±IQR)	Normal troponin	Elevated troponin	p-value
Leukocyte (cells/mm^3)	8,200±4,910	9,800±7,050	<0.001*
Neutrophil (cells/mm^3)	6,400±4,850	8,000±6,560	<0.001*
Lymphocyte (cells/mm^3)	1,000±740	800±680	<0.001*
Hemoglobin (g/dL)	12.6±1.9	11.7±2.4	<0.001
Platelet (cells/mm^3)	253,400±104,800	231,200±104,800	<0.001
C-reactive protein (mg/L)	131.8±100.8	159.8±120.9	<0.001
Lactate dehydrogenase (U/L)	401.7±213.2	529.6±483.9	<0.001
Aspartate aminotransferase (U/L)	36±30	40±39	<0.001*
Alanine aminotransferase (U/L)	34±31	30±32	0.01*
D-dimer (ng/mL)	1,134.5±1,536	2,073.5±5,052.5	<0.001*
Prothrombin time (seg)	13.3±5.6	14.6±8.4	<0.001
Activated partial thromboplastin time (seg)	30.3±6.4	33±14.9	<0.001
Fibrinogen (mg/dL)	596.2±182.2	523.5±201.5	<0.001
Creatine phosphokinase (U/L)	89.5±154.25	147±431.5	<0.001*
Lactate (mg/dL)	12.0±7.0	14.0±8.0	<0.001*
Urea (mg/dL)	37.7±27.3	80.1±59.1	<0.001
Creatinine (mg/dL)	0.81±0.38	1.35±1.58	<0.001*
Sodium (mEq/L)	139±4.5	139.8±6.1	<0.001
Potassium (mEq/L)	4.22±0.66	4.45±0.92	<0.001
Ionic calcium (mg/dL)	4.74±0.34	4.63±0.47	<0.001
Magnesium (mg/dL)	2.1±0.35	2.13±0.43	0.079
N-terminal B-type natriuretic peptide – NT-proBNP (pg/mL)	183.5±388.5	2,056±6,040.25	<0.001*

The t-test was used for all comparisons, except N-terminal B-type natriuretic peptide – NT-proBNP (pg/mL), for which *Mann-Whitney U test was used.

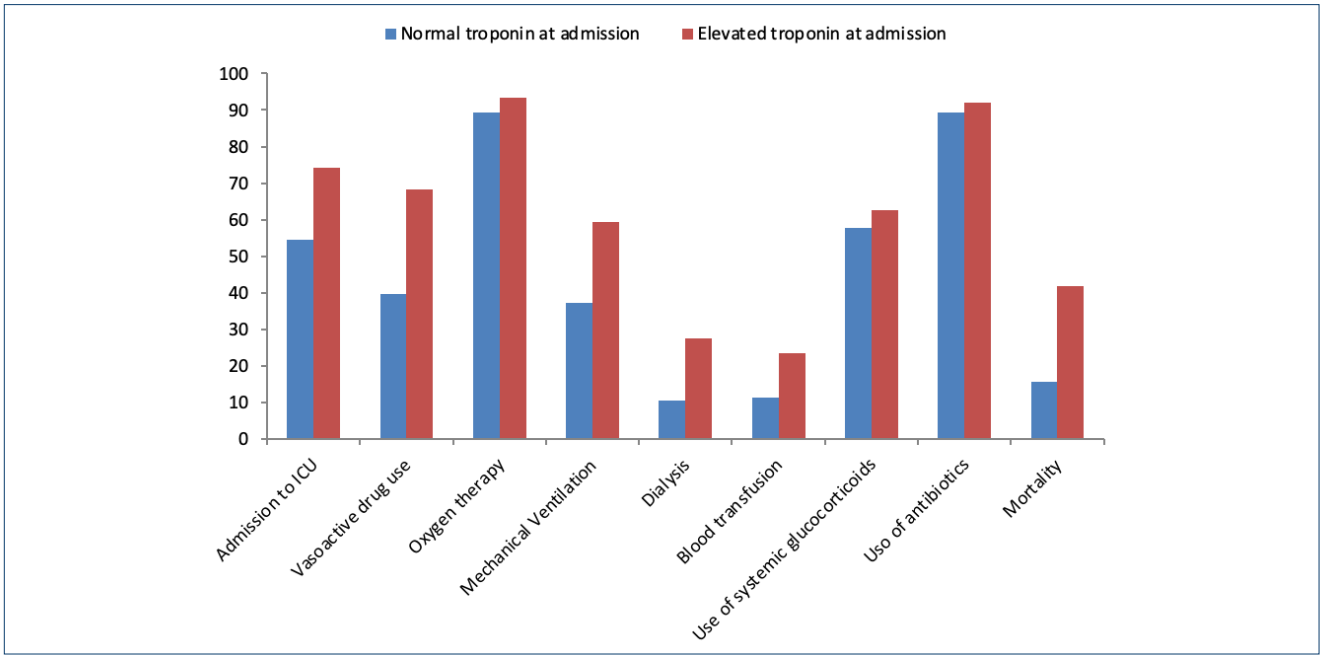

Figure 2. Outcomes during the hospitalization. ICU: intensive care unit. p<0.001 for all comparisons between normal and elevated troponin levels at admission.

normal, mildly elevated, and elevated and found increased mortality related to higher troponin levels[19].

The mechanism that links troponin elevation and higher rates of adverse outcomes in COVID-19 is not entirely elucidated. As observed in our cohort, the troponin rise occurs concomitantly with the increase in other inflammatory biomarkers, such as D-dimer, leukocytes, C-reactive protein, procalcitonin, ferritin, interleukin-6, and lactate dehydrogenase[3,20], which suggests that this reflects cytokine storm and critical illness more than the direct myocardial injury itself.

In this report, elevated troponin was not independently associated with mortality after logistic regression. A previous study demonstrated that myocardial injury was significantly associated with death, even after adjusting disease severity and relevant clinical factors[19]. Shi et al.[2] also observed a higher risk of death in patients with elevated troponin after adjusting for age, previous comorbidities, ARDS, creatinine levels, and NT-proBNP levels[2,19]. On the contrary, Metkus et al.[21] found results that are similar to our study. Mortality was greater with higher troponin levels, but the association between myocardial injury and mortality was not statistically significant after adjusting for age, sex, and multisystem organ dysfunction[21]. A Norwegian study points in the same direction, suggesting the limited role of troponin in prognostic assessment[21,22]. These findings corroborate the hypothesis that myocardial injury is reflective of baseline risk and comorbidities, especially underlying multisystem organ dysfunction, and troponin values reduce its prognostic importance when clinical severity features are included in the regression analysis.

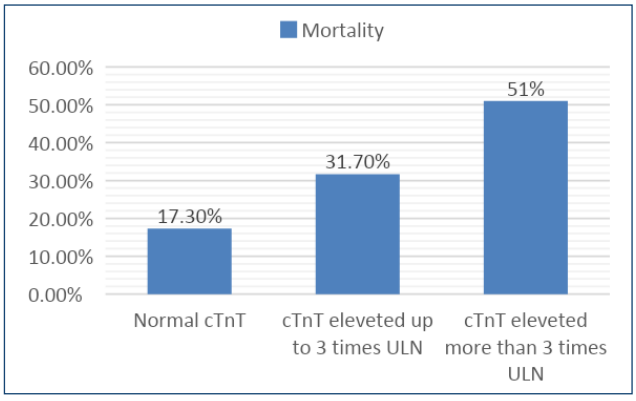

Figure 3. Association between troponin levels at admission and mortality. cTnT: cardiac T troponin; ULN: upper limit of normal. p<0.001 for all comparisons between individual groups.

Limitations

As an observational study, it presents a risk of selection bias. Our data are drawn from a single academic health institution, dedicated to treating high-complexity cases, which could influence the findings and limit its generalizability. Also, the retrospective nature of the study is another limitation, since the exams were collected at the discretion of the treating physician and the results were retrieved by the investigator from the patients' records. The admission troponin was not available in 32% of patients, which could represent a lower-risk population. Another limitation is that we did not assess secondary diagnoses that could contribute to troponin elevation, such as myocarditis or acute coronary syndrome.

Similar to other studies, we evaluated troponin only at admission, while serial troponin measurements during hospital stay were not available. Dynamic changes in troponin during hospitalization could provide better prognostic information. Zhou et al.[20] showed that troponin levels increased progressively among non-survivors, whereas they did not change significantly among survivors. These results were corroborated by other authors as well[3,19].

Table 3. Multiple regression analysis for prediction of in-hospital death—final model after backward stepwise method.

	OR	95%CI		p-value
		Inferior	Superior	
Hypertension	2.23	1.28	3.89	0.004
Obesity	0.45	0.23	0.89	0.021
Cancer	4.58	1.00	21.05	0.050
Use of vasoactive drugs	20.18	5.75	70.83	<0.001
Dialysis	4.15	2.38	7.26	<0.001
Use of ACEi	0.32	0.14	0.70	0.004
Use of ARB	0.13	0.05	0.32	<0.001
Age above 70 years	2.29	1.31	3.98	0.003

CONCLUSION

Our study showed that cTnT elevation at admission was common and associated with mortality, but it was not an independent marker of in-hospital mortality in patients with COVID-19. Some comorbidities, such as hypertension (OR 2.23) and age>70 years (OR 2.29), were strongly associated with mortality in these patients. Further research is needed to fully understand the prognostic role of troponin in COVID-19.

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AUTHORS' CONTRIBUTIONS

CVSJ: Conceptualization, Funding acquisition, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. **HTP**: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Software, Writing – original draft, Writing – review & editing. **FRG**: Data curation, Formal Analysis, Writing – original draft. **BRSM**: Data curation, Writing – original draft. **EGL**: Formal Analysis, Methodology, Validation, Writing – review & editing. **CLG**: Formal Analysis, Methodology. **RKF**: Resources, Supervision, Validation, Visualization.

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