Predictive Value of Myocardial injury in Patients with COVID-19 Admitted to a Quaternary Hospital in the City of Rio de Janeiro

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Abstract

Background: In Brazil the factors involved in the risk of death in patients with COVID-19 have not been well established.

Objective: To analyze whether elevations of high-sensitivity troponin I (hTnI) levels influence the mortality of patients with COVID-19.

Methods: Clinical and laboratory characteristics of hospitalized patients with COVID-19 were collected upon hospital admission. Univariate and binary logistic regression analyzes were performed to assess the factors that influence mortality. P-value<0.05 was considered significant.

Results: This study analyzed192 patients who received hospital admission between March 16 and June 2, 2020 and who were discharged or died by July 2, 2020. The mean age was 70±15 years, 80 (41.7%) of whom were women. In comparison to those who were discharged, the 54 (28.1%) who died were older (79±12 vs 66±15years; P=0.004), and with a higher Charlson´s index (5±2 vs 3±2; P=0.027). More patients, aged≥60years (P <0.0001), Charlson´s index>1 (P=0.004), lung injury>50% in chest computed tomography (P=0.011), with previous coronary artery disease (P=0.037), hypertension (P=0.033), stroke (P=0.008), heart failure (P=0.002), lymphocytopenia (P=0.024), high D-dimer (P=0.024), high INR (P=0.003), hTnI (P<0.0001), high creatinine (P<0.0001), invasive mechanical ventilation (P<0.0001), renal replacement therapy (P<0.0001), vasoactive amine (P<0.0001), and transfer to the ICU (P=0.001), died when compared to those who were discharged. In logistic regression analysis, elevated hTnI levels (OR=9.504; 95% CI=1.281–70.528; P=0.028) upon admission, and the need for mechanical ventilation during hospitalization (OR=46.691; 95% CI=2.360–923.706; P=0.012) increased the chance of in-hospital mortality.

Conclusion: This study suggests that in COVID-19 disease, myocardial injury upon hospital admission is a harbinger of poor prognosis.

Keywords: COVID-19; SARS-CoV-2; Mortality; Myocardial Contusions; troponin I.

Introduction

Since the first reported cases in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly worldwide. According to the World Health Organization (WHO), on October 9, 2020, there were 36,754,395 confirmed cases of COVID-19 in the world, with 1,064,838 deaths, while in Brazil there were 5,028,444 confirmed cases with 148,957 deaths.[1]

Although SARS-CoV-2 explicitly refers to an aggression in the lungs, often inducing acute respiratory distress syndrome (ARDS), it also affects other organs, including blood vessels, brain, gastrointestinal tract, kidneys, heart, and liver,[2] and cardiovascular complications are manifestations that contribute significantly to the mortality of these patients.[3]

Several biomarkers of myocardial injury are elevated in patients with COVID-19, and a rise in troponin levels

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have been associated with the prediction of malignant cardiac arrhythmias,[4] and the need for mechanical ventilation (MV).[3,5-8]

This study sought to verify whether the elevation of high-sensitive troponin I (hTnI) levels upon hospital admission is an independent predictive factor of higher mortality in hospitalized patients with COVID-19.

Methods

This retrospective study involved a cohort of patients over 18 years of age who received hospital admission between March 16 and June 2, 2020, with a diagnosis of COVID-19, confirmed by nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR), or IgM and IgG measurement by chemiluminescent microplate immunoassay technique, and who were discharged or died by July 2, 2020.

The following characteristics were routinely collected upon hospital admission: sex, age, symptoms, comorbidities, blood count, biochemistry, prothrombin time with INR (INR), ultrasensitive PCR, D-dimer, simple X-ray, and chest computed tomography (CT) scan. hTnI (VITROS® High Sensitivity Troponin I assay), N-terminal prohormone of brain natriuretic peptide (Roche NT-proBNP), fibrinogen, and transthoracic echocardiogram (TTE) were not collected in all patients upon hospital admission. The laboratory tests were those collected within 24 hours of the patients' admission.

Comorbidities and clinical manifestations were collected by the physician responsible for hospital admission and were described, non-systematically, in the research forms from which the data were extracted for analysis.

The need for invasive MV, renal replacement therapy (RRT), extracorporeal membrane oxygenator (ECMO), the development of acute left ventricular systolic dysfunction (LVSD), or acute cor pulmonale, and the transfer to the intensive care unit (ICU) due to the worsening of the clinical condition during hospitalization, were also collected. Worsening of the clinical condition meant persistent desaturation, despite oxygenation by a high-flow nasal catheter, endotracheal intubation, resuscitation after cardiorespiratory arrest, and shock of any nature requiring vasoactive amines.

To analyze the chest CT scan, exams performed in the first 24 hours of hospitalization were included, and those with a "ground glass" infiltrate pattern,

compatible with SARS-CoV-2 infection,[9] were considered positive. All chest CT reports were reviewed by a senior radiologist, with an emphasis on compatible changes and the percentage of pulmonary parenchymal involvement.

TTE were performed following the recommendations of the Department of Cardiovascular Imaging (DIC, in Portuguese) of the Brazilian Society of Cardiology (SBC, in Portuguese) to perform cardiovascular imaging tests during the COVID-19 pandemic,[10] prioritizing the analysis of the left ventricular systolic dysfunction (LVSD) and the presence of acute cor pulmonale. The degree of LVSD was assessed visually. These analyzes were performed within the first 48 hours of hospitalization, and all tests were reviewed and validated by a senior echocardiographer.

The review of the imaging exams was carried out without the doctors having any knowledge of the clinical, laboratory, or patient outcomes.

Symptoms and comorbidities were those reported by patients or provided by family members, caregivers, or companions depending on the degree of interaction of the patients at the time of hospital admission.

The comorbidities presented by the patients were assessed using the Charlson's comorbidity index.[11]

This study was approved by the institution's Ethics Committee (number 31543220.1.0000.5533).

Statistical analysis

Data were collected directly from the medical records by an independent clinical research team and subsequently included in the SPSS statistical package, version 22 (IBM SPSS®).

Continuous variables were exposed by mean and standard deviations, and categorical variables by numbers and the appropriate proportions. The unpaired Student t test was used to compare continuous variables, and the Fisher's exact test or the Chi-square method was used to verify the existence of the association between categorical variables.

Binary logistic regression analysis was used to define which factors independently influenced mortality. To be included in this analysis, it was necessary that in the univariate analyses conducted by the Student's t test, Fisher exact test, or Chi-square test, the P-values were ≤ 0.05. Two-tailed P-values < 0.05 were considered statistically significant.

Results

During the study period, 339 consecutive patients were admitted to cohort units for SARS-Cov-2 infection, of whom 205 had a confirmed diagnosis. Among the 205, 192 (93.6%), who either died or were discharged by July 2, 2020, were included in this analysis.

Of the 192, 80 (41.7%) were women, aged 70 ± 15 years and Charlson's index of 3 ± 2. This study included 135 patients aged ≥60 years (70.3%), and 61 (31.8%) were aged ≥80 years. Charlson's index >1 was observed in 133 (69.3%) patients.

During the study period, 54 (28.1%) patients died.

Table 1 shows that, on average, deceased patients were 13 years older than those who were discharged and with a significantly higher Charlson's index.

Of the 54 who died, 27 (50%) received palliative care during hospitalization. In 7 of the 27 (25.9%), no invasive procedures, endotracheal intubation, renal replacement therapy, or resuscitation procedures were used, and the deaths occurred in semi-intensive care units.

As shown in Table 1, more patients of ≥60 years, and with Charlson's index >1 died when compared to those who were discharged. Table 1 also shows that patients who died had more than 50% of the pulmonary parenchyma compromised, a previous history of

Table 1 – Factors involved in mortality upon hospital admission in a univariate analysis					
Characteristics	Discharged (N=138)	Died (N=54)	p-value	OR	95% CI
Age ≥ 60 years, N (%)	84 (60.9)	51 (94.4)	<0.0001	10.929	3.247–36.779
Charlson's index >1, N (%)	121 (87.7)	54(100)	0.004	1.446	1.310–1.547
Men, N (%)	81 (58.7)	31 (57.4)	0.672	1.054	0.558–1.994
Obesity, N (%)	37 (26.8)	14 (25.9)	1.0	0.995	0.467–1.954
SAH, N (%)	79 (57.2)	40 (74.1)	0.033	2.134	1.064–4.279
Diabetes, N (%)	48 (34.8)	20 (37.0)	0.867	1.103	0.573–2.121
CAD, N (%)	26 (18.8)	18 (33.3)	0.037	2.154	1.060–4.375
Stroke, N (%)	7 (5.1)	10 (18.5)	0.008	4.253	1.527–11.848
COPD, N (%)	11 (8.0)	8 (14.8)	0.181	2.008	0.760–5.303
CHF, N (%)	4 (2.9)	9 (16.7)	0.002	6.700	1.968–22.814
CRF, N (%)	7 (5.1)	6 (11.1)	0.197	2.339	0.749–7.310
CT pulmonary>50%, N (%)	30 (21.9)	22 (41.5)	0.011	2.531	1.282–4.997
Leukocytosis, N (%)	16 (11.6)	11 (20.4)	0.164	1.951	0.840–4.530
Lymphocytopenia, N (%)	63 (45.7)	35 (64.8)	0.024	2.193	1.143 4.206
Thrombocytopenia, N (%)	44 (31.9)	21 (38.9)	0.398	1.360	0.707–2.614
D-dimer≥500ng/mL, N (%)	108 (80.0)	48 (91.4)	0.024	4.000	1.157–13.827
hsRCP-t>0.5ng/mL, N (%)	135 (97.8)	54 (100)	0.560	0.978	0.954–1.003
hTnI≥34pg/mL, N (%)	11 (10.8)	18 (48.6)	<0.0001	7.837	3.192–19.345
INR>1.3, N (%)	21 (15.3)	19 (35.8)	0.003	3.087	1.489–6.398
Creatinine>1.3mg/dL, N (%)	29 (53.7)	28 (20.6)	<0.0001	4.474	2.273–8.809

SAH: systemic arterial hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; CRF: chronic renal failure; CT pulmonary: pulmonary parenchymal alterations in chest computed tomography; hsCRP: high-sensitive C-reactive protein; hsTnI: high-sensitivity troponin I; INR: international normalized ratio; Leukocytosis means white blood cell count ≥10500/L; Lymphocytopenia, lymphocyte count <900/L; thrombocytopenia, platelet count <150000/L.

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coronary artery disease (CAD), stroke, congestive heart failure (CHF), and systemic arterial hypertension (SAH), as well as lymphocytopenia, higher levels of creatinine, D-dimer, INR, and hTnI upon hospital admission than those who survived and were discharged.

The average length of stay was not different between those who died and those who were discharged (14 ± 13 days vs 14 ± 11 days; P=0.174).

No difference in mortality was found between men and women (27.7% vs 28.7%, respectively; P=0.872).

Table 2 shows that during hospitalization, more patients who died received invasive MV, RRT, vasoactive amine, and transfer to the ICU compared to those who were discharged.

There was no difference between those who died and those who were discharged with regard to the development of acute LVSD during hospitalization (10.6% vs 2.7%; P=0.109).

Table 3 shows that, in the binary logistic regression analysis, it was found that elevated hTnI levels upon hospital admission, and the need for invasive MV during hospitalization, increased the chance of hospital mortality.

Patients with hTnI elevation upon hospital admission are more likely to have previous CHF (17.2% vs 2.7%; P=0.010; OR=7.431; 95% CI=1.661 – 33.243), COPD (20.7% vs 6.4%; P=0.029; 95% CI= 1.179 – 12.497), and the need for invasive MV during hospitalization (55.2% vs 21.8%; P=0.001; OR=4.410; 95% CI=1.865 – 10.426) as compared to patients who have normal hTnI levels.

No difference was found in relation to previous history of stroke (13.3% vs 9.1%; P=0.49), CAD (27.6% vs 23.6%; P=0.63), SAH (72.4% vs 60,0%; P=0.28), diabetes (44.8% vs 33.6%; P=0.28), and the development of acute LVSD (7.7% vs 6.3%; P=1.0) during hospitalization between patients with high and normal TnI levels, respectively, upon hospital admission.

Discussion

According to the findings of this study, it is suggested that, in a selected population of symptomatic hospitalized adult patients with a confirmed diagnosis of COVID-19, the presence of myocardial injury, characterized by high levels of hTnI upon hospital admission, is associated with an increased risk of death.

There is growing evidence of an association between myocardial injury and an increased risk of death in patients with COVID-19. Several studies involving patients with confirmed COVID-19 have implied the elevation of serum hTnI not only with mortality,[4,12-19] but also criticality.[8,14,16]

Although some investigators[4,14,16,18] have found an association between inflammatory biomarkers with poor prognosis, in the present study, only higher levels of hTnI were independently associated with mortality (table 3).

Another finding of this study, unlike others,[6,12,13,18] is that the presence of cardiovascular comorbidities was not independently associated with higher mortality (Table 3). In addition, it was demonstrated (table 3) that there was no independent association between older age (>60year-old) and mortality as has been demonstrated in other studies.[12,14,16] In the present study, the mortality of patients aged ≥ 60years of age was 37.8%, while the mortality of

Table 2 – Factors involved in mortality during hospitalization in univariate analysis					
Characteristics	Discharged (N=138)	Died (N=54)	p-value	OR	95% CI
LVSD, N (%)	2 (2.7)	5 (10.6)	0.109	4.226	0.785–22.758
RRT, N (%)	2 (1.4)	11 (20.4)	<0.0001	17.395	3.710–81.562
Transfer to ICU, N (%)	17 (12.3)	19 (35.2)	0.001	3.864	1.817–8.219
Vasoactive amine, N (%)	20 (14.5)	30 (55.6)	<0.0001	7.375	3.604–15.092
MV, N (%)	16 (11.6)	41 (75.9)	<0.0001	24.048	10.667–54.214

LVSD: left ventricular systolic dysfunction; RRT: renal replacement therapy; ICU: intensive care unit; MV: invasive mechanical ventilation;

Table 3 – Results of binary regression analysis			
Characteristics	OR	95% CI	p-value
Age ≥ 60 years	6.305	0.501 – 79.403	0.154
CAD	8.093	0.944 – 69.376	0.056
Stroke	13.980	0.327 – 597.291	0.169
CHF	8.567	0.426 – 172.445	0.161
INR>1.3	6.221	0.765 – 50.613	0.087
D-dimer>500ng/mL	1.507	0.034 – 66.740	0.832
Creatinine >1.3mg/dL	1.206	0.196 – 7.404	0.840
hTnI >34pg/mL	9.504	1.281 – 70.528	0.028
CT pulmonary alterations >50%	3.878	0.502 – 29.943	0.194
MV	46.691	2.360 – 923.706	0.012
Vasoactive amine	0.843	0.113 – 6.262	0.867
Transfer to ICU	3.231	0.153 – 68.109	0.451
RRT	10.175	0.800 – 129.444	0.074

CAD: coronary artery disease; CHF: congestive heart failure; CT pulmonary: pulmonary parenchymal alterations in chest computed tomography; hTnI: high-sensitivity troponin I; MV: invasive mechanical ventilation; ICU: intensive care unit; RRT: renal replacement therapy.

patients with higher hTnI was 69.4% (data not shown). In other words, it is suggested that myocardial injury upon hospital admission is much more dangerous than older age or cardiovascular comorbidities in the population with COVID-19 reported in this study.

Therefore, according to the findings of the present study and data collected from recent literature, it seems clear that the presence of myocardial injury in hospitalized adult patients with COVID-19 was associated with an increased risk of death. The pathophysiological substrate of myocardial injury produced by SARS-CoV-2 is not yet well defined, but it is speculated that an imbalance between myocardial demand and supply due to tachycardia, hypotension, and hypoxemia resulting in type 2 myocardial infarction, acute coronary syndrome due to a virally induced thrombotic and inflammatory state, microvascular dysfunction due to diffuse microthrombi or vascular injury, stress-related cardiomyopathy (Takotsubo syndrome), nonischemic myocardial injury due to hyperinflammatory cytokine storm, or a direct viral cardiomyocyte toxicity and myocarditis may be involved.[5,20]

Although no association was found between a rise in troponin upon hospital admission and the development of acute LVSD, it must be taken into account that there was no analysis of the evolution of hTnI levels during hospitalization.

Another finding of the present study is the independent association of the need for invasive MV during hospitalization, and an increased chance of death. Patients who required MV had a much higher chance of death when compared to those who did not require MV (Table 2 and Table 3). Of 57 patients that needed MV, 41 died (71.9%). This association has been reported by other studies, which have demonstrated that the mortality involved in the need for invasive MV varied from 33.9% to 90%.[16,21-24]

The finding of an association between the need for MV and increased mortality seems obvious, as it implies greater severity of the disease, especially acute respiratory distress syndrome. In the studied population, patients who required MV present greater lung injury (40.4% vs 21.8%; P = 0.013), higher hTnI (40% vs 13.1%; P = 0.001), a greater need for ECMO (5.3% vs 0%; P = 0.025), and RRT (21.1% vs 0.7%; P <0.0001) than those that did not require MV.

Limitations

Like any retrospective study, this study suffers from the lack of systematization in the registration of clinical and laboratory characteristics of patients, implying that the associations between these data and mortality are suggestive and require external validation, involving a larger number of patients with similar clinical and laboratory characteristics.

Laboratory changes that occurred during the course of hospitalization were also not routinely analyzed, which could somehow modify the results of the study.

This is a study of a quaternary heart center, which increases the chance of involving more patients with heart diseases, although no difference was found in the presence of previous CAD, stroke, chronic kidney dysfunction, SAH, diabetes or the development of acute LVSD among those with and without myocardial injury.

Conclusions

In a selected population of symptomatic hospitalized adult patients with COVID-19, the presence of myocardial injury upon hospital admission was independently associated with increased mortality. Therefore, it was suggested that hospitalized COVID-19 patients should have troponin levels measured routinely upon hospital admission in order to stratify the risk of death.

Author contributions

Conception and design of the research: Rocha ASC, Volschan A, Coelho RPS, Thielmann DCA. Acquisition of data: Rocha ASC, Volschan A. Analysis and interpretation of the data: Rocha ASC, Volschan A, Campos LAA, Thielmann DCA, Ferreira CALC, Colafranceschi AS. Statistical analysis: Rocha ASC, Volschan A. Writing of the manuscript: Rocha ASC, Volschan A. Critical revision of the manuscript for intellectual content: Rocha ASC, Volschan A, Campos LAA, Thielmann DCA, Ferreira CALC, Colafranceschi AS.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital Pró-Cardíaco* under the protocol number 31543220.1.0000.5533. 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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