

# Troponin elevation on admission and mortality after hospital discharge among patients with COVID-19

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## INTRODUCTION

According to the World Health Organization, coronavirus disease 2019 (COVID-19) has resulted in over 6.8 million deaths worldwide as of January 2023<sup>1</sup>. However, variable rates of in-hospital and post-discharge morbidity and mortality have been described since the beginning of the pandemic. Regional differences in medical care, patient characteristics, access to vaccination, and effective interventions are important factors that contribute to these discrepancies. Nonetheless, several biomarkers have demonstrated prognostic value in this scenario primarily during the hospitalization period<sup>2</sup>.

High-sensitivity troponin I (hs-TnI) has been widely studied in the context of COVID-19, and elevated levels on admission are predictive of short-term outcomes<sup>3</sup>. However, the long-term prognostic significance of myocardial injury during the acute phase of COVID-19 remains unknown. The objective of this study was to determine the association between hs-TnI elevation above the 99th percentile upper reference limit on admission in hospitalized patients with COVID-19 and long-term survival among those who were successfully discharged.

## METHODS

Medical records from consecutive patients with confirmed COVID-19 admitted to a single institution between March and July 2020 were retrospectively analyzed. Only those with a positive polymerase chain reaction result for severe acute respiratory syndrome coronavirus 2 were screened for inclusion. The analysis was further restricted to patients with an initial hs-TnI measurement who were successfully discharged from the hospital. Clinical data, including age, comorbidities, oxygen saturation, and tomographic findings on admission, were collected in addition

to further laboratory information (leukocyte count, C-reactive protein, D-dimer, and creatinine). Myocardial injury was defined by hs-TnI levels above the 99th percentile upper reference limit (URL) of the assay (>34 pg/mL). Long-term survival was determined by consulting a public, governmental online database of births and deaths from the state's justice court. Previously collected clinical and laboratory data were then correlated with mortality after the index hospitalization.

The Stata<sup>®</sup> 11.0 software was used for statistical analysis. Categorical variables were analyzed with<sup>2</sup> and Fisher's exact test. Continuous variables were expressed by the median and 25th to 75th percentile interquartile range. Such data were evaluated by the Wilcoxon-Mann-Whitney and Kruskal-Wallis tests. Variables with significance in the univariate analysis were included in a multivariate logistic regression model to determine independent predictors of death. Survival curves were constructed from Kaplan-Meier estimates, and differences were analyzed using the log-rank test. A p-value<0.05 was considered significant. The study conforms to the guidelines of the Declaration of Helsinki and obtained appropriate Institutional Review Board approval on July 6, 2021, under project number 19101573. Informed consent was not required due to the retrospective nature of the study.

## RESULTS

Among the 230 patients admitted with a positive RT-PCR during the study period, 194 survived until hospital discharge, of which 149 had hs-TnI values on admission and were included in the analysis. The median age was 65 years (52–78), and 56.4% were males. Troponin elevation occurred in 21 patients (14.1%), and 36.2% were treated in the intensive care unit

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(ICU). Patients with myocardial injury were older, had greater prevalence of hypertension and previous cardiovascular disease, and presented with greater pulmonary compromise on admission chest tomography. Additional baseline characteristics are described in Table 1 according to the troponin values.

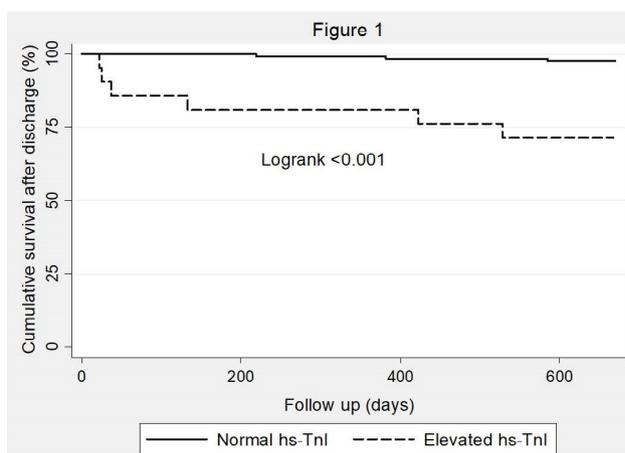
After a median follow-up of 631 days (612–643), 9 (6%) deaths occurred subsequently to hospital discharge, of which 6 were recorded within 1 year. In the univariate analysis, age (OR 1.08; 95%CI 1.02–1.14,  $p=0.008$ ), hypertension (OR 8.47; 95%CI 1.03–69.53,  $p<0.047$ ), and hs-TnI elevation (OR 16.7; 95%CI 3.8–73.6,  $p<0.001$ ) were associated with mortality. In the multivariate model, hs-TnI elevation remained predictive of subsequent death (OR 7.45; 95%CI 1.4–39.4,  $p=0.018$ ), after adjusting for age, hypertension, ICU admission, C-reactive protein, and creatinine values. Figure 1 represents the Kaplan–Meier survival estimates after hospital discharge according to hs-TnI elevation.

## DISCUSSION

Hospitalization due to COVID-19 often imposes significant short-term morbidity and an increased risk of death, especially in the presence of chronic comorbidities. However, even among those who are successfully discharged, long-term sequelae may persist. Among 1,733 patients who survived an initial hospitalization period in China, Huang et al. reported persistent

symptoms in 76% of the cohort after 6 months of follow-up. Manifestations included fatigue, muscle weakness, chest pain, psychiatric illnesses, and respiratory impairment<sup>4</sup>. Similarly, in a meta-analysis published by Leon-Lopez et al., more than 50 long-term effects were associated with the disease among almost 48,000 patients from multiple studies<sup>5</sup>.

Readmission and death rates are also relevant, with a 27% risk of either outcome within 60 days post-discharge<sup>6</sup>. Most importantly, in a study involving 153,760 patients with



**Figure 1.** Kaplan-Meier survival estimates of patients discharged after hospitalization for COVID-19. High-sensitivity troponin I elevation on admission was associated with decreased long-term survival. hs-TnI: high-sensitivity troponin I.

**Table 1.** Baseline characteristics of COVID-19 patients on admission, according to high-sensitivity troponin I elevation.

Characteristics	hs-TnI >99th percentile URL		p-value <sup>a</sup>
	No (n=128)	Yes (n=21)	
Age, median (IQR), years	61 (51–74)	84 (78–89)	<0.001
Male, No. (%)	73 (57.0)	11 (52.4)	0.69
BMI, median (IQR), kg/m <sup>2</sup>	26.8 (24.2–30.1)	27 (24.4–28.3)	0.52
Medical history, No. (%)			
Hypertension	60 (46.9)	16 (76.2)	0.02
Diabetes	36 (28.1)	8 (38.1)	0.35
Coronary artery disease	12 (9.4)	6 (28.6)	0.01
Oxygen saturation <sup>b</sup> , median (IQR), %	93 (91–96)	94 (86–95)	0.12
Total lung opacities <sup>c</sup> , median (IQR), %	15 (6.1–27.5)	26.8 (11.4–49.7)	0.05
Laboratory values, median (IQR)			
Leukocyte count, cells/mm <sup>3</sup>	5,430 (4,210–7,310)	9,890 (6,210–12,390)	<0.001
C-reactive protein, mg/mL	6.2 (3–14)	8.1 (3.8–14.2)	0.41
D-dimer, ng/mL	644 (440–1,155)	1,382 (678–3,467)	<0.001
Creatinine, mg/dL	0.85 (0.7–1.0)	0.9 (0.7–1.3)	0.15
hs-TnI, pg/mL	NA	104 (48–479)	NA

<sup>a</sup> $p<0.05$  indicates statistical significance (bold values); <sup>b</sup>On ambient air; <sup>c</sup>Chest computed tomography analysis. BMI: body mass index; hs-TnI: high-sensitivity troponin I; IQR: interquartile range; NA: not applicable; URL: upper reference limit.

COVID-19, Xie et al. found an increased risk of multiple cardiovascular complications after the first 30 days of infection. The higher risk persisted up to 12 months after the initial diagnosis and included the occurrence of ischemic heart disease, heart failure, cerebrovascular disease, thromboembolism, and arrhythmias. These findings strongly suggest that cardiovascular complications may manifest at a much later stage and could represent the main cause of morbidity and mortality following the acute phase of COVID-19<sup>7</sup>.

Troponin elevation is identified in approximately 30% of hospitalized patients with COVID-19 and is associated with a higher risk of both fatal and non-fatal short-term outcomes. However, abnormal TnI levels may persist months after hospital discharge and have been implicated in the long-term complications of the disease<sup>8</sup>. Our results further support this concept, indicating that initial myocardial injury is predictive of survival after discharge.

The exact mechanisms involved are unclear, though arrhythmias, heart failure, and atherosclerotic disease are all potential late consequences that seem to be associated with the extension of myocardial and vascular damage during the acute phase of the disease. COVID-19 endotheliopathy is a well-known factor associated with increased thrombogenicity and may persist beyond the initial stages of infection, leading to thromboembolic, coronary, and cerebrovascular events<sup>9</sup>. In addition, the extension of myocardial scarring following viral myocarditis is another potential mechanism that could affect long-term outcomes and has been previously described in imaging studies performed months after infection<sup>10</sup>.

Troponin values on admission could also perform as an indirect marker of non-cardiovascular damage during the disease's inflammatory cascade. Previous studies have demonstrated an association between higher troponin levels, greater total pulmonary opacification percentages, and lower lung volumes in hospitalized patients with COVID-19<sup>11</sup>. In the current study, those with hs-TnI elevation also presented with significantly greater lung involvement on computed tomography. Such an association may have contributed to the adverse prognosis

associated with the diagnosis of early myocardial injury, in addition to the subsequent cardiovascular complications. Most importantly, hs-TnI elevation in the acute phase represents a promising surrogate for a variety of outcomes and can be considered an early prognostic marker before hospital discharge.

This study has limitations, which have to be acknowledged. Data were retrospectively collected from a single center and may not reflect the same results as other institutions. Since patients were managed before evidence-based treatments and vaccines were available, current survivors discharged after hospitalization for COVID-19 could have different prognoses. Finally, the number of events was low, which limited a thorough statistical analysis of the results.

## CONCLUSION

Although most patients have favorable outcomes after hospitalization for COVID-19, hs-TnI elevation on admission appears to remain predictive of long-term survival after discharge. Such cases should be carefully followed, and until novel preventive strategies are developed, appropriate vaccination and management of traditional modifiable cardiovascular risk factors remain essential.

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## AUTHORS' CONTRIBUTIONS

**GSSO:** Data curation, Resources, Software, Writing – original draft. **RMF:** Data curation, Investigation, Project administration, Writing – review & editing. **JMF:** Conceptualization, Resources, Supervision. **RACL:** Conceptualization, Project administration, Supervision. **LHAS:** Formal Analysis, Methodology, Validation. **NASS:** Formal Analysis, Methodology, Supervision, Visualization.

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