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ORIGINAL RESEARCH

Relationship Between Myocardial Injury During Index Hospitalization for SARS-CoV-2 Infection and Longer-Term Outcomes

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BACKGROUND: Myocardial injury in patients with COVID-19 is associated with increased mortality during index hospitalization; however, the relationship to long-term sequelae of SARS-CoV-2 is unknown. This study assessed the relationship between myocardial injury (high-sensitivity cardiac troponin T level) during index hospitalization for COVID-19 and longer-term outcomes.

METHODS AND RESULTS: This is a prospective cohort of patients who were hospitalized at a single center between March and May 2020 with SARS-CoV-2. Cardiac biomarkers were systematically collected. Outcomes were adjudicated and stratified on the basis of myocardial injury. The study cohort includes 483 patients who had high-sensitivity cardiac troponin T data during their index hospitalization. During index hospitalization, 91 (18.8%) died, 70 (14.4%) had thrombotic complications, and 126 (25.6%) had cardiovascular complications. By 12 months, 107 (22.2%) died. During index hospitalization, 301 (62.3%) had cardiac injury (high-sensitivity cardiac troponin T≧14 ng/L); these patients had 28.6%, 32.2%, and 33.2% mortality during index hospitalization, at 6 months, and at 12 months, respectively, compared with 4.1%, 4.9%, and 4.9% mortality for those with low-level positive troponin and 0%, 0%, and 0% for those with undetectable troponin. Of 392 (81.2%) patients who survived the index hospitalization, 94 (24%) had at least 1 readmission within 12 months, of whom 61 (65%) had myocardial injury during the index hospitalization. Of 377 (96%) patients who were alive and had follow-up after the index hospitalization, 211 (56%) patients had a documented, detailed clinical assessment at 6 months. A total of 78 of 211 (37.0%) had ongoing COVID-19–related symptoms; 34 of 211 (16.1%) had neurocognitive decline, 8 of 211 (3.8%) had increased supplemental oxygen requirements, and 42 of 211 (19.9%) had worsening functional status.

CONCLUSIONS: Myocardial injury during index hospitalization for COVID-19 was associated with increased mortality and may predict who are more likely to have postacute sequelae of COVID-19. Among patients who survived their index hospitalization, the incremental mortality through 12 months was low, even among troponin-positive patients.

Key Words: biomarkers ■ COVID-19 ■ long covid ■ outcomes ■ PASC ■ troponin T

Cardiovascular complications of COVID-19 contribute substantially to high morbidity and mortality. Patients with cardiovascular risk factors, preexisting heart disease, and de novo myocardial injury have the highest case-fatality rates.[1–3] This suggests an interaction between the SARS-CoV-2 virus and the heart that

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CLINICAL PERSPECTIVE

What Is New?

- SARS-CoV-2 infection is associated with a high prevalence of cardiac injury, defined as circulating high-sensitivity cardiac troponin T, and has been previously shown to associate with all-cause and cardiovascular mortality.
- This study provides insights into the relationship between myocardial injury during the index hospitalization and longer-term outcomes up to 12 months.

What Are the Clinical Implications?

- The relationship between myocardial injury in patients hospitalized with COVID-19 and longer-term outcomes suggests that assessment of myocardial injury may serve as an additional tool for clinical practice.
- Future larger-scale prospective studies are needed to address the spectrum of myocardial injury across clinical severities of COVID-19 and the underlying mechanisms by which myocardial damage associates with longer-term outcomes.

Nonstandard Abbreviation and Acronym

hs-cTnT	high-sensitivity cardiac troponin T

is incompletely understood, but inflammation-induced as well as direct injury of the vascular endothelium and the myocardium are likely to play a central role.[4–8] Myocardial injury has been associated with increased morbidity and mortality during the index hospitalization for patients with COVID-19.[3,9] However, the impact of myocardial injury on longer-term outcomes in these patients is unknown. The purpose of this study was to assess the relationship between cardiac injury during the index hospitalization and longer-term outcomes, including the incidence of postacute sequelae of COVID-19 at 6 months, readmission rate at 6 and 12 months, and mortality at 6 and 12 months.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Study Design and Setting

The Brigham and Women's Hospital COVID-19 registry is a prospective cohort study of consecutive patients who were admitted with documented evidence of SARS-CoV-2 infection since March 2020. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.[10] The study was approved by the Massachusetts General Brigham institutional review board, and informed consent was waived. Patients were included if they tested positive for SARS-CoV-2 on a nasopharyngeal swab polymerase chain reaction test, received inpatient care at Brigham and Women's Hospital for COVID-19 from March to May 2020, and had troponin levels measured. Patients had follow-up through March 31, 2021.

Data Sources and Outcome Measurements

For the study cohort, baseline demographics, clinical characteristics, laboratory measurements, readmission data, mortality, and outpatient clinical follow-up assessments were obtained from the electronic medical health record (EHR) (Epic Systems, Verona, WI) by a combination of automated queries using the National Death Index, Research Patient Data Registry, and confirmation through physician medical record review. In addition, deaths were confirmed through online obituaries.[11] Hospital readmissions, 6-month clinical follow-up assessments, and loss to follow-up were assessed by examining the EHR shared by the Mass General Brigham healthcare system, which includes 11 institutions in Massachusetts that provide both inpatient and ambulatory services. Median follow-up time and mortality data were assessed from March 2020 to May 2021.

As part of the Brigham and Women's Hospital COVID-19 inpatient protocols, high-sensitivity cardiac troponin T (hs-cTnT) was measured in all COVID-19 inpatients every other day until at least hospital day 8.[12] Hs-cTnT was systematically collected and analyzed as a surrogate for myocardial injury using the Elecsys 2010 system (Roche Diagnostics GmbH, Mannheim, Germany). The assay has a 6 ng/L lower limit of detection, with a 99th percentile cutoff at 14 ng/L.[13] For each patient, the maximum hs-cTnT level during his/her hospitalization was used for analyses. Levels of hs-cTnT were categorized as follows: undetectable (<6 ng/L), low-level positive (6–14 ng/L), and myocardial injury (≥14 ng/L).[14]

Clinical outcomes during the index hospitalization and readmissions were ascertained on the basis of laboratory results, imaging, medications, and documentation of clinical assessment in the EHR and then were independently reviewed by a panel of physicians, including cardiologists and infectious disease physicians; and any discrepancies were adjudicated by at least 2 physicians. Cardiovascular outcomes

included heart failure, acute coronary syndrome, atrial and ventricular arrythmia, arterial and venous thrombosis, cardiogenic shock, and cardiovascular death. The composite thrombotic complication was defined as pulmonary embolism, lower extremity or upper extremity deep venous thrombosis, line-associated upper extremity/lower extremity deep venous thrombosis, or a circuit thrombosis (extracorporeal membrane oxygenation or continuous venovenous hemofiltration). Infectious outcomes included a composite of clinical and microbiological confirmed pneumonia, endocarditis, bloodstream infection, or urinary tract infection.

The clinical symptom assessments for postacute sequelae of COVID-19 at 6 months were ascertained through documentation in the shared EHR and adjudicated by at least 2 physicians. This assessment at 6 months included whether the patient had ongoing symptoms since his/her COVID-19 infection, including dyspnea, chest pain, palpitations, fatigue, anosmia, ageusia, headaches, neurocognitive decline, increased supplemental oxygen requirement, or decline in functional status, as documented by a decrease in the activities of daily living from his/her pre–COVID-19 baseline.[15–17]

Statistical Analysis

Categorical variables are reported as frequencies with percentages. Continuous variables are expressed as median (interquartile range [IQR]). To test for the presence of a significant trend across the troponin categories, the Jonckheere-Terpstra test was used for continuous variables, and the Cochran-Armitage test was used for binary variables. For race/ethnicity and prodrome categories, the Fisher exact test was used. *P* values represent the comparison between cardiac injury (≥14 ng/L) versus noncardiac injury (low-level positive and undetectable). For in-hospital and 6-month outcomes stratified by myocardial injury, a binomial proportion test was used. Troponin was evaluated by both a continuous linear regression and using categories of cardiac injury, low-level positive, and undetectable. Multivariable logistic regression was then performed to determine the association between high-sensitivity troponin and all-cause mortality, readmissions, and postacute sequelae of COVID-19 while adjusting for clinically significant covariates (age, sex, history of coronary artery disease [CAD], hypertension, hyperlipidemia, heart failure, and type 2 diabetes). Adjusted *P* values with logistic regression were not calculated with categories with <7 events to avoid overfitting. For all statistical analyses, 2-sided and false discovery rate corrected $P<0.05$ was considered statistically significant.[18] Data analysis was conducted in R version 4.0.2 (R Project for Statistical Computing).

RESULTS

Cohort Characteristics and Index Hospitalization Outcomes

A total of 500 consecutive patients were hospitalized with COVID-19 from March to May 2020, of whom 483 had hs-cTnT measured systematically during the index admission (Figure 1). Among these 483 patients who were included in the study cohort, 50.5% were women and had a median age of 63 years (IQR, 51–75 years), 24.6% were Hispanic, and 28.8% were Black non-Hispanic race/ethnicity. Median body mass index was 29 kg/m^2 (IQR, 25–33 kg/m^2), 64.6% had hypertension, 48% had hyperlipidemia, 34.2% had diabetes, 29.6% had CAD, and 14.9% had heart failure (Table 1). A total of 224 (46.4%) had an oxygen saturation of >92% on admission, and 221 (45.8%) required the intensive care unit at some point during their index hospitalization. The median length of hospitalization was 9 days (IQR, 5–19 days) (Table 1). During the index hospitalization, 116 (24%) had infectious complications, 70 (14.4%) had thrombotic complications, and 124 (25.6%) had cardiovascular complications (Table 2).

Mortality and Clinical Outcomes, Stratified by Myocardial Injury

During the index hospitalization, 91 (18.8%) patients died (Table 2). An additional 12 patients (103/483 [21.3%]) died by 6 months and 4 more died between 6 and 12 months after their index hospitalization (107/483 [22.2%]).

Overall, 301 (62.3%) patients had cardiac injury (hs-cTnT ≥14 ng/L) during the index hospitalization, 123 (25.5%) had low-level positive hs-cTnT, and 59 (12.2%) had an undetectable hs-cTnT level. Patients with evidence of cardiac injury were older and more likely to have diabetes, hypertension, dyslipidemia, and CAD (Table 1). The patients with cardiac injury had a 28.6%, 32.2%, and 33.2% mortality during index hospitalization, at 6 months, and at 12 months, respectively, compared with 4.1%, 4.9%, and 4.9% mortality for those who had low-level positive hs-cTnT, and 0%, 0%, and 0% for those who had undetectable troponin ($P<0.001$ for index hospitalization, 6-month mortality, and 12-month mortality) (Figure 2). Adjusting for age, sex, CAD, hypertension, hyperlipidemia, heart failure, and diabetes, cardiac injury (hs-cTnT ≥14 ng/L) compared with undetectable hs-cTnT was associated with an increased risk of mortality (hazard ratio [HR], 13.76; 95% CI, 1.85–102.3; $P=0.01$), whereas low-level positive hs-cTnT compared with undetectable was not statistically significant (HR, 2.31; 95% CI, 0.27–19.48; $P=0.44$) (Table 3). There was no relationship between cardiac injury and duration of symptoms before hospitalization (Table 1).

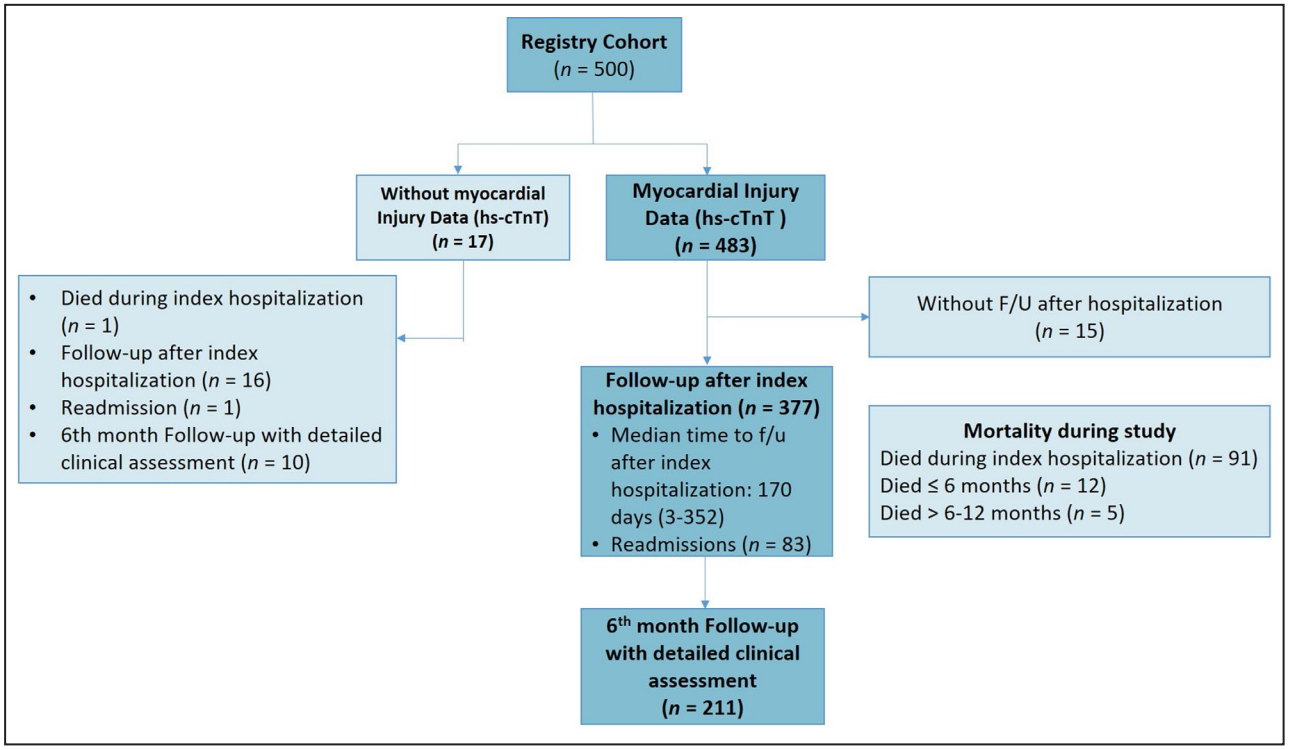

Figure 1. Brigham and Women's Hospital COVID-19 Registry flow diagram.
Shown is a detailed outline of the study cohort that included 500 consecutive patients enrolled in March to May 2020 and follow-up through March 2021. The proportion of patients with data on myocardial injury during index hospitalization is shown (n=483). Data are provided on mortality, mean follow-up (F/U) time, and detailed 6-month symptom assessment among the study cohort. hs-cTnT indicates high-sensitivity cardiac troponin T.

Patients with evidence of cardiac injury were more likely to have infectious, thrombotic, and cardiac complications during index hospitalization, which remained significant after adjustment for age, sex, CAD, hypertension, hyperlipidemia, and diabetes (cardiac: 117/124 [94%] versus 7/124 [6%] [*P*<0.001]; thrombotic: 59/70 [84%] versus 11/70 [16%] [*P*<0.001]; infectious: 99/116 [85%] versus 17/116 [15%] [*P*<0.001]) (Table 2). Among the cardiac complications, there were a total of 50 cases of type II myocardial infarction and 5 cases of acute coronary syndrome.

To further ascertain cardiac injury, we also examined cardiovascular imaging. Among the 483 patients, 122 had transthoracic echocardiograms during the index admission. Among the 122 patients, a total of 81 (66.4%) had left ventricular ejection fraction ≥40% and 16 (13.1%) had left ventricular ejection fraction <40%. Among the patients with left ventricular ejection fraction <40%, 16 of 17 (99%) had evidence of myocardial injury, defined as the highest category of troponin (Table S1). Additional cardiovascular imaging modalities were limited: 5 patients underwent coronary computed tomographic angiogram, and 3 patients had coronary angiograms.

Longer-Term Clinical Assessments, Stratified by Myocardial Injury

Of the 392 (81.2%) patients who survived the index hospitalization, 377 (96%) had documented follow-up, with a median follow-up time of 170 days (IQR, 3–352 days). A total of 15 (3.8%) patients were lost to follow-up. A detailed flow chart of the study cohort is provided in Figure 1. A total of 83 of 392 (21.2%) patients had ≥1 readmission within 6 months and 94 of 392 (24%) patients had ≥1 readmission within 12 months. Of the 6-month readmissions, 8 of 83 (9.6%) involved thrombotic complications and 20 of 83 (24.1%) had cardiac complications. Of the 12-month readmissions, 9 of 94 (9.6%) involved thrombotic complications and 28 of 94 (29.8%) had cardiac complications. Patients with myocardial injury were more likely to have a readmission than patients without myocardial injury (64.9% compared with 21.3% and 13.8% in low-level positive and undetectable troponin, respectively; *P*=0.01). However, this was not statistically significant after multivariable adjustment (HR, 1.5; 95% CI, 0.8–2.5; *P*=0.23; Table 2).

Of the 377 (96%) patients who had follow-up after the index hospitalization through May 2021, 211 (56%) had clinical follow-up with detailed symptom

Table 1. Baseline Characteristics of Study Cohort, Stratified by Myocardial Injury

Characteristics	Patients with troponin measured (n=483/500)	Undetectable troponin (<6 ng/L) (n=59 [12.2%])	Low-level positive (6–13 ng/L) (n=123 [25.5%])	Cardiac injury (≥14 ng/L) (n=301 [62.3%])	*P* value
Women, n (%)	244 (50.5)	46 (78.0)	60 (48.8)	138 (45.8)	0.008
Age, median (IQR), y	63 (51–75)	43 (34–55)	57 (48–66)	68 (58–79)	<0.001
SpO_2 >92% admission, n (%)	224 (46.4)	45 (76.3)	61 (49.6)	118 (39.2)	<0.001
Prodrome, n (%)					0.3923
Asymptomatic	4 (0.8)	0 (0.0)	0 (0.0)	4 (1.3)	
0–7 d	344 (71.2)	40 (67.8)	83 (67.5)	221 (73.4)	
>7 d	135 (28.0)	19 (32.2)	40 (32.5)	76 (25.2)	
Race/ethnicity, n (%)					0.0609
White	170 (35.2)	12 (20.3)	40 (32.5)	118 (39.2)	
Black, non-Hispanic	139 (28.8)	20 (33.9)	31 (25.2)	88 (29.2)	
Hispanic/Latino	119 (24.6)	19 (32.2)	34 (27.6)	66 (21.9)	
Other or unknown*	55 (11.4)	8 (13.6)	18 (14.6)	29 (9.6)	
Comorbidities					
Body mass index, median (IQR), kg/m^2	29 (25–33)	30 (27–34)	30 (27–34)	28 (25–32)	0.008
Diabetes, n (%)	165 (34.2)	6 (10.2)	33 (26.8)	126 (41.9)	<0.001
Hypertension, n (%)	312 (64.6)	17 (28.8)	67 (54.5)	228 (75.7)	<0.001
CAD, n (%)	146 (29.6)	2 (1.7)	18 (7.3)	126 (20.9)	0.008
Heart failure, n (%)	72 (14.9)	2 (3.4)	7 (5.7)	63 (20.9)	0.003
Hyperlipidemia, n (%)	232 (48.0)	5 (8.5)	57 (46.3)	170 (56.5)	<0.001
COPD, n (%)	43 (8.9)	2 (3.4)	6 (4.9)	35 (11.6)	0.239
History of active malignancy, n (%)	49 (10.1)	3 (5.1)	11 (8.9)	35 (11.6)	0.837
Inpatient medications					
Antiviral therapy, n (%)	171 (35.4)	18 (30.5)	60 (48.8)	93 (30.9)	0.167
Intravenous steroids, n (%)†	32 (6.6)	0 (0.0)	1 (0.8)	31 (10.3)	0.167
Tocilizumab, n (%)	74 (15.3)	2 (3.4)	13 (10.6)	59 (19.6)	0.039
Length of hospital stay, median (IQR), d	9 (5–19)	4 (2–6)	7 (4–12)	14 (7–26)	<0.001
ICU admission, n (%)	221 (45.8)	4 (6.8)	39 (31.7)	178 (59.1)	<0.001
Length of ICU stay, median (IQR), d	10 (4–22)	3 (2–5)	5 (2–9)	14 (6–23)	<0.001
Mechanical ventilation, n (%)	173 (35.8)	1 (1.7)	16 (13.0)	156 (51.8)	<0.001
Peak troponin during hospital stay, median (IQR), ng/L	23 (9–62)	5 (5–5)	9 (8–11)	47 (24–106)	<0.001

Baseline characteristics are shown. N=483 because of 17 patients with missing troponin values. *P* values were calculated by the Jonckheere trend test for continuous variables and the Fisher exact test for categorical variables with false discovery rate correction. Values shown are number (percentage) or median (IQR), as noted. For inpatient medications, therapy was defined as whether any dose or duration was given during index hospitalization. CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; and SpO_2, oxygen saturation.

*Other or unknown indicates Asian non-Hispanic, or unknown.

†Represents only patients in the ICU who received intravenous steroids.

assessment documented in the EHR at 6 months and could be assessed for postacute sequelae of COVID-19. Compared with the total cohort who survived the index hospitalization, the 211 patients with detailed symptom assessment were similar in age, comorbidities, length of stay, and intensive care unit admission (Table S2). Of those patients, 78 (37.0%) had ongoing COVID-19–related symptoms, including dyspnea, chest pain, palpitations, fatigue, anosmia, ageusia, or headaches (Table 4). Compared with their pre–COVID-19 baseline, 8 (3.8%) patients required increased supplemental oxygen, 34 (16.1%) patients had neurocognitive decline, and 42 (19.9%) patients had worsening functional status requiring additional assistance. Although not statistically significant, patients with higher levels of hs-cTnT during their index hospitalization had higher rates of ongoing COVID-19–related symptoms at 6 months (undetectable: 10/78 [12.8%]; low-level positive: 24/78 [30.7%]; and definite myocardial injury: 44/78 [56.4%]). In aggregate, 98 (46.4%) of the 211 assessed patients had symptoms and clinical features concerning for post-acute sequelae of COVID-19 6 months after their initial diagnosis of COVID-19 (Figure 3). Patients with myocardial

Table 2. In-Hospital, 6-Month, and 12-Month Outcomes, Stratified by Myocardial Injury

Outcome	Patients with troponin measured (n=483)	Undetectable troponin (<6 ng/L) (n=59)	Low-level positive (6–13 ng/L) (n=123)	Cardiac injury (≥14 ng/L) (n=301)	Univariate *P* value	Adjusted *P* value	Adjusted odds ratio (95% CI)
Index hospitalization outcomes							
Infectious complication	116 (24.0)	3/116 (2.6)	14/116 (12)	99/116 (85)	<0.001	<0.001	7.6 (3.6–15.8)
Cardiac complication	124 (25.6)	2/124 (1.6)	5/124 (4.0)	117/124 (94)	<0.001	<0.001	15.3 (6.3–37.1)
Thrombotic complication	70 (14.4)	2/70 (2.9)	9/70 (12.9)	59/70 (84)	<0.001	<0.001	6.0 (2.8–13.2)
Index hospitalization mortality	91 (18.8)	0/91 (0)	5/91 (5.5)	86/91 (95)	<0.001	<0.001	9.3 (3.3–25.8)
6-mo Readmissions							
Readmission	83 (17.2)	13/83 (15.7)	19/83 (23)	51/83 (61)	0.061	0.291	1.4 (0.7–2.5)
Thrombotic complication	8/83 (9.6)	0/8 (0)	2/8 (25)	6/8 (75)	0.311	NA	NA
Cardiac complication	20/83 (24.1)	1/20 (0.05)	5/20 (25)	14/20 (70)	0.137	NA	NA
Infectious complication	25/83 (30.1)	3/25 (12)	2/25 (0.1)	20/25 (80)	0.008	NA	NA
6-mo Mortality	103/483 (21.3)	0/103 (0)	6/103 (5.8)	97/103 (94)	<0.001	<0.001	8.2 (3.4–19.9)
12-mo Readmissions							
Readmission	94 (19.4)	13/94 (13.8)	20/94 (21.3)	61/94 (64.9)	0.008	0.220	1.4 (0.8–2.6)
Thrombotic complication	9/94 (9.6)	0/9 (0)	3/9 (33.3)	6/9 (66.7)	0.505	NA	NA
Cardiac complication	28/94 (29.8)	2/28 (7.2)	5/28 (17.9)	21/28 (75)	0.020	NA	NA
Infectious complication	33/94 (35.1)	4/33 (12.1)	4/33 (12.1)	25/33 (75.8)	0.008	NA	NA
12-mo Mortality	107/483 (22.2)	1/107 (0.1)	6/107 (5.6)	100/107 (94)	<0.001	<0.001	8.2 (3.4–19.7)

Data are given as number (percentage) or number/total (percentage). Univariate *P* values (after false discovery rate correction) represent the comparison between cardiac injury (≥14 ng/L) vs noncardiac injury (low-level positive and undetectable) based on a binomial proportion test for whether patients with cardiac injury had an unadjusted proportion of 50% (ie, shared equal proportions with patients without cardiac injury) in each outcome group. Adjusted *P* value and odds ratios (95% CIs) are based on multivariable logistic regression, adjusting for clinical covariates that included age, sex, history of coronary artery disease, hypertension, hyperlipidemia, and diabetes and further adjusted using false discovery rate correction. Adjusted *P* values were not calculated for categories with <7 events because of overfitting. NA indicates not applicable.

injury accounted for 58.2% of those with postacute sequelae of COVID-19. There was overall a gradation of risk for patients with undetectable troponin during the index hospitalization who were least likely to require readmissions, have postacute sequelae of COVID-19, or experience mortality at 6 months. Furthermore, older age (>65 years) was associated with higher degrees of cardiac injury and mortality (Figure 3).

DISCUSSION

Limited data exist on long-term outcomes,[19–21] and to our knowledge, this is the first longitudinal study to assess the relationship with myocardial injury. Although our findings further support other US center studies on postacute sequelae of COVID-19,[22] our mortality rate after index hospitalization was much lower than a recent analysis of a large registry cohort in the United Kingdom.[23] In that study, they assessed rates of multiorgan dysfunction after discharge through September 2020 (mean of 140 days of follow-up) rather than ongoing COVID-19 symptoms or neurocognitive decline stratified by myocardial injury. Their findings suggest a greater severity of disease in their cohort, leading to a higher rate of mortality and multiorgan dysfunction, which is consistent with the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial analyses from the United Kingdom, which showed higher mortality rates compared with other US or European trial sites.[23,24]

The exact mechanism by which mortality and adverse outcomes are increased in patients with COVID-19 who have elevated circulating hs-cTnT is not known. However, this association has previously been seen in patients with other infections, such as influenza, and other noncardiovascular disease states.[14,24–27] Hs-cTnT likely serves as a subclinical marker of cardiac damage in response to these conditions, with higher levels associated with a greater degree of damage. Close to half of the cardiac events observed in our cohort were attributable to either type II myocardial infarction or acute coronary syndrome. Underreporting of these events is certainly possible, given the limited diagnostic interventions used in the beginning of the pandemic because of infection control concerns. More in-depth diagnostic evaluation with cardiac imaging and further biomarker analysis across the wide range of disease states associated with elevated hs-cTnT could provide further understanding of the myocardial function and structural changes that lead to the adverse outcomes and increased mortality.

Limitations of this single-center, observational study include its sample size, assessment of hospital readmissions being constrained to the 11 medical facilities

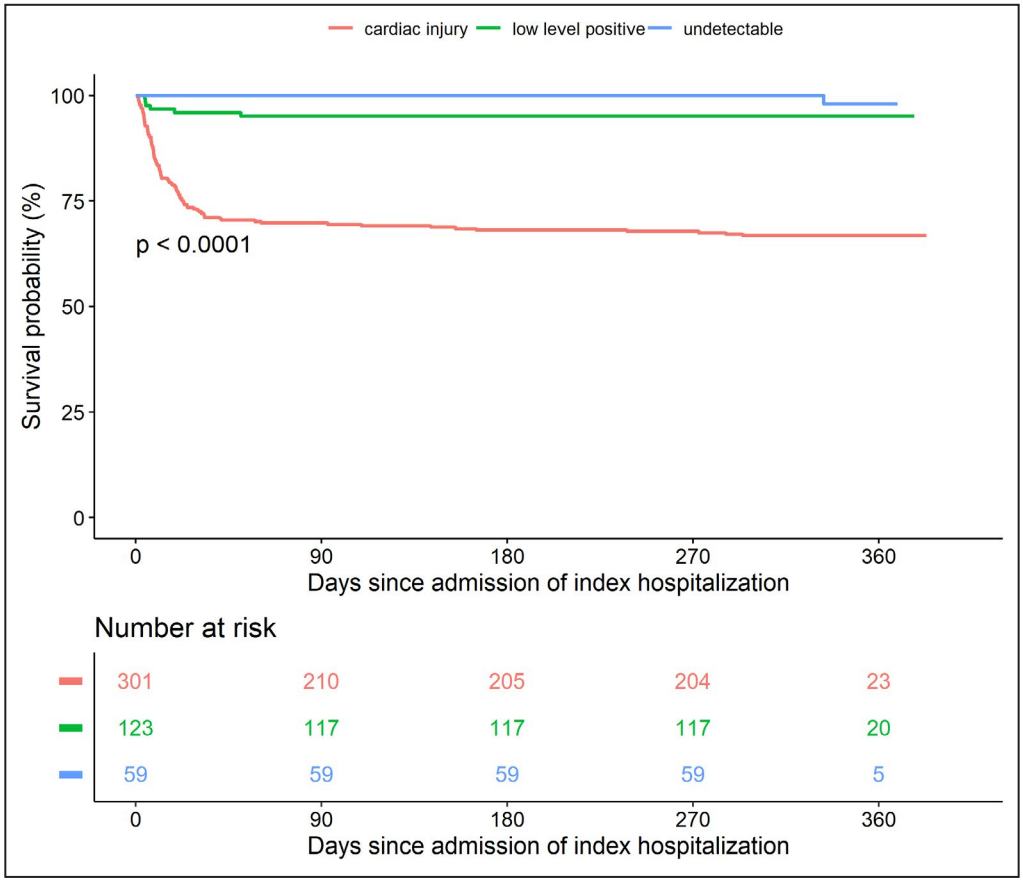

Figure 2. Relationship between myocardial injury and mortality.
Kaplan-Meier curves of all-cause mortality are shown, stratified by patients with myocardial injury (≥14 ng/L), low-level positive (6–13 ng/L), and undetectable troponin (log-rank *P*<0.0001). Index mortality is shown as time point 0, and the subsequent mortality over time is demonstrated. Despite high mortality during index hospitalization, there were small incremental changes in mortality over time.

in our integrated healthcare system, and 6-month assessment of postacute sequalae of COVID-19 being limited to what was documented in the EHR. Although the overall loss to follow-up at 1 year of those who survived the index hospitalization was low at 3.8%, which increases our confidence in the reported mortality data, we only had enough detailed, documented assessments in 53.8% of the follow-up cohort to assess postacute sequelae of COVID-19 given the observational nature of this study. Therefore, there may have been a deselection bias at the 6-month clinical assessment attributable to a healthy effect. However, it is reassuring that the demographic and clinical characteristics were similar among the patients who were able to be assessed for postacute sequelae of COVID-19 compared with the total cohort. The highest troponin value obtained during the index hospitalization was used to categorize patients, but further delineation of the trajectory of troponin over time in a larger sample size could provide further insights. In addition, we did not have routine data for all patients on echocardiography or cardiac magnetic resonance imaging to evaluate how often patients with myocardial injury had underlying cardiac abnormalities.[28] The definition of postacute sequelae of COVID-19 will continue to evolve as we better understand its pathophysiological features, which may impact the clinical characteristics

Table 3. Relationship Between Hs-cTnT and Mortality in Patients Hospitalized With COVID-19 Infection

Variable	Hazard ratio (95% CI)	*P* value
Cardiac injury (hs-cTnT ≥14 ng/L) vs undetectable	13.76 (1.85–102.29)	0.01
Low-level positive (hs-cTnT 6–13 ng/L) vs undetectable	2.31 (0.27–19.45)	0.44
Age	1.03 (1.01–1.04)	<0.00
Men	1.22 (0.82–1.82)	0.33
Coronary artery disease	1.29 (0.79–2.11)	0.30
Hypertension	0.94 (0.55–1.59)	0.81
Hyperlipidemia	0.71 (0.46–1.10)	0.13
Heart failure	0.98 (0.59–1.62)	0.93

Hazard ratios (95% CIs) and *P* values are from a multivariable adjusted Cox model. Hs-cTnT indicates high-sensitivity cardiac troponin T.

Table 4. Postacute COVID-19 Sequela Symptoms at 6 Months, Stratified by Cardiac Injury

6-mo Symptom assessment	Patients with troponin measured (n=483)	Undetectable troponin (<6 ng/L) (n=59)	Low-level positive (6–13 ng/L) (n=123)	Cardiac injury (≥14 ng/L) (n=301)	Univariate *P* value	Adjusted *P* value	Adjusted odds ratio (95% CI)
Ongoing supplemental oxygen requirement	8/211 (3.8)	0/8 (0)	1/8 (25)	7/8 (87.5)	0.108	NA	NA
Ongoing COVID-19 symptoms	78/211 (36.9)	10/78 (12.8)	24/78 (30.7)	44/78 (56)	0.332	0.235	0.7 (0.4–1.2)
Neurocognitive decline	34/211 (16.1)	3/34 (0.1)	12/34 (35.2)	19/34 (56)	0.607	NA	NA
Worsening functional status	42/211 (19.9)	2/42 (4.8)	7/42 (16.7)	33/42 (79)	0.001	NA	NA

Data are given as number/total (percentage). Univariate *P* values (after false discovery rate correction) represent the comparison between cardiac injury (≥14 ng/L) vs noncardiac injury (low-level positive and undetectable) based on a binomial proportion test for whether patients with cardiac injury had an unadjusted proportion of 50% (ie, shared equal proportions with patients without cardiac injury) in each outcome group. For ongoing COVID-19 symptoms, adjusted *P* value and odds ratios (95% CIs) are based on multivariable logistic regression, adjusting for clinical covariates that included age, sex, history of coronary artery disease, hypertension, hyperlipidemia, and diabetes. Adjusted *P* values were not calculated for categories with <7 events because of overfitting. NA indicates not applicable.

we used to ascertain postacute sequelae of COVID-19 in our cohort. Last, symptoms that were not reported by patients or documented in their medical record would have been missed by our data capture.

Although the exact mechanisms of cardiac injury during COVID-19 are not clearly understood, these findings highlight the need for further mechanistic studies to explore the relationship between myocardial injury and postacute sequelae of COVID-19. Approximately 100 million people are estimated to have recovered from COVID-19. Given the substantial public health consequences, future work is needed to address the predictors, duration, and long-term impact of postacute sequelae of COVID-19.

CONCLUSIONS

In conclusion, this study provides unique insights into the relationship between cardiovascular injury during the index hospitalization for patients with COVID-19 and longer-term outcomes. Patients with evidence of myocardial injury during index hospitalization had an increased risk of cardiac, thrombotic, and infectious complications during the hospitalization and all-cause mortality. Furthermore, these

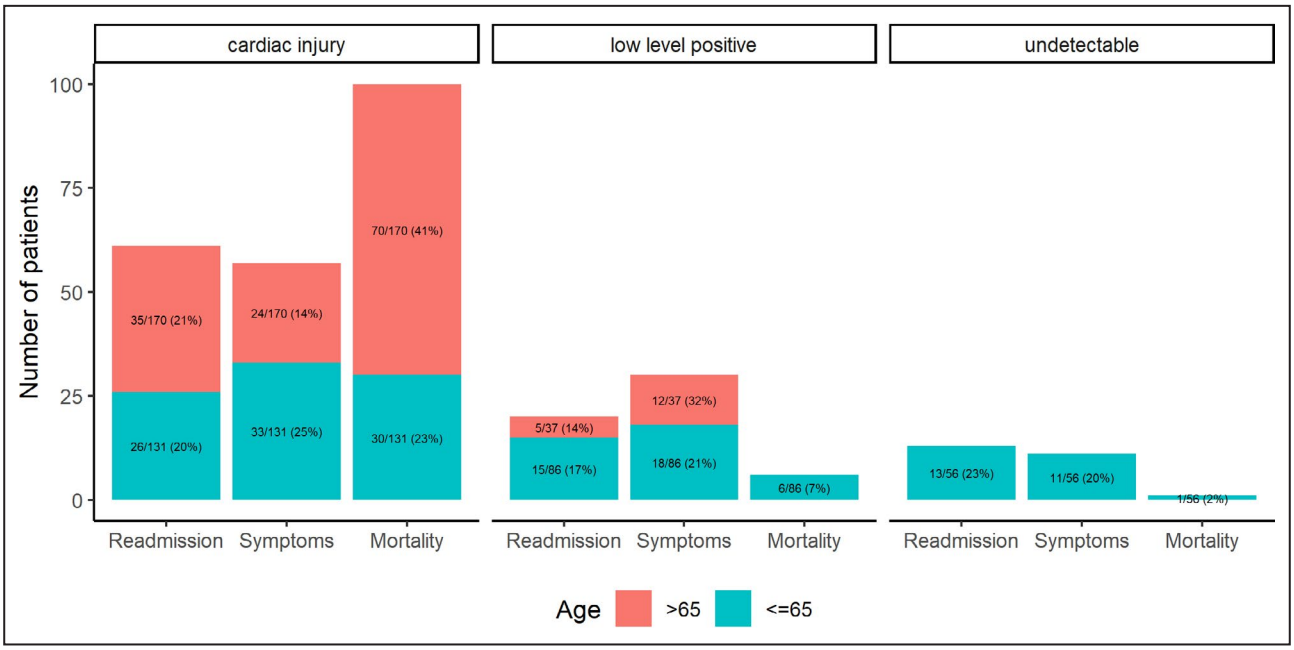

Figure 3. The relationship between myocardial injury during COVID-19 infection and long-term outcomes.
Shown is the distribution of the number of individuals with a readmission at 12 months, postacute sequelae of COVID-19 at 6 months, and all-cause mortality at 6 to 12 months, stratified by high-sensitivity cardiac troponin T level into cardiac injury, low-level positive, or undetectable during index hospitalization. Each bar graph demonstrates the age distribution by >65 and ≤65 years. The mortality and readmission represent the number of patients of the total 483. The patients noted to have postacute sequelae of COVID-19 (composite of ongoing COVID-19 symptoms, supplemental oxygen requirement, neurocognitive decline, or worsening function status) are among the 211 patients with 6-month follow-up.

patients had higher rates of hospital readmissions and postacute sequelae of COVID-19 at 6 months, although this was not statistically significant. An additional unique aspect of our cohort findings is that even among those patients with positive troponins during their index hospitalization, the incremental mortality at 6 months and 1 year among COVID-19 survivors was low. These data suggest that patients who are hospitalized with COVID-19, even if critically ill, but survive the index hospitalization are likely to survive up to 1 year. Whether this trend is observed longer-term is not known and will be an important question to investigate as we gather longer-term data.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1 Univariate P value represents the comparison between cardiac injury (>14ng/L) versus non-cardiac injury (low level positive and undetectable) from a univariate logistic regression model with LV function as outcome (>=40% vs <40%).

	TTE during index hospitalization (n=122)	Undetectable Troponin (<6ng/L) (n=2)	Low-level Positive (6ng/L-13ng/L) (n=8)	Cardiac Injury (>14ng/L) (n=112)	Univariate P value
Normal LV function (LVEF>=40%)	105 (86.1%)	2(100%)	7 (87.5%)	96 (85.7%)	0.709
Reduced LV function (LVEF<40%)	17 (13.9%)	0(0%)	1 (12.5%)	16 (14.3%)	

Table S2. P values were calculated by the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables and with FDR correction.

Characteristics	**Patients survived hospitalization (n=392)**	**Patients with follow-up data (n=211)**	**P-value**
Female	204 (52.0%)	108 (51.2%)	0.966
Age	60 (49 - 71)	61 (51 - 72)	0.966
SpO2 >92% admission	196 (50.0%)	110 (52.1%)	0.966
Prodrome			0.966
Asymptomatic	2 (0.5%)	2 (0.9%)	
0-7 days	273 (69.6%)	148 (70.1%)	
>7 days	117 (29.8%)	61 (28.9%)	
Race/ethnicity			0.966
White	132 (33.7%)	81 (38.4%)	
Black, non-Hispanic	113 (28.8%)	64 (30.3%)	
Hispanic/Latino	101 (25.8%)	49 (23.2%)	
Other or Unknown	46 (11.7%)	17 (8.1%)	
Comorbidities			
Body mass index, kg/m^2	29 (25 - 33)	29 (26 - 33)	0.966
Diabetes	126 (32.1%)	66 (31.3%)	0.966

Hypertension	243 (62.0%)	144 (68.2%)	0.966
CAD	50 (12.8%)	32 (15.2%)	0.966
Hyperlipidemia	181 (46.2%)	109 (51.7%)	0.966
COPD	27 (6.9%)	14 (6.6%)	1
Hx of active malignancy	38 (9.7%)	26 (12.3%)	1
Inpatient Medications			
Antiviral therapy,	153 (39.0%)	92 (43.6%)	0.966
IV steroids	16 (4.1%)	7 (3.3%)	0.966
Tocilizumab	55 (14.0%)	33 (15.6%)	0.966
Length of hospital stay, days	9 (5 - 18)	9 (5 - 22)	0.966
ICU admission	152 (38.8%)	85 (40.3%)	0.966
Length of ICU stay, days	11 (3 - 23)	16 (4 - 25)	0.966
Peak troponin during hospital stay	16 (8 - 42)	19 (9 - 54)	0.966