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Distinct etiologies of high-sensitivity troponin T elevation predict different mortality risks for patients hospitalized with COVID-19

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ABSTRACT

Background: Cardiovascular events in the context of COVID-19 infection increase the risk of negative patient outcomes, but large cohort studies describing this association are limited. The purpose of the current study was to investigate the potential associations between cardiovascular events and mortality in patients hospitalized due to COVID-19.

Methods: A retrospective chart review was performed in 2450 patients hospitalized for confirmed COVID-19 infection within a single hospital network between March 15 and June 15, 2020. Logistic regression analysis was used to identify predictors of mortality.

Results: In the study population, 57% of patients had elevated high sensitivity troponin (hs-TnT) levels. Acute heart failure occurred in 23% of patients and arrhythmias were observed in 8% of patients. Of the 1401 patients with elevated hs-TnT levels, a primary cardiac etiology (e.g., myocardial infarction) was identified in 653 (47%) patients. In the remaining 748 (53%) patients, there was evidence of a primary non-cardiac etiology for hs-TnT elevation such as renal failure ($n = 304$) and critical illness ($n = 286$). Elevated hs-TnT was associated with increased risk of mortality. A significantly higher mortality rate was observed for hs-TnT elevation associated with a primary cardiac etiology (OR 4.6, 95% CI: 2.7–7.6; $P < 0.001$) than a primary non-cardiac etiology (OR 2.7, 95% CI: 1.6–4.5; $P < 0.001$).

Conclusions: Elevated hs-TnT in the context of COVID-19 infection is associated with a significantly increased mortality risk. Hs-TnT elevation in the context of a primary cardiac etiology confers a nearly 2-fold higher mortality risk than hs-TnT elevation due to a primary non-cardiac etiology.

1. Introduction

There is a growing body of evidence demonstrating an association between SARS-COV-2 infection and increased risk of cardiovascular events such as myocardial injury and heart failure [1,2]. The mechanisms by which SARS-COV-2 infection lead to an increase in the risk of cardiovascular events have not been elucidated definitively. Proposed mechanisms include vascular endothelial activation/inflammation, microvascular injury, direct myocardial inflammation and injury, thromboembolic events, and exacerbation of underlying cardiovascular conditions in the context of hypoxemia and release of excess endogenous catecholamines [3]. Cardiovascular events in patients with COVID-19 are associated with worse outcomes [2,4,5]. Previous reports have shown that patients who present with clinical evidence of myocardial injury in the context of COVID-19 are at 1.5- to 4.5-fold greater risk of dying compared to patients without myocardial injury [2,5–11]. Variability in the reported impact of myocardial injury on mortality in patients with COVID-19 has been attributed to the small sample sizes and differences in the definitions of a cardiovascular events (e.g., cardiac biomarker elevation versus imaging studies) in reported studies to date [2,4,6,12]. In studies where cardiac biomarker elevation alone was used as a marker of myocardial injury, it is impossible to know whether the cardiac biomarker elevation was the consequence of a primary cardiac event or a secondary cardiac event precipitated by non-cardiac illness such as pulmonary embolism, acute renal failure, or sepsis [13,14]. As a result of these limitations, it is possible that the reported data either

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under- or overestimate the impact of cardiovascular events on patient outcomes in the context of COVID-19.

The purpose of this study was to assess the incidence of cardiovascular events and predictors of mortality in patients hospitalized with PCR-confirmed COVID-19 infection. This study was conducted on a larger number of patients with documented COVID-19 than had been included in prior studies, with the goal of obtaining a more accurate assessment of the impact of COVID-19-related cardiac events on mortality.

2. Methods

2.1. Study design, setting, and participants

The design of this retrospective cohort study was approved by the authors' Institutional Review Board before the study was begun. The written consent requirement was waived. The study was conducted during a three-month interval (March 15, 2020 to June 15, 2020) in four hospitals (Massachusetts General Hospital, Brigham and Womens' Hospital, Newton-Wellesley Hospital, and North Shore Medical Center) within a single health care network (Mass General Brigham). A total of 2450 adults (18 years of age and over) with PCR-confirmed COVID-19 were included.

2.2. Data sources and collection

All patient data (e.g., medical history, laboratory and imaging studies, interventions) were extracted through review of the electronic health records (EHR) using a standard data collection form. For all patients with an abnormal value on a test (e.g., a 12-lead ECG demonstrating heart block), pre-hospitalization data was reviewed to determine if the abnormality was a new finding associated with the index hospitalization for COVID-19.

Patients were categorized by vital status (deceased vs discharged). The immediate cause of death was reviewed for all patients who died during hospitalization to confirm that COVID-19 was an associated diagnosis. Patients were also categorized according to the presence of myocardial injury, which was defined to be present in any patient with a blood level of high-sensitivity troponin T (hs-TnT) above the 99th percentile upper reference limit (9 ng/L for women, 14 ng/L for men) [15].

Medical comorbidities were identified using International Classification of Diseases, Tenth Revision, and Clinical Modification (ICD-10-CM) codes. All patients in this study who were assigned a diagnostic code underwent review of the primary data to confirm the presence of the diagnosis. This included review of the problem list, medical history, and clinician notes, and the results of all relevant diagnostic studies. For imaging studies, data was derived from study reports. During data collection, care was taken to obtain comprehensive data for each patient in order to minimize the risk of misclassification of primary cardiac versus primary non-cardiac etiologies for myocardial injury.

2.3. Primary study outcome

The primary study outcome was the mortality rate among patients hospitalized with COVID-19. The impact of cardiovascular events and other potential predictors of mortality were assessed.

2.4. Statistical analysis

Continuous variables were presented using the median and interquartile range. Categorical variables were presented using the total number of observations per patient category. Baseline characteristics of patient groups were compared using the Student's *t*-test for continuous variables and the Chi-square test for categorical variables and Mann-Whitney *U* test for skewed variables as appropriate. Backward stepwise logistic regression model selection was used to identify independent predictors of mortality. Univariate logistic regression analyses were performed for each potential risk factor for mortality including age, sex, medication, comorbidities, and the following cardiac and vascular events: elevated troponin, echocardiographic abnormalities, clinical diagnosis of MI, myocarditis, Takotsubo syndrome, arrhythmias, acute heart failure, acute kidney injury, stroke, thromboembolic events and shock. Covariates with a P value <0.2 in the initial, univariate analysis were then included in the multivariable model. P values <0.05 were considered to be statistically significant. All statistical analyses were performed using STATA version 14 (College Station, TX).

3. Results

3.1. Characteristics of the patient population

Baseline characteristics of the study cohorts are included in Table 1. A total of 2450 hospitalized patients with confirmed COVID-19 were included. The median age was 64 years (interquartile range 50–77 years) and 54% were male. The most common comorbidities were hypertension (44%), diabetes (29%), and chronic kidney disease (CKD, 18%). Ischemic heart disease (IHD), congestive heart failure (CHF), chronic pulmonary disease, arrhythmia, and stroke were present in 13%, 10%, 7.8%, 20%, and 3.9% of patients, respectively.

3.2. In-hospital mortality for patients with COVID-19

Of the 2450 patients included in this study, 335 (14%) died during hospitalization. Compared with patients who survived hospitalization, the non-survivors were significantly older (median age 79 years for non-survivors vs 61 years for survivors, $P < 0.001$). Non-survivors also had significantly higher rates of medical comorbidities than survivors (Table 1).

3.3. In-hospital cardiovascular events for patients hospitalized with COVID-19

All cardiovascular outcomes observed in patients hospitalized with COVID-19 are summarized in Table 2. The most common cardiovascular events in hospitalized patients with COVID-19 were the following:

Table 1
Baseline characteristics of patients admitted with COVID-19.

	Total	Survivors	Non-survivors	P-value
Median age (Interquartile)	64 (50-77)	61 (48-75)	79 (76-81)	<0.001
Female/male (%)	46/54	46/54	43/57	0.269
Comorbidities (%)				
Diabetes mellitus	29	28	32	0.122
Hypertension	44	42	52	0.001
Chronic pulmonary disease	7.8	6.1	14	<0.001
Primary pulmonary hypertension	1.8	1.4	3.1	0.023
Asthma	8.6	8.6	5.6	0.067
Ischemic heart disease	13	11	23	<0.001
Chronic kidney disease	18	15	33	<0.001
Liver disease	6.2	5.6	6.2	0.628
Peripheral vascular disease	2.9	2.4	4.4	0.04
Arrhythmia	20	8.9	27	<0.001
Atrial fibrillation	14	4	15	<0.001
Atrial flutter	1.3	1.2	1.9	0.029
Atrioventricular block	2.5	1.7	7.2	<0.001
Left bundle branch block	1.4	1.1	1.8	0.041
Right bundle branch block	1.3	1.1	3	0.005
Chronic heart failure	10	8.9	19	<0.001
History of stroke	3.9	2.8	9.3	0.003

Values are shown as median (interquartile range) for continuous variables, and % for categorical variables.

Table 2
Cardiovascular outcomes for patients hospitalized with COVID-19.

Outcome, N (%)	Total	Survivors	Non-survivors	P-value
Elevated troponin	1401 (57)	1101(51)	298(89)	<0.001
Elevated troponin due to primary cardiac causes	653 (27)	471(22)	182 (54)	<0.001
Elevated troponin due to non-cardiac causes	748 (31)	630(29)	116(35)	0.047
Myocardial infarction type 1	11(0.5)	7(0.3)	4(1.2)	0.040
Myocardial infarction type 2	21 (0.89)	14(0.5)	7(1.9)	0.006
Takotsubo syndrome	11(0.5)	10(0.5)	1(0.3)	0.825
Myocarditis	14(0.5)	8(0.3)	6(1.5)	0.047
Cardiac arrest	18(0.7)	12(0.5)	6(1.8)	0.021
Acute heart failure	570 (23)	404(19)	165(49)	<0.001
Arrhythmias/Blocks	206 (8.4)	156(7.4)	49(15)	<0.001
Atrial fibrillation	67(2.6)	47(2.2)	20(6.0)	<0.001
Atrial flutter	16(0.7)	8(0.4)	8(2.4)	<0.001
Ventricular fibrillation	3(0.1)	0	3(0.9)	
Ventricular tachycardia	32(1.2)	27(1.3)	5(1.5)	0.046
Supraventricular tachycardia	29(1.1)	20(1.0)	9(2.7)	0.036
Atrioventricular block	39(1.5)	33(1.6)	6(1.8)	0.654
1st degree	22(1)	17(0.8)	5(1.5)	0.030
2nd degree	7(0.3)	6(0.3)	1(0.3)	0.578
Complete	2(0.1)	2(0.1)	0	
Left bundle branch block	9(0.34)	5(0.2)	4(1.2)	0.015
Right bundle branch block	37(1.5)	31(1.4)	6(1.8)	0.564
Stroke	27(1.1)	21(1)	6(1.8)	0.021
Hemorrhagic	9(0.34)	6(0.3)	3(0.9)	0.004
Ischemic	18(0.7)	15(0.7)	3(0.9)	0.576
Transient ischemic attack	2(0.1)	2(0.1)	0	
Shock	348 (13)	247(12)	101(30)	<0.001
Septic shock	178 (7.3)	119(5.6)	58(17)	<0.001
Cardiogenic shock	28(1.1)	21(1)	7(1.1)	0.087
Distributive shock	74(3.0)	51(2.4)	23(6.8)	<0.001
Hypovolemic shock	11(0.5)	9(0.4)	2(0.6)	0.665
Undifferentiated shock	57(2.3)	47(2.2)	10(2.9)	0.564
Pulmonary embolism	57(2.2)	49(2.3)	8(2.4)	0.930
Venous thromboembolism	62(2.5)	55(2.6)	7(2.1)	0.585
Atrial thromboembolism	9(0.4)	6(0.3)	3(0.9)	0.103
Acute kidney injury	575 (23)	430(20)	145(44)	<0.001

Values are mean ± SD or median (interquartile range) for continuous variables, and n (%) for categorical variables.

myocardial injury (57%), acute kidney injury (AKI) (23%), acute heart failure (23%), shock (13%), and new-onset arrhythmias or cardiac conduction block (8.4%, Supplemental Fig. 1). The most prevalent arrhythmias were atrial fibrillation (AF), and ventricular tachycardia (VT) which were present in 2.6% and 1.5% of patients, respectively (Supplemental Fig. 2). Most types of cardiovascular events were more common in non-survivors (Table 2).

3.4. Troponin elevation in patients hospitalized with COVID-19

A total of 2152 of the patients included in this study (88%) underwent hs-TnT testing. Analysis of hs-TnT values revealed that a total of 1401 patients included in this study (57%) had elevated hs-TnT levels above the 99th percentile (Fig. 1). Of these patients, 653 (47%) had a primary cardiac etiology for hs-TnT elevation and 748 (53%) did not. Patients with elevated hs-TnT due to a primary cardiac etiology were older and were more likely to have other medical comorbidities than patients with elevated hs-TnT not associated with a primary cardiac etiology (Supplemental Table 1). The impact of hs-TnT elevation on mortality is displayed in Supplemental Fig. 3. All-cause mortality was higher in patients with elevated hs-TnT due to a primary cardiac etiology (28%) than in patients with elevated troponin without a cardiac etiology (16%) and patients without elevated troponin levels (3.4%, $P < 0.001$ for all comparisons).

3.5. Primary cardiac etiologies for elevated hs-TnT

Instances of hs-TnT elevation were defined to be caused by a primary cardiac etiology if chart review confirmed the presence of an acute cardiac issue (MI, CHF, Myocarditis/Pericarditis, Takotsubo syndrome). Of the 653 patients in this study with elevated hs-TnT due to a primary cardiac etiology, ischemic myocardial injury was documented in 32 patients: 11 patients had a type 1 MI based on coronary angiography and clinical findings, and 21 patients had a type 2 MI. Myocarditis was diagnosed in 14 patients. Clinical and echocardiographic findings consistent with Takotsubo syndrome were seen in 11 patients. In 42 of these 653 patients, echocardiography revealed wall motion abnormalities but did not comment on the etiology of the wall motion abnormality (e.g., myocarditis or Takotsubo syndrome). Of the patients with elevated hs-TnT, 500 were diagnosed with acute congestive heart failure (CHF). Tachyarrhythmias including AF, VT, and SVT were the only abnormal cardiac findings in 54 patients with elevated hs-TnT (Fig. 1).

3.6. Elevated hs-TnT in the absence of a primary cardiac etiology

Instances of hs-TnT elevation were defined to be caused by a non-cardiac etiology if chart review confirmed the absence of an acute cardiac diagnosis and the presence of a non-cardiac diagnosis to which the biomarker elevation could be attributed (renal failure, sepsis/shock, cerebrovascular accident (CVA), or pulmonary embolism). Of the 748 patients in this study with hs-TnT elevation in the absence of a primary cardiac etiology, renal failure was observed in 304 patients (41%). Shock, pulmonary embolism and cerebrovascular accident (CVA) occurred in 105 (14%), 24 (3.2%), and 5 patients (0.7%), respectively. Among the remaining 310 patients (41%) without a primary cardiac etiology, a large majority (286, 92%) were critically ill, and a combination of sepsis and hypoxemia may have been the cause of elevated hs-TnT levels. In 24 (8%) of these patients there was no identifiable cause of hs-TnT elevation (Fig. 1).

3.7. Comparison of hs-TnT levels in patients with primary cardiac and primary non-cardiac etiologies for myocardial injury

A quantitative assessment of hs-TnT level was performed for all patients included in this study. Measured levels of hs-TnT were compared for patients with primary cardiac and primary non-cardiac etiologies for myocardial injury. The mean hs-TnT elevation was significantly higher for patients with myocardial injury due to a primary cardiac etiology (121 ± 12, mean ± SD) than for patients with a primary non-cardiac etiology (52 ± 5.1, $P < 0.001$).

3.8. Echocardiographic evidence of ventricular dysfunction in COVID-19 infection

Transthoracic echocardiography (TTE) was performed in 287 of the 2450 patients (12%) hospitalized with COVID-19 (Supplemental Table 2). The median left ventricular ejection fraction (LVEF) was 62% (IQR: 52% to 65%), and 84% of patients had a LVEF greater than 50%. Wall motion abnormalities were observed in 61 (22%) patients. Of these, 35 (57%) had >50% of cardiac segments involved, 8 (13%) had 25–50% and 13 (21%) had less than 25% of cardiac segments affected. Right ventricular (RV) dysfunction was detected in 49 of 287 patients (17%). Pericardial effusion was observed in 19 (6.6%) patients.

3.9. Predictors of mortality in patients hospitalized with COVID-19

The results of the multivariable logistic regression model used to identify independent predictors of mortality in patients hospitalized

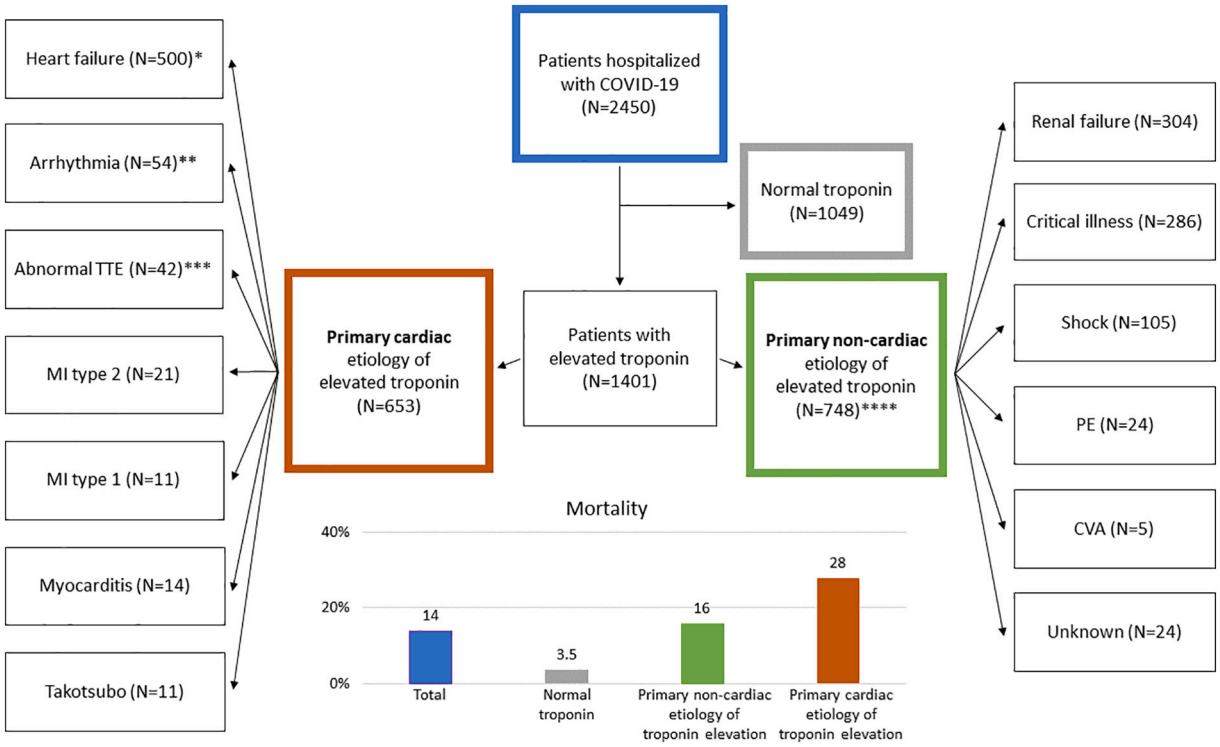

Fig. 1. Cardiac and non-cardiac etiologies of troponin elevation in patients hospitalized with COVID-19.
The number of patients with cardiac and non-cardiac etiologies for troponin elevation are displayed. Specific cardiac findings found in patients with troponin elevation due to a primary cardiac etiology are listed on the left side of the figure. Specific findings in patients with troponin elevation without a primary cardiac etiology are listed on the right side of the figure. The lower panel displays the overall mortality rate for all patients included in this study, as well as mortality rates for several patient subgroups (normal troponin, elevated troponin due to primary cardiac etiology, elevated troponin due to primary non-cardiac etiology). Patient groups are color-coded.
MI: Myocardial Infarction; CVA: Cerebrovascular Accident.
* Patients with acute heart failure who were not categorized as having acute MI, Myocarditis, Takotsubo or abnormal echocardiographic findings.
** Patients in whom tachyarrhythmia was the only evidence of cardiac etiology.
*** Patients with echocardiographic abnormalities without another cardiac problem.
**** Patients with critical illness, respiratory failure or sepsis.

Table 3
Predictors of in-hospital mortality in patients admitted with COVID-19.

Predictors of Mortality: Logistic Regression Based on Medical Comorbidities	OR	95% CI	P value
Age (per 1 year)	1.06	1.05-1.07	<0.001
Pre-existing AV block	2.5	1.4-5.3	0.003
Previous cerebrovascular accidents	2.3	1.4-3.8	0.001
Incident stroke	3.6	1.0-12.5	0.043
Incident shock	3.2	2.3-4.5	<0.001
Incident acute kidney injury	1.9	1.4-2.6	<0.001
Elevated troponin due to primary cardiac cause	4.6	2.7-7.6	<0.001
Elevated troponin due to primary non-cardiac cause	2.7	1.6-4.5	<0.001

Predictors of Mortality: Logistic Regression Based on Echocardiography and Medical Comorbidities	OR	95% CI	P value
Age (per 1 year)	1.04	1.01-1.07	0.008
Incident acute kidney injury	2.6	1.1-6.1	0.026
Right ventricular dysfunction	3.0	1.0-8.9	0.043
Wall motion abnormalities (% of total segments)			
<25	0.7	0.1-8.2	0.783
25-49	1.6	0.1-19.0	0.706
>=50	9.9	1.3-76.2	0.027
LVEF	1.1	0.1-1.2	0.100
Pericardial effusion	0.5	0.1-3.0	0.472

with COVID-19 are displayed in Table 3, Upper Panel. After adjusting for confounders, several patient characteristics were found to be predictors of mortality. These characteristics included age (OR 1.06 per 1 year, 95% CI: 1.05–1.07; $P < 0.007$), history of atrioventricular block (OR 2.5, 95% CI: 1.4–5.3; $P < 0.001$), and history of cerebrovascular events (OR 2.3, 95% CI: 1.4–3.8; $P = 0.001$). After adjustment for confounders, the following acute events were found to be predictors of mortality: incident stroke (OR 3.6, 95% CI: 1.0–12.5; $P = 0.043$), shock (OR 3.2, 95% CI: 2.3–4.5; $P < 0.001$), acute renal failure (OR 1.9, 95% CI: 1.4–2.6; $P < 0.001$), elevated hs-TnT with a primary cardiac etiology (OR 4.6, 95% CI: 2.7–7.6; $P < 0.001$) and hs-TnT with a primary non-cardiac etiology (OR 2.7, 95% CI: 1.6–4.5; $P < 0.001$).

An additional, multivariable logistic regression analysis was performed to assess predictors of mortality in patients with elevated hs-TnT during hospitalization for COVID-19 (patients with both primary cardiac and primary non-cardiac etiologies for hs-TnT elevation were included). After adjustment for confounders, mortality risk was found to be significantly higher in patients with a primary cardiac etiology for hs-TnT elevation than in patients with a primary non-cardiac etiology (OR 1.8, 95% CI: 1.3–2.4; $P < 0.001$). We further adjusted this model for hs-TnT levels and found that the mortality difference between primary cardiac and primary non-cardiac etiology remained significant (OR 1.7, 95% CI 1.3–2.3; $P = 0.001$).

A multivariable regression analysis was performed for the subgroup of 287 patients in whom TTE was performed to determine the prognostic significance of echocardiographic parameters in the context of COVID-19 infection. The regression model was adjusted for demographic

data, comorbidities, AKI, arrhythmias and cardiac biomarkers in addition to TTE findings. According to this model, predictors of mortality included age (OR 1.04, 95% CI: 1.01–1.07; $P = 0.008$), AKI (OR 2.6, 95% CI: 1.1–6.1; $P = 0.026$), RV dysfunction (OR 3.0, 95% CI: 1.0–8.9, $P = 0.043$) and left ventricular wall motion abnormalities in greater than 50% of segments (OR 9.9, 95% CI: 1.3–76; $P = 0.027$). Global left ventricular ejection fraction was not independently associated with mortality because 84% of patients had normal LV function. Troponin was also not an independent predictor of mortality in this analysis because 88% of patients in the TTE cohort had elevated hs-TnT levels. The results of the multivariable regression analysis are summarized in Supplemental Table 3.

4. Discussion

In this retrospective cohort study, 2450 patients with laboratory-confirmed COVID-19 infection who required inpatient admission were analyzed. Myocardial injury, defined as hs-TnT values above the 99th percentile limit, was present in 1401 (57%) of enrolled patients. Of these 1401 patients, 47% had evidence of a primary cardiac etiology. The remaining 53% did not have a primary cardiac etiology for troponin elevation but did have non-cardiac etiologies including sepsis, stroke, and acute renal failure. In total, 335 (14%) patients died during admission. The odds ratio for in-hospital mortality in patients with hs-TnT elevation due a primary cardiac etiology was 4.6-fold higher than patients with normal troponin. For patients with hs-TnT elevation without a primary cardiac etiology, mortality was 2.7-fold higher than in patients with normal troponin.

4.1. Incidence of myocardial injury in patients hospitalized with COVID-19

An association between COVID-19-related myocardial injury and increased mortality has been reported in several studies [2,16]. The reported incidence of myocardial injury varies widely among these studies, ranging from 7 to 63% [6,17,18]. In the present study, myocardial injury was observed in 1401 (57%) patients. The higher incidence of myocardial injury in our study may be attributed to several factors, including differences in cardiac biomarker testing patterns. The patients in our study were admitted to tertiary health care centers in which measurement of cardiac biomarkers was performed routinely for patients admitted with COVID-19 (88% of patients enrolled in this study underwent cardiac biomarker testing during admission). Our study also included troponin measurements throughout the course of hospitalization, which could have captured more myocardial injury events than studies that included only one troponin measurement at the beginning of hospitalization [13]. In addition, the 5th generation hs-TnT assay used to detect myocardial injury in our study is more sensitive than the assays used in other studies [19,20]. It is also possible that the population of patients enrolled in our study were more critically ill than patients in other studies, leading to a higher proportion with elevated cardiac biomarkers.

4.2. Acute MI in COVID-19

Inflammation caused by viral infection and subsequent endothelial dysfunction, along with other factors such as hypoxemia, may serve as triggers for atherosclerotic plaque rupture and thrombosis leading to ischemic myocardial injury in COVID-19 [16,20–22]. The risk for acute MI in the setting of acute infection is well established [23]; however, data pertaining to in-hospital incidence of MI in the setting of COVID-19 remain limited [24,25]. In our study, acute MI was rare: only 11 cases of type 1 MI (0.5%) and 21 cases of type 2 MI (0.9%) were identified.

4.3. Myocarditis in COVID-19

Several non-ischemic etiologies of COVID-19-related myocardial injury have been described, including myocarditis [13,26–35]. The true incidence of myocarditis in COVID-19 is not known, in part because the incidence varies depending on the parameters utilized to determine the diagnosis. In one study, cardiac MRI performed in patients who had recently recovered from COVID-19 revealed evidence of ongoing myocardial inflammation in 60% of participants [29]. Another study that defined myocarditis in the context of COVID-19 infection based on ECG, echocardiography, and hs-TnI elevation reported a lower incidence rate of myocarditis (13%) [30]. Studies involving autopsy findings suggest that clinical criteria for the diagnosis of myocarditis, including ECG and cardiac biomarker elevations, may overestimate the true incidence of myocarditis in the context of COVID. A post mortem study of 21 consecutive COVID-19 patients revealed the number of patients presenting with new ECG changes (12) or troponin elevation (16) was much higher than the number of patients with histologic evidence of myocarditis (lymphocytic infiltrates) on histopathology (3) [31]. A later study of 277 postmortem cardiac examinations in patients with COVID-19 reported that the true prevalence of myocarditis was less than 2% [31]. In our study, only 14 patients (0.5%) were diagnosed with probable myocarditis.

4.4. Acute heart failure in COVID-19

Acute heart failure is not uncommon in patients hospitalized with COVID-19 [13,28,36–40]. The incidence of heart failure in this study (23%) is comparable to the incidence reported in other studies [38,39]. Of the patients who presented with acute heart failure in this study, 88% also presented with elevated hs-TnT. The potential contribution of coronary artery disease to the clinical presentation was not excluded in most of the patients in our study, as few underwent cardiac catheterization due to critical non-cardiac comorbidities and the highly contagious nature of COVID-19 [37]. A small number of patients in this study (0.5%) were diagnosed with Takotsubo syndrome, which has previously been linked to COVID-19 [36,37]. An additional 42 patients (1.7%) presented with non-diagnostic echocardiographic abnormalities. It is possible that non-cardiac illnesses, such as acute respiratory distress syndrome (ARDS) and sepsis, contributed to heart failure in these patients [40].

4.5. Arrhythmias in COVID-19

Although arrhythmias are well-known complications of COVID-19 [41,42], data on the incidence and prevalence of different types of arrhythmias remains limited. In this cohort, all patient ECGs before and during admission were analyzed. In this study 8.4% of patients experienced at least one type of new-onset tachyarrhythmia or block during hospitalization (Table 2). Arrhythmia was potentially responsible for hs-TnT elevation in 54 (2.2%) of the patients in this study but was not shown to be an independent predictor of mortality.

The incidence of arrhythmias in this study is lower than the rate reported in a study from China (17%) [17], but is comparable to the rate described in a prior study from the United States (7.6%) [43]. It is not possible to determine the reasons for the differences between these studies, as the Chinese study did not specify the different types of arrhythmias observed and the U.S. study did not report heart block or sustained VT/VF [17,43].

In this study, 1.5% of patients presented with AV block (AVB). Left bundle branch block (LBBB) and right bundle branch block (RBBB) were identified in 0.3 and 1.5% of patients, respectively. In another study, the rates of COVID-19-related AVB, LBBB, and RBBB were higher [44]. This previously reported study did not differentiate acute vs chronic findings, which could contribute to the difference [44,45]. Although other studies have reported conduction system disturbances in the context of COVID-

19, our study is the only one to identify pre-existing AVB as a predictor of mortality [12,46,47].

4.6. Non-cardiac causes of elevated troponin

SARS-CoV-2 is known to cause non-cardiac disorders that can precipitate myocardial injury including shock, renal failure, and pulmonary embolism [26,28,48,49]. In this study, there were 748 patients (53%) with elevated hs-TnT in whom a primary cardiac cause was not identified. Renal failure, critical illness, shock, and pulmonary embolism occurred in 41%, 38%, 14%, and 3.2% of these patients, respectively.

4.7. Association between echocardiographic abnormalities and mortality risk

A recent study in patients with COVID-19 who had undergone transthoracic echocardiographic (TTE) evaluation showed that myocardial injury was a predictor of mortality only in the presence of echocardiographic abnormalities (Supplemental Table 3) [18]. This finding emphasizes the importance of detecting an underlying cardiac abnormality in patients with myocardial injury, which is consistent with the current study. However, they did not observe a significant association between elevated troponin and mortality in the absence of echocardiographic abnormalities. This difference can be explained by differences in study populations, as we selected all the patients hospitalized with COVID-19 and they studied only patients with COVID-19 in whom TTE was performed. As previously reported, clinical diagnoses were not always supported by diagnostic procedures or autopsy findings. To address this issue, we analyzed the effect of echocardiographic abnormalities on mortality. In this subset analysis, the presence of right ventricular dysfunction and left ventricular wall motion abnormalities in more than 50% of segments were found to be independent predictors of mortality. However, the LVEF was normal in 84% of patients in this study and was therefore not predictive of mortality.

4.8. All-cause mortality in COVID-19

The all-cause mortality rate in our study was 14%, which is similar to the rates in many published studies [2,5–11]. Multiple studies have shown that elevated troponin is an independent prognostic factor in patients hospitalized due to COVID-19 [2,5–7,39]. In the current study, we observed that the odds ratio for in-hospital mortality was 4.6-fold higher in patients with elevated hs-TnT due to a primary cardiac etiology than in patients without myocardial injury. Elevated troponin without evidence of a primary cardiac cause was associated with a nearly 2.7-fold increase in the odds ratio for in-hospital mortality risk. Moreover, hs-TnT elevation due to a primary cardiac etiology was associated with 1.7-fold higher risk of mortality compared to a primary non-cardiac etiology. The observed difference in mortality risk was independent of hs-TnT level. These data indicate that the etiology of myocardial injury impacts mortality in patients hospitalized with COVID-19.

5. Limitations

The retrospective study design and the exclusion of outpatients may limit the extent to which the results of this study can be generalized to all patients with COVID-19. The critical condition of hospitalized patients and highly contagious nature of the SARS-CoV-2 virus limited the extent of advanced diagnostic testing in some of the patients. Therefore, the incidence rates for some outcomes might be underreported. In addition, the analysis was limited to in-hospital complications and post-discharge mortality rates were not evaluated.

6. Conclusions

In the current study, elevated troponin levels were observed in 57% of patients hospitalized with COVID-19. Among these patients, 47% had evidence of a primary cardiac etiology. Critical illness and renal failure were the most prevalent conditions in those without a primary cardiac cause of myocardial injury. While troponin elevation from any cause is a strong independent predictor of mortality, hs-TnT elevation due to a primary cardiac cause is associated with a mortality risk that is nearly 2-fold higher than troponin elevation due to a primary non-cardiac cause (OR 4.6 vs 2.7). Other independent risk factors for mortality include echocardiographic evidence of right ventricular dysfunction and left ventricular wall motion abnormalities in 50% or more of measured segments.

Disclosures

P. Khaloo, A. Shaqdan, P.A. Ledesma, U.A. Uzomah, J. Galvin: no relationships to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.12.029.

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