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Impact of High Troponin Level on the Outcome in COVID-19 Positive Patients

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Purpose: COVID-19 is a new disease caused by the recently discovered SARS-CoV-2 virus. The COVID-19 disease manifests in several ways and it may affect various systems, including the gastrointestinal, musculoskeletal, neurological, cardiovascular, and pulmonary systems. Individuals who have ad-additional health conditions, such as cardiovascular disorders, are particularly more likely to experience illness and death. This study aimed to assess the clinical effect of COVID-19 on myocardial injury, as measured by troponin elevation, and to determine if this effect has an impact on the outcome.

Patients and Methods: This retrospective study was conducted at King Saud Medical City. The electronic medical records used to identify all admitted patients between March 23 and June 15, 2020, with a laboratory-confirmed positive COVID-19 diagnosis who had troponin I measured.

Results: During the study period, 768 COVID-19-positive patients were hospitalized. Of those, 187 patients were excluded because the troponin level was not measured. The remaining 581 (75.7%) had troponin I measured. Overall, 89 of 581 (15.3%) patients died. Of those, 67.8% were in the markedly elevated cTnI group, 8.5% were in the mildly elevated cTnI group, whereas no deaths were reported in the group with normal cTnI levels.

Conclusion: Myocardial injury was observed in COVID-19-admitted patients at a significant level that warrants attention to this consequence. In older individuals with pre-existing cardiovascular comorbidities, the diagnosis of myocardial injury was linked to a higher likelihood of being admitted to the intensive care unit, experiencing a worse prognosis, and ultimately, death.

Keywords: myocardial infarction, cardiovascular comorbidities, ARDS, biomarker, cytokine storm, risk stratification

Introduction

The emergence of a novel coronavirus, SARS-CoV-2, in late 2019 triggered the COVID-19 pandemic. As of October 21, 2023, this global health crisis has surpassed 771 million confirmed cases and tragically, over 6 million deaths.[1,2] COVID-19 manifests a diverse range of symptoms, including fever, cough, loss of taste or smell, and fatigue. It can involve other body systems, such as the gastrointestinal, musculoskeletal, neurological, cardiovascular, and pulmonary systems. ARDS (Acute respiratory distress syndrome) is one of the lethal complications that can progress rapidly and carries a bad prognosis and high mortality.[3] In addition, multi-organ involvement leading to multiorgan failure has been reported, most likely due to cytokine storms.[4,5] Patients with comorbidities, such as cardiovascular diseases, are especially at increased risk of morbidity and mortality.[6] The term "myocardial injury" encompasses all conditions that cause the death of cardiomyocytes. According to the latest update to the fourth universal definition of myocardial infarction (MI), established by expert consensus, clinical

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diagnosis of myocardial injury typically relies on at least one cardiac troponin measurement exceeding the 99th percentile upper reference limit (URL).[7] Myocardial damage with no overt ischemia represents approximately 60% of abnormal troponin elevation cases.[8] Emerging findings indicate that myocardial damage, characterized by the enhancement of the cardiac biomarker has been observed in a significant number of COVID-19 patients and was associated with adverse results and heightened mortality.[9,10] Up to 20% to 30% of hospitalized COVID-19 patients showed symptoms of myocardial involvement with elevated troponin.[9,11] COVID-19 can potentially damage the heart (myocardial injury) through several mechanisms. One possibility is direct injury to heart muscle cells mediated by the angiotensin-converting enzyme 2 (ACE2) receptor.[12,13] Another theory suggests an overwhelming inflammatory response triggered by the virus itself.[14] Furthermore, severe lung injury and other complications caused by the virus can lead to oxygen deprivation (hypoxia) and subsequent damage to the heart muscle due to its increased oxygen demand.[15] This study investigated the clinical impact of COVID-19 on myocardial injury, as measured by elevated troponin levels, and its potential influence on in-hospital outcomes.

Materials and Methods

Population Study

This retrospective study was conducted at King Saud Medical City. We used electronic medical records to identify all patients admitted to King Saud Medical City between March 23 and June 15, 2020, with a laboratory-confirmed positive COVID-19 diagnosis who had troponin I measured.

Data Collection

Patient data was collected from electronic medical records, encompassing demographics, clinical presentation (symptoms and signs), co-existing medical conditions (comorbidities), laboratory test results, and final clinical outcomes. The clinical outcomes of the hospitalized patients in our study were classified into two categories: Category I: Survivals and Category II: Death.

All patients admitted to the hospital were confirmed to be COVID-19 positive based on a positive polymerase chain reaction (PCR) test. The high-sensitivity ARCHI-TECTSTAT troponin I assay (Abbott Laboratories) was used to assess the concentration of cardiac troponin I (cTnI).[16] Cardiac injury was diagnosed if at least one value of serum cTnI was above the upper 99th percentile reference limit during hospitalization. For each patient with a high troponin level, serial samples were taken. In the present study, the peak troponin level was used as the gold standard.

Based on the peak troponin level, patients were categorized into three groups: Group 1 (normal, 0.02–0.06 ng/mL), Group 2 (mildly elevated, 1–3 times of the upper limit of normal or >0.06 to 0.18 ng/mL), and Group 3 (markedly elevated, >3 times of the upper limit of normal or >0.18 ng/mL).[16] All collected laboratory results are compared between all groups. Still, in COVID-19, we try to pick any significant laboratory test and research for any predictor of outcome.

Our tertiary center followed Ministry of Health guidelines for patients with confirmed COVID-19: ICU admission for severe cases with severe clinical signs of pneumonia (fever, cough, dyspnea, tachypnea) and one of the following: respiratory rate >30/min, (adults), blood oxygen saturation <90% on room air and severe respiratory distress. Also, critical cases with symptoms of the following: ARDS, respiratory failure requiring ventilation, sepsis, and/or septic Shock. In situations such as the coexistence of chronic kidney disease, elevations of troponin can be detected, so serial troponin levels are considered crucial, and delta troponin has a certain emphasis as well.

The Declaration of Helsinki was followed in this study. Prior to the study, ethical approval was obtained from the ethical research committee of the Institutional Review Board (IRB) of King Saud Medical City, Saudi Arabia, wherein they reviewed and approved this project (HAPO H-01-R-053, Project No.H1R1-28-June21-01) and informed consents were obtained from the patient or the official guardian.

Statistical Analysis

Statistical analyses were conducted using SPSS version 26.0 for Windows (IBM SPSS Statistics, Chicago, IL). Continuous data with normal distribution were presented as mean ± standard deviation (SD) with a 95% confidence interval (CI). Categorical data were summarized as frequencies and percentages. Non-normally distributed data were

presented as median with interquartile range (IQR). A p-value of less than 0.05 was considered statistically significant. For comparisons, Student's *t*-test was used for normally distributed variables between two groups, and ANOVA for more than two groups. For non-normally distributed variables, the Mann–Whitney *U*-test was employed. Chi-squared (χ^2) or Fisher's exact test was used for comparing categorical variables between two groups, while the Kruskal–Wallis test analyzed non-normally distributed continuous variables with more than two groups. Survival analysis was performed using the Log Rank (Mantel-Cox) Kaplan–Meier test. Additionally, a Cox proportional hazards model was employed for multivariate survival analysis.

Results

Baseline Characteristics and Troponin Levels

During the study period, 768 COVID-19-positive patients were hospitalized. Of those, 187 patients were excluded because the troponin level was not measured due to mild symptoms presentation. The remaining 581 (75.7%) had troponin I measured at least once within 24 hours of admission, followed by serial measurements. The mean age of the patients was 46.4 ± 14.8, and 471 were male (81.1%). Although the prevalence of fever did not differ between the three groups, cough, shortness of breath, heart failure, and the acute coronary syndrome were significantly higher in patients with positive cTnI (Group 2 and 3, see Table 1).

Table 1 Comparison of Baseline Features Between Groups with Different Troponin I Concentrations

	ICU Patients			P. value
	Normal (Group 1) N=100	Mild Elevated (Group 2) N=70	Elevated (Group 3) N=81	
Age (years) Mean ± SD	47.2±12.5	47.8±14.1	49.0±16.1	0.694
Sex (Male), n (%)	82(82.8%)	52(74.3%)	70(86.4%)	0.158
Smoker, n (%)	70(70.0%)	42(60.0%)	30(37.0%)	0.001*
Obesity, n (%)	53(53.0%)	25(35.7%)	32(39.5%)	0.052
Hypertension, n (%)	100(100.0%)	26(37.1%)	43(53.1%)	0.001*
Chronic Kidney Disease, n (%)	10(10.0%)	10(14.3%)	17(21.0%)	0.116
Diabetes Mellitus, n (%)	0(0.0%)	21(30.0%)	41(50.6%)	0.001*
Cerebro Vascular Accident, n (%)	6(6.0%)	0(0.0%)	3(3.7%)	0.117
History of cardiovascular Diseases, n (%)	34(34.0%)	22(31.4%)	42(51.9%)	0.015*
Lung disease, n (%)	8(8.0%)	2(2.9%)	5(6.2%)	0.378
Hb, (g/dl) Mean ± SD	13.2±2.3	12.0±2.0	12.1±2.8	0.006*
Creatine kinase (U/L) Median (IR)	153.5(97.3–304.8)	563.5(399.8–728.0)	888.0(677.0–1029.5)	0.001*
Creatine kinase-MB (ng/mL) Median (IR):	19.5(6.9–27.0)	59.0(40.8–95.0)	96.0(77.0–98.0)	0.001*
D-dimer (mg/L) Median (IR):	1.1(0.8–1.3)	3.0(2.6–4.5)	4.5(3.0–6.7)	0.001*
C-reactive protein (mg/L)	3.1(2.5–5.4)	111.0(39.0–159.0)	113.5(77.8–161.5)	0.001*
Creatinine (mmol/L) Median (IR):	85.0(70.0–100.0)	81.0(56.0–138.3)	112.0(82.4–190.0)	0.001*
Acute Respiratory Distress Syndrome, n (%)	19(19.0%)	23(32.9%)	43(53.1%)	0.001*
Septic shock, n (%)	9(9.0%)	13(18.6%)	23(28.4%)	0.003*

(*Continued*)

Table 1 (Continued).

	ICU Patients			P. value
	Normal (Group 1) N=100	Mild Elevated (Group 2) N=70	Elevated (Group 3) N=81	
Respiratory Failure, n (%)	10(10.0%)	2(2.9%)	7(8.6%)	0.202
Acute Kidney Injury, n (%)	4(4.0%)	6(8.6%)	18(22.2%)	0.001*
Death Rate	0(0.0%)	9(12.9%)	73(90.1%)	0.001*
Time from admission to death/ days	–	5.0(4.5–11.5)	10.0(6.0–15.0)	0.081

Note: *Statistically significant P-value.

Of the 581 patients, 357 (61.4%) had a normal cTnI level, 106 (18.2%) had a mildly elevated cTnI level, and 118 (20.3%) had a markedly elevated cTnI level (Table 1). Among reported risk factors, hypertension was the most common, found in 216 patients (37.2%), followed by smoking in 177 patients (30.5%), and diabetes mellitus in 150 patients (25.8%). Other baseline characteristics are shown in (Table 1).

There was a higher prevalence of hypertension, smoking, diabetes mellitus, previous history of CAD, and obesity in groups 2 and 3. (Table 1). Cardiac enzymes (CK, CK-MB) and inflammatory markers were elevated in concordance with the cTnI levels among patients in Groups 2 and 3. D-dimer, C-reactive protein, and lactate dehydro-genase were significantly higher in Group 3 (4.5 µg/mL, 121 mg/l, and 575 U/l respectively) than in Group 2 (3.1 µg/mL, 85.5 mg/l, and 635 U/l respectively) and those with normal cTnI (1.1 µg/mL, 5.6 mg/l and 374 U/l respectively). Similar findings were observed in the ICU subgroup (Table 2).

Table 2 Comparison of Baseline Characteristics of ICU Patients with Different Troponin I Level

	ICU Patients			P. value
	Normal (Group 1) N=100	Mild Elevated (Group 2) N=70	Elevated (Group 3) N=81	
Age (years) Mean ± SD	47.2±12.5	47.8±14.1	49.0±16.1	0.694
Sex (Male), n (%)	82(82.8%)	52(74.3%)	70(86.4%)	0.158
Smoker, n (%)	70(70.0%)	42(60.0%)	30(37.0%)	0.001*
Obesity, n (%)	53(53.0%)	25(35.7%)	32(39.5%)	0.052
Hypertension, n (%)	100(100.0%)	26(37.1%)	43(53.1%)	0.001*
Chronic Kidney Disease, n (%)	10(10.0%)	10(14.3%)	17(21.0%)	0.116
Diabetes Mellitus, n (%)	0(0.0%)	21(30.0%)	41(50.6%)	0.001*
Cerebro Vascular Accident, n (%)	6(6.0%)	0(0.0%)	3(3.7%)	0.117
History of cardiovascular Diseases, n (%)	34(34.0%)	22(31.4%)	42(51.9%)	0.015*
Lung disease, n (%)	8(8.0%)	2(2.9%)	5(6.2%)	0.378
Hb, (g/dl) Mean ± SD	13.2±2.3	12.0±2.0	12.1±2.8	0.006*
Creatine kinase (U/L) Median (IR)	153.5(97.3–304.8)	563.5(399.8–728.0)	888.0(677.0–1029.5)	0.001*

(*Continued*)

Table 2 (Continued).

	ICU Patients			P. value
	Normal (Group 1) N=100	Mild Elevated (Group 2) N=70	Elevated (Group 3) N=81	
Creatine kinase-MB (ng/mL) Median (IR):	19.5(6.9–27.0)	59.0(40.8–95.0)	96.0(77.0–98.0)	0.001*
D-dimer (mg/L) Median (IR):	1.1(0.8–1.3)	3.0(2.6–4.5)	4.5(3.0–6.7)	0.001*
C-reactive protein (mg/L)	3.1(2.5–5.4)	111.0(39.0–159.0)	113.5(77.8–161.5)	0.001*
Creatinine (mmol/L) Median (IR):	85.0(70.0–100.0)	81.0(56.0–138.3)	112.0(82.4–190.0)	0.001*
Acute Respiratory Distress Syndrome, n (%)	19(19.0%)	23(32.9%)	43(53.1%)	0.001*
Septic shock, n (%)	9(9.0%)	13(18.6%)	23(28.4%)	0.003*
Respiratory Failure, n (%)	10(10.0%)	2(2.9%)	7(8.6%)	0.202
Acute Kidney Injury, n (%)	4(4.0%)	6(8.6%)	18(22.2%)	0.001*
Death Rate	0(0.0%)	9(12.9%)	73(90.1%)	0.001*
Time from admission to death/ days	–	5.0(4.5–11.5)	10.0(6.0–15.0)	0.081

Note: *Statistically significant P-value.

When patients were categorized by their history of confirmed CVD, CVD risk factors, and no history of either, normal cTnI levels were more prominent in the group with no risk factors (n=151, 86.3%, p=0.001). Mildly elevated and markedly elevated cTnI levels were significantly more present in-patient groups with CVD risk factors and CVD disease; furthermore, ICU admission was significantly higher in the group with markedly elevated cTnI and a history of CVD (n=98, 98%, p=0.001, Table 3).

Table 3 Comparison of Patients Stratified by History of Cardiovascular Disease, Cardiovascular Risk Factors, or Neither

	No Risk Factors N=175	Risk Factors N=406	Cardiovascular Disease N=100	P. value
Age (years) Mean ± SD	41.7±14.8	48.0±15.5	48.5±13.2	0.001*
Sex (Male), n (%)	140(80.0%)	326(80.3%)	86(86.0%)	0.392
Smoker, n (%)	0(0.0%)	147(36.2%)	66(66.0%)	0.001*
Obesity, n (%)	0(0.0%)	90(22.2%)	65(65.0%)	0.001*
Hypertension, n (%)	0(0.0%)	206(50.7%)	61(61.0%)	0.001*
Chronic Kidney Disease, n (%)	0(0.0%)	58(14.3%)	18(18.0%)	0.001*
Diabetes Mellitus, n (%)	0(0.0%)	155(38.2%)	33 (33.0%)	0.001*
Cerebro Vascular Accident, n (%)	0(0.0%)	32(7.9%)	2(2.0%)	0.001*
History of Ischemic Heart Diseases, n (%)	0(0.0%)	0(0.0%)	100(100.0%)	0.001*
Lung disease, n (%)	0(0.0%)	33(8.1%)	8(8.0%)	0.001*

(*Continued*)

Table 3 (Continued).

		No Risk Factors N=175	Risk Factors N=406	Cardiovascular Disease N=100	P. value
Hb, (g/dl) Mean ± SD		12.7±2.3	12.8±2.3	12.4±2.6	0.321
Creatine kinase (U/L) Median (IR)		154.0(82.0–332.0)	297.5(139.5–655.0)	560.0(282.5–858.0)	0.001*
Creatine kinase-MB (ng/mL) Median (IR):		24.0(15.0–44.0)	36.0(20.8–85.0)	46.5(18.3–95.8)	0.001*
D-dimer (mg/L) Median (IR):		1.1(0.7–1.8)	1.9(1.1–3.5)	2.9(1.2–5.8)	0.001*
C-reactive protein (mg/L)		6.9(3.6–39.0)	28.0(4.9–113.3)	58.5(5.0–134.8)	0.004*
Creatinine (mmol/L) Median (IR):		85.0(66.0–107.0)	89.0(72.0–117.3)	99.0(70.0–148.8)	0.046*
Acute Respiratory Distress Syndrome, n (%)		35(20.0%)	123(30.3%)	40(40.0%)	0.001*
Septic shock, n (%)		13(7.4%)	60(14.8%)	22(22.0%)	0.003*
Respiratory Failure, n (%)		13(7.4%)	25(6.2%)	10(10.0%)	0.395
Acute Kidney Injury, n (%)		11(6.3%)	37(9.1%)	14(14.0%)	0.101
Troponin ng/mL	Normal (0.02–0.06)	151(86.3%)	172(56.2%)	34(34.0%)	0.001*
	Mild Elevation (>0.06–0.18)	17(9.7%)	66(21.6%)	23(23.0%)	
	Elevation (> 0.18)	7(4.0%)	68(22.2%)	43(43.0%)	
ICU admission, n (%)		16(9.1%)	182(44.8%)	98(98.0%)	0.001*
Death Rate, n (%)		4(2.3%)	53(13.1%)	45(45.0%)	0.001*
Death after admission/ days, Median (IR)		15.5(5.5–21.8)	8.0 (6.0–13.0)	10.0(6.0–14.5)	0.018*

Note: *Statistically significant P-value.

Outcomes and Mortality Rate

Overall, 89 of 581 (15.3%) patients died. Of those, 80 (67.8% of 118) were in the markedly elevated cTnI group, and nine (8.5% of 106) were in the mildly elevated cTnI group, whereas no deaths were reported in the group with normal cTnI levels (Figure 1 and Table 1). The majority of the deaths were in the ICU (87 of 89 deaths, 97.8%). The most common cause of death was ARDS (28.9%), followed by septic shock (13.8%), and AKI (9.1%; Table 1 and Table 2).

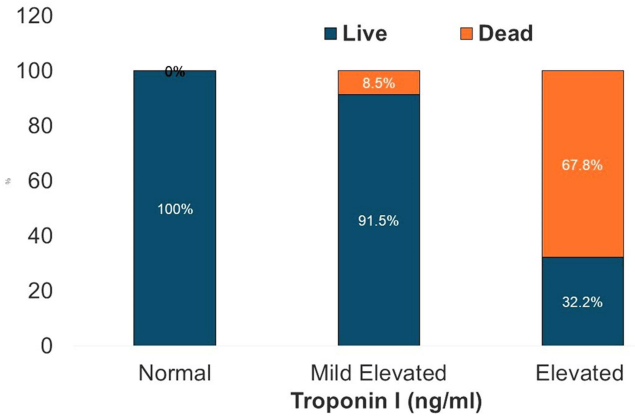

Figure 1 Death rate in the three different groups based on the troponin level.

Table 4 Survival Analysis (Kaplan–Meier Test) Regarding Troponin I Level

Troponin I Level	No. of Events	Estimate	Log Rank (Mantel-Cox)	P. value
		Median (95% C.I)		
Normal	0	15.0 (14.542–15.458)	229.316	<0.001
Mild Elevation (>0.02–0.18) ng/mL	9	12.0 (11.725–12.275)		
Elevation (> 0.18)	80	13.0 (12.267–13.733)		

Notes: Test of equality of survival distributions for the different levels of Troponin. 95% C.I: Confidence Interval.

The hazard ratio (HR) for mortality in those with an increased cTnI compared to those with a normal cTnI was −0.085 (95% CI: (−0.104) – (−0.065); <0.001), which reflects that high troponin level is a potent predictor of death among COVID-19 patients (Table 4). Furthermore, medical history of smoking (HR −0.088, 95% CI: (−0.135) - (−0.041, p < 0.001), hypertension (HR 0.106, 95% CI: (0.061) - (0.151), p=<0.001), diabetes mellitus (HR 0.089, 95% CI: (0.042)-(0.136), p < 0.001), cardiovascular disease (HR 0.204, 95% CI:(0.149) - (0.259), p < 0.001) were associated with an increased risk of death. Moreover, inflammatory markers such as Creatine kinase (HR −0.00007, 95% CI: (−0.00010) – (−0.00004), p < 0.001), Creatine kinase-MB (HR −0.00208, 95% CI: (−0.00253) - (−0.002), p < 0.001), D-dimer (HR −0.019, 95% CI: (−0.025) – (−0.013), p < 0.001) and C-reactive protein (HR −0.00040, 95% CI: (−0.00069) – (−0.00010), p < 0.009) are associated with higher mortality (Table 1).

The Kaplan-Meier test survival analysis (Figure 2) showed no difference in the mortality between mildly elevated and markedly elevated cTnI groups in COVID-19 infected patients. This was further confirmed by the log rank test, where the median (95% CI) in the group with mildly elevated troponin level was 5.0 (4.5–11.5) and 10.0 (6–15) in the group with markedly elevated troponin level, with a p-value of 0.081 (Table 1). On further analysis, we used the Cox Proportional Hazards Regression Model for Mortality as a function for different parameters and we found that the presence of a history of diabetes mellitus, elevated CKMB, elevated D-dimer and the presence of ARDS were major parameters for mortality (Table 5).

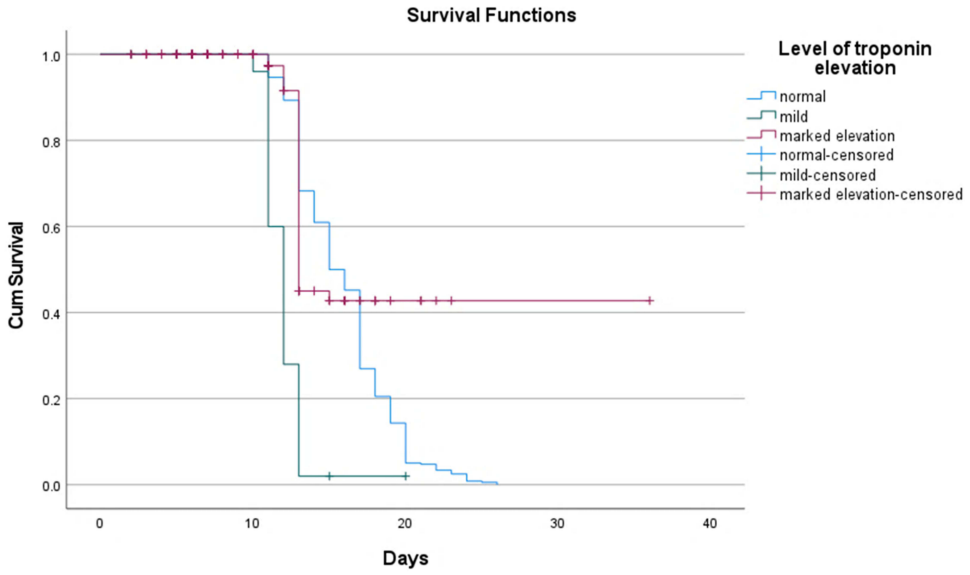

Figure 2 Survival analysis comparing the survival of all groups in days.

Table 5 Results from Cox Proportional Hazards Regression Analysis for Mortality as a Function of the Studied Parameters

	Wald Test	p	HR	95.0% CI for HR	
				Lower	Upper
Age	0.528	0.467	1.006	0.990	1.022
DM	15.755	<0.001*	0.394	0.249	0.624
Hb	2.466	0.116	0.925	0.840	1.019
CKMB	63.084	<0.001*	1.006	1.005	1.008
D-dimer	30.472	<0.001*	1.080	1.051	1.110
Creatinine	0.961	0.327	1.000	1.000	1.001
ARDS	8.782	0.003*	0.440	0.256	0.757
Septic shock	0.204	0.651	1.139	0.648	02.001
Dependent variable (Death)					

Notes: p-value calculated depending on Cox Proportional Hazards Regression Analysis.*Statistically significant P-value.
Abbreviations: HR, Hazard Ratio; C.I, Confidence Interval,

Discussion

This study demonstrated that myocardial injury was frequently observed in hospitalized patients with COVID-19 but was most commonly mild and associated with a mild level of troponin elevation. Pre-existing cardiovascular disease (CVD) or related risk factors significantly elevated the risk of myocardial injury in COVID-19 patients. This injury, as evidenced by increased troponin levels, was a key contributor to the higher mortality rate observed in this population.

Analysis of troponin levels, a marker of myocardial injury, revealed its presence in 38.5% of hospitalized COVID-19 patients. While most patients (majority <1.0 ng/mL) exhibited low troponin levels, even slight elevations (>0.06 ng/mL) were associated with a significantly increased risk of mortality. This risk further escalated with progressively higher troponin levels (troponin I >0.18 ng/mL). Our finding was also congruent with the previous reports in which Lala et al; 2020[17] reported that there was an elevated troponin concentration in 985 (36%) patients, even when the myocardial injury was not severe (eg troponin I > 0.03 to 0.09 ng/mL; n = 455; 16.6%). Death was significantly associated with a troponin I concentration of >0.03 to 0.09 ng/mL (n = 455; 16.6%) those with higher troponin I levels (n = 530; 19.4%) were significantly more likely to be fatal (adjusted HR: 3.03; 95% CI 2.42 to 3.80; p < 0.001).[17]

Elevated troponin levels in COVID-19 patients may not always indicate a classic heart attack (ischemic injury) but could signal a different type of myocardial injury secondary to viral infection or respiratory diseases.[18] The exact mechanisms remain under investigation.[16] While exceeding the 99th percentile URL is considered the gold standard for diagnosing myocardial injury,[19] the underlying cause should be interpreted based on the patient's clinical presentation. Studies have shown that troponin levels exceeding three times the URL are associated with a three-fold increase in mortality risk, even after accounting for other relevant factors. These findings align with a similar study conducted by Thygesen K. et al.[20] Myocardial injury is well understood in the context of ischemia (lack of oxygen to the heart muscle). However, in COVID-19, non-ischemic mechanisms may be at play, including cell death (apoptosis), pressure overload on the heart, direct cell necrosis, and increased release of troponin from the cell membrane.[21,22] While myocardial injury in some of the patients in our study was due to an ischemic mechanism, in others, the injury could have been induced by a non-ischemic mechanism. This warrants further investigation to better understand the etiology behind the myocardial injury in light of the COVID-19 infection.

COVID-19 can harm the heart (cardiovascular morbidity) through several mechanisms. One way is direct damage to the heart muscle (myocardial injury) caused by the release of inflammatory molecules (cytokines) and damage to small blood

vessels (microvascular damage) due to blood clots and thrombosis.[5,6] Additionally, the virus can directly infect heart cells by attaching to ACE2 receptors. Furthermore, the low oxygen levels (hypoxemia) associated with COVID-19's increased metabolic demands can lead to heart damage resembling a type 2 myocardial infarction (MI). This can ultimately lead to acute coronary syndrome due to inflammation-induced instability of fatty deposits (atheroma) in the coronary arteries.[23–25]

In addition, a state of hypercoagulability brought on by a gradual dysregulated coagulative response to SARS-CoV-2 may exacerbate intracardiac thrombosis and this will complete the Virchow's triad which is consistent with endothelial injury, blood stasis and hypercoagulability.[26]

A rare case report by Sonaglioni et al, in which a patient with ischemic dilated cardiomyopathy was identified with severe acute respiratory syndrome owing to coronavirus 2 (SARS-CoV2) associated with biventricular thrombi, could confirm the COVID-19 hypercoagulability state effect, taking in consideration she was never diagnosed with ventricular thrombi before admission and was tested negative for thrombophilia screening during her hospitalization.[27]

Whether the virus affects heart tissue directly or causes severe generalized dysfunction during viral sepsis is unknown. New evidence challenges the idea that SARS-CoV2 will directly impact the CV system at the outset of the epidemic. In COVID-19 tissue biopsies, myocarditis—multiple areas of inflammation and cellular damage—was studied Only 14% of cases had myocarditis-like histology, whereas the rest had diffuse inflammatory infiltration without myocyte involvement, comparable to acute myocardial inflammation. This suggests that significant systemic inflammation and other factors, not the virus only may cause SARS-CoV-2-injured cardiomyocytes. No matter its cause, elevated blood cardiac enzyme levels might identify high-risk COVID-19 patients during early recovery.[28]

A small study examining 18 COVID-19 patients with abnormal EKG readings indicative of potential heart damage (ST-segment elevation) revealed that 10 patients actually had a non-coronary myocardial injury. This means their heart injury was not caused by blocked coronary arteries (confirmed by coronary angiography) or abnormal heart muscle movement (evaluated by echocardiography).[29] Additionally, this study reported that despite the lower levels of troponin in the non-myocardial injury group, nine patients out of 10 died compared to four out of eight patients in the MI group, indicating that the outcome was worse in non-ischemic mediated myocardial injury in a COVID-19 setting. However, this result needs to be further studied by randomized control trials to account for confounders.

Our findings indicated that myocardial injury occurred in 38.5% of COVID-19-infected patients. The frequency of myocardial injury reported here is close to that reported in a large cohort study of hospitalized patients in the United States (36%),[17] and the one reported from China[30] with a prevalence of myocardial injury of 19.7% and 27.8%, respectively. Our study aligns with findings from the United States and China. COVID-19 patients with myocardial injury, a sign of heart damage, tended to be older, have a history of cardiovascular disease (CVD), and exhibit lower hemoglobin levels and higher levels of inflammatory markers. This association is further supported by mortality data from China. A report by the Chinese Center for Disease Control and Prevention involving over 44,000 COVID-19 cases revealed a significantly higher mortality risk (10.5% vs 0.9%) for patients with pre-existing heart conditions.[31]

Myocardial ischemia or cardiac dysfunction is more likely to occur in patients compromised with COVID-19, leading eventually to a dramatic deterioration.[32] Al-ternately, acute inflammatory reactions in the presence of pre-existing coronary disease can also contribute to ischemia. During the systemic inflammatory response, inflammatory activities inside the coronary atherosclerotic plaques are exacerbated, which makes them vulnerable to rupture.[33] Inflammation triggered by COVID-19 can further damage the inner lining of blood vessels (endothelial damage) and increase the production of clotting factors in the blood (procoagulant production). This can lead to the formation of blood clots (occlusive thrombus) that block previously weakened areas in coronary arteries (ruptured coronary plaque).[34] Based on this evidence, we propose that a severe inflammatory response, superimposed on pre-existing cardiovascular disease or its risk factors, can significantly contribute to myocardial injury in COVID-19 patients.

Several studies suggest a link between heart damage (myocardial injury) and poorer outcomes in COVID-19 patients. A study by Shi et al examining 416 patients in Wuhan, China, found a significantly higher mortality rate in those with myocardial injury compared to those without.[30] Similar results were reported by Guo et al in their study of 187 patients in Wuhan.[35] Interestingly, Guo et al also observed that among patients with myocardial injury, those with no prior cardiovascular disease (CVD) fared worse than those with a history of CVD. Our study reinforces these findings,

demonstrating that myocardial damage is a negative prognostic factor for COVID-19 patients, regardless of their CVD background or risk factors.

Although we found that the death rate and adverse outcomes were significantly higher in patients with an increased troponin level, myocardial injury was not the only possible cause of death in COVID-19 infected patients. This finding is aligned with recent studies that report the myocardial injury as an independent predictor of death in COVID-19-infected patients.[17,31,36,37] Our study has several strengths, including diverse laboratory and clinical findings, sample size, and coherent and representative sample. During the (COVID-19) pandemic, the COVID protocol recommended that limited focused imaging should be performed in order to minimize contact time with the infected patient, so we do not have echocardiographic documentation to support the clinical and laboratory findings.[38]

Fortunately, the reported in-hospital mortality among patients with SARS-CoV-2 infection has demonstrated an overall decline, which may partially indicate the influence of modifications in hospital strategy and clinical practice. These improvements may result from the identification of high-risk patients by recognizing predictors of mortality among COVID-19 positive patients.[39]

Conclusion

Myocardial injury, as indicated by troponin elevation, occurred in hospitalized COVID-19 patients at a level that is high enough to draw attention to this complication. Particularly in elderly people with pre-existing cardiovascular comorbidities, acute myocardial injury was associated with an elevated risk of ICU admission, worse outcomes, and death. The observed elevation of troponin associated with COVID-19 infection, even in patients with no previous cardiac disease, can point to the myocardial injury effect. One message is ringing among us: prevention. Encourage people, particularly those with a history of cardiovascular disease or cardiovascular risk factors, to vaccination. They should be most observant of strict hand hygiene and social distancing.

Institutional Review Board Statement

Ethical approval was obtained from the ethical research committee of the Institutional Review Board (IRB) of King Saud Medical City, Saudi Arabia, wherein they reviewed and approved this project (HAPO H-01-R-053, Project No.H1R1-28-June21-01).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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