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ORIGINAL INVESTIGATIONS

Characterization of Myocardial Injury in Patients With COVID-19

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ABSTRACT

BACKGROUND Myocardial injury is frequent among patients hospitalized with coronavirus disease-2019 (COVID-19) and is associated with a poor prognosis. However, the mechanisms of myocardial injury remain unclear and prior studies have not reported cardiovascular imaging data.

OBJECTIVES This study sought to characterize the echocardiographic abnormalities associated with myocardial injury and their prognostic impact in patients with COVID-19.

METHODS We conducted an international, multicenter cohort study including 7 hospitals in New York City and Milan of hospitalized patients with laboratory-confirmed COVID-19 who had undergone transthoracic echocardiographic (TTE) and electrocardiographic evaluation during their index hospitalization. Myocardial injury was defined as any elevation in cardiac troponin at the time of clinical presentation or during the hospitalization.

RESULTS A total of 305 patients were included. Mean age was 63 years and 205 patients (67.2%) were male. Overall, myocardial injury was observed in 190 patients (62.3%). Compared with patients without myocardial injury, those with myocardial injury had more electrocardiographic abnormalities, higher inflammatory biomarkers and an increased prevalence of major echocardiographic abnormalities that included left ventricular wall motion abnormalities, global left ventricular dysfunction, left ventricular diastolic dysfunction grade II or III, right ventricular dysfunction and pericardial effusions. Rates of in-hospital mortality were 5.2%, 18.6%, and 31.7% in patients without myocardial injury, with myocardial injury without TTE abnormalities, and with myocardial injury and TTE abnormalities. Following multivariable adjustment, myocardial injury with TTE abnormalities was associated with higher risk of death but not myocardial injury without TTE abnormalities.

CONCLUSIONS Among patients with COVID-19 who underwent TTE, cardiac structural abnormalities were present in nearly two-thirds of patients with myocardial injury. Myocardial injury was associated with increased in-hospital mortality particularly if echocardiographic abnormalities were present. (J Am Coll Cardiol 2020;76:2043–55) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AKI = acute kidney injury

ARDS = acute respiratory distress syndrome

CI = confidence interval

COVID-19 = coronavirus disease-2019

ECG = electrocardiography

IQR = interquartile range

LV = left ventricle

OR = odds ratio

RV = right ventricle

TTE = transthoracic echocardiography

Coronavirus disease-2019 (COVID-19) is a global pandemic caused by the novel severe acute respiratory syndrome-coronavirus-2 that is resulting in substantial morbidity and mortality (1). A significant proportion of patients presenting with COVID-19 infection requiring hospitalization have biomarker evidence of myocardial injury, which has been shown to be associated with increased risk of in-hospital morbidity and mortality (2–11). The pathogenesis of myocardial injury in patients affected by COVID-19 remains unclear. Proposed mechanisms include cytokine-mediated damage, oxygen supply-demand imbalance, ischemic injury from microvascular thrombi formation and direct viral invasion of the myocardium (9,11). In addition, the risk of coronary thrombotic events from atherosclerotic plaque rupture has previously been shown to be increased during viral infections (12,13), although a reduction in the numbers of patients presenting to hospitals with acute coronary syndromes (ACSs) has thus far been described with COVID-19 (14,15).

SEE PAGE 2056

Previous published series have defined myocardial injury only on the basis of myocardial necrosis biomarker elevations without imaging to characterize structural and functional cardiac abnormalities (2,3,9). In this regard, performing an extensive cardiac work-up in patients with COVID-19 is logistically challenging due to their clinical status and the need to limit exposure of health care personnel. Therefore, the underlying cardiac abnormalities in patients with cardiac injury in the setting of COVID-19 infection remain unknown. To address this gap in current knowledge, in the present study, we comprehensively characterized patients with COVID-19 and evidence of myocardial injury using laboratory, electrocardiographic (ECG), and echocardiographic data.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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METHODS

STUDY DESIGN. The Cardiac Injury Research in COVID-19 (CIRC-19) registry is an international, multicenter retrospective cohort study of hospitalized patients with confirmed severe acute respiratory syndrome-coronavirus-2 infection who underwent a transthoracic echocardiographic (TTE) evaluation during their index hospitalization at 7 clinical sites in New York City (United States) and Milan (Italy) between March 5, 2020, and May 2, 2020. Patients who did not have confirmed severe acute respiratory syndrome-coronavirus-2 infection (by polymerase chain reaction assay of nasal or pharyngeal swab specimens or serologic testing) and those who did not undergo a full TTE study were excluded. Patients who only had point-of-care cardiac ultrasound were not included. Approval for the study was obtained from each center's Institutional Review Board.

DATA COLLECTION AND ENDPOINTS. Data was collected from each center's electronic health record and included patient demographic information, presenting vital signs and symptoms, comorbidities, home medications, chest x-ray findings, ECG findings, laboratory values (reference values are reported in Supplemental Table 1), echocardiographic findings, inpatient treatments received, and in-hospital outcomes. Patients were then categorized according to the presence or absence of myocardial injury, defined as a serum cardiac troponin above the upper reference limit for the assay used at each participating site. Echocardiographic data examined included left ventricular (LV) ejection fraction, LV volumes, presence of regional wall motion abnormalities or global LV dysfunction, LV diastolic function, right ventricular (RV) size and function, and presence of pericardial effusions. Definitions of echocardiographic values are reported in Supplemental Tables 2 to 5. We defined "major echocardiographic abnormalities" as the composite of LV wall motion abnormalities, LV global dysfunction, LV grade II or III diastolic dysfunction, RV dysfunction or presence of a small or larger pericardial effusion. The primary clinical endpoint of interest was in-hospital all-cause mortality. Additional endpoints of interest included admission to an intensive care unit, need for mechanical ventilation, acute respiratory distress syndrome (ARDS), stroke, acute kidney injury (AKI), shock, and ventricular fibrillation or ventricular tachycardia. We defined ARDS according to the Berlin definition (16). AKI was defined according to the Kidney Disease: Improving Global Outcomes definition (17). All endpoints were site-reported.

STATISTICAL ANALYSIS. Continuous variables are reported as median (interquartile range) and were compared with the Wilcoxon rank sum test. Categorical variables are reported as percentages and were compared using the chi-square test. The Kaplan-Meier method was used to generate failure curves for descriptive purposes with censoring performed at either the date of discharge, date of last follow-up, or date of death. Multivariable logistic regression models were performed to evaluate the association between myocardial injury and mortality alone and with or without the presence of major echocardiographic abnormalities. The following covariates were included in the multivariable logistic regression model: age; sex; race; Hispanic ethnicity; history of heart failure; ARDS; AKI stage II or III; cardiocirculatory shock; myocardial injury (with or without major echocardiographic abnormalities), and center identifier. Results of the logistic regression models are reported as odds ratio (OR) and corresponding 95% confidence intervals (CIs). Multivariable Cox regression models for in-hospital death were also performed and the results were reported with hazard ratios and 95% CIs. Center identifiers were entered in the multivariable models to account for intercenter heterogeneity.

In separate analyses, we evaluate the characteristics and outcomes of subsets of patients according to the presence of major echocardiographic abnormalities. Also, we reported the clinical, echocardiographic characteristics and outcomes of those with confirmed ACS on coronary angiography defined as confirmed thrombotic lesion of a major epicardial coronary artery versus other types of myocardial injury. All analyses were performed with the use of Stata software version 14.2 (IBM Corp., Armonk, New York).

RESULTS

PATIENT CHARACTERISTICS. A total of 305 patients were included from March 2020 to May 2020 from 7 hospitals in New York City (United States) and Milan (Italy) (Supplemental Table 6). The demographics, clinical characteristics, and laboratory characteristics according to the presence of myocardial injury are shown in **Table 1**. Baseline medications are reported in Supplemental Table 7. Median age was 63 years and 67.2% were men. A total of 190 patients (62.6%) had biomarker evidence of myocardial injury of whom 118 had myocardial injury at the time of hospital admission and 72 developed myocardial injury during the hospitalization. The median time of in-hospital stay

TABLE 1 Clinical, Radiographic and Laboratory Characteristics of Patients With Versus Without Cardiac Injury and COVID-19

	Overall (N = 305)	Myocardial Injury (n = 190)	No Myocardial Injury (n = 115)	p Value
Demographics				
Age, yrs	63 (53-73)	66 (56-74)	58 (47-70)	0.0008
Male	205/305 (67.2)	132 (69.5)	73 (63.5)	0.28
Race				
White	174/305 (57.1)	98 (51.6)	76 (66.1)	0.10
Black	43/305 (14.1)	30 (15.8)	13 (11.3)	
Asian	27/305 (8.9)	20 (10.5)	7 (6.1)	
Unknown	61/305 (20.0)	42 (22.1)	19 (16.5)	
Hispanic ethnicity	84/304 (27.6)	56 (29.5)	28 (24.6)	0.35
Body mass index, kg/m^2	28 (24.5-32.8)	29.1 (24.6-33.2)	26.5 (24.3-31.2)	0.13
Past medical history				
Hypertension	181/305 (59.3)	130 (68.4)	51 (44.4)	<0.0001
Diabetes mellitus	114/305 (37.4)	80 (42.1)	34 (29.6)	0.03
Prior myocardial infarction	22/299 (7.4)	16 (8.6)	6 (5.4)	0.31
Prior percutaneous coronary intervention	33/300 (11.0)	23 (12.2)	10 (8.9)	0.38
Prior coronary artery bypass graft surgery	13/305 (4.3)	10 (5.3)	3 (2.6)	0.27
Prior stroke	29/304 (9.5)	21 (11.1)	8 (7.0)	0.23
Chronic kidney disease	59/305 (19.3)	49 (25.8)	10 (8.7)	<0.0001
Anemia	60/305 (19.7)	34 (17.9)	26 (22.6)	0.32
Chronic obstructive pulmonary disease	18/305 (5.9)	10 (5.3)	8 (7.0)	0.54
Asthma	27/305 (8.9)	14 (7.4)	13 (11.3)	0.24
History of atrial fibrillation	31/304 (10.2)	22 (11.6)	9 (7.9)	0.30
History of heart failure	24/305 (7.9)	19 (10.0)	5 (4.4)	0.08
Vital signs at presentation				
Temperature, °C	36.9 (36.5-37.6)	36.9 (36.4-37.6)	36.9 (36.5-37.6)	0.97
Systolic blood pressure, mm Hg	130 (115-148)	130 (114-146)	131 (120-152)	0.29
Diastolic blood pressure, mm Hg	75 (65-84)	75 (63-84)	77 (69-84)	0.32
Mean arterial pressure, mm Hg	94 (83-106)	93 (82-106)	95 (85-105)	0.29
Heart rate, beats/min	91.5 (79-109)	95 (80-109)	89 (78-106)	0.15
Oxygen saturation, %	95 (91-98)	95 (89-97)	96 (93-98)	0.007
Presenting symptoms				
Days from symptoms onset	5 (2-8)	5 (2-7)	7 (3-10)	0.03
Shortness of breath	182/303 (60.1)	119 (63.0)	63 (55.3)	0.19
Cough	142/241 (58.9)	94 (59.1)	48 (58.5)	0.93
Fever	128/241 (53.1)	84 (52.8)	44 (53.7)	0.90
Chest pain	42/241 (17.4)	30 (18.9)	13 (15.9)	0.56
Myalgia	53/241 (22.0)	38 (23.9)	15 (18.3)	0.32
Dizziness	16/241 (6.6)	9 (5.7)	7 (8.5)	0.40
Nausea or vomiting	32/241 (13.3)	21 (13.1)	11 (13.4)	0.96
Diarrhea	37/241 (15.4)	26 (16.4)	11 (13.4)	0.55

Continued on the next page

(to discharge, death, or still in the hospital) was 14 days (interquartile range [IQR]: 7 to 23 days). The median time to peak cardiac troponin elevation among patients presenting with normal cardiac troponin was 5 days (IQR: 1 to 12 days). Patients with myocardial injury were older and had a higher prevalence of hypertension, diabetes mellitus, and chronic kidney disease. In addition, patients with myocardial injury had higher levels of natriuretic peptides, inflammatory biomarkers (e.g., interleukin-6, C-reactive protein, ferritin), serum creatinine, coagulation biomarkers (e.g., D-dimer), and serum lactate (Table 1).

ELECTROCARDIOGRAPHIC, ECHOCARDIOGRAPHIC, AND ANGIOGRAPHIC FINDINGS. As shown in Table 2, patients with myocardial injury more frequently had ST-segment elevation or depression at presentation and the most common ST-segment changes were regional (i.e., ascribed to a coronary artery distribution) compared with those without myocardial injury. The presence of conduction disturbances and low voltage were also more frequent in patients with myocardial injury. Among patients with myocardial injury and a normal ECG at presentation, 30.9% developed new ECG ischemic changes during the hospitalization.

TABLE 1 Continued

	Overall (N = 305)	Myocardial Injury (n = 190)	No Myocardial Injury (n = 115)	p Value
Chest radiography				
Clear	46/303 (15.2)	26 (13.8)	20 (17.4)	0.40
Unilateral opacities	42/303 (13.9)	26 (13.8)	16 (13.9)	0.98
Bilateral opacities	211/303 (69.6)	133 (70.7)	78 (67.8)	0.59
Laboratory characteristics				
Cardiac troponin I, ng/ml				
Baseline	0.02 (0.0–0.10)	0.06 (0.02–0.51)	0.0 (0.0–0.0)	<0.0001
Peak	0.09 (0.02–0.86)	0.46 (0.11–2.73)	0.01 (0.0–0.02)	<0.0001
Cardiac troponin T, ng/ml				
Baseline	0.01 (0.0–0.10)	0.04 (0.0–0.16)	0.0 (0.0–0.0)	<0.0001
Peak	0.11 (0.01–0.61)	0.29 (0.06–1.22)	0.0 (0.0–0.0)	<0.0001
High-sensitivity cardiac troponin T, ng/l				
Baseline	12.5 (5.3–32.1)	30.8 (16.7–69.5)	6.2 (3.0–9.4)	<0.0001
Peak	16.6 (8.3–62.5)	62.5 (25.6–123.0)	9.4 (5.6–14.8)	<0.0001
CK-MB, ng/ml				
Baseline	3.1 (1.1–15.2)	3.6 (2.1–20.1)	1 (0.7–2.2)	0.002
Peak	4.1 (1.9–18.6)	5.1 (2.8–21.4)	1.1 (0.6–2.9)	0.0001
Brain natriuretic peptide, pg/ml				
Baseline	112.2 (32–626)	250 (64–1,241)	40 (15–109)	<0.0001
Peak	223.1 (50–1,089)	437 (114–1,689)	59 (17–164)	<0.0001
Creatinine, mg/dl				
Baseline	1.0 (0.8–1.4)	1.1 (0.8–1.9)	0.9 (0.7–1.1)	<0.0001
Peak	1.2 (0.9–2.6)	1.8 (1.0–4.4)	1.0 (0.8–1.2)	<0.0001
Hemoglobin, g/dl	13.2 (11.5–14.7)	13 (11.3–14.7)	13.3 (11.6–14.5)	0.70
White blood cell count, $10^3/\mu l$	8.7 (6.3–12.5)	9.2 (6.6–13.3)	8.0 (5.9–11.4)	0.01
Neutrophil count, $10^3/\mu l$	6.8 (4.4–9.9)	7.4 (4.5–10.8)	6.2 (4.0–8.8)	0.03
Lymphocyte count nadir, $10^3/\mu l$	0.9 (0.6–1.4)	0.9 (0.6–1.4)	0.9 (0.6–1.3)	0.64
Platelet count, $10^3/\mu l$	222.5 (166–306)	217 (155–291)	240 (181–327)	0.03
Lactate, mmol/l				
Baseline	1.7 (1.2–2.8)	1.9 (1.2–3.3)	1.5 (1.0–2.3)	0.04
Peak	2.8 (1.8–4.4)	3.2 (2.2–4.5)	2 (1.4–3.1)	<0.0001
Albumin, g/dl	3.2 (2.8–3.7)	3.2 (2.7–3.6)	3.4 (2.9–3.8)	0.049
C-reactive protein (peak), mg/l	216 (113–301)	240 (142–311)	170 (54–289)	0.002
Erythrocyte sedimentation rate (peak), mm/h	56 (31–78)	56 (37–80)	44 (24–75)	0.38
Interleukin-6 (peak), pg/ml	89.8 (36.8–223)	116 (49–298)	58 (25–147)	0.0002
Lactate dehydrogenase (peak), U/l	641 (404–983.5)	763 (513–1,113)	445 (306–750)	<0.0001
Ferritin (peak), ng/ml	1,322 (458–2,737)	1,624 (688–3,568)	701 (219–1,848)	<0.0001
D-dimer, μg/ml				
Baseline	0.9 (0.4–2.2)	1.2 (0.5–3.4)	0.6 (0.3–1.3)	<0.0001
Peak	2.3 (0.9–8.3)	3.7 (1.2–13.0)	1.5 (0.6–3.9)	<0.0001
Procalcitonin (peak), ng/ml	0.7 (0.15–3.23)	1.3 (0.2–6.8)	0.2 (0.1–1.0)	<0.0001
Alanine aminotransferase, U/l	55 (29–117)	61 (31–117)	47 (25–114)	0.19
Aspartate aminotransferase, U/l	63.5 (34–136)	73 (39–161)	49 (29–116)	0.001

Values are n/N (%) or median (interquartile range) as appropriate.
CK-MB = creatine kinase-myocardial band; COVID-19 = coronavirus disease-2019.

The median number of days between admission and TTE evaluation was 4 days (IQR: 1 to 10 days). The presence of cardiac symptoms (e.g., chest pain or shortness of breath) and troponin elevations were the most common reasons for TTE (Supplemental Table 8). The range of echocardiographic abnormalities in patients with myocardial injury is provided in the **Central Illustration**. The median LV ejection fraction of the overall study cohort was 60% (IQR: 48% to 65%). Compared with patients without myocardial injury, those with myocardial injury had an increased prevalence of any versus no major echocardiographic abnormalities (63.2% vs. 21.7%; OR: 6.17; 95% CI: 3.62 to 10.51; $p < 0.0001$), including global LV dysfunction, regional LV wall motion abnormalities, grade II or III diastolic dysfunction, RV

TABLE 2 Electrocardiographic and Echocardiographic Characteristics of Patients With Versus Without Cardiac Injury and COVID-19

	Overall (N = 305)	Myocardial Injury (n = 190)	No Myocardial Injury (n = 115)	p Value
Electrocardiogram at presentation				
Sinus rhythm	261/305 (85.6)	156 (82.1)	105 (91.3)	0.03
Atrial fibrillation or flutter	37/305 (12.1)	28 (14.7)	9 (7.8)	0.07
ST-segment elevations	20/305 (6.6)	19 (10.0)	1 (0.9)	0.002
ST-segment depressions	21/305 (10.5)	20 (10.5)	1 (0.9)	0.001
ST-segment elevations or depressions	30/305 (9.8)	28 (14.7)	2 (1.7)	<0.0001
Regional*	22/305 (7.2)	21 (11.1)	1 (0.9)	0.001
Diffuse	8/305 (2.6)	7 (3.7)	1 (0.9)	
T-wave inversions	86/305 (28.2)	57 (30.0)	29 (25.2)	0.37
Q-waves	41/305 (13.4)	28 (14.7)	13 (11.3)	0.39
New ECG ischemic changes during hospitalization†	62/305 (20.3)	59 (31.1)	3 (2.6)	<0.0001
Conduction disturbances	49/305 (16.1)	39 (20.5)	10 (8.7)	0.006
Low voltage	29/305 (9.5)	23 (12.2)	6 (5.2)	0.04
Echocardiographic characteristics				
Ejection fraction, %	60 (47.5–65)	58 (42–65)	61 (58–65)	0.0003
≥50	228 (74.8)	124 (65.3)	104 (90.4)	<0.0001
40–49	37 (12.1)	27 (14.2)	10 (8.7)	
<40	40 (13.1)	39 (20.5)	1 (0.9)	
LV internal diastolic diameter, cm	4.5 (4–5)	4.6 (4.1–5.1)	4.4 (4.0–4.9)	0.32
LV internal systolic diameter, cm	3.1 (2.7–3.8)	3.2 (2.7–4.0)	3.0 (2.8–3.6)	0.08
LV end-diastolic volume, ml	101 (76–124)	108 (76–131)	94 (77–113)	0.009
LV end-systolic volume, ml	40 (30–58)	44 (30–71)	36 (29–45)	0.004
Septal wall thickness, cm	1.1 (0.9–1.2)	1.1 (1.0–1.3)	1.0 (0.9–1.2)	0.0001
Posterior wall thickness, cm	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.9 (0.8–1.0)	0.0001
Stroke volume, ml	54 (43–67)	53 (40–69)	55 (45–66)	0.44
Left atrial volume, ml	50 (39–71.3)	60 (40–78)	46 (38–61)	0.0005
Diastolic function				
Normal	99/194 (51.0)	55 (49.1)	44 (53.7)	0.001
Grade I dysfunction	68/194 (35.1)	32 (28.6)	36 (43.9)	
Grade II dysfunction	18/194 (9.3)	16 (14.3)	2 (2.4)	
Grade III dysfunction	9/194 (4.6)	9 (8.0)	0 (0.0)	
Moderate or severe aortic regurgitation	10/296 (3.4)	10 (5.4)	0 (0.0)	0.10
Moderate or severe aortic stenosis	7/296 (2.4)	7 (3.8)	0 (0.0)	0.24
Moderate or severe mitral regurgitation	23/294 (7.8)	17 (9.4)	6 (5.3)	0.23
Moderate or severe tricuspid regurgitation	33/300 (11.0)	27 (14.5)	6 (5.3)	0.006
Pulmonary artery systolic pressure, mm Hg	36 (28–46)	36 (28–47)	36 (28–44)	0.46
LV wall motion abnormalities	50/305 (16.4)	45 (23.7)	5 (4.4)	<0.0001
Apical	28/50 (56.0)	27 (60.0)	1 (20.0)	
Mid	40/50 (80.0)	37 (82.2)	3 (60.0)	
Basal	33/50 (66.0)	29 (64.4)	4 (80.0)	
LV global dysfunction	45/305 (14.8)	35 (18.4)	9 (7.8)	0.01
LV thrombus	4/276 (1.5)	4 (2.4)	0 (0.0)	0.11
RV size				
Normal	239/299 (79.9)	141 (75.4)	97 (87.4)	0.07
Mild dilatation	35/299 (11.7)	25 (13.3)	10 (9.0)	
Moderate dilatation	18/299 (6.0)	15 (8.0)	3 (2.7)	
Severe dilatation	7/299 (2.3)	6 (3.2)	1 (0.9)	
RV function				
Normal	236/298 (79.2)	136 (73.1)	100 (89.3)	0.004
Mildly abnormal	37/298 (12.4)	27 (14.5)	10 (8.9)	
Moderately abnormal	21/298 (7.1)	19 (10.2)	2 (1.8)	
Severely abnormal	4/298 (1.3)	4 (2.2)	0 (0.0)	
RV s′	12 (10–15)	12 (9.5–15)	12.3 (11–14.5)	0.54

Continued on the next page

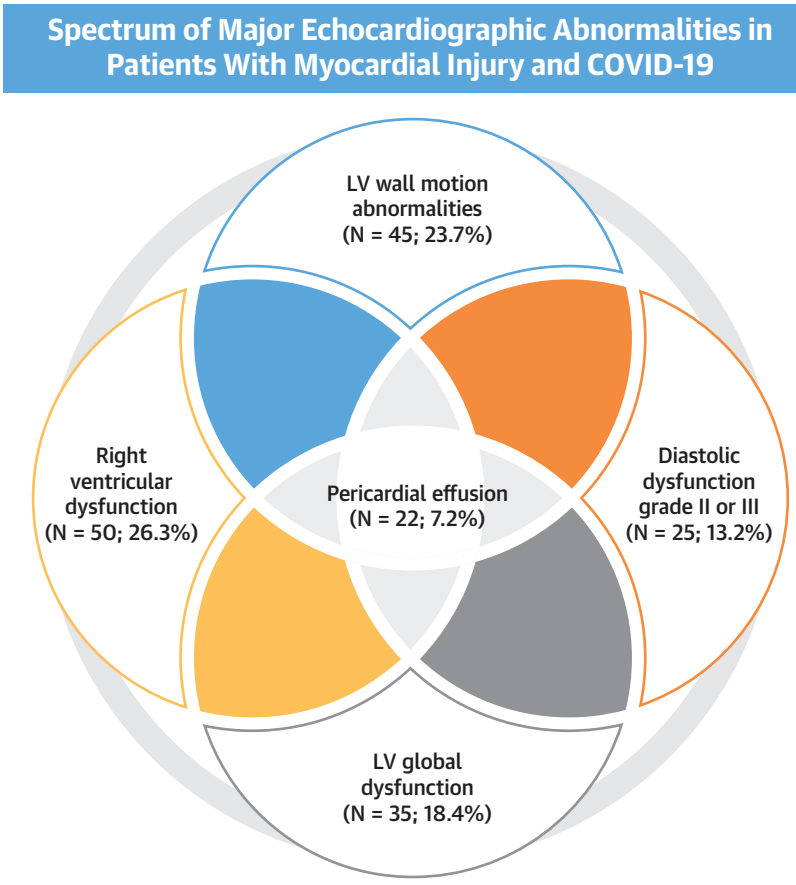
TABLE 2 Continued

	Overall (N = 305)	Myocardial Injury (n = 190)	No Myocardial Injury (n = 115)	p Value
Pericardial effusion				
None or minimal	280/302 (92.7)	169 (89.4)	111 (98.2)	0.02
Small	13/302 (4.3)	13 (6.8)	0 (0.0)	
Moderate	6/302 (2.0)	4 (2.1)	2 (1.8)	
Large	3/302 (1.0)	3 (1.6)	0 (0.0)	
Inferior vena cave size, cm	1.8 (1.4–2.1)	1.8 (1.4–2.1)	1.7 (1.3–2.0)	0.14
Any major echocardiographic abnormality‡	145/305 (47.5)	120 (63.2)	25 (21.7)	<0.0001

Values are n/N (%) or median (interquartile range) as appropriate. *Defined as ST-segment elevations or deviations occurring in a coronary artery distribution territory, including reciprocal ST-segment changes. †Defined as the composite of ST-segment elevations, depressions, or T-wave inversions. ‡Defined as the composite of wall motion abnormalities, global LV dysfunction, grade II or III diastolic dysfunction, RV dysfunction or pericardial effusions.

COVID-19 = coronavirus disease-2019; ECG = electrocardiographic; LV = left ventricular; RV = right ventricular.

CENTRAL ILLUSTRATION Spectrum of Echocardiographic Abnormalities in Patients With Biomarker Evidence of Myocardial Injury and Coronavirus Disease-2019



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Among patients with coronavirus disease-2019 (COVID-19) who underwent transthoracic echocardiography (TTE), cardiac structural abnormalities were present in nearly two-thirds of patients with myocardial injury. Cardiac structural abnormalities included right ventricular dysfunction, left ventricular (LV) wall motion abnormalities, global left ventricular dysfunction, diastolic dysfunction, and pericardial effusions.

TABLE 3 Association Between ECG and Echocardiographic Abnormalities

	No ST-Segment Changes (n = 275)	Regional ST-Segment Changes* (n = 22)	Diffuse ST-Segment Changes (n = 8)	p Value
Ejection fraction, %	60 (51–65)	47 (36–55)	30 (24–43)	<0.0001
≥50	216 (78.8)	9 (42.9)	2 (25.0)	<0.0001
40–49	30 (11.0)	7 (31.8)	0 (0.0)	
<40	28 (10.2)	6 (27.3)	6 (75.0)	
Wall motion abnormalities	34 (12.4)	14 (63.6)	2 (25.0)	<0.0001
Global LV dysfunction	39 (14.2)	0 (0.0)	5 (62.5)	<0.0001
RV size				
Normal	217 (80.4)	19 (86.4)	3 (42.9)	0.04
Mild dilatation	33 (12.2)	1 (4.8)	1 (14.3)	
Moderate dilatation	15 (5.5)	1 (4.8)	2 (28.6)	
Severe dilatation	5 (1.9)	1 (4.8)	1 (14.3)	
RV function				
Normal	215 (79.9)	19 (86.4)	2 (28.6)	<0.0001
Mildly abnormal	35 (13.0)	1 (4.8)	1 (14.3)	
Moderately abnormal	17 (6.3)	2 (9.5)	2 (28.6)	
Severely abnormal	2 (0.7)	0 (0.0)	2 (28.6)	
Any pericardial effusion	20 (7.3)	2 (9.1)	0 (0.0)	0.69

Values are n (%) or median (interquartile range) as appropriate. *Defined as ST-segment elevations or deviations occurring in a coronary artery distribution territory, including reciprocal ST-segment changes.

Abbreviations as in Table 2.

dysfunction, and pericardial effusions (Table 2). Patients with myocardial injury also had greater LV volumes, wall thickness, and left atrial volumes.

The relationships among ECG changes, clinical presentation, and echocardiographic characteristics are reported in Table 3 and Supplemental Table 9. Patients with ST-segment changes more frequently had chest pain at the time of presentation and, among these patients, those with regional ST-segment changes had higher degrees of troponin elevations. Patients with regional ST-segment changes more frequently had wall motion abnormalities on echocardiography, conversely those with diffuse ST-segment changes more frequently had global LV dysfunction (including lower ejection fraction) and RV dysfunction.

Coronary angiography was performed in 11 patients; 8 had confirmed ACS (7 with total thrombotic occlusion of a major epicardial artery who required percutaneous coronary intervention) and 3 had normal coronary arteries. Compared with patients with other types of myocardial injury, those with confirmed ACS more frequently had chest pain at the time of clinical presentation, had higher troponin elevations, lower levels of peak D-dimer levels, and all had wall motion abnormalities on TTE (Supplemental Tables 10 and 11).

MYOCARDIAL INJURY AND IN-HOSPITAL OUTCOMES. In-hospital treatments and outcomes are reported in Table 4. Among the entire study cohort of 305 patients, intensive care unit admission and mechanical ventilation were required in 43.9% and 34.5% of patients respectively, and in-hospital mortality occurred in 18.7%. Compared with patients without myocardial injury, those with myocardial injury had higher rates of in-hospital death (26.8% vs. 5.2%; $p < 0.0001$) (Figure 1A), intensive care unit admission, mechanical ventilation, ARDS, AKI, and cardiocirculatory shock. The rates of in-hospital mortality were 5.2%, 21.0%, and 31.2% among patients without myocardial injury with or without echocardiographic abnormalities, with myocardial injury but without echocardiographic abnormalities and with myocardial injury and echocardiographic abnormalities, respectively (trend adjusted OR: 2.27; 95% CI: 1.30 to 3.94; $p = 0.004$) (Figure 1B). As shown in Figure 2, by multivariable analysis, mortality was increased in patients with myocardial injury and echocardiographic abnormalities even after adjustment for other major complications of COVID-19 (adjusted OR: 3.87; 95% CI: 1.27 to 11.80) but not in patients without echocardiographic abnormalities (adjusted OR: 1.00; 95% CI: 0.27 to 3.71). Results were consistent using multivariable Cox regression models (Supplemental Table 12). In-hospital outcomes in patients with myocardial injury and major echocardiographic abnormalities are reported in Supplemental Table 13. Outcomes in patients with confirmed ACS versus other types of myocardial injury are shown in Supplemental Table 14.

DISCUSSION

In the present multicenter international study, patients with COVID-19 and myocardial injury had a higher prevalence of ECG and echocardiographic abnormalities than did patients without myocardial injury. The echocardiographic abnormalities were diverse and included global LV dysfunction, regional wall motion abnormalities, diastolic dysfunction, RV dysfunction, and pericardial effusions, among others (Central Illustration). Myocardial injury was independently associated with increased risk of in-hospital mortality after adjustment for other major in-hospital complications of COVID-19 including ARDS, cardiocirculatory shock, and AKI, but only in patients with major abnormalities detected on TTE. Finally, we identified substantial differences in clinical and echocardiographic characteristics between patients with confirmed ACS on cardiac catheterization and those with other types of myocardial injury.

TABLE 4 In-Hospital Treatments and Outcomes of Patients With Versus Without Cardiac Injury and COVID-19

	Overall (N = 305)	Myocardial Injury (n = 190)	No Myocardial Injury (n = 115)	Univariate OR (95% CI)	p Value
In-hospital treatments					
Hydroxychloroquine	217/295 (73.6)	128 (68.8)	89 (81.7)	–	0.02
Azithromycin	137/233 (58.8)	95 (60.9)	42 (54.6)	–	0.35
Glucocorticoids	106/233 (45.5)	78 (50.0)	28 (36.4)	–	0.049
Tocilizumab	19/294 (6.5)	12 (6.5)	7 (6.4)	–	0.98
Sarilumab	3/295 (1.0)	2 (1.1)	1 (0.9)	–	0.90
Remdesivir	10/295 (3.4)	9 (4.8)	1 (0.9)	–	0.07
Anticoagulation	164/295 (55.6)	119 (64.0)	45 (41.3)	–	<0.0001
Unfractionated heparin	60/295 (20.3)	48 (25.8)	12 (11.0)	–	0.002
Low molecular weight heparin	147/295 (49.8)	89 (47.9)	58 (53.2)	–	0.37
Direct oral anticoagulant	50/295 (17.0)	31 (16.7)	19 (17.4)	–	0.87
Convalescent plasma	12/295 (4.1)	10 (5.4)	2 (1.8)	–	0.14
Extracorporeal membrane oxygenation	3/305 (1.0)	3 (1.6)	0 (0.0)	–	0.41
In-hospital outcomes					
Death	57/305 (18.7)	51 (26.8)	6 (5.2)	6.67 (2.76–16.11)	<0.0001
ICU admission	134/305 (43.9)	99 (52.1)	35 (30.4)	2.49 (1.53–4.05)	<0.0001
Discharged alive	152/305 (49.8)	69 (36.3)	83 (72.2)	0.23 (0.14–0.38)	<0.0001
Mechanical ventilation	105/304 (34.5)	82 (43.4)	23 (20.0)	3.07 (1.79–5.26)	<0.0001
ARDS	124/305 (40.7)	93 (49.0)	31 (27.0)	2.60 (1.57–4.29)	<0.0001
Worst PaO_2/FiO_2 ratio	88 (66–134)	86 (66–110)	98 (65–152)	–	–
Acute kidney injury	111/304 (36.5)	95 (49.7)	16 (14.2)	6.13 (3.36–11.16)	<0.0001
Stage II or III	55/302 (18.2)	50 (26.6)	5 (4.4)	8.03 (3.10–20.82)	<0.0001
Need for renal replacement therapy	40/305 (13.1)	38 (19.9)	2 (1.8)	14.13 (3.34–59.77)	<0.0001
Shock	86/305 (28.2)	72 (37.9)	14 (12.2)	4.40 (2.34–8.27)	<0.0001
Ventricular arrhythmia	7/305 (2.3)	6 (3.2)	1 (0.9)	3.72 (0.44–31.28)	0.20
Diagnostic catheterization	11/305 (3.6)	11 (5.8)	0 (0.0)	–	0.009
Acute coronary syndrome	8/11 (72.7)	8/11 (72.7)	0 (0.0)	–	–
Normal coronaries	3/11 (27.3)	3/11 (27.3)	0 (0.0)	–	–
Percutaneous coronary intervention	7/8 (87.5)	7/8 (87.5)	0(0.0)	–	–

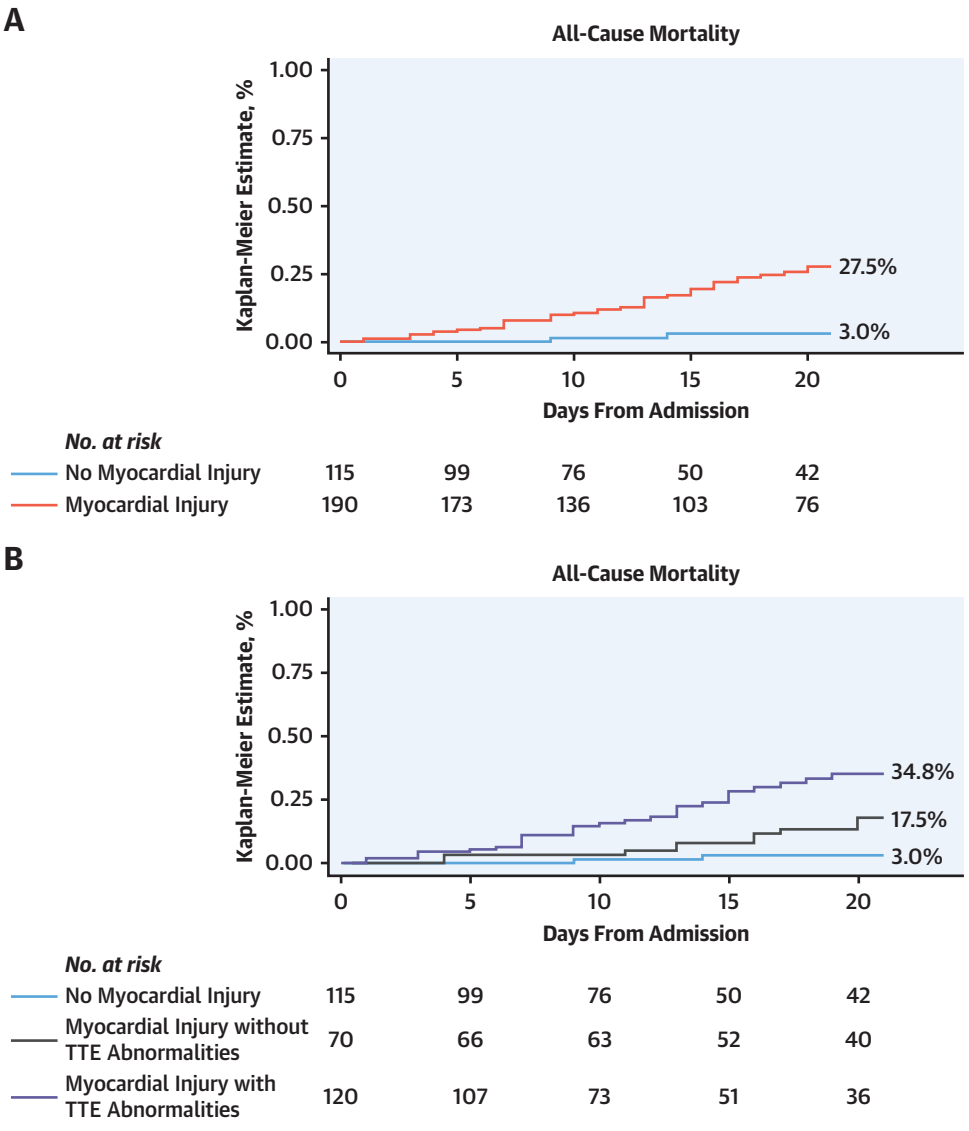
Values are n/N (%) or median (interquartile range) as appropriate.

ARDS = acute respiratory distress syndrome; CI = confidence interval; COVID-19 = coronavirus disease-2019; FiO_2 = fractional inspired oxygen; ICU = intensive care unit; OR = odds ratio; PaO_2 = partial arterial oxygen pressure.

COVID-19 is a global pandemic responsible for significant morbidity, mortality, and health care costs (1). A significant proportion of patients presenting with COVID-19 infection requiring hospitalization have evidence of myocardial injury based on serum cardiac troponin elevations, with an incidence ranging from 7% to 40% (2–11). In most prior studies, cardiac injury has been associated with increased risk of in-hospital complications and mortality (2–11). However, the underlying mechanisms of myocardial injury in patients with COVID-19 remain poorly understood because prior studies have not included cardiovascular imaging data and troponin elevations per se do not differentiate between etiologies of myocardial damage.

In the present study, we comprehensively characterized the structural and functional cardiac abnormalities of patients with COVID-19 infection and biomarker evidence of myocardial injury with the use of TTE. Consistent with prior reports, patients with myocardial injury had higher levels of inflammatory and coagulation biomarkers (2,3). On TTE, most patients with myocardial injury had preserved LV function, and the LV ejection fraction was <50% in only 35% of patients. Nonetheless, patients with cardiac injury had a substantially greater prevalence of LV, RV, and pericardial abnormalities. Higher degrees of diastolic dysfunction were also more frequent in patients with myocardial injury, possibly reflecting the higher prevalence of hypertension and chronic kidney disease among these patients. ST-segment changes on the 12-lead ECG appeared to identify 2 different patterns of myocardial injury, with diffuse ST-segment changes associated with global biventricular dysfunction (possibly reflecting a diffuse myocardial inflammatory damage) and regional ST-segment changes associated with regional wall motion abnormalities (possibly reflecting regional ischemic damage of the myocardium due to macro- or microvascular thrombosis). Therefore,

FIGURE 1 **In-Hospital Mortality in Patients With COVID-19, Myocardial Injury, and Echocardiographic Abnormalities**

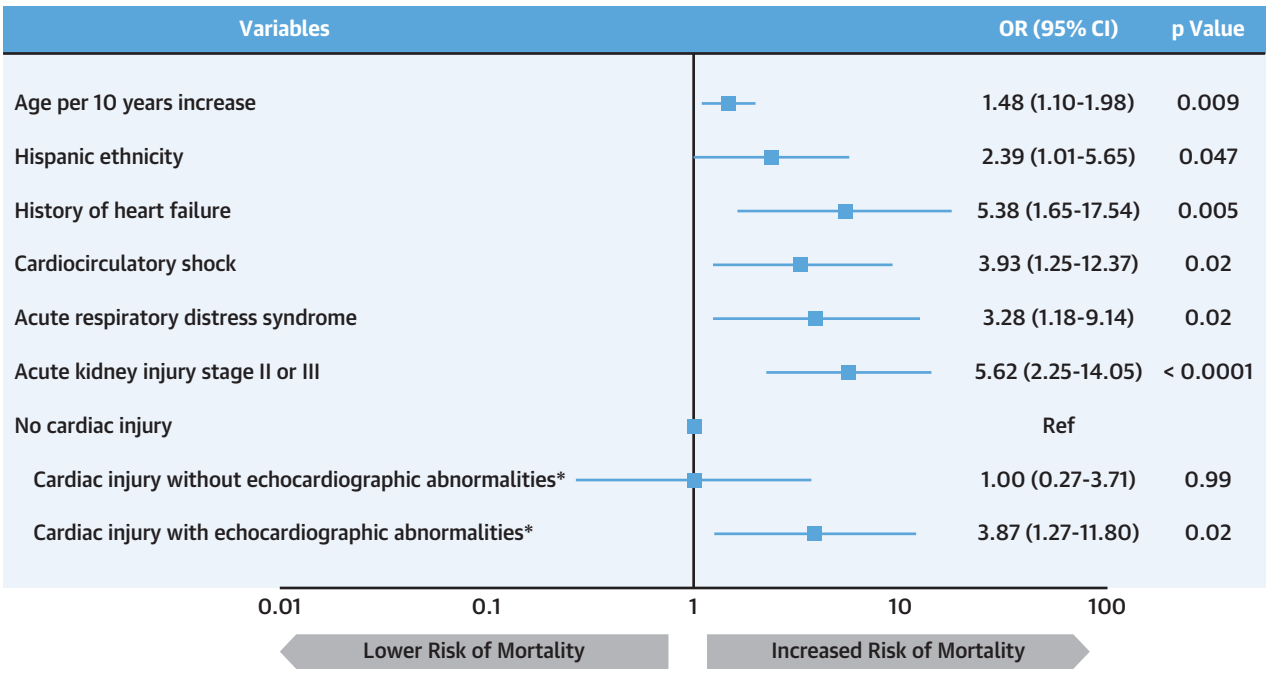


Kaplan-Meier curves for all-cause mortality in patients with versus without myocardial injury **(A)** and in patients with versus without myocardial injury according to the presence or absence of major echocardiographic abnormalities **(B)**. Includes wall motion abnormalities, global left ventricular dysfunction, diastolic dysfunction, right ventricular dysfunction, and presence of pericardial effusion. Event rates are censored at 20 days from hospital admission. TTE = transthoracic echocardiography.

ECG and echocardiographic abnormalities in the context of the appropriate clinical scenario may help differentiate across the different etiologies of myocardial injury in COVID-19.

By multivariable analysis, myocardial injury in patients with major echocardiographic abnormalities was strongly associated with increased risk for in-hospital mortality, even after correcting for other major COVID-19-related complications such as ARDS, AKI, and cardiocirculatory shock (which themselves were also independent predictors of mortality). Conversely, myocardial injury without major echocardiographic abnormalities was not a significant predictor of increased mortality. Thus, TTE in patients with troponin-positive COVID-19 syndromes provides useful prognostic information. The association between myocardial injury and mortality (especially in those with echocardiographic abnormalities)

FIGURE 2 Independent Predictors of In-Hospital Death From Multivariable Logistic-Regression Analysis



Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). The following variables were included in the final model: age, sex, race, history of heart failure, acute respiratory distress syndrome, acute kidney injury stage II or III, cardiocirculatory shock, myocardial injury (with or without major echocardiographic abnormalities), and center identifier. *Includes wall motion abnormalities, global left ventricular dysfunction, diastolic dysfunction, right ventricular dysfunction, or presence of mild or more severe pericardial effusion.

is likely multifactorial and possibly both correlative and causative in nature. First, myocardial injury seems to correlate with the severity of the clinical manifestations of COVID-19 and may identify patients with worse baseline clinical status. Second, COVID-19 has been shown to broadly affect the cardiovascular system (18). Proposed mechanisms include cytokine-mediated myocardial damage, oxygen supply-demand imbalance, microvascular and macrovascular thrombosis, endothelial damage, and possibly direct viral invasion of the myocardium (9). It is therefore possible that the cardiac damage resulting from COVID-19, through direct or indirect pathways, contributes to the poor prognosis observed in certain patients.

Acute myocardial infarction is a leading cause of death worldwide and a treatable and recognizable cause of irreversible cardiac damage (19). However, a reduction in the incidence of hospital admissions for ACS (especially ST-segment elevation myocardial infarction) has been described around the world (14). In our study, cardiac catheterization was performed only in 11 of 305 patients (3.6%), and of those 11 patients, 8 (72.7%) had confirmed ACS and 3 had normal coronary arteries. Patients with confirmed ACS compared with other causes of troponin elevation had a different clinical profile from patients with other causes of myocardial injury, including more frequent chest pain at the time of clinical presentation, more ECG changes, lower levels of inflammatory biomarkers, and all had regional wall motion abnormalities on TTE. For example, 100% of patients with ACS had regional wall motion abnormalities, compared with 20% of troponin-positive patients without confirmed ACS. Therefore, in the appropriate clinical scenario, TTE (or a point-of-care ultrasound) may be considered among patients with COVID-19 infection and biomarker evidence of myocardial injury to potentially identify those who might benefit from expedited invasive management.

STUDY LIMITATIONS. Data collection was retrospective and used manual electronic health record extraction from multiple institutions. Therefore, it

is subject to both reporting and ascertainment bias. Our sample size is modest but nonetheless represents one of the largest studies to date evaluating the association between myocardial injury and functional and structural cardiac assessment using echocardiography in patients with COVID-19. We did not include cardiac magnetic resonance imaging data, and only a small number of patients underwent cardiac catheterization. However, extensive cardiovascular work-up in patients with COVID-19 is often challenging due to both their clinical status and efforts to mitigate exposure risk of health care workers. There was no systematic basis on which patients were selected to undergo TTE evaluation. In fact, it is likely that only patients that were perceived to be at higher risk on clinical grounds underwent TTE. Also, echocardiograms were all interpreted locally and not centrally by an echocardiographic core laboratory. Finally, our study is limited to in-hospital outcomes; the long-term cardiovascular sequelae in patients with troponin-positive COVID-19 with and without echocardiographic abnormalities warrants future prospective investigation.

CONCLUSIONS

Patients with COVID-19 and myocardial injury have a broad spectrum of cardiac abnormalities, although approximately one-third of such patients show no evidence of structural cardiac disease. Myocardial injury is associated with increased risk of in-hospital mortality particularly in the presence of cardiac structural abnormalities detected by TTE. TTE evaluation should be considered in patients with COVID-19 and biomarker evidence of myocardial injury to characterize the underlying cardiac substrate, for risk stratification, and to potentially guide management strategies.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TTE can be useful in the evaluation of patients with COVID-19 who have biomarker evidence of myocardial injury to characterize the pathological mechanisms involved, guide management, and facilitate risk stratification.

TRANSLATIONAL OUTLOOK: Further studies are needed to develop strategies that reduce the short-term risk of mortality associated with myocardial injury in patients with COVID-19 and clarify the long-term consequences for survivors of the acute phase.

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KEY WORDS COVID-19, echocardiography, myocardial infarction, myocardial injury

APPENDIX For supplemental tables and references, please see the online version of this paper.