

Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China

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 Editorial

 Supplemental content

IMPORTANCE Coronavirus disease 2019 (COVID-19) has resulted in considerable morbidity and mortality worldwide since December 2019. However, information on cardiac injury in patients affected by COVID-19 is limited.

OBJECTIVE To explore the association between cardiac injury and mortality in patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted from January 20, 2020, to February 10, 2020, in a single center at Renmin Hospital of Wuhan University, Wuhan, China; the final date of follow-up was February 15, 2020. All consecutive inpatients with laboratory-confirmed COVID-19 were included in this study.

MAIN OUTCOMES AND MEASURES Clinical laboratory, radiological, and treatment data were collected and analyzed. Outcomes of patients with and without cardiac injury were compared. The association between cardiac injury and mortality was analyzed.

RESULTS A total of 416 hospitalized patients with COVID-19 were included in the final analysis; the median age was 64 years (range, 21-95 years), and 211 (50.7%) were female. Common symptoms included fever (334 patients [80.3%]), cough (144 [34.6%]), and shortness of breath (117 [28.1%]). A total of 82 patients (19.7%) had cardiac injury, and compared with patients without cardiac injury, these patients were older (median [range] age, 74 [34-95] vs 60 [21-90] years; $P < .001$); had more comorbidities (eg, hypertension in 49 of 82 [59.8%] vs 78 of 334 [23.4%]; $P < .001$); had higher leukocyte counts (median [interquartile range (IQR)], 9400 [6900-13 800] vs 5500 [4200-7400] cells/ μ L) and levels of C-reactive protein (median [IQR], 10.2 [6.4-17.0] vs 3.7 [1.0-7.3] mg/dL), procalcitonin (median [IQR], 0.27 [0.10-1.22] vs 0.06 [0.03-0.10] ng/mL), creatinine kinase-myocardial band (median [IQR], 3.2 [1.8-6.2] vs 0.9 [0.6-1.3] ng/mL), myohemoglobin (median [IQR], 128 [68-305] vs 39 [27-65] μ g/L), high-sensitivity troponin I (median [IQR], 0.19 [0.08-1.12] vs <0.006 [<0.006 -0.009] μ g/L), N-terminal pro-B-type natriuretic peptide (median [IQR], 1689 [698-3327] vs 139 [51-335] pg/mL), aspartate aminotransferase (median [IQR], 40 [27-60] vs 29 [21-40] U/L), and creatinine (median [IQR], 1.15 [0.72-1.92] vs 0.64 [0.54-0.78] mg/dL); and had a higher proportion of multiple mottling and ground-glass opacity in radiographic findings (53 of 82 patients [64.6%] vs 15 of 334 patients [4.5%]). Greater proportions of patients with cardiac injury required noninvasive mechanical ventilation (38 of 82 [46.3%] vs 13 of 334 [3.9%]; $P < .001$) or invasive mechanical ventilation (18 of 82 [22.0%] vs 14 of 334 [4.2%]; $P < .001$) than those without cardiac injury. Complications were more common in patients with cardiac injury than those without cardiac injury and included acute respiratory distress syndrome (48 of 82 [58.5%] vs 49 of 334 [14.7%]; $P < .001$), acute kidney injury (7 of 82 [8.5%] vs 1 of 334 [0.3%]; $P < .001$), electrolyte disturbances (13 of 82 [15.9%] vs 17 of 334 [5.1%]; $P = .003$), hypoproteinemia (11 of 82 [13.4%] vs 16 of 334 [4.8%]; $P = .01$), and coagulation disorders (6 of 82 [7.3%] vs 6 of 334 [1.8%]; $P = .02$). Patients with cardiac injury had higher mortality than those without cardiac injury (42 of 82 [51.2%] vs 15 of 334 [4.5%]; $P < .001$). In a Cox regression model, patients with vs those without cardiac injury were at a higher risk of death, both during the time from symptom onset (hazard ratio, 4.26 [95% CI, 1.92-9.49]) and from admission to end point (hazard ratio, 3.41 [95% CI, 1.62-7.16]).

CONCLUSIONS AND RELEVANCE Cardiac injury is a common condition among hospitalized patients with COVID-19 in Wuhan, China, and it is associated with higher risk of in-hospital mortality.

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Since December 2019, coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in considerable morbidity and mortality in more than 30 countries worldwide. Recently, COVID-19-associated clusters of severe respiratory illness have been independently associated with risk of mortality, and mounting evidence substantiates the presence of cardiac injury in patients with COVID-19.^{1,2} Although a recent study reported that 12% of patients had COVID-19-associated acute cardiac injury,¹ manifesting as an ejection fraction decline and troponin I elevation, and the American College of Cardiology clinical bulletin has highlighted the cardiac implications of COVID-19,³ the association between COVID-19-associated cardiac injury and risk of mortality remains unclear. The present study therefore retrospectively analyzed data from a single center in Wuhan, China, to examine the potential association between cardiac injury and mortality among patients with COVID-19.

Methods

Study Participants

Consecutive patients admitted to Renmin Hospital of Wuhan University with laboratory-confirmed COVID-19 were included in this retrospective cohort study, which was conducted from January 20, 2020, to February 10, 2020. Renmin Hospital of Wuhan University, located in Wuhan, Hubei Province, China, was assigned responsibility for the treatment of patients with severe COVID-19 by the Wuhan government. The patients with COVID-19 enrolled in this study were diagnosed according to World Health Organization interim guidance.⁴ The cases without cardiac biomarkers, including values of high-sensitivity troponin I (hs-TNI) and creatinine kinase-myocardial band (CK-MB), were excluded.

This study was approved by the National Health Commission of China and the institutional review board at Renmin Hospital of Wuhan University (Wuhan, China). Written informed consent was waived by the ethics commission of the designated hospital for patients with emerging infectious diseases.

Data Collection

The demographic characteristics (age and sex), clinical data (symptoms, comorbidities, laboratory findings, treatments, complications, and outcomes), laboratory findings, and results of cardiac examinations (cardiac biomarkers and electrocardiography) for participants during hospitalization were collected from electronic medical records by 2 investigators (S.S. and B.S.). Cardiac biomarkers measured on admission were collected, including hs-TNI, CK-MB, and myohemoglobin. The radiologic assessments included chest radiography or computed tomography. All data were independently reviewed and entered into the computer database by 2 analysts (T.L. and Y.C.). Patients were categorized according to the presence or absence of cardiac injury. Cardiac injury was defined as blood levels of cardiac biomarkers (hs-TNI) above the 99th-percentile upper reference limit, regardless of new abnormalities in

Key Points

Question What is the incidence and significance of cardiac injury in patients with COVID-19?

Findings In this cohort study of 416 consecutive patients with confirmed COVID-19, cardiac injury occurred in 19.7% of patients during hospitalization, and it was one independent risk factor for in-hospital mortality.

Meaning Cardiac injury is a common condition among patients hospitalized with COVID-19, and it is associated with higher risk of in-hospital mortality.

electrocardiography and echocardiography. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition.⁵ Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition.⁶ The clinical outcomes (ie, discharges, mortality, and length of stay) were monitored up to February 15, 2020, the final date of follow-up.

To confirm COVID-19, the Viral Nucleic Acid Kit (Health) was used to extract nucleic acids from clinical samples according to the kit instructions. A 2019-nCoV detection kit (Bioperfectus) was used to detect the *ORF1ab* gene (*nCovORF1ab*) and the *N* gene (*nCov-NP*) according to the manufacturer's instructions, using real-time reverse transcriptase-polymerase chain reaction.⁷ An infection was considered laboratory-confirmed if the *nCovORF1ab* and *nCov-NP* tests both showed positive results.

Statistical Analysis

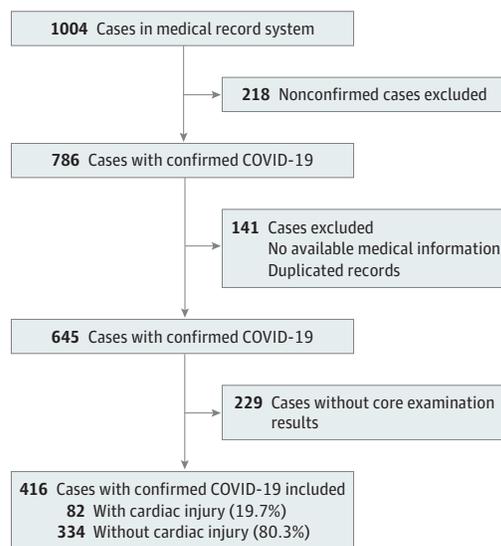
Descriptive statistics were obtained for all study variables. All categorical variables were compared for the study outcome by using the Fisher exact test or χ^2 test, and continuous variables were compared using the *t* test or the Mann-Whitney *U* test, as appropriate. Continuous data are expressed as mean (SD) or median (interquartile range [IQR]) values. Categorical data are expressed as proportions. Survival curves were plotted using the Kaplan-Meier method and compared between patients with vs without cardiac injury using the log-rank test. Multivariate Cox regression models were used to determine the independent risk factors for death during hospitalization. Data were analyzed using SPSS version 25.0 (IBM). Statistical charts were generated using Excel 2016 (Microsoft) or Prism 5 (Graphpad). For all the statistical analyses, $P < .05$ was considered significant.

Results

Patient Characteristics

Figure 1 shows a flowchart for patient recruitment. Briefly, of all 1004 patients in the medical record system who were screened initially from January 20, 2020, to February 10, 2020, 218 patients whose cases were not confirmed, 141 patients without available medical information and duplicated records, and 229 patients with missing core results of laboratory examination (hs-TNI and CK-MB) were excluded. The median age of

Figure 1. Flowchart of Patient Recruitment



these 229 patients was 45 years (range, 22-90 years), and 130 (56.8%) were female; the details of baseline characteristics were presented in the eTable in the Supplement.

Finally, the study population included 416 patients hospitalized with confirmed COVID-19: 82 patients (19.7%) with cardiac injury and 334 patients (80.3%) without cardiac injury. The median age was 64 years (range, 21-95 years), and 211 (50.7%) were female. Among these patients, fever (334 patients [80.3%]) was the most common symptom. Cough, shortness of breath, fatigue, sputum production, and muscle ache were present in 144 patients (34.6%), 117 patients (28.1%), 55 patients (13.2%), 23 patients (5.5%), and 19 patients (4.6%), respectively. Diarrhea (16 patients [3.8%]), chest pain (14 patients [3.4%]), sore throat (12 patients [2.9%]), rhinorrhea (10 patients [2.4%]), and headache (9 patients [2.2%]) were rare. Hypertension (127 patients [30.5%]) and diabetes (60 patients [14.4%]) were the most common coexisting conditions. Of these 416 patients, 44 (10.6%) and 22 (5.3%) had coronary heart disease and cerebrovascular disease, respectively. The proportion of chronic heart failure, chronic renal failure, chronic obstructive pulmonary disease, cancer, pregnancy, and hepatitis B infection was 4.1% (17 patients), 3.4% (14 patients), 2.9% (12 patients), 2.2% (9 patients), 1.7% (7 patients), and 1.0% (4 patients), respectively.

Compared with patients without cardiac injury, patients with cardiac injury were older (median [range] age, 74 [34-95] years vs 60 [21-90] years; $P < .001$), and more likely to have chest pain (11 of 82 patients [13.4%] vs 3 of 334 patients [0.9%]; $P < .001$). Moreover, comorbidities, including hypertension (49 [59.8%] vs 78 [23.4%]), diabetes (20 [24.4%] vs 40 [12.0%]), coronary heart disease (24 [29.3%] vs 20 [6.0%]), cerebrovascular disease (13 [15.9%] vs 9 [2.7%]), chronic heart failure (12 [14.6%] vs 5 [1.5%]), chronic obstructive pulmonary disease (6 [7.3%] vs 6 [1.8%]), and cancer (7 [8.5%] vs 2 [0.6%]), were present more often among patients with cardiac injury (all $P < .001$) (Table 1).

Laboratory and Radiographic Findings

The laboratory and radiologic findings are shown in Table 1. In the overall study population of 416 patients, median (IQR) levels of C-reactive protein (4.5 [1.4-8.5] mg/dL; to convert to milligrams per liter, multiply by 10) and procalcitonin (0.07 [0.04-0.15] ng/L) were elevated, while the median values of other laboratory indicators were within the normal range, such as counts of leukocytes, lymphocytes, platelets, erythrocytes; hemoglobin level; cardiac indicators; alanine aminotransferase level; aspartate aminotransferase level; creatinine concentration; and electrolyte levels. The proportion of patients with bilateral pneumonia was 74.8% (311 patients) according to chest radiography and computed tomography findings, and 68 patients (16.3%) had multiple mottling and ground-glass opacity. Distribution of hs-TNI based on detection time from hospitalization (median [IQR], 2 [1-15] days) is shown in eFigure 1 in the Supplement. The duration of hospitalization before testing was longer in patients with cardiac injury than those without cardiac injury (median [range] time, 3 [1-15] days vs 2 [1-8] days; $P < .001$).

In terms of laboratory findings, patients with cardiac injury compared with patients without cardiac injury showed higher median leukocyte count (median [IQR], 9400 [6900-13 800] cells/ μ L vs 5500 [4200-7400] cells/ μ L), and levels of C-reactive protein (median [IQR], 10.2 [6.4-17.0] mg/dL vs 3.7 [1.0-7.3] mg/dL), procalcitonin (median [IQR], 0.27 [0.10-1.22] ng/mL vs 0.06 [0.03-0.10] ng/mL), CK-MB (median [IQR], 3.2 [1.8-6.2] ng/mL vs 0.9 [0.6-1.3] ng/mL), myohemoglobin (median [IQR], 128 [68-305] μ g/L vs 39 [27-65] μ g/L), hs-TNI (median [IQR], 0.19 [0.08-1.12] μ g/L vs <0.006 [<0.006-0.009] μ g/L), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (median [IQR], 1689 [698-3327] pg/mL vs 139 [51-335] pg/mL), aspartate aminotransferase (median [IQR], 40 [27-60] U/L vs 29 [21-40] U/L), and creatinine (median [IQR], 1.15 [0.72-1.92] mg/dL vs 0.64 [0.54-0.78] mg/dL) during hospitalization, but a lower median lymphocyte count (median [IQR], 600 [400-900] cells/ μ L vs 1000 [800-1400] cells/ μ L), platelet count (median [IQR], 172 [111-215] cells $\times 10^3/\mu$ L vs 216 [165-273] cells $\times 10^3/\mu$ L), and albumin level (median [IQR], 3.2 [2.9-3.4] g/dL vs 3.7 [3.3-3.9] g/dL), with significant differences in each case (all $P < .001$; Table 1; eFigure 1 in the Supplement). In terms of radiologic findings, bilateral pneumonia (75 of 82 patients [91.5%] vs 236 of 334 patients [70.7%]) and multiple mottling and ground-glass opacity (53 [64.6%] vs 15 [4.5%]) were more prevalent in patients with than those without cardiac injury (both $P < .001$, Table 1).

Of patients with cardiac injury, only 22 (26.8%) underwent examination of electrocardiogram (ECG) after admission, and 14 of 22 ECGs (63.6%) were performed during the periods of elevation of cardiac biomarkers. All 14 ECGs were abnormal, with findings compatible with myocardial ischemia, such T-wave depression and inversion, ST-segment depression, and Q waves. The ECG changes in 3 patients with representative cardiac injury are shown in eFigure 2 in the Supplement.

Treatment, Complications, and Clinical Outcome

The median time from symptom onset to admission was 10 (IQR, 1-30) days and similar between the 2 groups ($P = .27$;

Table 1. Baseline Characteristics and Laboratory and Radiographic Findings of 416 Patients With COVID-19

Characteristic	Patients, No. (%)			P value
	All (n = 416)	Cardiac injury With (n = 82)	Without (n = 334)	
Age, median (range), y	64 (21-95)	74 (34-95)	60 (21-90)	<.001
Female	211 (50.7)	38 (46.3)	173 (51.8)	.39
Signs and symptoms at admission				
Fever	334 (80.3)	63 (76.8)	271 (81.1)	.44
Cough	144 (34.6)	28 (34.1)	116 (34.7)	>.99
Shortness of breath	117 (28.1)	26 (31.7)	91 (27.2)	.41
Fatigue	55 (13.2)	15 (18.3)	40 (12.0)	.15
Sputum production	23 (5.5)	3 (3.7)	20 (6.0)	.59
Muscle ache	19 (4.6)	5 (6.1)	14 (4.2)	.55
Diarrhea	16 (3.8)	1 (1.2)	15 (4.5)	.22
Chest pain	14 (3.4)	11 (13.4)	3 (0.9)	<.001
Sore throat	12 (2.9)	4 (4.9)	8 (2.4)	.26
Rhinorrhea	10 (2.4)	3 (3.7)	7 (2.1)	.42
Headache	9 (2.2)	2 (2.4)	7 (2.1)	.69
Chronic medical illness				
Hypertension	127 (30.5)	49 (59.8)	78 (23.4)	<.001
Diabetes	60 (14.4)	20 (24.4)	40 (12.0)	.008
Coronary heart disease	44 (10.6)	24 (29.3)	20 (6.0)	<.001
Cerebrovascular disease	22 (5.3)	13 (15.9)	9 (2.7)	<.001
Chronic heart failure	17 (4.1)	12 (14.6)	5 (1.5)	<.001
Chronic renal failure	14 (3.4)	5 (6.1)	9 (2.7)	.16
Chronic obstructive pulmonary disease	12 (2.9)	6 (7.3)	6 (1.8)	.02
Cancer	9 (2.2)	7 (8.5)	2 (0.6)	<.001
Pregnancy	7 (1.7)	0	7 (2.1)	.35
Hepatitis B infection	4 (1.0)	2 (2.4)	2 (0.6)	.18
Laboratory findings at admission, median (IQR)				
Leukocytes/ μ L	5800 (4300-8300)	9400 (6900-13 800)	5500 (4200-7400)	<.001
Lymphocytes/ μ L	900 (600-1300)	600 (400-900)	1000 (800-1400)	<.001
Platelets $\times 10^3$ / μ L	207 (153-265)	172 (111-215)	216 (165-273)	<.001
Erythrocytes $\times 10^6$ / μ L	4.1 (3.6-4.4)	4.0 (3.4-4.3)	4.1 (3.6-4.4)	.01
Hemoglobin, g/dL	12.4 (11.1-13.4)	12.5 (10.8-13.2)	12.4 (11.2-13.5)	.34
C-reactive protein, mg/dL	4.5 (1.4-8.5)	10.2 (6.4-17.0)	3.7 (1.0-7.3)	<.001
Procalcitonin, ng/mL	0.07 (0.04-0.15)	0.27 (0.10-1.22)	0.06 (0.03-0.10)	<.001
Creatinine kinase-myocardial band, ng/mL	1.0 (0.7-2.0)	3.2 (1.8-6.2)	0.9 (0.6-1.3)	<.001
Myohemoglobin, μ g/L	47 (28-93)	128 (68-305)	39 (27-65)	<.001
High-sensitivity troponin I, μ g/L ^a	<0.006 (<0.006-0.02)	0.19 (0.08-1.12)	<0.006 (<0.006-0.009)	<.001
N-terminal pro-B-type natriuretic peptide, pg/mL	219 (73-699)	1689 (698-3327)	139 (51-335)	<.001
Alanine aminotransferase, U/L	28 (18-46)	29 (19-44)	28 (18-46)	.93
Aspartate aminotransferase, U/L	30 (22-43)	40 (27-60)	29 (21-40)	<.001
Albumin, g/dL	3.6 (3.2-3.8)	3.2 (2.9-3.4)	3.7 (3.3-3.9)	<.001
Creatinine, mg/dL	0.67 (0.55-0.81)	1.15 (0.72-1.92)	0.64 (0.54-0.78)	<.001
Potassium, mEq/L	4.0 (3.6-4.4)	4.0 (3.6-4.6)	4.0 (3.6-4.3)	.65
Sodium, mEq/L	140 (138-144)	141 (138-146)	140 (138-143)	.08
Chest radiography and computed tomography findings				
Pneumonia				
Unilateral	105 (25.2)	7 (8.5)	98 (29.3)	<.001
Bilateral	311 (74.8)	75 (91.5)	236 (70.7)	
Multiple mottling and ground-glass opacity	68 (16.3)	53 (64.6)	15 (4.5)	<.001

Abbreviation: IQR, interquartile range.

SI conversion factors: To convert leukocytes or lymphocytes to $\times 10^9$ /L, multiply by 0.001; to convert platelets to $\times 10^9$ /L, multiply by 1.0; to convert erythrocytes to $\times 10^{12}$ /L, multiply by 1.0; to convert hemoglobin to g/L, multiply by 10.0; to convert C-reactive protein to mg/L, multiply by 10.0; to convert creatinine kinase-myocardial band to μ g/L, multiply by 1.0; to convert troponin I to ng/mL, multiply by 1.0; to convert alanine aminotransferase or aspartate

aminotransferase to μ kat/L, multiply by 0.0167; to convert albumin to g/L, multiply by 10; to convert creatinine to μ mol/L, multiply by 88.4; to convert potassium and sodium to mmol/L, multiply by 1.0.

^a Indicated that the lowest value of troponin actually measured is <0.006 ng/mL in our hospital, although the range of reference values is 0.00 to 0.04 ng/mL.

Table 2. Treatment, Complications, and Clinical Outcome of 416 Patients With COVID-19

Characteristic	Patients, No. (%)			P value
	All (n = 416)	With (n = 82)	Without (n = 334)	
Time from symptom onset to admission, median (range), d	10 (1-30)	10 (1-30)	10 (1-28)	.27
Treatment				
Oxygen inhalation	316 (76.0)	26 (31.7)	290 (86.8)	<.001
Noninvasive ventilation	51 (12.3)	38 (46.3)	13 (3.9)	<.001
Invasive mechanical ventilation	32 (7.7)	18 (22.0)	14 (4.2)	<.001
Continuous renal replacement therapy	2 (0.5)	2 (2.4)	0	.04
Antiviral treatment	403 (96.9)	82 (100)	321 (96.1)	.08
Glucocorticoids	304 (73.1)	72 (87.8)	232 (69.5)	<.001
Intravenous immunoglobulin therapy	259 (62.3)	68 (82.9)	191 (57.2)	<.001
Antibiotic treatment	235 (56.5)	68 (82.9)	167 (50)	<.001
Complications				
ARDS	97 (23.3)	48 (58.5)	49 (14.7)	<.001
Acute kidney injury	8 (1.9)	7 (8.5)	1 (0.3)	<.001
Electrolyte disturbance	30 (7.2)	13 (15.9)	17 (5.1)	.003
Hypoproteinemia	27 (6.5)	11 (13.4)	16 (4.8)	.01
Anemia	13 (3.1)	4 (4.9)	9 (2.7)	.30
Coagulation disorders	12 (2.9)	6 (7.3)	6 (1.8)	.02
Clinical outcome				
Remained in hospital	319 (76.7)	38 (46.3)	281 (72.2)	<.001
Discharged	40 (9.6)	2 (2.4)	38 (23.4)	
Died	57 (13.7)	42 (51.2)	15 (4.5)	<.001

Abbreviation: ARDS, acute respiratory distress syndrome.

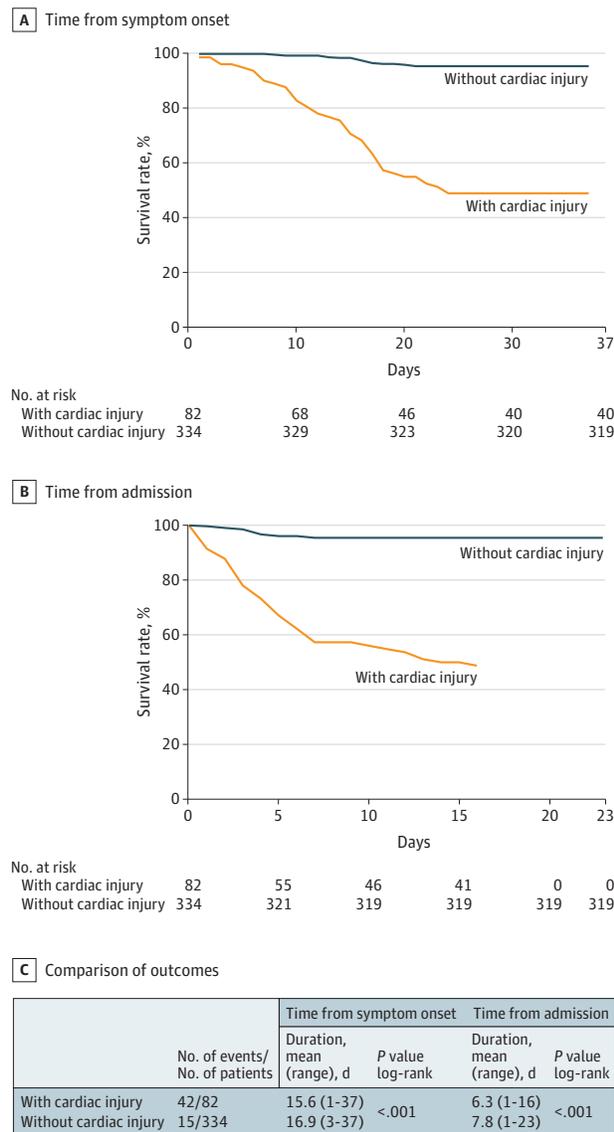
Table 2). A total of 399 patients (95.9%) were treated with oxygen, and the percentages of use of oxygen inhalation, noninvasive ventilation, and invasive mechanical ventilation were 76.0% (316 patients), 12.3% (51 patients), and 7.7% (32 patients), respectively. The proportion of antiviral therapy use was the highest (403 [96.9%]), followed by glucocorticoids (304 [73.1%]), intravenous immunoglobulin therapy (259 [62.3%]), and antibiotic therapy (235 [56.5%]). Only 2 patients (0.5%) among all participants were given continuous kidney therapy. Overall, 97 patients (23.3%) had ARDS, and 8 patients (1.9%) had acute kidney injury during hospitalization; other common complications included electrolyte disturbance (30 patients [7.2%]), hypoproteinemia (27 [6.5%]), anemia (13 [3.1%]), and coagulation disorders (12 [2.9%]). During follow-up, a total of 57 patients (13.7%) died, 40 patients (9.6%) were discharged, and the rest (319 [76.7%]) remained hospitalized. Compared with those without cardiac injury, patients with cardiac injury required more noninvasive ventilation (38 [46.3%] vs 13 [3.9%]; $P < .001$) and invasive mechanical ventilation (18 [22.0%] vs 14 [4.2%]; $P < .001$) (Table 2). The use of antibiotic treatment (68 [82.9%] vs 167 [50.0%]), glucocorticoids (72 [87.8%] vs 232 [69.5%]), and intravenous immunoglobulin treatment (68 [82.9%] vs 191 [57.2%]) was also significantly higher in patients with cardiac injury than in those without cardiac injury (all $P < .001$; Table 2). In addition to anemia, other complications were more common among patients with cardiac injury than those without cardiac injury; these included ARDS (48 [58.5%] vs 49 [14.7%]; $P < .001$), acute kidney injury (7 [8.5%] vs 1 [0.3%]; $P < .001$), electrolyte disturbances

(13 [15.9%] vs 17 [5.1%]; $P = .003$), hypoproteinemia (11 [13.4%] vs 16 [4.8%]; $P = .01$), and coagulation disorders (6 [7.3%] vs 6 [1.8%]; $P = .02$) (Table 2).

Cardiac Injury and Mortality

Patients with cardiac injury vs those without cardiac injury had shorter durations from symptom onset to follow-up (mean, 15.6 [range, 1-37] days vs 16.9 [range, 3-37] days; $P = .001$) and admission to follow-up (6.3 [range, 1-16] days vs 7.8 [range, 1-23] days; $P = .039$). The mortality rate was higher among patients with vs without cardiac injury (42 [51.2%] vs 15 [4.5%]; $P < .001$) as shown in Table 2 and the Kaplan-Meier survival curves in Figure 2. The mortality rate increased in association with the magnitude of the reference value of hs-TNI (eFigure 3 in the Supplement). After adjusting for age, preexisting cardiovascular diseases (hypertension, coronary heart disease, and chronic heart failure), cerebrovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, renal failure, cancer, ARDS, creatinine levels greater than 133 $\mu\text{mol/L}$, and NT-proBNP levels greater than 900 pg/mL, the multivariable adjusted Cox proportional hazard regression model showed a significantly higher risk of death in patients with cardiac injury than in those without cardiac injury, either during time from symptom onset (hazard ratio [HR], 4.26 [95% CI, 1.92-9.49]) or time from admission to study end point (HR, 3.41 [95% CI, 1.62-7.16]) (Table 3). Under this hazard regression model, ARDS was another independent risk factor for mortality with COVID-19, with a high HR (7.89 [95% CI, 3.73-

Figure 2. Mortality During Hospitalization Between Patients With vs Without Cardiac Injury



A-B, Kaplan-Meier survival curves for mortality during the time from symptom onset (A) and admission (B). In (B), the maximum duration was 16 days. C, Patients with cardiac injury had a higher rate of mortality in log-rank test, both from symptom onset and from admission.

16.66]) in model 1 and an HR of 7.11 (95% CI, 3.31-15.25) in model 2 (Table 3).

Discussion

The present study demonstrates the statistically significant association between cardiac injury and mortality in patients with COVID-19. Cardiac injury, as a common complication (19.7%), was associated with an unexpected high risk of mortality during hospitalization.

As of March 12, 2020, there have been a total of more than 130 000 laboratory-confirmed cases of COVID-19 globally, including more than 80 000 within mainland China. Because of its high infectivity, this virus has managed to supersede severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in death toll. Severe respiratory distress is usually considered the main cause of coronavirus-induced death. According to a recent study of the largest clinical sample in China,⁸ severe pneumonia was independently associated with admission to an intensive care unit, mechanical ventilation, or death. It is notable that a recent report on 138 patients hospitalized with COVID-19 found that 7.2% of patients developed acute cardiac injury, and patients who received care in the intensive care unit were more likely to have cardiac injury (22.2%) than non-ICU patients.² This observation suggests that cardiac injury is possibly associated with the clinical outcomes of COVID-19. Consistently, our study also found 19.7% of patients with cardiac injury and first demonstrated that cardiac injury was independently associated with an increased risk of mortality in patients with COVID-19. Compared with patients without cardiac injury, patients with cardiac injury presented with more severe acute illness, manifested by abnormal laboratory and radiographic findings, such as higher levels of C-reactive protein, NT-proBNP, and creatinine levels; more multiple mottling and ground-glass opacity; and a greater proportion requiring noninvasive or invasive ventilation.

In a study of cardiovascular complications of SARS in 121 patients,⁹ hypertension occurred in 61 patients (50.4%) in the hospital. Of these patients, 71.9% developed persistent tachycardia, including 40% with continued tachycardia during outpatient follow-up. Although tachycardic cardiovascular complications were common in patients with SARS, they were usually self-limiting and not associated with risk of death. In contrast with that from SARS, more than half of the patients with cardiac injury experienced in-hospital death in this study, indicating that COVID-19-induced cardiac injury is associated with major adverse clinical outcomes. However, the mechanism of cardiac injury among these patients with COVID-19 remains uncertain.

Evidence from a case report showed that MERS-CoV causes acute myocarditis, manifested as myocardial edema and acute myocardial injury of the apical and lateral walls of the left ventricle.¹⁰ This regional myocardial injury may result from direct viral myocardial infection. On the basis of recent studies, angiotensin-converting enzyme 2 (ACE2) is a human cell receptor with a strong binding affinity to the Spike protein of SARS-CoV-2, and ACE2 is also highly expressed in heart.^{11,12} Thus, it is rational to hypothesize that COVID-19-induced cardiac injury might be mediated by ACE2. However, a recent pathological study found scarce interstitial mononuclear inflammatory infiltrates in heart tissue without substantial myocardial damage in a patient with COVID-19,¹³ suggesting that COVID-19 might not directly impair the heart. The present study lacks evidence from magnetic resonance imaging or echocardiography to determine the features of myocardial injury. On the basis of the present results of hs-TNI and ECG findings in a subset of patients, we can only estimate the severity

Table 3. Multivariate Cox Regression Analysis on the Risk Factors Associated With Mortality in Patients With COVID-19

Factor	From symptom onset		From admission	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age, y	1.02 (0.99-1.05)	.07	1.02 (0.99-1.04)	.18
Cardiovascular diseases	1.51 (0.70-3.30)	.30	1.40 (0.65-3.03)	.39
Cerebrovascular diseases	1.12 (0.46-2.70)	.80	1.71 (0.71-4.09)	.25
Diabetes	0.79 (0.41-1.52)	.48	0.75 (0.38-1.50)	.42
Chronic obstructive pulmonary disease	0.37 (0.04-3.50)	.38	0.39 (0.04-3.68)	.41
Renal failure	1.10 (0.49-2.44)	.82	0.66 (0.29-1.46)	.30
Cancer	1.75 (0.43-7.16)	.44	0.82 (0.18-3.65)	.79
Acute respiratory distress syndrome	7.89 (3.73-16.66)	<.001	7.11 (3.31-15.25)	<.001
Cardiac injury	4.26 (1.92-9.49)	<.001	3.41 (1.62-7.16)	.001
Creatinine \geq 1.50 mg/dL	0.59 (0.29-1.23)	.16	1.22 (0.60-2.50)	.58
N-terminal pro-B-type natriuretic peptide \geq 900 pg/mL	1.16 (0.54-2.47)	.70	1.52 (0.74-3.10)	.25

SI conversion factor: To convert creatinine to $\mu\text{mol/L}$, multiply by 88.4.

of cardiac injury. Thus, because of the current limited evidence, the question of whether the SARS-CoV-2 virus can directly injure the heart requires further demonstration.

In contrast, a previous study found that reversible, subclinical diastolic left ventricular impairment appears to be common in acute SARS infection, even among those without underlying cardiac disease,¹⁴ suggesting that left ventricular dysfunction in the acute phase might be attributable to the cytokine storm syndrome. This is a serious life-threatening disease with clinical features of systemic inflammation, methemoglobinemia, hemodynamic instability, and multiple organ failure.^{15,16} The hallmark of cytokine storm syndrome is an uncontrolled and dysfunctional immune response involving the continuous activation and proliferation of lymphocytes and macrophages. Huang et al¹ found that patients with COVID-19 who were admitted to the intensive care unit had higher plasma levels of cytokines, including interleukin (IL)-2, IL-7, IL-10, granulocyte-colony stimulating factor, IgG-induced protein 10 (also known as C-X-C motif chemokine 10), monocyte chemoattractant protein-1, macrophage inflammatory protein 1-alpha (also known as chemokine ligand 3), and tumor necrosis factor α . In the present study, we also found that markers of inflammatory response, such as C-reactive protein, procalcitonin, and leukocytes, were significantly increased among patients who suffered from cardiac injury. The activation or enhanced release of these inflammatory cytokines can lead to apoptosis or necrosis of myocardial cells.

In addition, preexisting cardiovascular diseases might also be more susceptible COVID-19-induced heart injury, as approximately 30% and 60% of patients with cardiac injury in the present study had a history of coronary heart disease and hypertension, respectively, which were significantly more prevalent than in those without cardiac injury. Similarly, in a recent report,² 25% and 58.3% of patients who were critically ill with COVID-19 had underlying heart diseases and hypertension, respectively. According to the "Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial Version 4),"¹⁷ elderly patients with underlying diseases are more likely to be infected with SARS-CoV-2 and tend to be severely ill, especially those with hypertension, coronary heart disease, and diabetes. Although there are few pieces of evidence to establish a direct association between cardiac injury and cardiovascu-

lar comorbidities, it is rational to presume that patients with coronary artery disease or heart failure are susceptible to cardiac injury, and once such patients are infected with severe pneumonia, myocardial ischemia or cardiac dysfunction are more likely to occur, ultimately leading to a sudden deterioration. On the other hand, acute inflammatory responses can also lead to ischemia in the presence of preexisting cardiovascular diseases. The inflammatory activity within coronary atherosclerotic plaques is exacerbated during systemic inflammatory response, making them prone to rupture.¹⁸ Inflammation also causes endothelial dysfunction and increases the procoagulant activity of the blood, which can contribute to the formation of an occlusive thrombus over a ruptured coronary plaque.¹⁹ Based on these lines of evidence, we hypothesize that an intense inflammatory response superimposed on preexisting cardiovascular disease may precipitate cardiac injury observed in patients with COVID-19 infections.

Limitations

Some limitations existed in the present study. First, because of the logistical limitations at the onset of these emerging infections in Wuhan, some data, such as echocardiography data, electrocardiography data, and cytokine level measurements, were lacking from clinical examinations of patients in isolation wards or the intensive care unit, which limits the determination of potential mechanisms of cardiac injury. Second, because the clinical observation of patients is still ongoing, many with and without cardiac injury have not reached clinical end points. Third, data from larger populations and multiple centers are warranted to further confirm the outcomes of cardiac injury in COVID-19.

Conclusions

Cardiac injury is a common condition among patients hospitalized with COVID-19, and it is associated with a higher risk of in-hospital mortality. Although the exact mechanism of cardiac injury needs to be further explored, the findings presented here highlight the need to consider this complication in COVID-19 management.

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