



ORIGINAL RESEARCH

Clinical Characteristics and Risk Factors of Cardiac Involvement in COVID-19

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BACKGROUND: Increasing studies demonstrated that the cardiac involvements are related to coronavirus disease 2019 (COVID-19). Thus, we investigated the clinical characteristics of patients with COVID-19 and further determined the risk factors for cardiac involvement in them.

METHODS AND RESULTS: We analyzed data from 102 consecutive laboratory-confirmed and hospitalized patients with COVID-19 (52 women aged 19–87 years). Epidemiologic and demographic characteristics, clinical features, routine laboratory tests (including cardiac injury biomarkers), echocardiography, electrocardiography, chest imaging findings, management methods, and clinical outcomes were collected. Patients were divided into acute cardiac injury, with and without cardiac marker abnormalities groups according to different level of cardiac markers. In this research, cardiac involvement was found in 72 of the 102 (70.6%) patients: tachycardia (n=20), electrocardiography abnormalities (n=23), echocardiography abnormalities (n=59), elevated myocardial enzymes (n=55), and acute cardiac injury (n=9). Eight patients with acute cardiac injury were aged >60 years; seven of them had ≥2 underlying comorbidities (hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease). Novel coronavirus pneumonia was much more severe in the patients with acute cardiac injury than in patients with nondefinite acute cardiac injury ($P<0.001$). Multivariate analyses showed that CRP (C-reactive protein) levels, old age, novel coronavirus pneumonia severity, and underlying comorbidities were the risk factors for cardiac abnormalities in patients with COVID-19.

CONCLUSIONS: Cardiac involvements are common in patients with COVID-19. Elevated CRP levels, old age, underlying comorbidities, and novel coronavirus pneumonia severity are the main risk factors for cardiac involvement in patients with COVID-19. More attention should be given to cardiovascular protection during COVID-19 treatment for mortality reduction.

REGISTRATION: URL: <https://www.chictr.org>; Unique identifier: ChiCTR2000029955.

Key Words: acute cardiac injury ■ cardiac involvement ■ COVID-19 ■ risk factor

The widespread outbreak of the coronavirus disease 2019 (COVID-19, previously known as 2019-nCoV) is a big challenge for public health and medical care. Since its first emergence in late December 2019, COVID-19 has already spread to surpass 150 countries and territories. As of July 10,

2020, there were 12015193 confirmed cases worldwide, with 54247 fatalities,¹ and the World Health Organization had declared the outbreak a pandemic. To date, several of the latest studies have reported the clinical characteristics of hospitalized patients with novel coronavirus pneumonia (NCP), including signs,

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Preprint posted on MedRxiv March 8, 2020. <https://doi.org/10.1101/2020.03.05.20031591>.

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For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- Since coronavirus disease 2019 spreads rapidly around world, this study focuses on the cardiac involvements of coronavirus disease 2019 infection, which has been sustainably found in recent research.
- We further confirm that cardiac involvement is common in patients with coronavirus disease 2019 and associated with different clinical manifestations, and more cardiac involvements besides acute cardiac injury, such as elevated enzymes and echocardiographic and electrocardiographic abnormalities, were found.
- Meanwhile, high CRP (C-reactive protein) level, age, underlying comorbidities, and novel coronavirus pneumonia severity are verified as the main risk factors of cardiac involvement.

What Are the Clinical Implications?

- Through this research, the patients with high CRP level, old age, underlying comorbidities, or novel coronavirus pneumonia severity should be of more concern in clinics, for those kinds of patients may have more severe outcomes.
- On the other hand, cardiac support therapy may be taken in the early stage to avoid the disease's progression.

Nonstandard Abbreviations and Acronyms

ACI	acute cardiac injury
ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
IQR	interquartile range
NCP	novel coronavirus pneumonia
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TNT-HSST	hypersensitive troponin T

symptoms, laboratory test results, imaging features, therapeutic strategies and effects, and multiple organ dysfunction.²⁻⁵ Notably, acute cardiac injury, defined as "TNT-HSST (hypersensitive troponin T) serum levels >99th percentile upper reference limit (>28 pg/mL), or new abnormalities were shown in electrocardiography or echocardiography" by previous literature about the COVID-19 combined with the European Society of Cardiology guidelines' definition of myocardial infarction,^{3,6} was detected in ~7.2% to 27.8% patients with COVID-19 in previous studies.^{2,3} Furthermore, both

severe acute respiratory syndrome and Middle East respiratory syndrome (MERS) have been linked to acute myocarditis, acute myocardial injury, and rapid-onset heart failure.⁷⁻⁹ Reportedly,² nearly 40% of hospitalized patients with confirmed COVID-19 have underlying comorbidities such as cardiovascular or cerebrovascular diseases. Recently, a meta-analysis of 8 studies showed that cardiovascular diseases (5±4; 95% CI, 4%–7%) commonly happened in 46 248 patients.¹⁰ Clerkin et al¹¹ concluded that COVID-19 interacts with underlying cardiovascular system dysfunction on a different level, increasing morbidity in patients with underlying cardiovascular conditions, and may provoke myocardial injury and dysfunction. More and more evidence links COVID-19 with increased morbidity and mortality from cardiovascular complications. Thus, undoubtedly, special medical attention should be paid to patients with COVID-19 with cardiac complications and underlying cardiovascular diseases. On February 13, 2020, the American College of Cardiology released a clinical bulletin titled "Cardiac Implications of Novel Wuhan Coronavirus (COVID-19)"¹² for addressing cardiac implications of this disease and offering early clinical guidance given the current uncertainty over COVID-19. However, detailed clinical characteristics such as laboratory results, cardiac markers, echocardiography, and electrocardiography of patients with COVID-19 with cardiac involvement have not been investigated in detail. Thus, the aim of this study is to describe the different clinical, laboratory, echocardiographic and electrocardiographic characteristics of patients with COVID-19-related cardiac involvement and to further determine the clinical risk factors for cardiac involvement in COVID-19.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The institutional ethics board of our institutes approved this study (No. 2020.43), and all the subjects gave informed consent. We retrospectively enrolled 102 patients with laboratory-confirmed COVID-19 who were consecutively hospitalized between January 2, 2020, and March 17, 2020, in the Public Health Clinical Center of Chengdu, China, and all of the enrolled patients had laboratory tests, chest computed tomography or digital radiography, echocardiography, and electrocardiography on admission because of previous research findings of lung involvement and cardiac injury in COVID-19 infection. The patients were diagnosed and classified according to

the World Health Organization interim guidance.⁷ NCP types were classified as mild, common, severe, and critically severe according to the COVID-19 patient management guideline issued on February 8, 2020.¹³

Procedures

Data on epidemiologic and demographic characteristics, clinical signs and symptoms, underlying comorbidities, complications, and treatment managements (such as antiviral or antibiotic therapy, respiratory support, continuous renal replacement therapy, and extracorporeal membrane oxygenation) were collected from the patients' medical records. Laboratory test results including those of blood routine tests, CRP (C-reactive protein) and D-dimer tests, and blood gas analysis were recorded and compared. The levels of cardiac injury markers including lactate dehydrogenase, hydroxybutyrate dehydrogenase, creatine kinase, myoglobin, amino NT-proBNP (N-terminal pro-B-type natriuretic peptide), and TNT-HSST were determined at admission (normal range: lactate dehydrogenase, 109–245 U/L; HDBH, 72–182 U/L; creatine kinase, 25–196 U/L; myoglobin, 28–72 ng/mL, NT-proBNP, 0–85.8 pg/mL; TNT-HSST, 0–14 pg/mL). The acute cardiac injury (ACI) group were defined as having TNT-HSST serum levels >99th percentile of the upper reference limit (>28 pg/mL), or new abnormalities were shown in electrocardiography or echocardiography.^{3,6} The group with cardiac marker abnormalities but nondefinite ACI was defined as patients with TNT-HSST serum levels <28 pg/mL but increase in the levels of any of the other above-mentioned cardiac markers. The group without cardiac marker abnormalities comprised patients without elevation in the levels of any of the cardiac markers. Chest computed tomography was performed on the day of admission. The period of illness onset to admission was defined from the day when signs or symptoms were first noticed to the day of admission. All enrolled patients underwent 2-dimensional echocardiography and electrocardiography during hospitalization. Acute respiratory distress syndrome (ARDS) was identified according to the Berlin definition¹⁴ and acute kidney injury according to the Kidney Disease Improving Global Outcomes definition.¹⁵ The use of cardioprotective or antihypertensive medicines, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or positive inotropic drugs, was collected from the medical record.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (IBM, Armonk, NY) Prism version 7.00 (GraphPad Software, San Diego, CA). Data were presented as median (interquartile range [IQR]) if non-normally distributed and as mean (SD) if normally distributed. Categorical variables were presented as n (%). Kruskal-Wallis

analysis, chi-square test, and 1-way ANOVA with post hoc Bonferroni correction were used for multiple group comparisons according to data characteristics. Univariate analysis was calculated using single-factor regression analysis to detect the potential risk factor for cardiac involvement. The related factors enrolled in the univariate correlation analysis covered sex, age, days from illness onset to admission, NCP type, comorbidities, complications, CRP and D-dimer, which we think may have influence on the cardiac involvements. Further, the significant factors ($P < 0.1$) in the univariate analysis were brought into multiple logistic regression model to explore the risk factors of cardiac involvement in COVID-19. Hosmer-Lemeshow analysis were used to test the goodness of fit of logistic regression models. In all other analyses, 2-tailed P values of < 0.05 were considered significant.

RESULTS

Baseline Data

The baseline data of the 102 patients with COVID-19 are listed in Table 1. Of them, 9 (8.8%) patients had ACI (8 aged >60 years; median age, 78.0 years [IQR, 63.5–82.5]); 46 (45.1%) patients were defined as the cardiac marker abnormalities group (14 [30.4%] aged >60 years; median age, 54.0 years old [IQR, 40.0–65.0]). Cardiac markers of 47 (46.1%) patients were within the normal range (7 [14.9%] aged >60 years; median age, 41.00 years [IQR, 31.0–51.0]). There were no significant sex differences among the 3 subgroups. Epidemiology of all the groups was similar (all $P > 0.05$), such as being a local resident, Wuhan residence exposure, and COVID-19 exposure. No patients had direct Huanan seafood market exposure. No exact epidemiologic link was found between the first case and the later ones. Almost all the patients' first onset symptoms were fever ($n = 75$, 73.5%) and dry cough ($n = 72$, 70.6%). Furthermore, the mean systolic blood pressure of the patients with ACI was higher than those of the other 2 groups ($P < 0.001$). Twenty (19.6%) of the patients had tachycardia.

High occurrence of hypertension was detected in the patients with ACI (total patients with hypertension: $n = 18$, 17.7%; ACI group: $n = 6$, 66.7%; cardiac marker abnormalities group: $n = 9$, 19.6%; without cardiac marker abnormalities group: $n = 3$, 6.4%; $P < 0.001$). Cardiovascular diseases were more frequently found in the patients with ACI, all of whom had coronary artery disease, with 1 having prior coronary artery bypass grafting (total patients with cardiovascular disease: $n = 9$, 8.8%; ACI group: $n = 5$, 55.6%), compared with the groups with and without cardiac marker abnormalities ($P < 0.001$). Additionally, diabetes mellitus ($n = 18$, 17.7%) and chronic obstructive pulmonary disease ($n = 5$, 4.9%) were found in all the patients, with a higher tendency

Table 1. Baseline Characteristics

	ACI Group (n=9)	Cardiac Marker Abnormalities Group (n=46)	Without Cardiac Marker Abnormalities Group (n=47)	P Value
Age, y	78.0 (63.5–82.5)	54.0 (40.0–65.0)*	41.0 (31.0–51.0)*	<0.001
Sex (male, n [%])	4 (44.4)	23 (50.0)	23 (48.9)	0.954
Smoking, n (%)	1 (11.1)	5 (10.9)	4 (8.5)	0.921
Local residents of Wuhan, n (%)	1 (11.1)	12 (26.1)	9 (19.1)	0.522
Recently been to Wuhan, n (%)	2 (22.2)	10 (21.7)	18 (38.3)	0.191
Wuhan residence exposure, n (%)	1 (11.1)	3 (6.5)	8 (17.0)	0.290
NCP patient exposure, n (%)	2 (22.2)	19 (41.3)	25 (53.1)	0.182
Huanan seafood market exposure, n (%)	0	0	0	NA
Days from illness onset to admission, d	2.0 (1.0–7.0)	7.0 (5.0–11.0)*	4.5 (3.0–9.5)†	0.007
Days of admission, d	21.0 (15.3–30.5)	13.0 (10.0–24.8)	12.0 (9.5–18.0)	0.152
Temperature, °C	37.4 (36.8–37.8)	36.9 (36.5–37.5)	36.7 (36.5–37.2)	0.126
HR, beats/min	105.0 (75.0–120.5)	87.5 (80.0–95.3)	86.0 (77.0–93.0)	0.333
Respiratory rate, n/min	21.0 (19.5–23.0)	20.0 (20.0–21.0)	20.0 (20.0–20.0)*	0.333
Systolic BP, mm Hg	150.0 (126.5–161.5)	129.0 (115.8–140.3)*	118.0 (112.0–128.0)*	0.002
Diastolic BP, mm Hg	78.0 (63.0–85.0)	78.0 (73.0–87.0)	77.5 (71.5–84.3)†	0.637
Signs and symptoms				
Fever, n (%)	9 (100)	35 (76.1)	31 (66.0)	0.092
Dry cough, n (%)	5 (55.6)	38 (82.6)	29 (61.7)	0.051
Fatigue, n (%)	2 (22.2)	2 (4.3)	2 (4.3)	0.093
Dyspnea, n (%)	1 (11.1)	7 (15.2)	3 (6.4)	0.389
Myalgia, n (%)	2 (22.2)	7 (15.2)	6 (12.8)	0.757
Expectoration, n (%)	4 (44.4)	16 (34.8)	14 (29.8)	0.667
Diarrhea, n (%)	2 (22.2)	2 (4.3)	7 (14.9)	0.133
Comorbidities				
Hypertension, n (%)	6 (66.7)	9 (19.6)*	3 (6.4)*	<0.001
Diabetes mellitus, n (%)	3 (33.3)	10 (21.7)	5 (10.6)	0.162
Cardiovascular diseases, n (%)	5 (55.6)	3 (6.5)*	1 (2.1)*	<0.001
COPD, n (%)	3 (33.3)	1 (2.2)*	1 (2.1)*	0.025
CKD, n (%)	5 (55.6)	1 (2.2)*	0*	<0.001
With >2 comorbidities, n (%)	7 (77.8)	5 (10.9)*	2 (4.3)*	<0.001
Image characteristics of NCP				
Bilateral involvement on CT or DR, n (%)	9 (100)	36 (78.3)	33 (70.2)	0.144

Data are presented as median (IQR) or n (%). ACI indicates acute cardiac injury; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DR, digital radiography; HR, heart rate; IQR, interquartile range; and NCP, novel coronavirus pneumonia.

*Mean $P < 0.05$ compared with the ACI group.

† $P < 0.05$ compared with the group with cardiac marker abnormalities.

in the ACI group (diabetes mellitus: $n=3$; and chronic obstructive pulmonary disease: $n=3$) than in the other 2 groups (Figure 1). ACI was accompanied by chronic kidney disease in 55.6% ($n=5$) of patients. Notably, 77.8% ($n=7$) of patients with ACI and 10.9% ($n=5$) of patients with cardiac marker abnormalities had >2 comorbidities, which was higher than in patients without cardiac marker abnormality ($n=2$, 4.3%).

Regarding computed tomography or digital radiography findings on admission, all the patients with ACI and 36 (78.3%) patients with nondefinite ACI with cardiac marker abnormalities had bilateral multilobular and subsegmental lung involvement; in the group

without cardiac marker abnormalities, bilateral lobes were affected in 33 (70.2%) patients (Figure 2).

Main Management Strategies, Comorbid Conditions, and Clinical Outcome Data

Table 2 shows the main management strategies, comorbid conditions, and clinical outcomes of all the patients with COVID-19. In the ACI group, in addition to antiviral and antibiotic therapies, amiodarone and cedi-lanid were used in 4 patients. However, only 1 patients with nondefinite ACI with cardiac marker abnormalities used cardioprotective or antihypertensive medications.

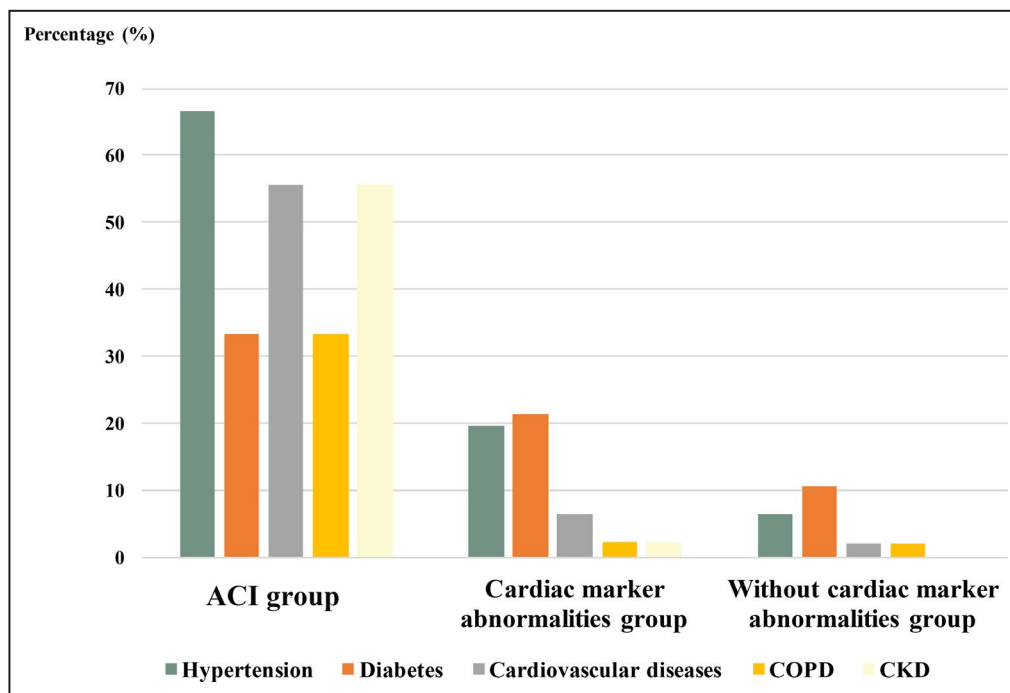


Figure 1. Comorbidities in patients with COVID-19.

In patients with ACI, hypertension and cardiovascular diseases were the frequently occurring comorbidities. ACI indicates acute cardiac injury; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases; and COVID-19, coronavirus disease 2019.

Ninety-one (89.2%) patients were administered nasal cannula oxygen therapy during admission for respiratory support; noninvasive ventilation or high-flow nasal cannula oxygen therapy was performed for 7 (77.8%) patients with ACI and 11 (23.9%) patients with nondefinite ACI with cardiac marker abnormalities. Notably, in the ACI group, invasive mechanical ventilation was used in 5 (55.6%) patients and extracorporeal membrane oxygenation in 1 patient because of extremely severe ARDS.

ARDS occurred in the 8 (88.9%) patients with ACI and 7 (15.2%) patients with nondefinite ACI with cardiac marker abnormalities. Hypoxemia was a common complication that affected 24 (23.5%) of the 102 study patients, with a significant difference in the number of affected patients between the ACI (n=9, 100%) and nondefinite ACI with cardiac marker abnormalities (n=9, 19.6%) groups and the group without cardiac marker abnormalities (n=6, 12.8%; $P<0.001$). Moreover, a total of 6 (66.7%) patients with ACI had acute kidney injury,



Figure 2. CT features of NCP in patient with COVID-19.

A, Patient with ACI with critically severe NCP showed bilateral infiltration mainly representing as consolidation and ground glass opacity in both lungs. **B**, Ground-glass opacity and reticulation were observed in both lung of a case with cardiac marker abnormality with server type NCP. **C**, Patchy ground-glass opacity shown in the patients with common-type NCP without cardiac marker abnormality. ACI indicates acute cardiac injury; COVID-19, coronavirus disease 2019; CT, computed tomography; and NCP, novel coronavirus pneumonia.

Table 2. Main Management Strategies, Comorbid Conditions, and Clinical Outcomes

	ACI Group (n=9)	Cardiac Marker Abnormalities Group (n=46)	Without Cardiac Marker Abnormalities Group (n=47)	P Value
Medication treatment				
Antiviral medication, n (%)	9 (100)	46 (100)	47 (100)	NA
Antibiotics, n (%)	7 (77.8)	13 (28.3)*	3 (6.4)*†	<0.001
Traditional Chinese medicine, n (%)	2 (22.2)	26 (56.5)	31 (66.0)	0.050
Cardioprotective or antihypertensive drug, n (%)	5 (55.6)	1 (2.2)*	0*	<0.001
Oxygen therapy				
Nasal cannula, n (%)	7 (77.9)	40 (87.0)	44 (93.6)	0.299
Noninvasive ventilation or high-flow nasal cannula, n (%)	7 (77.8)	11 (23.9)*	0*	<0.001
Invasive mechanical ventilation, n (%)	5 (55.6)	0*	0*	<0.001
ECMO, n (%)	2 (22.2)	0*	0*	0.007
Supportive treatment				
Use of continuous renal replacement therapy, n (%)	5 (55.6)	1 (2.2)*	0*	<0.001
Use of intravenous immunoglobulin, n (%)	6 (66.7)	10 (21.7)*	1 (2.1)*	<0.001
Complications				
ARDS, n (%)	8 (88.9)	7 (15.2)*	0*	<0.001
AKI, n (%)	6 (66.7)	0*	0*	<0.001
Electrolyte disorder, n (%)	8 (88.9)	9 (19.6)*	4 (8.5)*	<0.001
Acute liver injury, n (%)	3 (33.3)	9 (19.6)*	6 (12.8)*	0.300
Hypoxemia, n (%)	9 (100)	9 (19.6)*	6 (12.8)*	<0.001
Outcome				
Discharge, n (%)	4 (44.4)	32 (69.6)	37 (78.7)*	0.104
Death, n (%)	4 (44.4)	0*	0*	<0.001
Still admitted, n (%)	1 (11.1)	14 (30.4)*	10 (21.3)*	0.366
ICU care, n (%)	9 (100)	8 (17.4)*	0*	<0.001

Data are presented as median (IQR) or n (%). ACI indicates acute cardiac injury; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; and IQR, interquartile range.

*Mean $P < 0.05$ compared with the ACI group.

† $P < 0.05$ compared with the group with cardiac marker abnormalities.

and 5 of them received continuous renal replacement therapy.

Importantly, all 9 patients with ACI had critically severe NCP and needed care in the intensive care unit. However, half of the patients with cardiac marker abnormalities (n=26, 56.5%) had the common NCP type, with 8 (17.4%) of them having critically severe NCP needing care in the intensive care unit. Meanwhile, the majority of patients (n=44, 93.6%) in the group without cardiac marker abnormalities had the common NCP type (Figure 3). Regarding the clinical outcomes, in the ACI group, 4 patients died, 1 was still in admission, and 4 were discharged from the hospital. Conversely, a majority of patients with nondefinite ACI with (n=32, 69.6%) and without (n=37, 78.7%) cardiac marker abnormalities were discharged, with no cases of death.

Laboratory Results on Admission

The laboratory test and blood gas analysis results are shown in Table 3. CRP levels of all the patients with ACI

were increased above the normal range (0–5 mg/L) on admission and were higher than those of the other 2 groups (median, 60.3 mg/mL [IQR, 25.4–115.6]); however, CRP levels were also increased in some patients in the groups with (n=12, 26.1%; CRP: median, 14.2 mg/mL [IQR, 4.5–38.0]) and without (n=25, 53.2%; CRP: median, 3.1 mg/mL [IQR, 1.3–9.8]) cardiac marker abnormalities. D-dimer levels on admission were increased in the patients with ACI (median, 1.8 µg/mL [IQR, 1.2–4.9]) and patients with abnormal cardiac markers (median, 0.8 µg/mL [IQR, 0.7–1.1]) and were higher than those in patients with normal cardiac markers (median, 0.61 µg/mL [IQR, 0.5–0.7]; $P < 0.001$). Initial white blood cell counts of all the patients were within the normal range ($3.5\text{--}9.5 \times 10^9/\text{L}$). Initial lymphocyte counts of 7 (77.8%) patients with ACI were decreased below the normal range ($0.8\text{--}4.0 \times 10^9/\text{L}$); these counts were decreased in only 19 (41.3%) and 7 (14.9%) patients with and without cardiac marker abnormalities, respectively. Furthermore, red blood cell count, hemoglobin level, and platelet count of the ACI group were lower than those of the other 2 groups

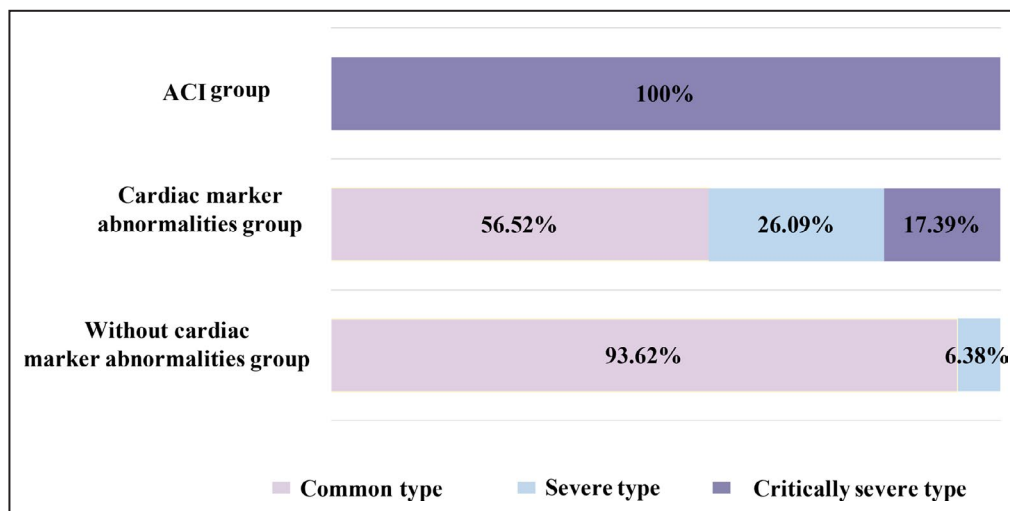


Figure 3. Heterogeneity of NCP types in patients with COVID-19. ACI indicates acute cardiac injury; COVID-19, coronavirus disease 2019; and NCP, novel coronavirus pneumonia.

($P < 0.05$); 2 (22.2%) patients with ACI had procalcitonin levels above the normal range (0–0.5 ng/mL).

Cardiac Markers, Echocardiographic, and Electrocardiographic Abnormalities

Over half ($n = 55$, 53.9%) of the patients with COVID-19 exhibited elevated cardiac marker levels (Table 3). Also, there were some differences in echocardiographic and electrocardiographic findings (Table 4). Of all the patients with COVID-19, 57.8% ($n = 59$) of patients exhibited echocardiographic abnormalities. Echocardiographic abnormalities more frequently occurred in the ACI group and included left chamber enlargement ($n = 3$), left ventricular diastolic dysfunction ($n = 8$), mitral valve regurgitation ($n = 5$), tricuspid regurgitation ($n = 3$), and aortic valve regurgitation ($n = 3$). It is noteworthy that nondefinite patients with ACI with cardiac marker abnormalities also had a high frequency of echocardiographic abnormalities ($n = 34$, 73.9%), with 17 (37.0%) of them having > 2 of the above-mentioned echocardiographic abnormalities. The most frequent echocardiographic abnormality in the cardiac marker abnormalities group was left ventricular diastolic dysfunction ($n = 24$, 52.2%).

As shown in Table 4, 23 (22.5%) patients with COVID-19 had electrocardiographic abnormalities, including 7 (77.8%) patients with ACI and 14 (20.4%) patients with nondefinite ACI with cardiac marker abnormalities. Five of the patients with ACI had > 2 kinds of electrocardiographic abnormalities including atrioventricular block ($n = 2$), ST-T/Q curve abnormalities ($n = 2$), and other arrhythmia (including sinus tachycardia, premature atrial contractions, sinus bradycardia; $n = 5$); furthermore, ST-T/Q curve abnormalities ($n = 6$, 13.0%) and other arrhythmias (including sinus tachycardia, premature atrial

contractions, sinus bradycardia; $n = 4$, 8.7%) were the main abnormalities in patients with cardiac marker abnormalities. Only 2 patients without cardiac marker abnormalities exhibited electrocardiographic abnormalities.

Risk Factors for Cardiac Involvement

To determine the risk factors for cardiac involvement in patients with COVID-19, a univariate analysis of cardiac involvement with clinical data and laboratory findings was performed, showing that age, CRP levels, complication (eg, ARDS or hypoxemia), NCP severity, and presence of commodities may be significant factors of cardiac involvement occurrence (all $P < 0.1$). Further multivariate analysis (Table 5) demonstrated that increased CRP levels (odds ratio, 1.1; 95% CI, 1.0–1.2; $P = 0.001$) as well as increasing age (odds ratio, 1.1; 95% CI, 1.0–1.1; $P = 0.040$) may be risk factors for cardiac involvement in patients with COVID-19. Patients with COVID-19 with more severe NCP type (odds ratio, 4.9; 95% CI, 1.8–13.7; $P = 0.002$) may have a higher risk of cardiac involvement than other patients. It is worth mentioning that the presence of comorbidities (odds ratio, 2.4; 95% CI, 1.0–5.4; $P = 0.042$) may be the most critical risk factor for cardiac involvement in patients with COVID-19.

DISCUSSION

Clinical variables and patterns of cardiac complication for COVID-19 were detected, and the risk model for the cardiac complication was developed in this research. Our study shows that cardiac involvement including tachycardia (19.6%), elevated myocardial enzyme levels (53.9%), and cardiac dysfunction (41.2%) are common in patients with COVID-19. Moreover, ACI was detected in 9 (9%) of

Table 3. Comparison of Cardiac Markers, Laboratory Findings, and Blood Gas Analysis of Patients With COVID-19

	Normal Range	ACI group (n=9)	Cardiac Marker Abnormalities Group (n=46)	Without Cardiac Marker Abnormalities Group (n=47)	P Value
Laboratory findings					
CRP, mg/mL	0–5	60.3 (25.4–115.6)	14.2 (4.5–38.0)*	3.1 (1.3–9.8)*	<0.001
D-dimer, µg/mL	0–1	1.8 (1.2–4.9)	0.8 (0.7–1.1)*	0.6 (0.5–0.7)*	<0.001
Procalcitonin, ng/mL	0–0.5	0.08 (0.04–0.6)	0.03 (0.02–0.06)*	0.2 (0.19–0.29)*	<0.001
Blood routine test					
White blood count, ×10 ⁹ /L	3.5–9.5	5.7 (2.7–7.7)	5.5 (4.0–7.9)	5.4 (4.2–6.8)	0.847
Neutrophil, ×10 ⁹ /L	2.0–7.0	5.3 (2.0–5.6)	3.6 (2.6–5.4)	3.5 (2.4–4.6)	0.365
Lymphocyte count, ×10 ⁹ /L	0.8–4.0	0.5 (0.4–1.1)	1.0 (0.6–1.3)*	1.4 (0.9–1.8)*	<0.001
Red cell count, ×10 ⁹ /L	3.5–5.5	3.4 (2.6–3.6)	4.5 (4.0–4.9)*	4.6 (4.1–5.0)*	<0.001
Hemoglobin, g/L	110–160	90.0 (66.0–113.5)	131.0 (122.5–143.5)*	134.0 (123.0–148.0)*	<0.001
Platelet count, ×10 ⁹ /L	100–300	115.0 (96.5–139.5)	164.0 (119.5–222.0)*	183.0 (147.0–232.0)*	0.011
Blood gas analysis					
pH	7.35–7.45	7.40 (7.34,7.42)	7.41 (7.38,7.43)	7.38 (7.35,7.39) [†]	<0.001
Lactate, mmol/L	0.5–1.6	1.8 (1.6–2.0)	2.0 (1.7–2.4)	2.3 (1.7–2.7) [†]	0.136
PaCO ₂ , mm Hg	35–45	34.7 (30.3–40.8)	39.7 (36.7–42.1)	41.6 (38.9–44.9)*	0.001
PaO ₂ , mm Hg	90–110	77.4 (65.4–101.5)	89.9 (77.3–100.7)	87.5 (77.5–103.2)	0.333
Cardiac markers					
LDH, U/L	109–245	289.0 (227.5–429.5)	248.0 (219.3–288.5)*	191.0 (158.0–213.0)*	<0.001
HBDH, U/L	72–182	235.0 (183.0–334.0)	192.0 (158.0–222.0)*	143.0 (122.5–156.5)*	<0.001
CK, U/L	25–196	139.0 (58.5–259.0)	74.0 (48.5–198.0)	61.0 (46.5–94.0)*	0.014
Myoglobin, ng/mL	28–72	149.0 (107.3–706.7)	31.0 (21.0–47.4)*	21.0 (21.0–20.8)*	<0.001
TNT-HSST, pg/mL	0–14	69.5 (34.9–145.1)	7.4 (5.3–9.4)*	4.4 (3.0–6.7)*	<0.001
NT-proBNP, pg/mL	0–85.8	2798.0 (442.2–10 226.0)	97.8 (38.0–229.7)*	28.3 (14.8–43.5)*	<0.001

ACI indicates acute cardiac injury; CK, creatine kinase; CRP, C-reactive protein; HDBH, hydroxybutyrate dehydrogenase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; and TNT-HSST, troponin T hypersensitivity.

*Mean P<0.05 compared with the ACI group.

[†]P<0.05 compared with the group with cardiac marker abnormalities.

the 102 hospitalized patients with COVID-19. All 9 patients had severe or critically severe NCP and required care in the intensive care unit. Of the 9 patients with ACI, 4 died, 1 remained hospitalized, and 4 were discharged. Notably, CRP levels, old age, NCP severity, and underlying comorbidities were the major risk factors for ACI in patients with COVID-19. Interestingly, there were 46 (45.1%) patients with COVID-19 with elevation in the levels of ≥1 myocardial enzymes and markers of myocardial damage whose features did not meet the strict definition of myocardial injury, with most having the common NCP type and experiencing quick recovery; however, 52.2% of these patients exhibited some form of left ventricular dysfunction on echocardiography, and long-term outcomes should be observed via follow-up in a future study.

Cardiac complications were high in the hospitalized patients with COVID-19, which has been demonstrated in our and previous reports. As shown in a recent report on 138 hospitalized patients with COVID-19,² 16.7% of the patients developed arrhythmia and 7.2% developed acute cardiac injury. In another series of 41 cases of hospitalized patients with COVID-19, it has

been reported that 5 (12%) patients were diagnosed with ACI.^{2–5} Similar to the cardiovascular complications of COVID-19, those of severe acute respiratory syndrome include hypotension, tachycardia, arrhythmias, systolic and diastolic dysfunctions, and sudden death, with tachycardia particularly being the most common condition persistent in nearly 40% of patients during follow-up.¹⁶ Furthermore, MERS-induced myocarditis and myocardial damage has been reported.¹⁷ However, case series reporting elevated levels of myocardial enzymes and myocardial injury markers remain limited for severe acute respiratory syndrome and MERS. Notably, although only 9 patients had clinically confirmed ACI based on strict inclusion criteria in our study, most patients had elevated levels of ≥1 cardiac injury biomarkers and left ventricular diastolic dysfunction. Those patients with nondefined ACI who had increased cardiac injury biomarkers also accompanied with echocardiographic and electrocardiographic abnormalities. Thus, more attention should be paid, and follow-up should be undertaken on this cohort. Although long-term outcomes of patients

Table 4. Echocardiographic and Electrocardiographic Results During Admission

	ACI Group (n=9)	Cardiac Marker Abnormalities Group (n=46)	Without Cardiac Marker Abnormalities Group (n=47)	P Value
Echocardiographic abnormalities	9 (100)	34 (78.3)	16 (34.0)*†	<0.001
Left chamber enlargement	3 (33.3)	4 (8.7)*	1 (2.1)*	0.006
LV diastolic dysfunction	8 (88.9)	24 (52.2)*	10 (21.3)*†	0.005
Mitral valve regurgitation	5 (55.6)	11 (23.9)	6 (12.8)*	0.015
Tricuspid regurgitation	3 (33.3)	5 (10.9)	2 (4.3)*	0.026
Aortic valve regurgitation	3 (33.3)	7 (15.2)	3 (6.4)	0.067
LV wall thickening	2 (22.2)	5 (10.9)	2 (4.3)	0.177
With 2 items	9 (100)	17 (37.0)*	7 (14.9)*†	<0.001
Electrocardiographic abnormalities	7 (77.8)	14 (30.4)*	2 (4.3)*†	<0.001
Atrioventricular block	2 (22.2)	2 (4.4)	1 (2.1)*	0.037
ST-T/Q curve abnormalities	2 (22.2)	6 (13.0)	1 (2.3)	0.059
Arrhythmia	5 (55.6)	4 (8.7)*	0*	<0.001
With 2 items	5 (55.6)	3 (6.5)*	0*	<0.001

Data are presented as n (%). ACI indicates acute cardiac injury; and LV, left ventricular.

*Mean *P*<0.05 compared with the ACI group.

†*P*<0.05 compared with the group with cardiac marker abnormalities.

with COVID-19 with ACI need to be further validated, significantly more clinical attention should be paid to avoid underdiagnosis because of classic symptoms and because of the possible overshadowing of cardiac complications in the context of coronavirus, as cautioned by the American College of Cardiology clinical bulletin.¹²

To date, the underlying mechanisms of ACI and potential impacts in patients with COVID-19 remain unknown. Clinically, the increased serum levels of proinflammatory cytokines, such as interleukin-1β, interleukin-6, interleukin-12, interferon-gamma, interferon-inducible protein,³ and monocyte chemoattractant protein-1, suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with cellular immune deficiency and coagulation activation.³ Thus, the direct effects of the virus, cytokine storm induced by viral invasion, and sustained inflammatory response–induced fulminant myocarditis

are presumed to be the main pathophysiological mechanisms underlying SARS-CoV-2 infection. A previous report of 191 patients with COVID-19 indicated that nonsurvivors showed higher rates of heart failure (52% versus 12%) and ACI (59% versus 1%), but respiratory failure, myocardial damages, and circulatory failure were reasons of death. Consistently, our studies detected high fatality in ACI group. High inflammatory burden and possible increase in myocarditis-related cardiac events are suggested.^{18,19} Myocarditis was also found by cardiac magnetic resonance imaging in a COVID-19 case after the resolution of upper respiratory infection.²⁰ Previous studies have indicated that severe acute respiratory syndrome coronavirus can mediate myocardial injury and damage associated with the downregulation of the myocardial angiotensin-converting enzyme 2 system; this may be responsible for the myocardial dysfunction and adverse cardiac outcomes in patients with severe acute respiratory syndrome,

Table 5. Risk Factors for Cardiac Involvement According to Logistic Regression

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.1 (1.0–1.1)	<i>P</i> <0.001	1.1 (1.0–1.1)	0.04
Sex	1.1 (0.5–2.3)	0.848	NA	NA
Days from illness onset to admission	1.1 (1.0–1.2)	0.125	NA	NA
NCP type	6.1 (2.32–15.9)	<i>P</i> <0.001	4.9 (1.8–13.7)	0.002
Comorbidities	3.2 (1.5–6.6)	0.002	2.4 (1.0–5.4)	0.042
Complication	10.1 (2.2–46.3)	0.003	3.6 (0.6–20.9)	0.148
CRP	1.1 (1.0–1.2)	<i>P</i> <0.001	1.1 (1.0–1.2)	0.001
D-dimer	2.3 (0.9–5.9)	0.093	NA	NA

CRP indicates C-reactive protein; NCP, novel coronavirus pneumonia; and OR, odds ratio.

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which has also been detected in patients with COVID-19.²¹⁻²⁴ Until now, the pathophysiology of severe acute respiratory syndrome coronavirus or MERS coronavirus has not been completely understood. Although full-genome sequencing and phylogenetic analysis has shown that SARS-CoV-2 is similar to severe acute respiratory syndrome coronavirus or MERS coronavirus, the pathophysiological mechanism of cardiac infection or damage caused by SARS-CoV-2 needs to be further validated in future studies.²⁵

In our study, ACI usually occurred in patients with COVID-19 with old age, underlying comorbidities, severe or critically severe NCP, and ARDS. Among 44 672 patients with confirmed COVID-19, as reported in the *China CDC Weekly* on February 11, 2020, ~31.2% patients were aged >60 years. The overall case fatality rate was 2.3% (1023 deaths); more importantly, the majority (81%) of deaths occurred in patients aged ≥60 years or in those with underlying medical conditions.²⁶ Similarly, in our study, 8 of our ACI patients were aged >60 years and had ≥1 underlying conditions, including diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and previous myocardial infarction or heart failure. As described in a recent retrospective study of 1099 laboratory-confirmed cases, ~25.2% of the patients had at least 1 underlying disorder, such as hypertension and cardiovascular disease, and an underlying disorder potentially acts as an important risk factor for poor outcomes.²⁷ We found that the severity of NCP was closely correlated with the ACI occurrence. Meanwhile, ARDS was present in most of the patients with ACI. ARDS, as a severe complication, occurred in ~19% to 29% patients with NCP as per previous reports.²⁻⁵ Patients with ACI all suffered critically severe NCP in both lungs. Since NCP severity was a risk factor for ACI in patients with COVID-19, mechanisms of heart–lung interactions in patients with ARDS should be further investigated, particularly the right ventricular function impairments caused by respiratory dysfunction.⁹ Indeed, the outcomes of these patients need to be further determined in long-term follow-up studies.

Our study has some limitations. First, this is a modest-size case series of hospitalized patients with COVID-19; more standardized data from a larger cohort would be beneficial for further determining the clinical characteristics. Second, our data showed the clinical characteristics of ACI induced by COVID-19, including the clinical presentations, electrophysiological abnormality, myocardial enzyme and myocardial injury marker levels, and cardiac dysfunction and enlargement. Our study would have no doubt been strengthened by the inclusion of cardiovascular magnetic resonance imaging findings (and corroboration of possible myocardial edema, necrosis, and/or microvascular impairment; however, cardiac magnetic resonance was not possible in the acute setting given

infection control limitations). Most of the patients with COVID-19 with ACI had critically severe NCP and a high fatality rate, but long-term follow-up should be performed to determine adverse cardiac events in the patients who could not be diagnosed with ACI but had elevated levels of ≥1 myocardial enzymes and myocardial injury markers. Finally, we did not perform the overfitting analysis and model diagnostics to test and verify the logistic regression, whether this logistic model is suitable elsewhere or not still needs to further investigate.

In summary, we found that cardiovascular involvements are common in patients with COVID-19 and include tachycardia, elevated myocardial enzyme levels, cardiac dysfunction, and even ACI. More importantly, CRP level elevation, old age, NCP severity, and underlying cardiovascular diseases are the major risk factors for cardiac involvement in these patients.

ARTICLE INFORMATION

Received March 28, 2020; accepted August 3, 2020.

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Acknowledgments

We thank all our colleagues who helped us during the current study. We are also grateful to the many frontline medical staff for their dedication in the face of this outbreak, despite the potential threat to their own lives and the lives of their families.

Sources of Funding

This work was supported by 2020 Novel Coronavirus Pneumonia Prevention and Control Technology Project of Chengdu (No. 2020-YF05-00007-SN); Clinical Research Finding of Chinese Society of Cardiovascular Disease (CSC) of 2019 (No. HFCSC2019B01); the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586, 81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and the 1-3-5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYGD18013).

Disclosures

None.

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