Impact of Cardiovascular Disease on Clinical Characteristics and Outcomes of Coronavirus Disease 2019 (COVID-19)

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Background: To investigate the effect of cardiovascular disease (CVD) on the global pandemic, coronavirus disease 2019 (COVID-19), we analyzed the cases of laboratory-confirmed COVID-19 patients in Wuhan.

Methods and Results: Data were extracted from the medical records. SARS-CoV-2 RNA was confirmed by RT-PCR. A total of 33 (53.2%) of 62 cases with CVD, who had higher prevalence of severe COVID-19 compared with non-CVD patients (P=0.027). The median age of all patients was 66.0 (53.3, 73.0) years old. Coronary artery disease (11.3%) and hypertension (38.7%) were the common coexisting CVDs in COVID-19 patients. High-sensitivity cardiac troponin I (hs-cTnI), creatinine, high-density lipoprotein-cholesterol, interleukin-6, C-reactive protein, prothrombin time, and D-dimer levels in the severe COVID-19 with CVD group were higher than in the non-severe COVID-19 with CVD group (P<0.05). For all patients, chest computed tomography (CT) showed ground-glass opacity (66.1%), local (21.0%), bilateral (77.4%), and interstitial abnormalities (4.8%). In COVID-19 patients with CVD, 27 (81.8%) were cured and discharged. 6 (18.2%) remained in hospital, including 2 (3.2%) patients requiring intubation and mechanical ventilation. The hs-cTnI levels in the remaining hospitalized patients were higher than in the discharged patients (P=0.047).

Conclusions: CVDs play a vital role in the disease severity of COVID-19. COVID-19 could result in myocardial injury, which affects the prognosis of COVID-19.

Key Words: Cardiovascular disease; Coronary artery disease; COVID-19; Hypertension; Myocardial injury

Since the first unknown pneumonia case was identified in early December 2019, the disease has spread rapidly throughout the world. After isolation of the virus, it was confirmed as the 2019 novel coronavirus (2019-nCoV) by high-throughput sequencing,[1] and subsequently named officially as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO), caused the coronavirus disease known as COVID-19. COVID-19 has become a global pandemic. With a large infected population, it makes control and prevention extremely serious.[2]

Cardiovascular diseases (CVD), including coronary artery disease (CAD), hypertension, and heart failure (HF) are common in older adults, which may increase the risk of COVID-19 or aggravate the disease progress. A study showed that half of 99 COVID-19 patients had chronic diseases such as CVD, cerebrovascular disease, or diabetes mellitus.[3] Other studies also showed that 29.3–45.7% of patients had COVID-19 combined with CVD, which may have increased the risk of death.[3–6] Myocardial injury may be the primary cause of death or sudden death. An early cohort study showed that 5 of 41 COVID-19 patients in Wuhan were diagnosed with virus-related cardiac injury,[4] and postmortem biopsy reports have recently revealed that the myocardial section was gray and fish meat-like in an 85-year-old male COVID-19 patient.[7] Another postmortem biopsy report showed few interstitial mononuclear inflammatory cells in a 50-year-old male COVID-19 patient,[8] indicating that SARS-CoV-2 might cause myocardial damage. However, the effect of CVD on the progression and outcomes of COVID-19 is still unclear, and the evidence of myocardial injury is not sufficient. In this study, we compared the differences between CVD and non-CVD in severe and non-severe COVID-19 patients to try and

Table 1. Patients' Demographic and Clinical Characteristics

Characteristics, symptoms, coexisting disorders	All patients (n=62)	Non-Severe			Severe			P value[c]
		CVD (n=16)	Non-CVD (n=22)	P value	CVD (n=17)	Non-CVD (n=7)	P value	
Age (years) [M (Q1, Q3)][a]	66.0 (53.3, 73.0)	66.0 (56.3, 73.0)	58.0 (42.8, 66.3)	0.031	73.0 (64.5, 83.0)	69.0 (51.0, 75.0)	0.203	0.061
Sex (n, %)[b]				0.309			0.653	0.157
Female	35 (56.5)	12 (75.0)	12 (54.5)		9 (52.9)	2 (28.6)		
Symptoms (n, %)[b]								
Fever	46 (74.2)	9 (56.2)	21 (95.5)	0.005	12 (70.6)	4 (57.1)	0.647	0.481
Cough	29 (46.8)	7 (43.8)	9 (40.9)	1.000	9 (52.9)	4 (57.1)	1.000	0.732
Headache	3 (4.8)	0 (0.00)	3 (13.6)	0.249	–	–	–	–
Sputum	12 (19.4)	1 (6.2)	4 (18.2)	0.374	5 (29.4)	2 (28.6)	1.000	0.175
Fatigue	16 (25.8)	2 (12.5)	8 (36.4)	0.143	5 (29.4)	1 (14.3)	0.629	0.398
Shortness of breath	11 (17.7)	1 (6.2)	5 (22.7)	0.370	2 (11.8)	3 (42.9)	0.126	1.000
Diarrhea	9 (14.5)	1 (6.2)	4 (18.2)	0.374	3 (17.6)	1 (14.3)	1.000	0.601
Myalgia	7 (11.3)	1 (6.2)	4 (18.2)	0.374	2 (11.8)	0 (0.00)	1.000	1.000
Chill	7 (11.3)	1 (6.2)	3 (13.6)	0.624	2 (11.8)	1 (14.3)	1.000	1.000
Coexisting disorders (n, %)[b]								
Diabetes	13 (21.0)	3 (18.8)	0 (0.0)	0.066	10 (58.8)	0 (0.0)	0.019	0.032
CAD	7 (11.3)	1 (2.6)	–	–	6 (25.0)	–	–	0.085
Hypertension	24 (38.7)	9 (23.7)	–	–	15 (62.5)	–	–	0.057
HF	2 (3.2)	0 (0.0)	–	–	2 (8.3)	–	–	0.485
AF	1 (1.6)	0 (0.0)	–	–	1 (4.2)	–	–	1.000
Medication history (n, %)[b]								
ACEI/ARB	3 (4.8)	0 (0.0)	–	–	3 (12.5)	–	–	0.227

[a]Statistical analysis by nonparametric Mann-Whitney U test; [b]statistical analysis performed with Fisher's exact probability test; [c]non-severe coronavirus disease 2019 (COVID-19) patients with CVD compared with severe group with CVD. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure.

understand the effect of CVD in COVID-19. We collected data from 62 patients with laboratory-confirmed COVID-19 in both non-severe and severe cases in Wuhan, China, hoping to provide new evidence and ideas for the prevention and treatment of COVID-19.

Methods

Research Objectives
The 82 consecutive patients from the Z11 Department of Infectious Disease at the Cancer Center, Union Hospital, Tongji Medical College, Huazhong Science and Technology University were screened (taken over by The First Affiliated Hospital of Anhui Medical University, Medical Aid Team from February 15 to March 14, 2020). Of these, 62 cases were diagnosed with COVID-19 based on the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission of the PRC.[9] The 33 patients with a CVD history were clearly diagnosed with CAD, hypertension, or HF. The study protocol was approved by The Committee on Medical Ethics of The First Affiliated Hospital of Anhui Medical University (reference no. Quick-PJ 2020-03-37).

Laboratory Confirmation
COVID-19 cases were laboratory-confirmed by a positive result to real-time reverse-transcriptase polymerase chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.[4] The assay was performed by the Union Hospital, Tongji Medical College, Huazhong Science and Technology University. Only laboratory-confirmed cases were included in this study. Cases with incomplete data or only suspected diagnosis were excluded.

Clinical Classification
Patients were classified based on disease severity according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission of the PRC.[9] Mild cases had mild symptoms and no abnormalities on imaging. Moderate cases had respiratory infection symptoms such as fever, coughing, and pneumonia manifestation on imaging. Severe cases had respiratory rate ≥30 breaths/min, or resting fingertip oxygen saturation ≤93%, or oxygen partial pressure (PaO_2)/fraction of inspired O_2 (FiO_2) ≤300 mmHg (1 mmHg=0.133 kPa). Critical cases had respiratory failure requiring mechanical ventilation, or symptoms of shock, or multiple organ dysfunction requiring intensive care. In this study, patients were divided into 2 groups: the non-severe group included mild and moderate cases, and the severe group included severe and critical cases.

Data Collection
Patients' data were obtained from electronic medical records. Epidemic data included age, sex, symptoms, coexisting disorders, and medication history. Laboratory findings included blood count, arterial blood gas, blood chemistry, coagulation test, liver and renal function, C-reactive protein (CRP), cardiac markers, and immune indicators. Computed tomography (CT) on admission was used for radiological assessment.

Laboratory and radiology findings [M (Q1, Q3)][a]	All patients (n=62)	Non-Severe			Severe			P value[c]
		CVD (n=16)	Non-CVD (n=22)	P value	CVD (n=17)	Non-CVD (n=7)	P value	
Table 2. Laboratory and Radiology Findings on Hospital Admission								
Routine blood tests								
Leukocyte count (×10⁹)	5.1 (4.3, 6.0)	5.6 (4.3, 6.9)	5.0 (4.1, 5.8)	0.183	5.5 (4.3, 6.9)	4.8 (4.7, 5.1)	0.295	0.943
Neutrocyte count (×10⁹)	3.3 (2.4, 4.3)	3.5 (2.5, 4.6)	3.0 (2.1, 4.0)	0.156	3.5 (3.0, 4.5)	3.2 (3.0, 3.8)	0.634	0.679
Lymphocyte count (×10⁹)	1.3 (0.8, 1.6)	1.5 (1.1, 1.9)	1.4 (0.8, 1.7)	0.274	1.1 (0.7, 1.5)	0.8 (0.6, 1.0)	0.144	0.046
Platelet count (×10⁹)	219.0 (191.8, 291.8)	214.0 (194.8, 271.0)	267.0 (206.0, 299.0)	0.243	200.0 (180.0, 292.0)	242.0 (151.0, 281.0)	0.799	0.665
HCT (%)	34.3 (32.7, 36.9)	34.5 (31.7, 35.7)	34.2 (33.0, 37.1)	0.594	36.4 (34.2, 38.6)	32.9 (31.7, 33.8)	0.007	0.066
Cardiac markers[a]								
hs-cTnI (ng/L)	2.7 (1.6, 6.8)	2.2 (1.6, 4.9)	2.0 (1.1, 3.2)	0.236	8.7 (3.8, 22.4)	6.0 (2.3, 28.1)	0.799	0.002
AST (U/L)	25.0 (20.0, 31.5)	24.0 (20.3, 27.8)	22.0 (18.5, 28.0)	0.505	33.0 (23.0, 46.5)	27.0 (19.0, 30.0)	0.192	0.028
CK (U/L)	65.0 (51.0, 91.5)	66.0 (62.5, 83.3)	62.0 (51.0, 80.0)	0.301	73.0 (43.0, 118.0)	99.0 (48.0, 123.0)	0.680	0.564
CK-MB (U/L)	0.6 (0.4, 0.9)	0.6 (0.4, 0.7)	0.5 (0.3, 0.8)	0.404	0.7 (0.5, 1.1)	0.6 (0.4, 1.3)	0.750	0.099
LDH (U/L)	180.0 (152.5, 221.5)	177.0 (158.3, 211.3)	155.0 (131.8, 201.8)	0.139	208.0 (171.0, 302.5)	190.0 (158.0, 257.0)	0.589	0.101
BNP (pg/L)[a]	38.6 (16.3, 84.3)	19.7 (14.3, 74.1)	19.5 (12.4, 39.0)	0.563	83.7 (34.1, 207.8)	53.0 (41.4, 107.0)	0.651	0.158
Renal & liver function[a]								
Cr (μmol/L)	71.0 (65.0, 86.3)	68.0 (62.8, 78.3)	68.5 (64.5, 74.8)	0.976	94.0 (66.0, 101.0)	78.0 (66.0, 87.0)	0.634	0.025
BUN (mmol/L)	4.7 (3.8, 5.8)	4.5 (4.2, 6.0)	3.9 (3.1, 4.7)	0.016	5.4 (4.4, 6.4)	5.0 (3.0, 7.9)	0.949	0.402
UA (μmol/L)	281.0 (218.0, 331.8)	282.0 (216.0, 326.3)	212.0 (184.0, 315.0)	0.243	283.0 (209.0, 409.0)	310.0 (266.5, 353.0)	0.680	0.732
ALT (U/L)	25.5 (17.0, 39.0)	21.5 (19.3, 29.8)	25.5 (16.3, 39.3)	0.988	31.0 (16.0, 55.0)	26.0 (11.0, 32.0)	0.227	0.377
Blood lipid levels[a]								
TC (mmol/L)	4.1 (3.7, 4.8)	4.1 (3.9, 5.2)	4.3 (3.6, 4.6)	0.183	3.9 (3.5, 4.6)	4.4 (3.5, 6.6)	0.624	0.494
TG (mmol/L)	1.2 (0.9, 1.8)	1.2 (0.8, 2.4)	1.1 (1.0, 1.6)	0.790	1.5 (0.9, 1.7)	1.2 (0.9, 1.7)	0.421	0.552
LDL-C (mmol/L)	2.2 (1.9, 2.5)	2.2 (1.9, 2.6)	2.2 (2.0, 2.3)	0.636	2.2 (1.8, 3.4)	2.5 (1.9, 3.5)	0.401	0.652
HDL-C (mmol/L)	1.2 (1.0, 2.5)	1.4 (1.2, 1.6)	1.3 (1.0, 1.5)	0.044	1.1 (0.9, 1.3)	1.1 (0.7, 1.7)	0.726	0.042
Lymphocyte subsets[a]								
CD4 (%)	43.5 (36.8, 50.4)	42.2 (36.0, 50.8)	41.4 (37.5, 50.3)	0.872	47.1 (42.4, 53.2)	36.7 (30.6, 52.6)	0.276	0.447
CD8 (%)	23.8 (18.5, 29.7)	23.5 (19.2, 28.6)	27.6 (23.8, 31.8)	0.134	22.8 (17.6, 25.4)	17.3 (14.1, 25.4)	0.392	0.345
Inflammatory markers[a]								
IL-6 (pg/mL)	7.4 (4.9, 18.6)	6.7 (4.2, 9.3)	5.0 (4.3, 8.2)	0.555	17.5 (8.4, 27.9)	14.1 (4.3, 26.7)	0.533	0.003
CRP (mg/L)	3.3 (0.9, 22.5)	3.3 (1.5, 4.2)	1.3 (0.8, 27.2)	0.664	15.4 (2.4, 38.9)	8.3 (0.8, 27.6)	0.823	0.028
PCT (ng/L)	0.07 (0.05, 0.17)	0.06 (0.04, 0.09)	0.07 (0.05, 0.18)	0.445	0.08 (0.06, 0.22)	0.10 (0.04, 33.5)	0.853	0.137
Coagulation test[a]								
APTT (s)	37.6 (35.4, 40.7)	36.3 (34.8, 39.7)	37.3 (34.7, 40.3)	0.712	39.2 (36.4, 42.1)	37.7 (33.9, 41.4)	0.751	0.063
PT (s)	13.6 (12.9, 40.7)	12.9 (12.6, 13.7)	13.7 (13.3, 14.2)	0.012	13.9 (13.1, 14.8)	14.1 (13.1, 14.9)	0.589	0.032
D-dimer (mg/L)	0.5 (0.3, 1.4)	0.4 (0.3, 1.1)	0.3 (0.2, 0.6)	0.252	1.1 (0.5, 2.0)	2.9 (0.3, 10.1)	0.306	0.010

Laboratory and radiology findings [M (Q1, Q3)][a]	All patients (n=62)	Non-Severe			Severe			P value[c]
		CVD (n=16)	Non-CVD (n=22)	P value	CVD (n=17)	Non-CVD (n=7)	P value	
Arterial blood[a]								
pH	7.4 (7.4, 7.4)	7.4 (7.4, 7.4)	7.4 (7.4, 7.4)	0.116	7.4 (7.4, 7.4)	7.4 (7.4, 7.4)	0.389	0.099
Lactic acid (mmol/L)	2.0 (1.6, 2.2)	1.9 (1.5, 2.2)	1.7 (1.1, 1.9)	0.284	2.1 (1.9, 2.2)	2.4 (1.5, 4.5)	0.319	0.185
Abnormalities on chest CT[b]								
Ground-glass opacity	41 (66.1)	13 (81.2)	14 (63.6)	0.296	9 (56.2)	5 (71.4)	0.657	0.252
Local pneumonia	13 (21.0)	3 (18.8)	3 (13.6)	0.682	5 (31.2)	2 (28.6)	1.000	0.685
Bilateral pneumonia	48 (77.4)	13 (81.2)	19 (86.4)	0.682	11 (68.8)	5 (71.4)	1.000	0.685
Interstitial abnormalities	3 (4.8)	0 (0.0)	1 (4.5)	1.000	0 (0.0)	2 (28.6)	0.083	–

[a]Statistical analysis by nonparametric Mann-Whitney U test; [b]statistical analysis performed with Fisher's exact probability test; [c]non-severe coronavirus disease 2019 (COVID-19) patients with CVD compared with severe group with CVD. APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, CK-myocardial bound; Cr, creatinine; CRP, C-reactive protein; CVD, cardiovascular disease; HCT, hematocrit; HDL-C, high-density lipoprotein-cholesterol; hs-cTnI, high-sensitivity cardiac troponin I; IL, interleukin; LDH, lactase dehydrogenase; LDL-C, low-density lipoprotein-cholesterol; PCT, procalcitonin; PT, prothrombin time; TC, total cholesterol; TG, triglycerides; UA, uric acid.

Statistical Analysis

Data analyses were performed using SPSS 22.0 software. First, the data were stratified by the severity of COVID-2019, differences in the basic information, including demographic characteristics, clinical symptoms, and coexisting disorders among patients with and without CVD. In order to explore whether the CVD history affected the phenotype of COVID-19, differences in the variables described above were further compared between non-severe COVID-19 patients with CVD and the severe group with CVD. Second, differences in laboratory and radiology findings were examined. Finally, among COVID-19 patients with CVD, differences in several laboratory findings in patients with different clinical outcomes (discharge or stay in hospital) were retrospectively analyzed to explore whether different prognoses of COVID-19 exist functionally. Among all data analyses, the Mann-Whitney U test was used for continuous variables, and Fisher's exact test was applied for binary variables. A P-value of tests (2-sided) <0.05 indicated significance.

Results

Patients' Demographic and Clinical Characteristics

All 82 patients with suspected or confirmed COVID-19 were residents of Wuhan and recruited as of March 14, 2020; 20 patients with suspected diagnosis or incomplete medical records were excluded, leaving 62 patients, of whom a total of 33 (53.2%) had CVD, comprising 16 (25.8%) cases in the non-severe group and 17 (27.4%) cases in the severe group, and a total of 29 (46.8%) cases were recorded without CVD, comprising 22 (35.5%) cases in the severe group and 7(11.3%) cases in the non-severe group. Patients with CVD had a higher prevalence of severe COVID-19 compared with patients without CVD (51.5% vs. 24.1%, P=0.027).

The demographic and clinical characteristics are shown in **Table 1**. For all patients, the median age was 66.0 (53.3, 73.0) years old. In the non-severe COVID-19 subgroups,

the age of CVD patients significantly higher than that of the non-CVD group [66.0 (56.3, 73.0) vs. 58.0 (42.8, 66.3) years, P=0.031], but there was no difference in the severe subgroups, or between non-severe and severe groups with CVD. Of the patients, 56.5% were female, and 33.9% of females had CVD. The most common onset symptoms were fever (74.2%) and cough (46.8%). In the non-severe subgroups, 95.5% of non-CVD patients had accompanying fever, and the incidence of fever was significantly higher than in the CVD patients (56.2%).

CAD (11.3%) and hypertension (38.7%) were the common coexisting CVDs in COVID-19 patients. The rate of each CVD in the severe group was significantly higher than in the non-severe group (P<0.05). However, there were no statistical differences between the 2 groups in the rates of HF and atrial fibrillation. In the severe COVID-19 patients, the rate of coexisting diabetes in the CVD group was significantly higher than in the non-CVD group (58.8% vs. 0%) (P=0.032). Regarding the medication history of angiotensin-converting enzyme (ACE) inhibitor/angiotensin-receptor blocker (ARB) in patients with CVD, there were no differences between the non-severe and severe groups.

Laboratory and Radiological Findings at Presentation

The laboratory and radiological findings on admission are shown in **Table 2**. Lymphocyte count was significantly lower in the severe COVID-19 with CVD group, compared with the non-severe COVID-19 with CVD group (P=0.046). In the severe subgroups, hematocrit (HCT) was significantly higher in patients with CVD than in non-CVD patients (P=0.007). Of the cardiac markers, high-sensitivity cardiac troponin I (hs-cTnI) and aspartate aminotransferase levels were higher in the severe COVID-19 with CVD group compared with the non-severe COVID-19 with CVD group (P=0.002 and 0.028, respectively), but there were no statistical differences among other comparable groups. Creatinine (Cr), high-density lipoprotein-cholesterol (HDL-C), interleukin-6 (IL-6), CRP, prothrombin time (PT), and the D-dimer levels in the severe COVID-19 with CVD

Table 3. Clinical Outcomes of COVID-19 Patients With CVD

	Discharged (n=27)	Transferred (remained in hospital) (n=6)	P value
Arterial blood pH[a]	7.4 (7.4, 7.4)	7.4 (7.4, 7.5)	0.950
Lactic acid (mmol/L)[a]	1.7 (1.5, 2.0)	1.8 (1.3, 2.2)	0.391
PaO_2/FiO_2 (mmHg)[a]	404.8 (390.5, 514.3)	366.7 (347.6, 790.5)	0.708
hs-cTnI (ng/L)[a]	2.4 (1.6, 5.6)	9.0 (1.2, 25.0)	0.047
CK-MB (U/L)[a]	0.4 (0.3, 0.6)	0.5 (0.5, 1.0)	0.115
IL-6 (pg/mL)[a]	6.9 (2.3, 8.8)	5.9 (5.8, 15.6)	0.867
CRP (mg/L)[a]	2.4 (0.5, 5.6)	1.0 (0.4, 1.7)	0.590
HDL (mmol/L)[a]	1.2 (1.0, 1.5)	1.4 (1.0, 1.7)	0.889
Severity of COVID-19[b]			1.000
Non-severe	13 (48.1)	3 (50.0)	
Severe	14 (51.9)	3 (50.0)	
CVD (n, %)[b]			
Hypertension	20 (74.1)	4 (66.7)	1.000
CAD	7 (25.9)	0 (0.0)	0.394

[a]Statistical analysis by nonparametric Mann-Whitney U test; [b]statistical analysis performed with Fisher's exact probability test. CAD, coronary artery disease; CK-MB, creatine kinase-myocardial bound; COVID 19, coronavirus disease 2019; CRP, C-reactive protein; CVD, cardiovascular disease; FiO_2, fraction of inspired oxygen; HDL, high-density lipoprotein; hs-cTnI, high-sensitivity cardiac troponin I; IL, interleukin; PaO_2, oxygen partial pressure.

group were higher than in the non-severe COVID-19 with CVD group (P<0.05). Lymphocyte subsets such as CD4, and CD8 T cells showed no statistical differences between groups. All the patients underwent chest CT on admission, showing ground-glass opacity (66.1%), or local (21.0%), bilateral (77.4%), and interstitial abnormalities (4.8%), but there were no statistical differences for these indicators between each comparable group and subgroup. In addition, as shown in **Table 2**, in the non-severe COVID-19 subgroup, we only observed a higher blood urea nitrogen level and lower PT level among patients with CVD compared with non-CVD, and in the severe COVID-19 subgroup, only a higher HCT was observed among patients with CVD compared with non-CVD.

Clinical Outcomes

Among the 82 patients there was 2.4% all-cause mortality. Of the 2 deaths, 1 patient died because of gastric tumors causing gastrointestinal hemorrhage and the other patient died of tuberculosis and chronic obstructive pulmonary disease, which destroyed the lungs and caused respiratory failure. In both cases COVID-19 was suspected only, so they were excluded from this study. Among the 62 patients, 49 were discharged and 13 patients who failed the discharge criteria were transferred to another hospital because of closure of the ward.

The clinical outcomes of the COVID-19 patients with CVD are shown in **Table 3**: 27 (81.8%) CVD patients were cured and discharged, and 6 (18.2%) CVD patients remained in hospital, including 2 (3.2%) patients requiring intubation and mechanical ventilation. Comparing the discharged patients with the transferred patients, there were no differences in hypertension, CAD, atrial blood pH, lactic acid, PaO_2/FiO_2, CK-MB, IL-6, CRP, and HDL. However, the cTnI levels in the transferred patients were significantly higher than in the discharged patients (P<0.05).

Discussion

Our team took over the Z11 infectious diseases department of the Cancer Center, Union Hospital, Tongji Medical College, Huazhong Science and Technology University from February 15 to March 14, 2020, which is a designated hospital mainly admitting severe or critical COVID-19 patients. Therefore, in this study, 53.2% of COVID-19 patients had CVD, which is slightly higher than in other reports.[3-6] As in other studies,[3,4,6] we found that in COVID-19 patients with CVD, the lymphocyte count was significantly lower in severe cases compared with non-severe cases, and the most common onset symptoms were fever and cough. In addition, our study showed that the rates of hypertension and CAD in severe cases were significantly higher than in the non-severe group, which suggests that CVD played a critical role in the disease severity of COVID-19.

It is well-known that the renin-angiotensin system (RAS) is important in the pathophysiology of hypertension,[10] including the regulation of ACE2. RAS regulation is not only involved in cardiovascular system disorders but also contributes to the generation of other diseases such as inflammation, and renal dysfunction.[11] ACE2 had been reported as a functional receptor for coronavirus-induced infection, which binds the spike proteins of the SARS-CoV-2 virus to the enzyme, especially in the lungs and heart.[12] Therefore, the greater secretion of ACE2 in hypertensive patients may explain the risk factor of hypertension in COVID-19. ACEI/ARB are common medications for antihypertension, but the safety and potential effect in COVID-19 patients has been questioned. We collected the medication histories of all 33 CVD patients. Only 3 patients in the severe group were taking ACEI/ARB, but a lack of statistical difference suggests that ACEI/ARB did not affect COVID-19 progression. However the case numbers were limited in this study, so further study with large patients is still needed. Our findings are consistent with those from a study that contained 112 patients with a similar proportion of ACEI/ARB medication history in the severe and non-severe groups.[5] We found that the Cr level in severe patients with CVD was higher than in non-severe patients with CVD, which may also related to the ACE2 function in COVID-19 progression.

Interestingly, our study showed that the HDL-C level in the severe group with CVD was much lower than in the non-severe group with CVD. HDL is an atheroprotective cholesterol and a marker for atherosclerosis and a predictor of cardiovascular events.[13] It was lower in the severe group, indicating that coronary-related cardiovascular events may aggravate the progression of COVID-19. In this study, the rate of CAD was significantly higher in the severe group than in the non-severe group, which may also be related to HDL. Besides, HDL is not only as a modulator that could affect the cell surface receptors and functions of immune cells,[14,15] but also enables the neutralization and clearance of endotoxins by carrying lipopolysaccharide-binding protein.[16] A large population cohort study has shown that the HDL level is associated with a higher risk of infectious disease,[17] indicating that HDL also plays an important role in the immune system. However, with timely, effective monitoring and treatment, hypertension and CAD did not affect the prognosis of COVID-19.

Our study provided some clinical evidence of myocardial injury in COVID-19 patients. Although the relationship between CVD and COVID-19 is under-reported to date, a study in 1993 showed that rabbit coronavirus infection could result in viral myocarditis and dilated cardiomyopathy (DCM).[18] Another study has suggested that the Middle East respiratory syndrome-related coronavirus (MERS-CoV) can also cause acute myocarditis and HF.[19] Huang et al firstly reported that myocardial injury might occur in COVID-19 patients with high levels of cTnI.[4] cTnI is considered as the gold standard biomarker of myocardial injury because of its high specificity and sensitivity. An increase in the cTnI level correlates with myocardial necrosis, and increased levels may suggest chronic injury or high cardiovascular risk in the prognosis.[20] In our study, the hs-cTnI levels in severe cases with CVD were significantly higher than in the non-severe cases with CVD, but there were no differences in the comparison between CVD and non-CVD among the severe or non-severe subgroups, indicating that severe COVID-19 patients might have virus-related myocardial injury. The hs-cTnI levels were higher in the transferred COVID-19 patients than in the discharged patients, which also suggests that the cTnI level could be a predictor of the prognosis of COVID-19 patients. However, CVD is not an independent factor leading to myocardial injury. The mechanism of myocardial injury is still unclear: the underlying mechanism could involve ACE2-related direct injury, or hypoxia- or "cytokine storm"-induced indirect injury.

COVID-19 could cause indirect myocardial injury through a severe cytokine storm manifested by increasing CRP and IL-6 levels. In our study, the CRP and IL-6 levels were significantly higher in severe patients with CVD than in non-severe patients with CVD, which is consistent with the findings that 52% and 86% of COVID-19 patients had increased levels of IL-6 and CRP, respectively.[3] Xu et al found that CD4 and CD8 cells were reduced, and the concentration of Th17 was increased, which implies an overreaction of T cells.[8] A study of SARS suggested that proinflammatory cytokines may be related to decreased diastolic function of the left ventricle.[21] Therefore, the underlying mechanism of the cytokines still needs further study. Clinical treatment against the cytokine storm might also reduce myocardial injury and myocardial injury-related mortality.

Study Limitations

First, because of the ward closure, the number of cases was limited. Second, SARS-CoV-2 antibody testing, such as IgG and IgM detection, was available for clinical screening, but the results could not be included in this study because the kits' reference values were different. Finally, echocardiography is a good method for evaluating structural and functional changes during COVID-19, but only some of the patients underwent echocardiography.

In conclusion, CVDs, such as hypertension and CAD, play a vital role in the disease severity of COVID-19. COVID-19 results in myocardial injury manifested by higher level of cTnI, but CVD is not an independent risk factor. With proper monitoring and treatment, the outcome prognosis was approximately the same in both severe and non-severe cases.

Data Availability

The deidentified participant data are accessible for clinicians and researchers as Excel or csv files via e-mail and will be shared on request to the corresponding authors.

Conflicts of Interest

We declare no conflicts of interest.

Authors' Contributions

Y.X., C. Wang, H.Z. designed the study. Y.X., Q.Y., C. Wu, S.C., X.Y., X.H., H.Z. collected the clinical data. Y.X., S.C., C. Wu performed the statistical analysis. Y.X. draft the manuscript. H.Z., C. Wang, Y.X. responsible for the revision of the manuscript.

IRB Information

This study protocol was approved by The Committee on Medical Ethics of The First Affiliated Hospital of Anhui Medical University. Reference no. Quick-PJ 2020-03-37.

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