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

Yangjing Xie, MD, PhD; Qinghai You, MD, PhD; Chaoran Wu, MD; Shiyu Cao, MD; Guangbo Qu, PhD; Xiaoxiang Yan, MD; Xuan Han, MD; Changhui Wang, MD, PhD; Hong Zhang, MD, PhD

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
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 Mild cases had mild symptoms and no abnormalities on imaging. Severe cases had respiratory rate ≥30 breaths/min, or resting fingertip oxygen saturation ≤93%, or oxygen partial pressure (PaO₂)/fraction of inspired O₂ (FiO₂) ≤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.

Table 1. Patients’ Demographic and Clinical Characteristics

| Characteristics, symptoms, coexisting disorders | All patients (n=62) | CVD (n=16) | Non-CVD (n=22) | P value | CVD (n=17) | Non-CVD (n=7) | P value |
|-----------------------------------------------|-------------------|-----------|---------------|---------|-----------|---------------|---------|
| Age (years) [M (Q1, Q3)]<sup>a</sup>          | 66.0 (53.3, 73.0) | 66.0      | 58.0          | 0.031   | 73.0 (64.5, 83.0) | 69.0 (51.0, 75.0) | 0.203   |
| Sex (n, %)<sup>b</sup>                        |                   |           |               | 0.309   |           |               | 0.653   |
| Female                                         | 35 (56.5)         | 12 (75.0) | 12 (54.5)     |   9 (52.9) | 2 (28.6) |               | 0.157   |
| Symptoms (n, %)<sup>b</sup>                    |                   |           |               |         |           |               |         |
| Fever                                          | 46 (74.2)         | 9 (56.2)  | 21 (95.5)     | 0.005   | 12 (70.6) | 4 (57.1)      | 0.647   |
| Cough                                          | 29 (46.8)         | 7 (43.8)  | 9 (40.9)      | 1.000   | 9 (52.9)  | 4 (57.1)      | 1.000   |
| 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)      | 0.175   |
| Fatigue                                        | 16 (25.8)         | 2 (12.5)  | 8 (36.4)      | 0.143   | 5 (29.4)  | 1 (14.3)      | 0.398   |
| Shortness of breath                            | 11 (17.7)         | 1 (6.2)   | 5 (22.7)      | 0.370   | 2 (11.8)  | 3 (42.9)      | 0.126   |
| Diarrhea                                       | 9 (14.5)          | 1 (6.2)   | 4 (18.2)      | 0.374   | 3 (17.6)  | 1 (14.3)      | 1.000   |
| Myalgia                                        | 7 (11.3)          | 1 (6.2)   | 4 (18.2)      | 0.374   | 2 (11.8)  | 0 (0.00)      | 1.000   |
| Chill                                          | 7 (11.3)          | 1 (6.2)   | 3 (13.6)      | 0.624   | 2 (11.8)  | 1 (14.3)      | 1.000   |
| Coexisting disorders (n, %)<sup>b</sup>        |                   |           |               |         |           |               |         |
| Diabetes                                       | 13 (21.0)         | 3 (18.8)  | 0 (0.0)       | 0.066   | 10 (58.8) | 0 (0.0)       | 0.019   |
| 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, %)<sup>b</sup>          |                   |           |               |         |           |               |         |
| ACEI/ARB                                       | 3 (4.8)           | 0 (0.0)   | –             | –       | 3 (12.5)  | –             | 0.227   |

<sup>a</sup>Statistical analysis by nonparametric Mann-Whitney U test; <sup>b</sup>statistical analysis performed with Fisher’s exact probability test; <sup>c</sup>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.
| Laboratory and radiology findings [M (Q1, Q3)]a | All patients (n=62) | Non-Severe (n=22) | P value | Severe (n=17) | Non-Severe (n=7) | P value |
|---------------------------------------------|---------------------|-------------------|---------|---------------|------------------|---------|
| **Routine blood tests**                     |                     |                   |         |               |                   |         |
| Leukocyte count (×10^9)                     | 5.1 (4.3, 6.0)       | 5.6 (4.3, 6.9)    | 0.183   | 5.5 (4.3, 6.9) | 4.8 (4.7, 5.1)   | 0.295   |
| Neutrophil count (×10^9)                    | 3.3 (2.4, 4.3)       | 3.5 (2.5, 4.6)    | 0.156   | 3.5 (3.0, 4.5) | 3.2 (3.0, 3.8)   | 0.634   |
| Lymphocyte count (×10^9)                    | 1.3 (0.8, 1.6)       | 1.5 (1.1, 1.9)    | 0.274   | 1.1 (0.7, 1.5) | 0.8 (0.6, 1.0)   | 0.144   |
| Platelet count (×10^9)                      | 219.0 (191.8, 291.8) | 214.0 (194.8, 271.0) | 0.243 | 200.0 (180.0, 292.0) | 242.0 (151.0, 281.0) | 0.799 |
| HCT (%)                                     | 34.3 (32.7, 36.9)    | 34.5 (31.7, 35.7) | 0.594   | 36.4 (34.2, 38.6) | 32.9 (31.7, 33.8) | 0.007   |
| **Cardiac markers**                         |                     |                   |         |               |                   |         |
| hs-cTnI (ng/L)                              | 2.7 (1.6, 6.8)       | 2.2 (1.6, 4.9)    | 0.236   | 8.7 (3.8, 22.4) | 6.0 (2.3, 28.1)  | 0.799   |
| AST (U/L)                                   | 25.0 (20.0, 31.5)    | 24.0 (20.3, 27.8) | 0.505   | 33.0 (23.0, 46.5) | 27.0 (19.0, 30.0) | 0.192   |
| CK (U/L)                                    | 65.0 (51.0, 91.5)    | 66.0 (62.0, 83.3) | 0.301   | 73.0 (43.0, 110.0) | 99.0 (48.0, 123.0) | 0.680   |
| CK-MB (U/L)                                 | 0.6 (0.4, 0.9)       | 0.6 (0.4, 0.7)    | 0.404   | 0.7 (0.5, 1.1)  | 0.6 (0.4, 1.3)   | 0.750   |
| LDH (U/L)                                   | 180.0 (152.5, 221.5) | 177.0 (153.8, 211.3) | 0.139 | 208.0 (171.0, 302.5) | 190.0 (156.8, 257.0) | 0.589   |
| **Renal & liver function**                  |                     |                   |         |               |                   |         |
| Cr (µmol/L)                                 | 71.0 (65.0, 86.3)    | 68.0 (62.8, 78.3) | 0.976   | 94.0 (66.0, 101.0) | 78.0 (66.0, 87.0) | 0.634   |
| BUN (mmol/L)                                | 4.7 (3.8, 5.8)       | 4.5 (4.2, 6.0)    | 0.016   | 5.4 (4.4, 6.4)  | 5.0 (3.0, 7.9)   | 0.949   |
| UA (µmol/L)                                 | 281.0 (218.0, 331.8) | 282.0 (216.0, 326.3) | 0.243 | 283.0 (209.0, 409.0) | 310.0 (266.5, 353.0) | 0.680 |
| ALT (U/L)                                   | 25.5 (17.0, 39.0)    | 21.5 (19.3, 29.8) | 0.988   | 31.0 (16.0, 55.0) | 26.0 (11.0, 32.0) | 0.227   |
| **Blood lipid levels**                      |                     |                   |         |               |                   |         |
| TC (mmol/L)                                 | 4.1 (3.7, 4.8)       | 4.1 (3.9, 5.2)    | 0.183   | 3.9 (3.5, 4.6)  | 4.4 (3.5, 6.6)   | 0.624   |
| TG (mmol/L)                                 | 1.2 (0.9, 1.8)       | 1.2 (0.8, 2.4)    | 0.790   | 1.5 (0.9, 1.7)  | 1.2 (0.9, 1.7)   | 0.421   |
| LDL-C (mmol/L)                              | 2.2 (1.9, 2.5)       | 2.2 (1.9, 2.6)    | 0.636   | 2.2 (1.8, 3.4)  | 2.5 (1.9, 3.5)   | 0.401   |
| HDL-C (mmol/L)                              | 1.2 (1.0, 2.5)       | 1.4 (1.2, 1.6)    | 0.044   | 1.1 (0.9, 1.3)  | 1.1 (0.7, 1.7)   | 0.726   |
| **Lymphocyte subsets**                      |                     |                   |         |               |                   |         |
| CD4 (%)                                     | 43.5 (36.8, 50.4)    | 42.2 (36.0, 50.8) | 0.872   | 47.1 (42.4, 53.2) | 36.7 (30.6, 52.6) | 0.276   |
| CD8 (%)                                     | 23.8 (18.5, 29.7)    | 23.5 (19.2, 28.6) | 0.134   | 22.8 (17.6, 25.4) | 17.3 (14.1, 25.4) | 0.392   |
| **Inflammatory markers**                    |                     |                   |         |               |                   |         |
| IL-6 (pg/mL)                                | 7.4 (4.9, 18.6)      | 6.7 (4.2, 9.3)    | 0.555   | 17.5 (8.4, 27.9) | 14.1 (4.3, 26.7) | 0.533   |
| CRP (mg/L)                                  | 3.3 (0.9, 22.5)      | 3.3 (1.5, 4.2)    | 0.664   | 15.4 (2.4, 38.9) | 8.3 (0.8, 27.6)  | 0.823   |
| PCT (ng/L)                                  | 0.07 (0.05, 0.17)    | 0.06 (0.04, 0.09) | 0.445   | 0.08 (0.06, 0.22) | 0.10 (0.04, 0.33) | 0.853   |
| **Coagulation test**                        |                     |                   |         |               |                   |         |
| APTT (s)                                    | 37.6 (35.4, 40.7)    | 36.3 (34.8, 39.7) | 0.712   | 39.2 (36.4, 42.1) | 37.7 (33.9, 41.4) | 0.751   |
| PT (s)                                      | 13.6 (12.9, 40.7)    | 12.9 (12.6, 13.7) | 0.012   | 13.9 (13.1, 14.8) | 14.1 (13.1, 14.9) | 0.589   |
| D-dimer (mg/L)                              | 0.5 (0.3, 1.4)       | 0.4 (0.3, 1.1)    | 0.252   | 1.1 (0.5, 2.0)   | 2.9 (0.3, 10.1)   | 0.306   |

(Table 2 continued on the next page.)
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 patients were fever (74.2%) and cough (46.8%). In the CVD group, there were no differences between the non-severe and severe CVD groups, or between non-severe and severe groups with CVD. Of the patients, 56.5% were female, and 33.9% of patients were fever (74.2%) and cough (46.8%). 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 each CVD in the severe group was significantly higher than in the severe COVID-19 patients (56.2%).

LABORATORY AND RADIOLICAL FINDINGS AT PRESENTATION

The laboratory and radiological findings at presentation 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, hematoctrit (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

| Laboratory and radiology findings | All patients (n=62) | CVD (n=16) | Non-CVD (n=22) | P value | CVD (n=17) | Non-CVD (n=7) | P value |
|-----------------------------------|---------------------|------------|----------------|---------|------------|---------------|---------|
| Arterial blood                     |                     |            |                |         |            |                |         |
| pH                                | (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)              | (1.6, 2.2)          | (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          |                     |            |                |         |            |                |         |
| Ground-glass opacity              | (66.1)              | 14 (63.6)  | 14 (63.6)      | 0.296   | 9 (65.6)   | 5 (71.4)       | 0.657   | 0.252 |
| Local pneumonia                   | (21.0)              | 3 (13.6)   | 3 (13.6)       | 0.682   | 5 (31.2)   | 2 (28.6)       | 1.000   | 0.685 |
| Bilateral pneumonia               | (77.4)              | 19 (86.4)  | 19 (86.4)      | 0.682   | 11 (68.8)  | 5 (71.4)       | 1.000   | 0.685 |
| Interstitial abnormalities         | (4.8)               | 1 (4.5)    | 1 (4.5)        | 0.000   | 0 (0.0)    | 2 (28.6)       | 0.083   | –      |

Statistical analysis by nonparametric Mann-Whitney U test; bstatistical analysis performed with Fisher’s exact probability test; cnon-severe 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, hematoctrit; 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.
Impact of CVD on COVID-19

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

| Arterial blood pH | Transferred (remained in hospital) |
|-------------------|------------------------------------|
| Discharged (n=27) | (n=6)                              |
| 7.4 (7.4, 7.4)    | 7.4 (7.4, 7.5)                     |
| Lactic acid (mmol/L) | 1.7 (1.5, 2.0)                     |
| PaO2/FiO2 (mmHg)   | 366.7 (347.6, 790.5)               |
| hs-cTnI (ng/L)     | 2.4 (1.6, 5.6)                     |
| CK-MB (U/L)       | 0.4 (0.3, 0.6)                     |
| IL-6 (pg/mL)      | 2.4 (0.5, 5.6)                     |
| CRP (mg/L)        | 2.4 (0.5, 5.6)                     |
| HDL (mmol/L)      | 1.2 (1.0, 1.5)                     |

| Severity of COVID-19 | Discharged (n=27) | Transferred (remained in hospital) |
|----------------------|-------------------|------------------------------------|
| Non-severe           | 13 (48.1)         | 3 (50.0)                           |
| Severe               | 14 (51.9)         | 3 (50.0)                           |
| CVD (n, %)           |                   |                                   |
| Hypertension         | 20 (74.1)         | 4 (66.7)                           |
| CAD                  | 7 (25.9)          | 0 (0.0)                            |

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. As in other studies, 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, 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. 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. 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. 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. 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, but also enables the neutralization and clearance of endotoxins by carrying lipopolysaccharide-binding protein. A large population cohort study has shown that the HDL level is associated with a higher risk of infectious disease, 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). Another study has suggested that the Middle East respiratory syndrome-related coronavirus (MERS-CoV) can also cause acute myocarditis and HF. Huang et al firstly reported that myocardial injury might occur in COVID-19 patients with high levels of cTnI. 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. 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. 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. A study of SARS suggested that proinflammatory cytokines may be related to decreased diastolic function of the left ventricle. 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.

Acknowledgments
We thank the Cancer Center, Union Hospital, Tongji Medical College, Huazhong Science and Technology University for the clinical testing. We also thank all the patients involved in this study.

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.

Disclosures
This study funded by Natural Science Foundation of University of Anhui Province [Grant no. KJ2019A0265]; The Fund Project of the First Affiliated Hospital of Anhui Medical University [Grant numbers BSKY2019003 and 2009KJ19].

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.

References
1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565–574.
2. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020; 17: 259–260.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020; 395: 507–513.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
5. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi 2020; 48: E004 (in Chinese).
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061–1069.
7. Liu Q, Wang R, Qu G, Wang Y, Liu P, Zhu Y, et al. Autopsy
Impact of CVD on COVID-19

8. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; 8: 420–422.

9. National Health Commission of the People’s Republic of China. Diagnosis and treatment protocol for COVID-19 (Trial Version 7). Updated: 2020-03-29. http://en.nhc.gov.cn/2020-03/29/c_78469.htm (accessed March 29, 2020).

10. Lu, X, Bi YW, Chen KB, Wang HY. Protective effect of olmesartan against cardiac ischemia/reperfusion injury in spontaneously hypertensive rats. *Exp Ther Med* 2015; 9: 2081–2087.

11. Qaradakhi T, Gadaneck LR, McSweeney KR, Tacey A, Apostolopoulos V, Levinger I, et al. The potential actions of angiotensin-converting enzyme II (ACE2) activator diminazene aceturate (DIZE) in various diseases. *Clin Exp Pharmacol Physiol* 2020; 47: 751–758.

12. Turner AJ, Hiscox JA, Hooper NM. ACE2: From vasopeptidase to SARS virus receptor. *Trends Pharmacol Sci* 2004; 25: 291–294.

13. Kon V, Linton MF. HDL: Beyond atheroprotection. *J Am Soc Nephrol* 2016; 27: 341–344.

14. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. *Cardiovasc Res* 2014; 103: 372–383.

15. Wang SH, Yuan SG, Peng DQ, Zhao SP. HDL and ApoA-I inhibit antigen presentation-mediated T cell activation by disrupting lipid rafts in antigen presenting cells. *Atherosclerosis* 2012; 225: 105–114.

16. Wurfel MM, Kunitake ST, Lichenstein H, Kane JP, Wright SD. Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. *J Exp Med* 1994; 180: 1025–1035.

17. Madsen CM, Varbo A, Tybjaerg-Hansen A, Frikke-Schmidt R, Nordestgaard BG. U-shaped relationship of HDL and risk of infectious disease: Two prospective population-based cohort studies. *Eur Heart J* 2018; 39: 1181–1190.

18. Alexander LK, Keene BW, Small JD, Yount B Jr, Baric RS. Electrocardiographic changes following rabbit coronavirus-induced myocarditis and dilated cardiomyopathy. *Adv Exp Med Biol* 1993; 342: 365–370.

19. Alhogbani T. Acute myocarditis associated with novel Middle east respiratory syndrome coronavirus. *Ann Saudi Med* 2016; 36: 78–80.

20. Gherasim L. Troponins in heart failure: A perpetual challenge. *Maedica Buchar* 2019; 14: 371–377.

21. Li SS, Cheng CW, Fu CL, Chan YH, Lee MP, Chan JW, et al. Left ventricular performance in patients with severe acute respiratory syndrome: A 30-day echocardiographic follow-up study. *Circulation* 2003; 108: 1798–1803.