Defining heart disease risk for death in COVID-19 infection

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Summary

Background: Cardiovascular disease (CVD) was common in coronavirus disease 2019 (COVID-19) patients and associated with unfavorable outcomes. We aimed to compare the clinical observations and outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients with or without CVD.

Methods: Patients with laboratory-confirmed SARS-CoV-2 infection were clinically evaluated at Wuhan Seventh People’s Hospital, Wuhan, China, from 23 January to 14 March 2020. Demographic data, laboratory findings, comorbidities, treatments and outcomes were collected and analyzed in COVID-19 patients with and without CVD.

Results: Among 596 patients with COVID-19, 215 (36.1%) of them with CVD. Compared with patients without CVD, these patients were significantly older (66 vs. 52 years) and had higher proportion of men (52.5% vs. 43.8%). Complications in the course of disease were more common in patients with CVD, included acute respiratory distress syndrome (22.8% vs. 8.1%), malignant arrhythmias (3.7% vs. 1.0%) including ventricular tachycardia/ventricular fibrillation, acute coagulopathy(7.9% vs. 1.8%) and acute kidney injury (11.6% vs. 3.4%). The rate of glucocorticoid therapy (36.7% vs. 25.5%), Vitamin C (23.3% vs. 11.8%), mechanical ventilation (21.9% vs. 7.6%), intensive care unit admission (12.6% vs. 3.7%) and mortality (16.7% vs. 4.7%) were higher in patients with CVD (both P < 0.05). The multivariable Cox regression models showed that older age (≥65 years old) (HR 3.165, 95% CI 1.722–5.817) and patients with CVD (HR 2.166, 95% CI 1.189–3.948) were independent risk factors for death.

Conclusions: CVD are independent risk factors for COVID-19 patients. COVID-19 patients with CVD were more severe and had higher mortality rate, early intervention and vigilance should be taken.
Background
Coronavirus disease 2019 (COVID-19) pneumonia was first reported in Wuhan, Hubei Province, China, in December, 2019, followed by an outbreak across Hubei Province and other parts of the world. At present, there are more than three million confirmed cases worldwide. The outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been pandemic and become a major global public health emergency. Respiratory symptoms were the main manifestation of COVID-19, but mounting evidence substantiates the presence of cardiac injury in patients. Several retrospective studies have shown increasing serum levels of High-sensitivity troponin I, creatine kinase, creatine kinase-mb in confirmed patients. Wang et al. reported that 16.7% of patients with COVID-19 were diagnosed with arrhythmias and 7.2% had acute myocardial injury. From other recent data, the most prevalent cardiovascular metabolic comorbidities were hypertension and myocardial injury. From other recent data, the most prevalent COVID-19 patients combined with CVD.

Methods

Study participants
For this retrospective study, we recruited patients diagnosed with laboratory-confirmed COVID-19 in the Wuhan Seventh People’s Hospital from 23 January 2020 to 14 March 2020. All COVID-19 patients were diagnosed according to WHO interim guidelines. The study was approved by the local Medical Research Ethics Board of Zhongnan Hospital of Wuhan University and Wuhan Seventh People’s Hospital (No.2020068K), and complied with the edicts of the 1975 Declaration of Helsinki. Oral consent was obtained from patients on admission.

Data collection
The electronic medical records of the patients were reviewed by a team of well-trained physicians worked in the two hospitals during the epidemic time. Patient demographical, epidemiological, clinical, laboratory, treatment and outcome data were collected with standardized data collection forms shared by the international severe acute respiratory and emerging infection consortium from electronic medical records. The researchers were responsible to contact the patients or their families in case of uncertainties about the data to maximum the accuracy of the data.

Laboratory procedures
Real-time transcription polymerase chain reaction (RT-PCR) Assay for COVID-19. Throat swabs from the inpatients were collected at multiple time points after COVID-19-related symptom remission according to their treating physicians. SARS-CoV-2 in respiratory samples was qualitatively detected by RT-PCR assay according to publicly released COVID-19 sequence, as described previously. Diagnostic criteria are based on the recommendations by National Institute for Viral Disease Control and Prevention (China).

Routine blood examinations
Routine blood examinations were performed for COVID-19 inpatients, including complete blood count, coagulation profile, blood lipids and electrolytes, liver and renal function, cardiac biomarkers (Troponin T (TnT), creatine kinase-MB, myoglobin and NT-proBNP), inflammatory biomarkers and arterial blood gas analysis. The frequency of tests was determined by the treating physicians according to the clinical condition of the individuals.

Definition
Discharge and cure standards according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission of the PRC. Acute respiratory distress syndrome was defined according to the Berlin Definition. Malignant arrhythmia was diagnosed when rapid ventricular tachycardia lasting more than 30s, inducing hemodynamic instability and/or ventricular fibrillation. Acute myocardial injury was defined if serum levels of TnT were above the 99th percentile upper reference. Acute coagulopathy was determined as all prothrombin time (PT), activated partial thromboplastin time, D-dimer and platelet count were abnormal, while excluded antiocoagulant effect. Acute kidney injury was identified according the Kidney Disease: Improving Global Outcomes definition.

Treatment
Treatment decisions for COVID-19 patients were made in accordance with the Chinese Diagnosis and Treatment Protocol of Coronavirus Pneumonia from first to seventh versions. Since there were no effective antiviral drug or vaccine at present, most treatments were symptomatic and supportive. For mild and moderate patients, main treatment is symptomatic support and antifebrile. For severe and critical patients, on the basis of symptomatic treatment, complications should be proactively prevented, underlying diseases should be treated, secondary infections also be prevented and organ function support should be provided timely. COVID-19 patients were used of oseltamivir, ribavirin or arbidol for antiviral therapy. Most patients received a broad-spectrum antibiotic (moxifloxacin) to prevent secondary bacterial infection. Patients with PaO2/FiO2 and chest radiographs showing rapid deterioration were given respiratory support, vitamin C and low-dose glucocorticoids (methylprednisolone). The long-term medications prior to admission such as anti-hypertensive drugs and hypoglycemic drugs were not discontinued.

Statistical analysis
Continuous variables were expressed as mean (SD) or median (interquartile range (IQR)) if appropriate. One-sample Kolmogorov–Smirnov test was used to verify the normality of distribution of continuous variables. Comparison of the means of continuous variables between two groups were made with Mann–Whitney U test. Categorical variables were expressed as frequencies (percentages). Comparison of categorical variables between two groups were made using Chi-square test or Fisher’s exact test if appropriate. Survival curves were plotted using Kaplan–Meier method with the log-rank test and compared between COVID-19 patients with vs. without CVD. Multivariate Cox regression models were used to identify the independent risk factors for death in-hospital death. The number of possible predictors entering into Cox regression was limited.
due to small number of death cases \( (n = 54) \) and to avoid overfitting in the model. Five variables, including sex, age, CVD, diabetes and malignancy were chosen for the final regression models. The statistical analysis was performed using the SPSS package for Windows (v.22.0, Chicago, IL, USA) and GraphPad Prism (version 8.0). A two-tailed \( P \) values \( < 0.05 \) was considered statistically significant.

Results

Clinical characteristics

A total of 596 patients with COVID-19 were included in this study, 215 of them with CVD (36.1%) and 384 without CVD (63.9%) (Table 1). Among 215 patients with CVD, 176 patients had hypertension, 36 had coronary heart disease, 10 had atrial fibrillation and 21 had cerebrovascular disease (Table 2). The median age was 48 (IQR 47–68) and 280 (47.0%) were male. Compared with patients without CVD, patients with CVD were significantly older (66 (IQR 57–73) years vs. 52 (IQR 40–63) years; \( P < 0.001 \)) and higher proportion of men (52.5% vs. 43.8%; \( P = 0.040 \)). Patients with CVD had higher systolic blood pressure (138 (IQR 126–150) vs. 126 (IQR 118–136)), diastolic blood pressure (81 (IQR 75–90) vs. 78 (IQR 72–85)), heart rate (89 (IQR 79–100) vs. 87 (IQR 79–97)) and respiratory rate (20 (IQR 20–21) vs. 20 (IQR 20–20)).

Table 1. Characteristics, complications, treatments and outcomes among different groups

| Characteristic                  | Total (\( n = 596 \)) | With CVD (\( n = 215 \)) | Without NCVD (\( n = 381 \)) | \( P \) value |
|---------------------------------|------------------------|--------------------------|-----------------------------|--------------|
| Sex, counts (%)                 |                         |                          |                             |              |
| Male                            | 280 (47.0)             | 113 (52.6)               | 167 (43.8)                  | 0.040        |
| Age (years), mean (IQR)         |                         |                          |                             |              |
|                                  | 58 (47–68)             | 66 (57–73)               | 52 (40–63)                  | <0.001       |
| Age \( \geq 65 \) (%)           |                         | 200 (55.3)               | 81 (21.3)                   | <0.001       |
| Temperature (\(^{\circ}\)C), mean (IQR) |             |                          |                             |              |
|                                  | 36.6 (36.4–37.0)       | 36.6 (36.4–37.0)         | 36.6 (36.4–37.0)            | 0.510        |
| SBP, mean (IQR)                 |                         |                          |                             |              |
|                                  | 130 (120–141)          | 138 (126–150)            | 126 (118–136)               | <0.001       |
| DBP, mean (IQR)                 |                         |                          |                             |              |
|                                  | 80 (73–86)             | 81 (75–90)               | 78 (72–85)                  | <0.001       |
| HR, mean (IQR)                  |                         |                          |                             |              |
|                                  | 88 (78–98)             | 89 (75–100)              | 87 (78–97)                  | 0.021        |
| RR, mean (IQR)                  | 20 (20–20)             | 20 (20–20)               | 20 (20–20)                  | <0.001       |
| Comorbidities, count (%)        |                         |                          |                             |              |
| Diabetes                        | 79 (13.3)              | 58 (27.0)                | 21 (5.5)                    | <0.001       |
| COPD                            | 4 (0.7)                | 2 (0.9)                  | 2 (0.5)                     | 0.622        |
| Hepatic dysfunction             | 19 (3.2)               | 6 (2.8)                  | 13 (3.4)                    | 0.678        |
| Renal dysfunction               | 11 (1.8)               | 7 (3.3)                  | 4 (1.0)                     | 0.064        |
| Malignancy                      | 27 (4.5)               | 16 (7.4)                 | 11 (2.9)                    | 0.010        |
| Smoking                         | 32 (5.4)               | 15 (7.0)                 | 17 (4.5)                    | 0.192        |
| Treatment, count (%)            |                         |                          |                             |              |
| Antivirus therapy               | 467 (78.4)             | 174 (80.9)               | 293 (76.9)                  | 0.252        |
| Antibiotic therapy              | 446 (74.8)             | 171 (79.5)               | 275 (72.2)                  | 0.047        |
| Glucocorticoid therapy          | 176 (29.5)             | 79 (36.7)                | 97 (25.5)                   | 0.004        |
| Immunoglobin                    | 55 (9.2)               | 21 (9.8)                 | 34 (8.9)                    | 0.733        |
| Vitamin C                       | 95 (15.9)              | 50 (23.3)                | 45 (11.8)                   | <0.001       |
| Chinese medicine                | 266 (44.6)             | 96 (44.7)                | 170 (44.6)                  | 0.994        |
| Mechanical ventilation          | 76 (12.8)              | 47 (21.9)                | 29 (7.6)                    | <0.001       |
| NMV                             | 41 (6.9)               | 25 (11.6)                | 16 (4.2)                    | 0.001        |
| IMV                             | 35 (5.9)               | 22 (10.2)                | 13 (3.4)                    | 0.001        |
| CRRT                            | 4 (0.7)                | 2 (0.9)                  | 2 (0.5)                     | 0.622        |
| Complication, count (%)         |                         |                          |                             |              |
| ARDS                            | 80 (13.4)              | 49 (22.8)                | 31 (8.1)                    | <0.001       |
| VT/VF                           | 12 (2.0)               | 8 (3.7)                  | 4 (1.0)                     | 0.034        |
| Acute myocardial injury         | 126 (21.1)             | 78 (36.3)                | 48 (12.6)                   | <0.001       |
| Acute coagulopathy              | 24 (4.0)               | 17 (7.9)                 | 7 (1.8)                     | <0.001       |
| Acute liver injury              | 31 (5.2)               | 11 (5.1)                 | 20 (5.2)                    | 0.944        |
| Acute kidney injury             | 38 (6.4)               | 25 (11.6)                | 13 (3.4)                    | <0.001       |
| Clinical outcome                |                         |                          |                             |              |
| Hospitalization (days), mean (IQR) | 16 (9–24)             | 16 (9–24)                | 15 (9–24)                   | 0.374        |
| Duration* (days), mean (IQR)    |                         | 30 (20–39)               | 28 (20–37)                  | 0.250        |
| Death-count (%)                 |                         | 54 (9.1)                 | 36 (16.7)                   | <0.001       |
| ICU (%)                         | 41 (6.9)               | 27 (12.6)                | 14 (3.7)                    | <0.001       |

IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia; NMV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy.

*Duration from the onset of symptom to death or discharge.
20–20) to admission (all P values < 0.05). Diabetes (13.3%) and malignancy (4.5%) were most common coexisting in COVID-19 patients. The rate of diabetes (27.0% vs. 5.5%; P < 0.001) and malignancy (7.4% vs. 2.9%; P = 0.010) in the patients with CVD was higher than patient without CVD. There were no significant differences in chronic obstructive pulmonary disease, hepatic dysfunction, renal dysfunction and smoking history between the two groups (Table 1).

### Laboratory findings on admission

The laboratory findings on admission are shown in Table 3. Patients with CVD compared with patients without CVD showed higher leukocyte counts (5770 (IQR 4340–7800) vs. 4850 (IQR 3850–6415) cells/μl), neutrophil counts (3860 (IQR 2725–6260) vs. 3060 (IQR 2215–4205) cells/μl) and lower lymphocyte counts (930 (IQR 618–1430) vs. 1160 (IQR 725–1625) cells/μl) (P < 0.001 for both), but platelets counts and hematocrit did not differ according to CVD. Patients with CVD had significant higher procalcitonin (0.07 (IQR 0.04–0.18) vs. 0.04 (IQR 0.03–0.08) ng/ml), high-sensitivity C-reactive protein (24.5 (IQR 3.6–79.4) vs. 7.5 (IQR 1.0–38.3) mg/ml) and globulin (27.6 (IQR 24.9–31.9) vs. 26.0 (IQR 23.1–28.3) g/l) (P < 0.001 for both) than patients without CVD. Patients with CVD also had longer PT (12.6 (IQR 11.7–13.7) s, P = 0.003) and high levels of D-dimer (0.43 (IQR 0.18–2.78) vs. 0.18 (IQR 0.09–0.43) μg/ml, P < 0.001). The cardiac biomarkers, including creatine kinase-MB fraction (1.81 (IQR 0.95–3.43) vs. 1.01 (IQR 0.66–1.61) ng/ml), myoglobin (53.3 (IQR 27.6–114.8) vs. 25.0 (IQR 21.0–43.5) ng/ml), N-terminal pro-brain natriuretic peptide (300.8 (IQR 132.2–648.4) vs. 103.5 (IQR 39.2–287.6) pg/ml) and TnT (0.012 (IQR 0.008–0.024) vs. 0.007 (IQR 0.005–0.011) ng/ml) were significantly higher in patients with CVD (all P values < 0.001). Total, triglyceride, low-density lipoprotein cholesterol, potassium and calcium levels did not differ between the two groups, but patients with CVD had lower levels of density lipoprotein (1.09 (IQR 0.94–1.31) vs. 1.16 (IQR 0.98–1.44) mmol/l, P = 0.01). Patients with CVD had higher levels of alanine aminotransferase (23 (IQR 15–38) vs. 19 (IQR 13–31) U/l), aspartate aminotransferase (29 (IQR 19–44) vs. 23 (IQR 19–34) U/l), aspartate aminotransferase (29 (IQR 19–44) vs. 23 (IQR 19–34) U/l).
CVDs, we found that hypertension (HR 2.606, 95% CI 1.443–4.706) and coronary heart disease (HR 2.330, 95% CI 0.985–5.512) were related to death (Table 5).

Discussion

This study described the characteristics of COVID-19 patients with vs. without CVD and identified risk factors associated with in-hospital mortality. In this study, patients with CVD accounted for 36.1% and hypertension accounted for the highest proportion, which was consistent with previous studies.2–7 Patients with CVD were more likely to have complications in the course of the disease, requiring glucocorticoid therapy and mechanical ventilation for a larger proportion, and had a higher rate of intensive care unit admission and death. Old age (>65 years) and CVDs, especially hypertension and coronary heart disease, were independently associated with in-hospital death.

CVD was the most common comorbidity in patients with coronavirus. CVD was an independent risk factor for death or other adverse outcomes in patients with SARS,14,15 about 50% of patients with Middle East respiratory syndrome coronavirus had hypertension and diabetes mellitus.16 It had been confirmed that SARS-CoV-2 infection depends on the binding of spike glycoprotein on the surface of and angiotensin-converting enzyme 2 (ACE2).17 ACE2 plays a key role in regulating the invasion of coronavirus into human cells. ACE2 was highly expressed in the heart as well as in lung cells. It protected the cardiovascular system by counteracting the over activation of angiotensin II (AngII) in the renin angiotensin system.18 Therefore, the increase of ACE2 activity in patients with CVD was considered to be the mechanism of high prevalence in patients with CVD.

The remarkably increase in coagulation profiles such as D-dimer and PT were observed in patients with CVD. Early stage of CVD was usually accompanied by vascular endothelial dysfunction and organic lesions, while oxidative stress and blood pressure can damage vascular endothelium. The vicious cycle of them aggravated vascular endothelial damage, and endothelial damage can cause hypercoagulability.20 In our study, patients with CVD were mostly in severe, they were more likely to form venous thrombosis of lower extremities in need of respiratory support and long-term bed rest, which caused the increase of D-dimer. ACE2 was also expressed in vascular endothelial cells. Previous studies showed that the expression of ACE2 on the cell surface can be reduced after SARS-CoV infection,21 which led to the activation of renin–angiotensin system, promoted vascular contraction and endothelial injury. The injury of endothelium caused the up-regulation of tissue factor expression and imbalance of fibrinolysis system.22 In the pneumonia model of bacterial infection, the level of ACE2 was critical for the severity of inflammation.23 ACE2 reduction promoted the release of inflammatory factors, which results in the infiltration of a large number of neutrophils, leading to excessive inflammatory response and immune damage.24 Therefore, it was speculated that ACE2 is a key regulatory factor of inflammatory reaction and coagulation dysfunction in patients with COVID-19.

Combining CVD caused the reduction in the function of cardiac reserve, bad tolerance to severe pneumonia and acute cardiovascular events were more likely to occur in cases of viral infection. In this study, the levels of myocardial biomarkers in patients with CVD was significantly higher than that of patients without CVD on admission, and the rates of acute myocardial injury in hospital was remarkably increased. The infection of SARS-CoV-2 may cause direct primary myocardial injury or

Figure 1. Survival analysis by Kaplan–Meier curve in patients with vs. without cardiovascular disease.
aggravate the original myocardial injury. Previous reports showed that ACE2 expression was significantly decreased in the myocardium of mice infected with SARS-CoV, resulting in ACE2-dependent myocardial injury.25 In addition, SARS-CoV-2 had a stronger interaction with ACE2 than SARS-CoV,26 and may directly or indirectly cause heart damage through ACE2-related pathways. Ribose nucleic acid of SARS-CoV was detected in the hearts of dead SARS patients and viral inclusion bodies were found in cardiac myocytes in pathological examination. It proved that SARS-CoV can directly infect the heart. Pathological findings of COVID-19 patients showed degeneration and necrosis of the cardiomyocytes,27 so the same mechanism could not be ruled out for SARS-CoV-2. Autopsy report showed interstitial mononuclear inflammatory infiltrates in heart tissue. In this study, inflammatory biomarkers were significantly increased in mononuclear inflammatory infiltrates in heart tissue. In this study, inflammatory biomarkers were significantly increased in patients with CVD, indicating that inflammatory cell necrosis promoted inflammatory response and led to cytokine storm damage to the myocardium, which can be severe and even lead to fulminant myocarditis.28,29

Lesions of COVID-19 patients were mainly focus on the lung, but other organs may also have different degrees of damage. Patients with CVD had higher rate of acute liver injury and acute renal injury in hospitalization. A study reported that specific expression of ACE2 in bile duct cells may lead to liver injury after SARS-CoV-2 infection.30 Patients with CVD had poor compensatory ability of cardiac function and inflammatory storm, which exacerbated microcirculation ischemia and hypoxia of liver cells and further aggravated liver function injury. As the organ with high expression of ACE2, kidney was the primary target of injury. Furthermore, pneumonia caused by SARS-CoV-2 infection caused gas exchange disorders, acidosis and oxygen-free radicals during anoxic reperfusion made patients more prone to renal dysfunction. This study has several limitations. First, this is a single-center descriptive study, the patients included in this study were early stages of the epidemic, coronaviruses at this stage were more virulent. Data from more centers and more patient populations are needed to further confirm the relationship between CVD and COVID-19. Secondly, due to limited medical resources and time for diagnosis in the outbreak, there was a lack of some important laboratory data for the patients, such as echocardiography, electrocardiogram and cytokines. Finally, this study only observed the starting point and results of patients, lacking dynamic observation of disease progression.

Conclusions
Older age (>65 years old) and CVD are independent risk factors for COVID-19 patients. COVID-19 patients with CVD were more severe and had higher mortality rate, early intervention and vigilance should be taken.

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Conflict of interest. The authors declare that they have no conflict of interest.

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