Original Article

Clinical course and outcomes of COVID-19 patients with a history of cerebrovascular disease: a retrospective study in Wuhan

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Background: Data on patients with coronavirus disease 2019 (COVID-19) who have pre-existing cerebrovascular disease (CVD) are scarce. This study set out to describe the clinical course and outcomes of these patients.

Methods: This single-center retrospective study was performed at Huoshenshan Hospital in Wuhan, China. Patients with confirmed COVID-19 who had pre-existing CVD (N=69) were identified. COVID-19 patients without CVD were randomly selected and matched by age and sex to the patients with CVD. Clinical data were analyzed and compared between the 2 groups. The composite endpoint included intensive care unit admission, use of mechanical ventilation, and death. Multivariable Cox regression analyses with control for medical comorbidities were used to examine the relationship between pre-existing CVD and clinical outcome of COVID-19.

Results: Compared with patients without CVD, patients with pre-existing CVD were more likely to present with unapparent symptoms at first; however, at admission, these patients tended to be in a severer condition than those without CVD, with more underlying hypertension and diabetes. The levels of interleukin-6, creative kinase MB, aspartate transaminase, and creatinine, as well as prothrombin time, were also markedly higher in patients with CVD. Patients with pre-existing CVD were more likely to develop multi-organ dysfunction, deteriorate to critical condition, and yield poorer clinical outcomes than patients without CVD. Concerning therapeutics, greater proportions of patients with pre-existing CVD required mechanical ventilation, higher-order anti-bacterials, and drugs targeting underlying diseases and complications. In the multivariable analysis, pre-existing CVD was significantly associated with a poor clinical outcome.

Conclusions: Patients with a history of CVD are more vulnerable to an over-activated inflammatory response and subsequent multi-organ dysfunction, resulting in a poor clinical outcome. Close monitoring is advisable for these patients.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); cerebrovascular disease (CVD); clinical course; clinical outcome

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is continuing to rage on around the globe (1). The World Health Organization (WHO) reported that, as of April 2021, there had been over 3.1 million deaths from the disease, with older people with underlying diseases, such as hypertension, diabetes, and cardiovascular disease, impacted hardest (2,3). Cerebrovascular disease (CVD) is another common senile disease, and cerebrovascular accidents as neurological complications of COVID-19 have been put much emphasis in prior studies. Regarding CVD as a comorbidity of COVID-19 (4), several retrospective studies (5-11) and meta-analyses (12-15) have confirmed that pre-existing CVD is associated with COVID-19 severity and mortality. However, little is known of the clinical characteristics of COVID-19 patients with pre-existing CVD, or of the impact of pre-existing CVD on the clinical course and outcomes of the disease.

Previous reports have shown that COVID-19 patients with pre-existing CVD are older, are more likely to be male, and have more comorbidities than those without CVD (5-8). However, the impact of discrepancies in these demographical features between patients with and without pre-existing CVD was not considered in these studies. To explore the impact of CVD pathophysiology on the clinical course of COVID-19, clinical data of COVID-19 patients with pre-existing CVD treated at Huoshenshan Hospital (Wuhan, China) and age- and sex-matched non-CVD COVID-19 patients selected from the same cohort were compared. The association of pre-existing CVD with the clinical outcome of COVID-19 was also examined *via* a multivariable Cox regression analysis. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-2237).

Methods

Study participants

Consecutive patients admitted to Huoshenshan Hospital between 5 February and 15 March, 2020 were included in this retrospective cohort study. This hospital, located in Wuhan in the province of Hubei, was assigned the responsibility of treating patients with COVID-19 by the Chinese government. The inclusion and exclusion criteria for patients are shown in *Figure 1*.

All confirmed COVID-19 patients with pre-existing CVD included in this study had a clear diagnosis of CVD by a physician on the report of the patients themselves or their family members, as well as their electronic medical records. Compared with the overall study population, patients with pre-existing CVD were significantly older [median (IQR), 71.0 (67.0–81.0) *vs.* 60.0 (49.0–68.0); P<0.001], and a higher proportion were male (56.5% *vs.* 51.1%; P<0.001). Older age and male sex have been demonstrated to be associated with in-hospital death among patients with COVID-19 (16,17). Thus, to adjust for age and sex, an age- (±2 years) and sex-matched COVID-19 patient without CVD was randomly selected for each patient in the CVD group, using a method similar to ones reported previously (18,19). Whenever more than one non-CVD patient was available for a patient with CVD, a match was randomly selected from the patients available. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the National Health Commission of China and the Institutional Review Board in Huoshenshan Hospital (approval No. K202101-02). The requirement to obtain written informed consent from patients with emerging infectious diseases was waived by the ethics committee of the designated hospital.

Data collection

All data were extracted from patients' electronic medical records by 2 investigators and then independently reviewed by 2 analysts. According to a previous observational study (20), clinical data were collected in detail, which included: demographic information (age, sex, and comorbidities); onset symptoms (e.g., fever, cough, dyspnea, and myalgia); vital signs (blood pressure, heart rate, respiratory rate, and body temperature); laboratory data (i.e., infection-related indices, blood routine test, coagulation function test, myocardial injury markers, liver function indices, kidney function indices, electrolytes, and glucose); and complications (e.g., respiratory

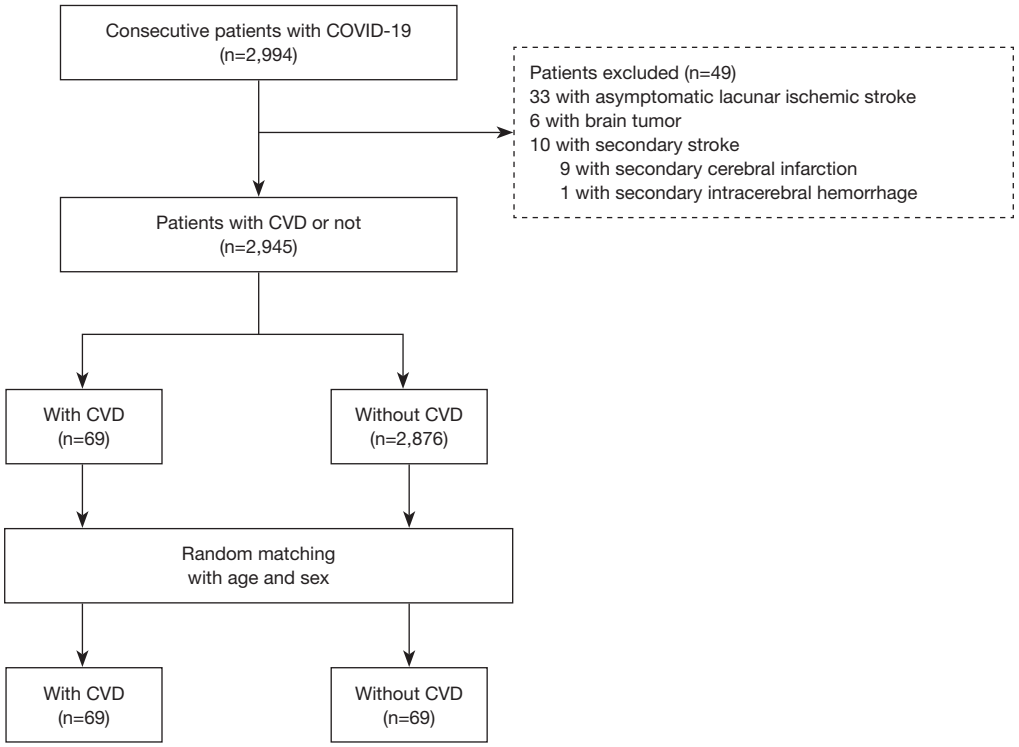

Figure 1 Flowchart of patient recruitment.

failure and septic shock).

Additionally, clinical information concerning therapeutics were also collected. According to the WHO's interim guidelines (21), all patients received individualized systematic treatment, including antivirals, oxygen support, secondary infection control, immunomodulators, and multi-organ support. As the key therapeutic approach, oxygen therapy was given through normal or high-flow nasal cannulas, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). For patients with a history of CVD, individualized therapy including antiplatelets, anti-coagulation agents, antihypertensives, antidiabetic agents, or brain-protective agents were administered according to the relevant guidelines (22,23).

In this study, a composite endpoint consisting of unfavorable clinical outcomes including admission to the intensive care unit (ICU), use of mechanical ventilation, and death was adopted as the primary outcome. Secondary outcomes included the occurrence of disease progression, disease deterioration, viral clearance, and death. All patients were followed up to discharge from hospital after recovery, or death. The durations of onset of COVID-19 symptoms to hospital admission, disease progression, disease deterioration, death, the occurrence of the composite endpoint, and viral clearance, were recorded, respectively.

Definitions

Cases of COVID-19 were diagnosed on the basis of the WHO's interim guidance (21). Disease severity was defined in accordance with the guidelines for the diagnosis and management of COVID-19 (6th edition) released by the National Health Commission of China (24). Disease progression and disease deterioration were defined as the exacerbation of disease from non-severe types (including mild and moderate types) to severe and critical types, respectively. Viral clearance was considered when negative nucleic acid results of respiratory tract specimens were produced 3 times consecutively with sampling intervals of more than 24 hours.

The occurrence of complications was confirmed according to the following criteria. Anemia was diagnosed based on hemoglobin <110 g/L. Myocardial injury was reported if the serum levels of cardiac troponin I (cTnI) or creatine kinase isoenzyme (CKMB) exceeded the upper

limit of normal (ULN) (25). The diagnosis of liver injury was made based on an alanine transaminase (ALT) or aspartate aminotransferase (AST) level more than 3-fold the ULN, or a total bilirubin (TBIL) level more than 2-fold the ULN (26). Hypoproteinemia was defined by a serum albumin level less than 25 g/L (16). Acute kidney injury (AKI) was defined by an increase in serum creatinine (Cr) levels to more than 1.5 times the baseline (27). Sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) were diagnosed according to the International Society of Thrombosis and Haemostasis (ISTH) scoring systems (28,29). Cardiac insufficiency was defined as a serum level of brain natriuretic peptide (BNP) exceeding the normal range combined with the presence of associated symptoms, such as dyspnea, orthopnea, and edema of the lower extremity (30). Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin definition (31). Respiratory failure was defined by an arterial partial pressure of oxygen of less than 60 mmHg. Multiple organ dysfunction syndrome (MODS) was diagnosed on the basis of the multiple organ dysfunction score (32). Shock was defined in accordance with the 2016 Third International Consensus Definition for Sepsis and Septic Shock (33).

Statistical analysis

No imputation was made for variables with missing data. Quantitative data with non-normal distribution were expressed as medians [interquartile ranges (IQRs)] and statistically compared using the Mann-Whitney U non-parametric test. Percentages (%) of enumeration data were calculated and compared using the χ^2 test or Fisher's exact test. Survival curves were plotted employing the Kaplan-Meier method with the log-rank test.

For the assessment of whether pre-existing CVD was an independent risk factor for the primary outcome, Cox regression analyses were carried out. Considering the death toll was not large in our study, and to avoid overfitting in the multivariable model, 3 variables (age, CVD, and malignancy) were chosen for the multivariable model. All variables included were based on their clinical and scientific merits, previous findings, and the results of univariable analyses. Variables (i.e., atrial fibrillation and chronic kidney disease) were excluded from the Cox regression models if the number of events was deemed too small. All statistical analyses were performed with SPSS software (version 22.0, IBM Corp). P<0.05 was considered to indicate statistical significance.

Results

Identification of patients with pre-existing CVD

Figure 1 depicts the flowchart of participant selection. A total of 2,994 consecutive hospitalized patients with confirmed COVID-19 in the medical record system were screened from 5 February to 15 March, 2020. Among these cases, 33 patients with asymptomatic lacunar ischemic stroke (diagnosed in previous health examinations), 10 patients with secondary stroke (diagnosed after the occurrence of COVID-19), and 6 patients with brain tumor were excluded. Among the 2945 cases remaining, 69 patients with a history of CVD were identified, including 56 cases with cerebral infarction, 8 cases with symptomatic lacunar ischemic stroke, 4 cases with intracerebral hemorrhage, and 1 case with subarachnoid hemorrhage (*Figure 2A*). Of these 69 patients, 9 exhibited no residual symptoms on admission, whereas the others presented with neurological sequelae such as limb dyskinesia, cognitive disorder, aphasia, loss of self-sufficiency, sensory disorder, bulbar paralysis, and prosopoplegia (*Figure 2B*). The median interval from the diagnosis of CVD to admission was 6 years (IQR, 1–10 years), and there were 13 patients who had been newly diagnosed with CVD within the previous 3 months.

Demographic and clinical features

Baseline demographic and clinical features of the COVID-19 patients with pre-existing CVD and matched patients without CVD are shown in *Table 1*. There was no difference in the duration from the onset of COVID-19 symptoms to admission between the 2 groups [22.0 (7.0–40.5) *vs.* 21.0 (14.0–36.0) days; P=0.427]. Patients with pre-existing CVD had a higher prevalence of comorbid hypertension (75.4% *vs.* 43.5%) and diabetes (34.8% *vs.* 11.6%) than patients without CVD (all P values <0.01). Interestingly, in the early stage of the disease, patients with CVD were more likely to be asymptomatic (17.4% *vs.* 2.9%; P=0.005) and exhibited fewer systematic symptoms (i.e., chill, myalgia and fatigue; all P values <0.05) and respiratory symptoms (i.e., dry cough and dyspnea; all P values <0.01). Despite having less obvious symptoms, patients with CVD were more likely than those without CVD to be in a severe condition (43.5% *vs.* 26.1%; P=0.032) on admission. No significant difference was found in vital signs on admission

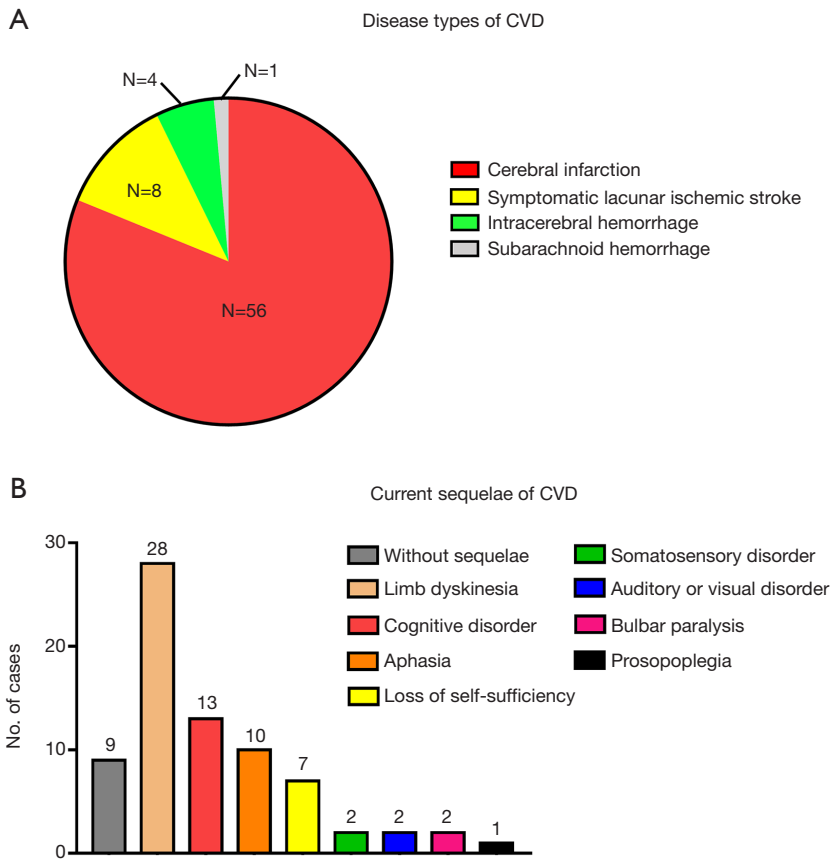

Figure 2 Disease type (A) and current neurological manifestations (B) of 69 patients with cerebrovascular diseases.

Table 1 Demographic and clinical features of matched COVID-19 patients with and without CVD

Variable	Patients with CVD (n=69)	Patients without CVD (n=69)	P[a]
Age, y	71.0 (67.0–81.0)	71.0 (66.5–81.0)	0.811
Male, No. (%)	39 (56.5)	39 (56.5)	1.000
Symptom onset to admission, d	22.0 (7.0–40.5)	21.0 (14.0–36.0)	0.427
Comorbidity, No. (%)			
Hypertension	52 (75.4)	30 (43.5)	0.000*
Diabetes	24 (34.8)	8 (11.6)	0.001*
CHD	14 (20.3)	10 (14.5)	0.500
AF	4 (5.8)	1 (1.4)	0.362[a]
COPD	8 (11.6)	7 (10.1)	1.000
CKD	2 (2.9)	1 (1.4)	1.000[a]
Malignancy	5 (7.2)	4 (5.8)	1.000[a]
Disease classification, No. (%)			
Non-severe group	39 (56.5)	51 (73.9)	0.032*

Table 1 (*continued*)

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Variable	Patients with CVD (n=69)	Patients without CVD (n=69)	P[a]
Severe group	30 (43.5)	18 (26.1)	0.032*
Severe type	23 (33.3)	14 (20.3)	
Critical type	7 (10.1)	4 (5.8)	
Onset symptoms, No. (%)			
Asymptomatic	12 (17.4)	2 (2.9)	0.005*
Fever	38 (55.1)	48 (69.6)	0.079
Max. temp, ℃	38.0 (37.7–38.5)	38.5 (38.0–38.9)	0.089
Chill	9 (13.0)	21 (30.4)	0.013*
Myalgia	10 (14.5)	22 (31.9)	0.016*
Fatigue	23 (33.3)	41 (59.4)	0.002*
Respiratory symptoms	36 (52.17)	54 (78.26)	0.001*
Dry cough	30 (43.5)	47 (68.1)	0.004*
Productive cough	13 (18.8)	9 (13.0)	
Dyspnea	14 (20.3)	37 (53.6)	0.000*
Nasal congestion	0 (0.0)	2 (2.9)	
Rhinorrhoea	0 (0.0)	1 (1.4)	
Pharyngalgia	1 (1.4)	3 (4.3)	
Chest tightness	9 (13.0)	12 (17.4)	
Chest pain	0 (0.0)	3 (4.3)	
Gastrointestinal symptoms	8 (11.6)	8 (11.6)	1.000
Anorexia	4 (5.8)	4 (5.8)	
Nausea	0 (0.0)	3 (4.3)	
Vomiting	1 (1.4)	4 (5.8)	
Diarrhea	4 (5.8)	2 (2.9)	
Abdominal distention	0 (0.0)	1 (1.4)	
Abdominal pain	0 (0.0)	1 (1.4)	
Vital signs on admission, median (IQR)			
HR, beats per min.	86.0 (79.0–93.5)	82.0 (76.5–90.0)	0.216
SBP, mmHg	137.0 (124.5–149.0)	132.0 (123.5–144.0)	0.620
DBP, mmHg	79.0 (68.0–87.0)	80.0 (75.0–89.0)	0.433
RR, breaths per min.	20.0 (19.0–21.0)	20.0 (20.0–22.0)	0.437
Temp, ℃	36.5 (36.3–36.8)	36.5 (36.3–36.8)	0.838
Max. HR, beats per min.	105.0 (98.3–115.0)	100.0 (98.0–106.5)	0.034*
Max. RR, breaths per min.	24.0 (22.0–27.0)	23.0 (22.0–25.5)	0.235
Max. Temp, ℃	37.0 (36.9–37.5)	37.0 (37.0–37.4)	0.986

[a], compared by Fisher's exact test. *, P<0.05. AF, atrial fibrillation; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; HR, heart rate; Max., maximum; RR, respiratory rate; SBP, systolic blood pressure; temp., temperature.

between patients with and without CVD; however, during hospitalization, those with CVD exhibited higher peak heart rates [105.0 (98.3–115.0) *vs.* 100.0 (98.0–106.5) beats per min; P<0.05)].

Laboratory findings

Initial laboratory parameters of the patients are shown in *Table 2*. In terms of infection-related indices, patients with pre-existing CVD presented with significantly higher interleukin-6 (IL-6) [8.7 (3.6–36.7) *vs.* 2.8 (1.5–5.4) pg/mL] than those without CVD. Regarding coagulation function, patients with CVD exhibited prolonged prothrombin time (PT) and thrombin time (TT), as well as an increased international normalized ratio (INR) (all P<0.05). Also, patients with CVD displayed higher levels of serum CKMB, myoglobin, AST, blood urea nitrogen, Cr, cystatin-c, urine red blood cells, and urine protein (all P<0.05).

Apart from initial laboratory indices, during hospitalization, the peak or lowest values of some parameters which are of importance to the diagnosis of complications were also recorded and analyzed. Patients with CVD had higher peak levels of IL-6 [8.8 (3.8–77.8) *vs.* 3.1 (1.5–8.2) pg/mL], procalcitonin (PCT) [0.08 (0.04–0.49) *vs.* 0.05 (0.04–0.08) ng/mL], CKMB [13.9 (9.2–20.3) *vs.* 9.5 (7.4–13.2) mg/L], cTnI [0.01 (0.01–0.06) *vs.* 0.01 (0.01–0.01) ng/mL], and AST [25.8 (18.5–43.1) *vs.* 20.4 (16.9–32.8) IU/L], and a longer PT [13.7 (12.7–15.1) *vs.* 12.8 (12.3–13.7) s], than patients without CVD (all P<0.05).

Complications and treatments

As shown in *Table 3*, in comparison to patients without CVD, those with pre-existing CVD had a higher likelihood of developing ARDS (14.5% *vs.* 4.3%; P<0.05). Furthermore, 23 (33.3%), 19 (27.5%), 18 (26.1%), and 16 (23.2%) patients with CVD had AKI, hypoproteinemia, SIC, and myocardial injury, respectively, which were significantly higher than those seen among patients without CVD (17.4%, 13.0%, 11.6%, and 5.8%), respectively (all P<0.05).

Regarding treatments (*Table 4*), patients with pre-existing CVD required more routine therapies for comorbidities than patients without CVD, including antihypertensives (71.0% *vs.* 46.4%), antidiabetic agents (34.8% *vs.*11.6%), antilipemics (37.7% *vs.* 14.5%), amiodarone (8.7% *vs.* 0.0%), and antiplatelet agents (42.0% *vs.* 23.2%) (all P<0.05). Importantly, patients with CVD were also more likely to need sedatives and analgesics (13.0% *vs.* 2.9%), mechanical ventilation (17.4% *vs.* 5.8%), and high-order antibacterials (30.4% *vs.* 8.7%) (all P<0.05), but not immunomodulators (all P>0.05). The use of therapies to prevent or treat complications, including anticoagulants (23.2% *vs.* 8.7%), hepatic protectants (21.7% *vs.* 8.7%), and albumin transfusion (31.9% *vs.*14.5%) was also significantly higher in patients with than without CVD (all P<0.05). However, the use of anti-asthmatic agents was lower among patients with CVD (11.6% *vs.* 29.0%; P<0.05).

Outcomes

As shown in *Table 3*, patients with pre-existing CVD were more likely than those without CVD to experience disease deterioration (20.3% *vs.* 7.2%; P<0.05) but not disease progression (P>0.05). Despite no significant difference existing in the length of hospital stay between the 2 groups (P>0.05), patients with CVD had worse outcomes, with higher rates of admission to the ICU (17.4% *vs.* 5.8%), use of mechanical ventilation (17.4% *vs.* 5.8%), and death (11.6% *vs.* 2.9%) (all P<0.05). The Kaplan-Meier survival curves also showed that patients with CVD had significantly escalated risks of disease deterioration [hazard ratio (HR), 3.104; 95% confidence interval (CI), 1.118–8.619; Log-rank P=0.021], death (HR, 4.378; 95% CI, 0.929–20.621; Log-rank P=0.041), and unfavorable outcomes (HR, 3.017; 95% CI, 1.075–8.466; Log-rank P=0.027) compared to their non-CVD counterparts (*Figure 3*). However, no significant difference in disease progression or viral clearance was observed between the 2 groups (*Figure 3*).

In the initial univariate Cox regression analyses of demographic variables, CVD was identified as a changed risk factor (HR, 3.017; 95% CI, 1.075–8.466; P=0.036) for an unfavorable outcome among the patients in the cohort. Thereafter, a multivariate model including age, CVD, and malignancy was established employing a forward stepwise approach, which indicated that CVD was an independent risk factor (HR, 3.155; 95% CI, 1.121–8.878; P=0.030) for an unfavorable clinical outcome of COVID-19 (*Table 5*).

Discussion

The present study analyzed the characteristics of COVID-19 patients with pre-existing CVD and sex- and age-matched COVID-19 patients without CVD. Among these patients with COVID-19, CVD was identified as an

Table 2 Laboratory results of matched COVID-19 patients with and without CVD

Variable	Patients with CVD (n=69)	Patients without CVD (n=69)	P
Initial laboratory examination (normal range), median (IQR)			
Infection-related indices			
IL–6, pg/mL (<7)	8.7 (3.6–36.7)	2.8 (1.5–5.4)	0.001*
PCT, ng/mL (0–0.05)	0.07 (0.03–0.16)	0.05 (0.03–0.07)	0.085
CRP, mg/L (0–4)	7.6 (1.4–49.4)	4.6 (1.5–19.3)	0.119
WBC, $\times10^9$/L (3.5–9.5)	6.3 (4.7–8.9)	5.7 (4.6–7.5)	0.296
NEU, $\times10^9$/L (1.8–6.3)	4.2 (2.8–6.8)	3.7 (2.8–4.8)	0.155
LYM, $\times10^9$/L (1.1–3.2)	1.2 (0.8–1.6)	1.2 (0.9–1.6)	0.786
NLR (1.8–5.7)	3.0 (2.2–5.8)	3.1 (1.9–4.4)	0.269
Blood routine test			
RBC, $\times10^{12}$/L (3.8–5.1)	3.9 (3.4–4.3)	3.8 (3.5–4.1)	0.647
Hb, g/L (115–150)	116.0 (103.0–131.0)	116.5 (105.5–127.5)	0.940
PLT, $\times10^9$/L (125–350)	210.0 (148.0–265.0)	211.0 (162.8–266.5)	0.697
Coagulation function test			
FIB, g/L (1.8–3.5)	3.3 (2.8–3.8)	3.3 (2.9–3.8)	0.785
APTT, s (21–37)	28.9 (26.2–31.2)	27.9 (26.0–29.7)	0.172
PT, s (9.2–15)	13.5 (12.4–14.6)	12.8 (12.2–13.6)	0.021*
TT, s (14–21)	15.5 (14.7–17.0)	15.1 (14.6–15.9)	0.047*
INR (0.8–1.25)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	0.040*
D-dimer, mg/L (0–0.55)	0.9 (0.5–1.6)	0.8 (0.4–1.2)	0.129
PTA, (70–125)	92.3 (87.5–99.1)	96.1 (92.1–99.0)	0.059
Myocardial injury markers			
CKMB, IU/L (0–24)	10.5 (7.8–15.7)	9.0 (7.0–11.7)	0.008*
LDH, IU/L (120–250)	196.0 (164.8–260.8)	189.7 (162.0–241.4)	0.369
MYO, ng/mL (0–65)	16.2 (9.5–52.6)	8.5 (4.7–12.3)	0.000*
cTnI, ng/mL (0–0.04)	0.01 (0.01–0.04)	0.01 (0.01–0.01)	0.057
BNP, pg/mL (0–100)	27.0 (12.2–75.0)	14.3 (0.0–65.5)	0.142
Liver function indices			
ALT, IU/L (7–40)	19.1 (11.6–39.0)	17.8 (13.9–26.4)	0.340
AST, IU/L (7–45)	21.1 (16.3–30.6)	18.9 (14.9–25.5)	0.047*
TB, g/L (20–30)	63.5 (59.7–68.8)	63.6 (58.4–68.0)	0.557
ALB, g/L (40–55)	35.6 (32.5–39.0)	35.6 (33.3–38.8)	0.786
TBIL, μmol/L (0–21)	9.2 (6.7–13.7)	10.2 (7.4–12.7)	0.651
DBIL, μmol/L (0–8)	3.7 (2.7–5.2)	3.6 (2.5–4.7)	0.477
γ-GT, IU/L (7–45)	29.4 (19.1–42.4)	29.0 (20.7–39.9)	0.930

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Patients with CVD (n=69)	Patients without CVD (n=69)	P
Kidney function indices			
BUN, mmol/L (3.1–8.8)	5.7 (4.4–8.9)	4.5 (3.6–6.1)	0.001*
Cr, μmol/L (41–81)	77.3 (59.3–94.7)	66.6 (56.3–78.2)	0.032*
CysC, mg/L (22–29)	1.2 (1.0–1.5)	1.0 (0.9–1.2)	0.000*
URBC, ×1/μL (0–10)	3.0 (0.0–41.0)	0.0 (0.0–3.5)	0.007*
UPRO (0)	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.001*
Electrolytes and glucose			
Na^+, mmol/L (137–147)	141.2 (138.1–143.8)	141.7 (139.0–143.7)	0.978
K^+, mmol/L (3.5–5.3)	4.3 (3.8–4.7)	4.3 (4.0–4.5)	0.624
Ca^{2+}, mmol/L (211–252)	2.2 (2.0–2.3)	2.1 (2.1–2.2)	0.280
Cl^-, mmol/L (99–110)	106.0 (102.4–108.3)	106.3 (104.0–108.1)	0.646
Glu, mmol/L (3.9–6.1)	5.5 (5.0–6.5)	4.9 (4.7–5.8)	0.002*
Peak/lowest value during hospitalization (normal range), median (IQR)			
Max. CRP, mg/L (0–4)	12.3 (1.2–71.6)	5.8 (1.9–30.7)	0.088
Max. PCT, ng/mL (0–0.05)	0.08 (0.04–0.49)	0.05 (0.04–0.08)	0.030*
Max. IL-6, pg/dL (<0.07)	8.8 (3.8–77.8)	3.1 (1.5–8.2)	0.001*
Max. WBC, $\times10^9$/L (3.5–9.5)	7.1 (5.5–11.3)	6.5 (5.1–8.1)	0.074
Min. Hb, g/L (115–150)	111.0 (87.0–121.5)	112.0 (99.5–123.0)	0.158
Min. PLT, $\times10^9$/L (125–350)	190.0 (132.5–232.5)	199.0 (160.5–236.5)	0.399
Min. FIB, g/L (1.8–3.5)	2.9 (2.6–3.5)	3.1 (2.7–3.5)	0.329
Max. PT, s (9.2–15)	13.7 (12.7–15.1)	12.8 (12.3–13.7)	0.003*
Max. TT, s (14–21)	15.6 (14.8–17.3)	15.1 (14.7–16.0)	0.080
Max. D-dimer, mg/L (0–0.55)	1.1 (0.5–2.5)	0.8 (0.4–1.8)	0.073
Max. CKMB, IU/L (0–24)	13.9 (9.2–20.3)	9.5 (7.4–13.2)	0.000*
Max. cTnI, ng/mL (0–0.04)	0.01 (0.01–0.06)	0.01 (0.01–0.01)	0.046*
Max. BNP, pg/mL (0–100)	44.3 (12.9–133.1)	18.2 (0.0–70.0)	0.091
Max. AST, IU/L (7–45)	25.8 (18.5–43.1)	20.4 (16.9–32.8)	0.034*
Min. ALB, g/L (40–55)	34.0 (29.3–37.4)	35.3 (32.6–37.8)	0.193
Max. TBIL, μmol/L (0–21)	10.9 (8.0–16.0)	11.4 (8.5–14.0)	0.981
Max. Cr, μmol/L (41–81)	79.1 (63.2–110.9)	68.2 (57.7–79.0)	0.016*

*, P<0.05. ALB, albumin; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; CKMB, creative kinase MB; Cr, creatinine; CRP, C-reactive protein; cTnI, cardiac tropinin I; CVD, cerebrovascular disease; CysC, cystatin C; DBIL, direct bilirubin; FIB, fibrinogen; Glu, glucose; Hb, hemoglobin; IL-6, interleukin-6; INR, international normalized ratio; LDH, lactate dehydrogenase; LYM, lymphocyte; MYO, myoglobin; NEU, neutrophil; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PLT, blood platelet; PT, prothrombin time; PTA, prothrombin activity; RBC, red blood cell; TBIL, total bilirubin; TT, thrombin time; UPRO, urine protein; URBC, urine red blood cell; WBC, white blood cell.

Table 3 Complications and outcomes of matched COVID-19 patients with and without CVD

Variable	Patients with CVD (n=69)	Patients without CVD (n=69)	P[a]
Complications, No. (%)			
GIB	5 (7.2)	1 (1.4)	0.210[a]
Anemia	33 (47.8)	31 (44.9)	0.733
Myocardial injury	16 (23.2)	4 (5.8)	0.004*
Liver injury	5 (7.2)	3 (4.3)	0.718[a]
Hypoproteinemia	19 (27.5)	9 (13.0)	0.038*
AKI	23 (33.3)	12 (17.4)	0.031*
SIC	18 (26.1)	8 (11.6)	0.029*
Cardiac insufficiency	4 (5.8)	0 (0.0)	0.128[a]
DIC	4 (5.8)	1 (1.4)	0.362[a]
ARDS	10 (14.5)	3 (4.3)	0.041*
Respiratory failure	10 (14.5)	4 (5.8)	0.091
MODS	3 (4.3)	1 (1.4)	0.612[a]
Septic shock	6 (8.7)	1 (1.4)	0.121[a]
Outcomes, No. (%)			
Length of stay, median (IQR), d	12.0 (7.0–18.0)	13.0 (7.0–19.5)	0.435
Disease progression	38 (55.1)	35 (50.7)	0.609
Disease deterioration	14 (20.3)	5 (7.2)	0.026*
Composite endpoint	13 (18.8)	5 (7.2)	0.043*
Admission to ICU	12 (17.4)	4 (5.8)	0.033*
Use of mechanical ventilation	12 (17.4)	4 (5.8)	0.033*
Death	8 (11.6)	2 (2.9)	0.049*
Symptom onset to, median (IQR), d			
Disease progression	31.0 (16.0–45.5)	31.0 (20.0–43.0)	0.483
Disease deterioration	36.0 (24.5–47.5)	39.0 (29.5–49.0)	0.185
Discharge	37.0 (25.5–49.5)	39.0 (31.0–50.5)	0.354
Composite endpoint	35.0 (23.5–47.5)	39.0 (29.5–49.0)	0.095

[a], compared by Fisher's exact test. *, P<0.05. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CVD, cerebrovascular disease; DIC, disseminated intravascular coagulation; GIB, gastrointestinal bleeding; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome; SIC, sepsis-induced coagulopathy.

independent predictor of adverse outcomes. Among patients hospitalized with COVID-19 in Huoshenshan Hospital between 5 February and 15 March, 2020, the prevalence of CVD was 2.3% (69/2, 994). Compared with COVID-19 patients without CVD, those with pre-existing CVD were more likely to have underlying diseases, and, although they tended to present with unapparent initial symptoms, they had severer COVID-19 on admission. Furthermore, during the course of their disease, patients with pre-existing CVD were more likely to have severer secondary infection, develop ARDS and subsequent multi-organ dysfunction, deteriorate to a critical condition, and ultimately yield a worse outcome. Correspondingly, higher proportions of patients with pre-existing CVD required higher-order anti-

Table 4 Treatment of matched COVID-19 patients with and without CVD

Treatments, No. (%)	Patients with CVD (n=69)	Patients without CVD (n=69)	P[a]
Oxygen therapy			
Oxygen inhalation	63 (91.3)	60 (87.0)	0.412
High-flow nasal cannula	3 (4.3)	3 (4.3)	1[a]
Mechanical ventilation	12 (17.4)	4 (5.8)	0.033*
Non-invasive	5 (7.2)	4 (5.8)	
Invasive	10 (14.5)	2 (2.9)	
ECMO	0 (0.0)	0 (0.0)	
Renal replacement therapy	4 (5.8)	1 (1.4)	0.362[a]
Bronchoalveolar lavage	4 (5.8)	0 (0.0)	0.128[a]
Antivirals	36 (52.1)	43 (62.3)	0.228
Umidenovir	29 (42.0)	37 (53.6)	
Oseltamivir	5 (7.2)	3 (4.3)	
Ribavirin	2 (2.9)	4 (5.8)	
Lopinavir and ritonavir	1 (1.4)	1 (1.4)	
Interferon	7 (10.1)	11 (15.9)	
Chloroquine	2 (2.9)	0 (0.0)	
Antibacterials			
First- and second-line antibacterials	22 (31.9)	26 (37.7)	0.475
Quinolones	22 (31.9)	24 (34.8)	
Cephalosporins	3 (4.3)	4 (5.8)	
Third-line antibacterials	21 (30.4)	6 (8.7)	0.001*
β-lactamase inhibitors	15 (21.7)	5 (7.2)	0.016*
Carbapenems	12 (17.4)	3 (4.3)	0.014*
Vancomycin	2 (2.9)	0 (0.0)	
Polymyxins	1 (1.4)	0 (0.0)	
Tigecycline	4 (5.8)	0 (0.0)	
Linezolid	4 (5.8)	1 (1.4)	
Antifungals	5 (7.2)	2 (2.9)	0.438[a]
Immunomodulators			
Glucocorticoids	15 (21.7)	16 (23.2)	0.838
Immunoglobulin	8 (11.6)	4 (5.8)	0.227
Thymosin	19 (27.5)	12 (17.4)	0.153
Tocilizumab	6 (8.7)	3 (4.3)	0.490[a]
Convalescent plasma	5 (7.2)	6 (8.7)	0.753
Pidotimod	4 (5.8)	5 (7.2)	1[a]
Mesenchymal stem cells	1 (1.4)	1 (1.4)	1[a]
rhG-CSF	2 (2.9)	1 (1.4)	1[a]

Table 4 (*continued*)

Table 4 (*continued*)

Treatments, No. (%)	Patients with CVD (n=69)	Patients without CVD (n=69)	P[a]
Antihypertensives	49 (71.0)	32 (46.4)	0.003*
Diuretics	5 (7.2)	0 (0.0)	
RAAS inhibitors	12 (17.4)	5 (7.2)	
Beta-blockers	13 (18.8)	9 (13.0)	
CCBs	41 (59.4)	28 (40.6)	
Urapidil	2 (2.9)	0 (0.0)	
Nitroglycerin	1 (1.4)	0 (0.0)	
Antidiabetics	24 (34.8)	8 (11.6)	0.001*
Insulin	12 (17.4)	5 (7.2)	
Metformin	10 (14.5)	5 (7.2)	
Acarbose	13 (18.8)	4 (5.8)	
Insulin secretagogues	4 (5.8)	2 (2.9)	
Drugs for cardiovascular disorders			
Cardiotonic drugs	5 (7.2)	0 (0.0)	0.068[a]
Amiodarone	6 (8.7)	0 (0.0)	0.028[a]*
Antianginal drugs	5 (7.2)	9 (13.0)	0.259
Creatine phosphate	4 (5.8)	3 (4.3)	1[a]
Antilipemic agents	26 (37.7)	10 (14.5)	0.002*
Anticoagulants	16 (23.2)	6 (8.7)	0.033*
Antiplatelet agents	29 (42.0)	16 (23.2)	0.018*
Drugs for gastrointestinal disorders			
Acid inhibitors	23 (33.3)	18 (26.1)	0.352
Laxatives	16 (23.2)	16 (23.2)	1
Antidiarrheics	4 (5.8)	2 (2.9)	0.676[a]
Gastrointestinal stimulants	9 (13.0)	11 (15.9)	0.629
Probiotics	17 (24.6)	15 (21.7)	0.687
Hepatic protectants	15 (21.7)	6 (8.7)	0.033*
Drugs for respiratory disorders			
Anti-asthmatics	8 (11.6)	20 (29.0)	0.011*
Expectorants	25 (36.2)	32 (46.4)	0.226
NSAIDs	14 (20.3)	8 (11.6)	0.163
Sedatives & analgesics	9 (13.0)	2 (2.9)	0.028*
RBC transfusion	7 (10.1)	1 (1.4)	0.069[a]
Albumin transfusion	22 (31.9)	10 (14.5)	0.016*

[a], compared by Fisher's exact test. *, P<0.05. CCBs, calcium channel blockers; CVD, cerebrovascular disease; ECMO, extracorporeal membrane oxygenation; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system; RBC, red blood cell; rhG-CSF, recombinant human granulocyte colony-stimulating factor.

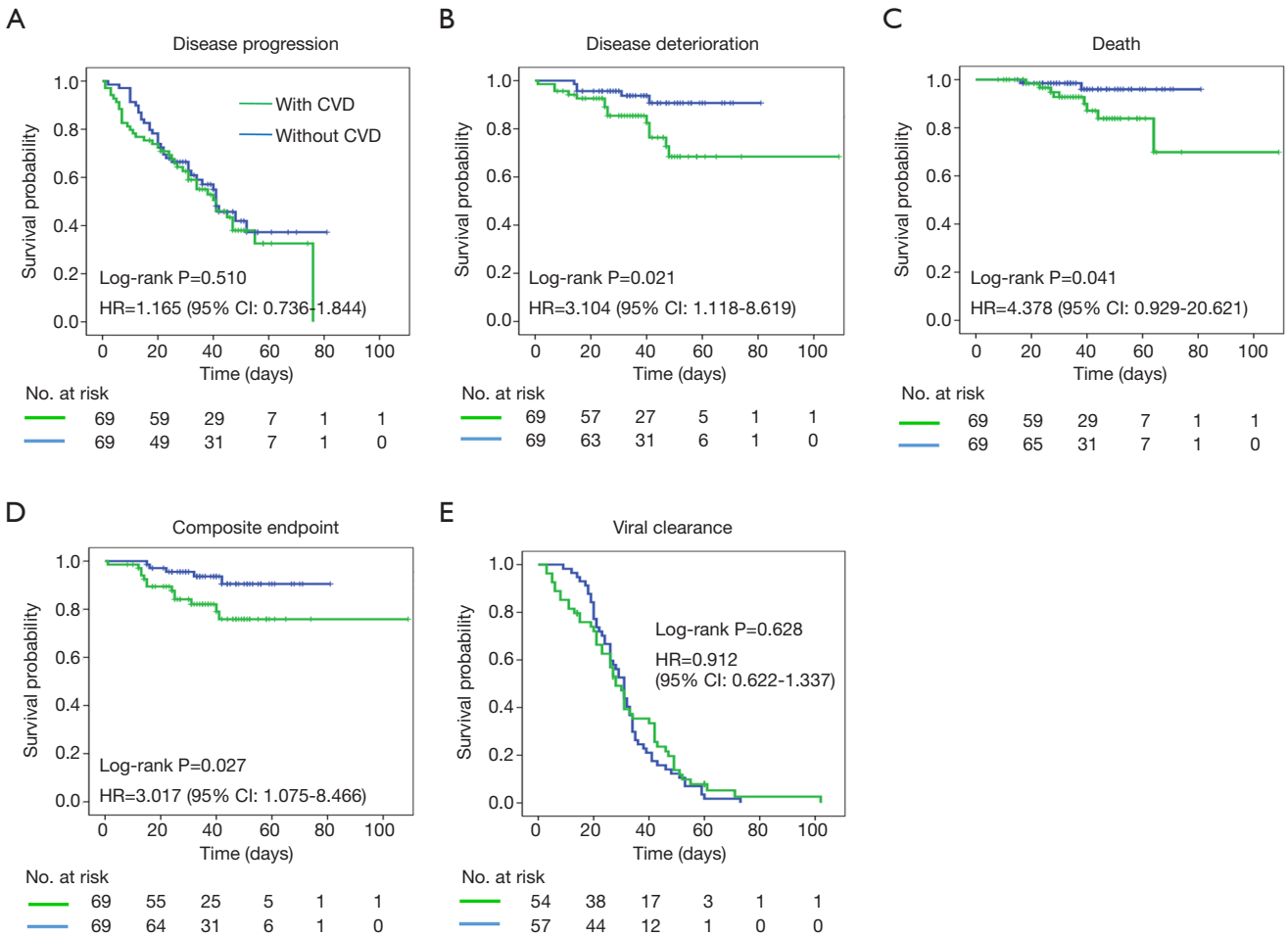

Figure 3 Kaplan-Meier plots for different clinical outcomes in patients with and without pre-existing cerebrovascular diseases. The figure displays Kaplan-Meier survival plots according to disease progression (A), disease deterioration (B), death (C), the composite endpoint (D), and viral clearance (E). CVD, cerebrovascular disease; HR, hazard ratio.

bacterials, mechanical ventilation, and ICU admission. Furthermore, therapeutics aiming at controlling and preventing comorbidities and complications were also more frequently administered to patients with pre-existing CVD.

Since the outbreak of the COVID-19 pandemic, neurological symptoms and complications of the disease have been widely described (34). COVID-19 has also been reported to be an independent predictor for the occurrence of stroke in hospitalized patients as well as mortality of these patients with stroke (35,36). It is suggested that COVID-19 represents a state of hypoxia, inflammation, and hypercoagulability. These pathophysiological changes may underpin the development of stroke (37). However, comprehensive data concerning the impact of pre-existing CVD on the clinical course of COVID-19 have seldom been reported. To date, several cohort studies have compared clinical data between patients with and without pre-existing CVD. They observed that COVID-19 patients with pre-existing CVD were older and more likely to be male, and had more comorbidities and severer disease than patients without CVD, resulting in a higher mortality rate (5-8). One limitation of these studies is that the authors lost sight of the impact of age and sex on the clinical course and outcomes of patients with COVID-19, since they had already been verified as independent predictors of adverse outcome of COVID-19 (16,17). Since the aim of our study was to explore the impact of CVD pathophysiology on the clinical course of COVID-19, a matching method was utilized to account for the impact of the demographic features on COVID-19. In addition to the risk conferred by age and sex, pre-existing

Table 5 Cox regression analyses of risk factors for the outcome of the composite endpoint in matched COVID-19 patients with and without CVD

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y	1.016 (0.966–1.068)	0.539	–	–
Male	1.496 (0.561–3.987)	0.421		
Hypertension	1.069 (0.414–2.761)	0.890		
Diabetes	1.467 (0.521–4.129)	0.468		
CHD	0.279 (0.037–2.099)	0.215		
CVD	3.017 (1.075–8.466)	0.036	3.155 (1.121–8.878)	0.030
COPD	1.040 (0.239–4.524)	0.958		
Malignancy	3.097 (0.892–10.752)	0.075	–	–

The multivariable model contains age, CVD, and malignancy. CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; HR, hazard ratio.

CVD itself was demonstrated to be associated with an unfavorable outcome of COVID-19 in the present study.

One interesting phenomenon we identified was that higher proportions of COVID-19 patients with pre-existing CVD were asymptomatic or presented with unapparent system symptoms (chill, myalgia, and fatigue) and respiratory symptoms (cough and dyspnea) at disease onset compared with their non-CVD counterparts. Accordingly, patients with pre-existing CVD were less likely to receive anti-asthmatic drugs during hospitalization. However, they were more likely to have severe disease and to deteriorate to a critical condition. Considering these observations, the possibility of severe illness masquerading as mild symptoms should not be overlooked, and much more attention should be paid to this subgroup of COVID-19 patients.

Additionally, COVID-19 patients with pre-existing CVD presented with clinical characteristics seen in severe or critical illness, including cytokine storm, ARDS, and subsequent extra-pulmonary organ dysfunction, as evidenced by abnormities in IL-6 and other laboratory indices during the disease's clinical course. Cell entry of SARS-CoV-2 directly damages the lungs, kidneys, heart, gastrointestinal tract, and vasculature (38). In most cases, it is self-limited, owing to the clearance of SARS-CoV-2 from the lung via adaptive immune response. However, in severe cases, an aberrant uncontrolled response, in the form of a "cytokine storm", can result in multiple organ failure (39). The key mechanism is that, in the late stage of COVID-19, cytokine storm induces endothelial damage, predisposes the thrombotic/fibrinolytic imbalance toward a status of microthrombosis and microcirculatory disturbance, and finally causes multi-organ ischemic or hemorrhagic complications, especially in the lungs, heart, and kidneys (38). Consequently, the use of therapeutics aimed at controlling secondary infection and multi-organ support have been emphasized for patients with severe COVID-19 (21,24), as also seen in our study.

The pathophysiology of CVD is closely related to the specific clinical characteristics of the subgroup of COVID-19 patients included in this study. Firstly, due to bulbar paralysis, impaired locomotion, insufficient nutrition, and cognitive disorder, patients with pre-existing CVD have poor immunity and cardiac function, resulting in an escalated risk of secondary infection, especially hospital-acquired pneumonia (6,40). Secondly, owing to the disturbance of central nervous system regulatory functions, patients affected by neurological disease have lower ability to compensate for COVID-19 with unapparent symptoms, which leads to severer infection and respiratory depression (5). Thirdly, as illustrated in this study, patients with pre-existing CVD are more likely to have other comorbidities, such as hypertension and diabetes, which themselves are associated with mortality from COVID-19 (4,11,18). CVD may serve as a proxy for vascular frailty and a pro-inflammatory status caused by hypertension and diabetes, which predisposes patients to developing severer endothelial injury and subsequent multi-organ injury upon infection with SARS-CoV-2 (41). Last but not least, the potential neurotropism of SARS-CoV-2 could exert a possible detrimental effect in patients with pre-existing neurological diseases (42,43), which may form a vicious cycle for the pathophysiology of COVID-19.

Concerning therapeutics, there are several important findings in this study. Firstly, more COVID-19 patients with pre-existing CVD received third-line antibacterials, corroborating the existence of severer secondary infection in this subgroup of patients. Secondly, owing to disease deterioration, more patients with pre-existing CVD required ICU admission, and subsequent use of mechanical ventilation, sedatives & analgesics, and multi-organ supporting therapeutics. We observed more use of hepatic protectants, albumin, and amiodarone, as well as a trend toward more use of cardiotomic drugs in those with pre-existing CVD. However, no significance of other supporting treatments, such as creatine phosphate and renal replacement therapy, was seen between the two groups, which we believe may be owing to the small sample size of this study. Thirdly, greater proportions of patients with pre-existing CVD required antihypertensives, antidiabetics, antilepemic agents, anticoagulants, and antiplatelet agents. Hence, drugs targeting underlying diseases should also be emphasized in the management. These findings not only have important instruction significance for the treatment of this subgroup of patients, but also corroborate with the features of the clinical course mentioned above, which may deepen our understanding of the pathophysiology of comorbid COVID-19 and CVD.

There are several limitations to this work. Firstly, it was a single-center retrospective study with a relatively small number of patients, which made it challenging to accurately assess various risk factors using a multifactor regression model. Secondly, our findings may not be generalizable to other regions worldwide with diverse epidemiological characteristics, since all participants in this study were from the epicenter Wuhan during the early days of the outbreak. Thirdly, the available data did not address the heterogeneity of CVD, including disease severity and disease subtype, owing to the small sample size; future analysis with a larger population on a nationwide basis should consider these features as additional susceptibility factors. Fourthly, continued observation and follow-up of this subpopulation with COVID-19 is critical. Nevertheless, we hope that our results will provide guidance for clinicians to understand the complete picture of the disease and be conducive to improving the management of patients with COVID-19 who have a history of CVD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the National Health Commission of China and the Institutional Review Board of Huoshenshan Hospital (approval no. K202101-02). The requirement for written informed consent was waived by the ethics committees of the designated hospital for patients with emerging infectious diseases.

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