

ORIGINAL RESEARCH

Do underlying cardiovascular diseases have any impact on hospitalised patients with COVID-19?

Jixiang Zhang,¹ Shimin Lu,¹ Xiaoli Wang,² Xuemei Jia,¹ Jiao Li,¹ Hongbo Lei,³ Zhengru Liu,¹ Fei Liao,¹ Mengyao Ji,¹ Xiaoguang Lv,¹ Jian Kang,¹ Shan Tian,¹ Jingjing Ma,⁴ Dandan Wu,⁵ Yang Gong,⁶ Yu Xu,⁷ Weiguo Dong ¹

For numbered affiliations see end of article.

Correspondence to

Professor Weiguo Dong, Renmin Hospital of Wuhan University, Wuhan 430060, China; dwg@whu.edu.cn and Professor Yu Xu, Department of Otorhinolaryngology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China; xy37138@163.com

JZ and SL contributed equally.

JZ and SL are joint first authors.

Received 15 March 2020
Revised 26 April 2020
Accepted 27 April 2020
Published Online First
25 May 2020

ABSTRACT

Objectives An outbreak of the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has sickened thousands of people in China. The purpose of this study was to explore the early clinical characteristics of COVID-19 patients with cardiovascular disease (CVD).

Methods This is a retrospective analysis of patients with COVID-19 from a single centre. All patients underwent real-time reverse transcription PCR for SARS-CoV-2 on admission. Demographic and clinical factors and laboratory data were reviewed and collected to evaluate for significant associations.

Results The study included 541 patients with COVID-19. A total of 144 (26.6%) patients had a history of CVD. The mortality of patients with CVD reached 22.2%, which was higher than that of the overall population of this study (9.8%). Patients with CVD were also more likely to develop liver function abnormality, elevated blood creatinine and lactic dehydrogenase ($p < 0.05$). Symptoms of sputum production were more common in patients with CVD ($p = 0.026$). Lymphocytes, haemoglobin and albumin below the normal range were pervasive in the CVD group ($p < 0.05$). The proportion of critically ill patients in the CVD group (27.8%) was significantly higher than that in the non-CVD group (8.8%). Multivariable logistic regression analysis revealed that CVD (OR: 2.735 (95% CI 1.495 to 5.003), $p = 0.001$) was associated with critical COVID-19 condition, while patients with coronary heart disease were less likely to reach recovery standards (OR: 0.331 (95% CI 0.125 to 0.880), $p = 0.027$).

Conclusions Considering the high prevalence of CVD, a thorough CVD assessment at diagnosis and early intervention are recommended in COVID-19 patients with CVD. Patients with CVD are more vulnerable to deterioration.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, Hubei Province in December 2019, has since spread to the southwest region in an extremely short time.¹ The spread of the virus prompted Chinese officials to partially lock down major cities and strengthen public health interventions before the Spring Festival.² Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), sustained by person-to-person transmission, has impacted multiple countries and

has become a major threat to public health around the world.³ As of 25 April 2020, the SARS-CoV-2 had sickened 2 686 785 and killed 184 681 people worldwide. Due to the acute onset and rapid progressive nature of COVID-19, some patients follow an unusually aggressive clinical course, developing acute respiratory distress syndrome (ARDS).⁴

Massive financial resources and a great number of researchers have been devoted to containing the disease quickly and achieving a rapid progress in our understanding of COVID-19. Wu *et al*² have found that the basic reproductive number R0 for SARS-CoV-2 is 2.68 (95% CI 2.47 to 2.86), exceeding WHO estimates of 1.4–2.5. Epidemiological studies have demonstrated that underlying diseases are present more so in critically ill patients than in mild patients.^{5,6} As the most common coexisting medical condition, cardiovascular diseases (CVDs) are not only increasing the economic burden of the government but also threatening the outcome of patients with COVID-19. Whether COVID-19 patients with CVD are more likely to develop severe disease in a short amount of time is a question demanding attention. The aims of this study were to explore the early clinical characteristics of patients with CVD diagnosed with COVID-19 and to provide clues to assist experts in the early stage of clinical management.

METHODS**Study design and participants**

We conducted a retrospective study using an electronic medical records system. A total of 663 patients who were hospitalised and diagnosed with COVID-19 in the Renmin Hospital of Wuhan University from 11 January to 6 February 2020 were enrolled in this study. Renmin Hospital of Wuhan University, where patients with severe COVID-19 were diagnosed and treated in Wuhan, is a comprehensive hospital that serves as an education facility for both the Department of Health Care and the Department of Education. Patients with uncertain diagnosis or incomplete information ($n = 119$) were excluded from the present study to minimise assessment bias. Hospitalised mild patients ($n = 3$) with COVID-19 were also excluded from the present study due to the unreliability of applying reference rates to this group. A total of 541 patients with COVID-19 were ultimately included, 309 of whom were also included in a previous publication.⁷



► <http://dx.doi.org/10.1136/heartjnl-2020-317110>



© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Zhang J, Lu S, Wang X, *et al.* *Heart* 2020;**106**:1148–1153.

According to the official treatment and management policy during follow-up, all costs of COVID-19 treatment were covered by the Chinese medical insurance, and all patients underwent hospitalisation to control the progression and spread of the disease. Mild and partly ordinary patients were treated in cabin hospitals. Therefore, this study also includes ordinary patients, in addition to severe and critical patients. A confirmed case of COVID-19 was defined as a positive result on real-time reverse transcription PCR (RT-PCR), consistent with epidemic history, clinical symptoms and radiographic results.^{8,9} All cases were reviewed by three physicians (JZ, XW, JL) using the New Coronavirus Pneumonia Prevention and Control Program (Sixth Edition) published by the Chinese National Health Commission.⁹

Data collection

The chart records of all patients were critically and simultaneously reviewed by three physicians, respectively. Data, including demographics (age and gender), family history, disease duration, presence of other underlying diseases (concomitant diseases, malignant tumour and so on), clinical characteristics, laboratory test results, CT, period of treatment, therapeutic effect and disease severity, were obtained through review of electronic medical records. Underlying diseases, clinical characteristics, laboratory test results and CT were defined by the values on a patient's admission. A customised data collection form was used for information clustering and statistical analysis. The clinical outcomes were followed up until 9 March 2020.

The real-time RT-PCR assay was performed using a SARS-CoV-2 nucleic acid detection kit, according to the manufacturer's protocol (Shanghai bio-germ Medical Technology Co Ltd) and following the WHO guidelines¹⁰ in the laboratory medical centre of Renmin Hospital of Wuhan University, one of the first centres assigned by the government for viral testing. The laboratory tests for clinical lab index were performed in this laboratory medical centre. The serum levels of laboratory biomarkers (aspartate aminotransferase (AST), alanine aminotransferase, creatinine, lactate dehydrogenase and C reactive protein (CRP)) which were used to predict organ damage and inflammation in the body were referred to the 95th percentile upper reference limit.

Definitions

The following are the clinical classifications of COVID-19 in adults, according to the New Coronavirus Pneumonia Prevention and Control Program (Sixth Edition)⁹: (1) mild: patients may have minor symptoms such as nasal congestion, muscle pain without changes on imaging and symptoms of pneumonia; (2) ordinary: patients have non-specific symptoms such as fever, cough, sore throat or malaise, with imaging features of pneumonia and no signs of severe pneumonia; (3) severe: patients have one of the following: respiratory distress, with respiratory rate higher than 30 times per minute, fingertip blood oxygen saturation of less than 93% at rest, and progress of lesions on imaging of more than 50% within 24–48 hours; and (4) critical: patients have one of the following: respiratory failure or requiring mechanical ventilation, shock condition, and other organ failure that requires treatment in an intensive care unit.

The recovery standards⁹ are as follows: (1) two or more consecutive viral nucleic acid tests are negative (sampling time should be at least 1 day apart); (2) improvement in clinical symptoms is identified by the attending physician; (3) clinical indexes have returned to normal or have markedly improved compared with former; and (4) gradual improvement of pulmonary

inflammation on imaging analysis (obviously reduced shadow area).

Statistical analysis

Data were collected in Excel and imported into SPSS V.23. Continuous variables that were normally distributed were expressed as mean \pm SD, and categorical variables were expressed as count (%). Independent sample t-test was applied for normally distributed continuous data, and χ^2 test or Fisher's exact test was applied for categorical data. Independent risk factors for developing severe or critical illness were determined by multi-variable logistic regression analysis. Baseline variables that were considered clinically relevant (male, age, underlying disease)^{4–7} or laboratory test data that showed a univariate relationship with outcome were entered into multivariate regression model. All available variables were collected and carefully chosen to ensure parsimony of the final model, while those associated with CVD such as CRP or factors collinear with other main variables were excluded. $P < 0.05$ was considered statistically significant.

RESULTS

Basic characteristics

After excluding 119 cases with incomplete information and 3 other cases diagnosed as a mild type of COVID-19, a total of 541 incident cases of COVID-19 were ultimately included, of whom 33.6% (182 cases) were ordinary patients, 52.5% (284 cases) were severe and 13.9% (75 cases) were critically ill. Nearly 47.1% of the 541 patients with COVID-19 were male, with an average (SD) age at index date of 57.62 (16.7) years. The symptoms of patients with COVID-19 were mainly in the respiratory and gastrointestinal systems, and included fever (80.2%), cough (62.3%), fatigue (32.9%), sputum production (26.1%), chest congestion (24.0%), dyspnoea (24.0%), diarrhoea (11.6%), nausea (4.8%) and emesis (2.4%). Disorders of other systems could also be observed in some patients: dizziness (3.5%), headache (3.5%), disturbance of consciousness (1.7%) and arthralgia (9.8%). In addition, lymphocytes and haemoglobin were below the normal range in a great number of patients, while more than 50% had elevated CRP (> 10 mg/L) and lactic dehydrogenase. Furthermore, some patients had abnormalities in creatinine and liver function, with varying degrees of liver and kidney damage. Fifty-three (9.8%) patients had died before they were due for follow-up.

Clinical characteristics and laboratory results in patients with and without CVD

A total of 144 (26.6%) patients with COVID-19 had a history of CVD, while 397 (73.4%) patients did not (table 1). Among the CVD group, 125 patients had hypertension, 41 had coronary heart disease, 8 had cerebrovascular disease, 12 had arrhythmia, 1 had dilated heart disease and 1 had pericardial effusion; 40 of them had two or more CVDs (table 2). There were no significant differences with regard to sex and various symptoms in the two groups, aside from symptoms of sputum production ($p = 0.026$). Laboratory test data show that elevated leucocytes and CRP were more prevalent in the CVD group ($p < 0.05$). The presence of lymphocytes, haemoglobin and albumin below the normal range was also more common in the CVD group ($p < 0.05$). Patients with CVD were also more likely to develop liver function abnormality, elevated blood creatinine and lactic dehydrogenase ($p < 0.05$). Furthermore, the mortality of patients with CVD reached 22.2%, which was higher than that of the overall population of this study (9.8%), while the mortality of patients with two or more CVDs was as high as 42.5%. The

Table 1 Differences between COVID-19 patients with or without CVD

Variable	Without CVD (n=397) n (%)	With CVD (n=144) n (%)	P value
Male	183 (46.1)	72 (50.0)	0.437
Age			
Mean (SD)	53.25±16.29	69.66±10.94	<0.001
≤40	105 (26.4)	0 (0)	
40–60	138 (34.8)	30 (20.8)	
60–80	138 (34.8)	90 (62.5)	
>80	16 (4.0)	24 (16.7)	
Fever	316 (79.6)	118 (81.9)	0.626
Fatigue	125 (31.5)	53 (36.8)	0.256
Cough	244 (61.5)	93 (64.6)	0.548
Sputum production	93 (23.4)	48 (33.3)	0.026
Chest congestion	91 (22.9)	39 (27.1)	0.362
Dizziness	13 (3.3)	6 (4.2)	0.603
Headache	13 (3.3)	6 (4.2)	0.603
Dyspnoea	89 (22.4)	41 (28.5)	0.172
Disturbance of consciousness	5 (1.3)	4 (2.8)	0.256
Arthralgia	40 (10.1)	13 (9.0)	0.870
Stomach-ache	2 (0.5)	3 (2.1)	0.120
Diarrhoea	45 (11.3)	18 (12.5)	0.762
Nausea	15 (3.8)	11 (7.6)	0.071
Emesis	7 (1.8)	6 (4.2)	0.118
Leucocytes <3.5×10 ⁹ /L	41 (10.3)	13 (9.0)	0.747
Leucocytes >9.5×10 ⁹ /L	36 (9.1)	32 (22.2)	<0.001
Lymphocytes <1.1×10 ⁹ /L	203 (51.1)	93 (64.6)	0.006
Haemoglobin <115.0 g/L	122 (30.7)	71 (49.3)	<0.001
Albumin <40.0 g/L	277 (69.8)	120 (83.3)	0.001
C reactive protein >10.0 mg/L	265 (66.8)	121 (84.0)	<0.001
Aspartate aminotransferase >35.0 U/L	99 (24.9)	50 (34.7)	0.029
Alanine aminotransferase >40.0 U/L	93 (23.4)	41 (28.5)	0.260
Serum creatinine >81.0 μmol/L	37 (9.3)	27 (18.8)	0.004
Lactate dehydrogenase >250.0 U/L	190 (47.9)	93 (64.6)	0.001
Disease grade			
Ordinary	154 (38.8)	28 (19.4)	
Severe	208 (52.4)	76 (52.8)	
Critical	35 (8.8)	40 (27.8)	<0.001
Death	21 (5.3)	32 (22.2)	<0.001
Recovered	119 (30.0)	35 (24.3)	0.197

CVD, cardiovascular disease.

proportion of critically ill patients in the CVD group (27.8%) was significantly higher than in the group with no CVD (8.8%). Patients meeting the recovery standards were more prevalent in the group without CVD (30.0%), but the difference was not statistically significant ($p=0.197$) (table 1). After comparison of the outcomes of patients with different CVDs, the results showed that among patients who had coronary heart disease

alone or cerebrovascular disease alone and patients with more than two different types of CVD simultaneously, the mortality rate was higher than 40% and the proportion of critical patients was higher than 30% (table 2).

Differences between patients in various conditions

Table 3 presents the differences between ordinary, severe and critical patients. Among the 541 patients on admission, 52.5% (284 patients) were classified as severe COVID-19, while 33.6% (182 patients) and 13.9% (75 patients) were classified as ordinary and critical, respectively. Critical patients were significantly older than patients in the other groups, and their age mainly ranged from 60 to 80 years ($p<0.05$). The proportion of patients with CVD increased stepwise in the ordinary, severe and critical groups ($p<0.001$). The proportion of patients with respiratory illness in the critical group was higher than in the other groups ($p<0.05$). The prevalence of albumin and lymphocytes below the normal range, elevated CRP and lactic dehydrogenase, and abnormal blood creatinine and liver function index in patients with severe COVID-19 was higher than in the ordinary group, and these become gradually common as COVID-19 classification is upgraded ($p<0.05$).

Associations between CVD and clinical classification and outcomes of disease

We performed multivariable logistic regression analysis to identify potential independent factors related to the outcome. First, comparing critically ill patients with non-critical patients showed that CVD (OR: 2.735 (95% CI 1.495 to 5.003), $p=0.001$), elevated AST (OR: 1.783 (95% CI 1.061 to 3.128), $p=0.044$), elevated creatinine (OR: 2.656 (95% CI 1.355 to 5.203), $p=0.004$) and albumin below the normal range (OR: 2.891 (95% CI 1.228 to 6.803), $p=0.015$) were associated with critical COVID-19 condition (table 4). After supplementary analysis of CVD details, we found that hypertension (OR: 2.051 (95% CI 1.104 to 3.808), $p=0.023$) was associated with critical disease (online supplementary table 1). Second, when we compared ordinary with other patients, analysis showed that age (OR: 1.042 (95% CI 1.027 to 1.057), $p<0.001$), elevated AST (OR: 1.716 (95% CI 1.063 to 2.769), $p=0.027$) and haemoglobin below the normal range (OR: 1.833 (95% CI 1.166 to 2.882), $p=0.009$) were associated with severe and critical COVID-19 condition, while CVD (OR: 1.114 (95% CI 0.649 to 1.910), $p=0.696$) has no significant association (table 4).

Lastly, we performed multivariable logistic regression analysis evaluating the predictors of recovery on follow-up of patients with COVID-19. Comparison of patients who were discharged from the hospital (those who met the recovery standards) and those who were not discharged showed that coronary heart disease (OR: 0.331 (95% CI 0.125 to 0.880), $p=0.027$) and albumin below the normal range (OR: 0.512 (95% CI 0.329 to 0.797), $p=0.003$) were associated with recovery of patients during follow-up (table 5).

Table 2 Classification of cardiovascular diseases

Underlying cardiovascular diseases (n=144)	Ordinary, n (%)	Severe, n (%)	Critical, n (%)	Healing, n (%)	Death, n (%)
Cardiovascular diseases (n=144)	28 (19.4)	76 (52.8)	40 (27.8)	35 (24.3)	32 (22.2)
Hypertension (n=125)	23 (18.4)	67 (53.6)	35 (28.0)	32 (25.6)	28 (22.4)
Coronary heart disease (n=41)	5 (12.2)	22 (53.7)	14 (34.1)	6 (14.6)	17 (41.5)
Abnormal heart rhythms (n=12)	3 (25.0)	4 (33.3)	5 (41.7)	2 (16.7)	4 (33.3)
Cerebrovascular disease (n=8)	0 (0)	6 (75.0)	2 (25.0)	1 (12.5)	5 (62.5)
Two or more cardiovascular diseases (n=40)	3 (7.5)	22 (55.0)	15 (37.5)	6 (15.0)	17 (42.5)

Table 3 Differences between patients in various conditions

Variable	Ordinary (n=182) n (%)	Severe (n=284) n (%)	Critical (n=75) n (%)	P value
Male	75 (41.2)	135 (47.5)	45 (60.0)	0.023
Age				
Mean (SD)	49.26±16.13	60.35±15.40	67.57±13.84	<0.001
≤40	63 (34.6)	37 (13.0)	5 (6.7)	
40–60	70 (38.5)	82 (28.9)	16 (21.3)	
60–80	45 (24.7)	142 (50.0)	41 (54.7)	
>80	4 (2.2)	23 (8.1)	13 (17.3)	
Respiratory system disease	12 (6.6)	20 (7.0)	13 (17.3)	0.010
Malignant tumour	1 (0.5)	9 (3.2)	2 (2.7)	0.149
Endocrine system disease	13 (7.1)	38 (13.4)	11 (14.7)	0.077
Urinary system disease	6 (3.3)	10 (3.5)	5 (6.7)	0.402
Cardiovascular diseases	28 (15.4)	76 (26.8)	40 (53.3)	<0.001
Hypertension	23 (12.6)	67 (23.6)	35 (46.7)	<0.001
Coronary heart disease	5 (2.7)	22 (7.7)	14 (18.7)	<0.001
Abnormal heart rhythms	3 (1.6)	4 (1.4)	5 (6.7)	0.037
Cerebrovascular disease	0 (0)	6 (2.1)	2 (2.7)	0.070
Leucocytes <3.5×10 ⁹ /L	16 (8.8)	33 (11.6)	5 (6.7)	0.368
Leucocytes >9.5×10 ⁹ /L	15 (8.2)	24 (8.5)	29 (38.7)	<0.001
Haemoglobin <115.0 g/L	41 (22.5)	123 (43.3)	29 (38.7)	<0.001
Lymphocytes <1.1×10 ⁹ /L	63 (34.6)	169 (59.5)	64 (85.3)	<0.001
C reactive protein >10.0 mg/L	92 (50.5)	225 (79.2)	69 (92.0)	<0.001
Albumin <40.0 g/L	117 (64.3)	212 (74.6)	68 (90.7)	<0.001
Lactate dehydrogenase >250.0 U/L	54 (29.7)	165 (58.1)	64 (85.3)	<0.001
Aspartate aminotransferase >35.0 U/L	33 (18.1)	83 (29.2)	33 (44.0)	<0.001
Alanine aminotransferase >40.0 U/L	34 (18.7)	76 (26.8)	24 (32.0)	0.042
Serum creatinine >81.0 μmol/L	10 (5.5)	31 (10.9)	23 (30.7)	<0.001
Death	5 (2.7)	13 (4.6)	35 (46.7)	<0.001

DISCUSSION

CVD has been proven to be the most common chronic disease in patients with COVID-19.^{4,6} It is worth noting the progress of COVID-19 in patients with CVD. In this study of individuals with COVID-19, we first described the epidemiological and clinical characteristics of COVID-19 patients with CVD and further explored the impact of CVD.

This study demonstrates that COVID-19 patients with CVD are more likely to be critically ill and have a higher mortality rate, especially those who simultaneously have different types of CVD. It appears that coronary artery disease and cerebrovascular

disease were strongly associated with adverse outcomes within the CVD category. Our study also identified that CVD is an independent risk factor associated with the progression of COVID-19 to a critical illness at the early stage.

COVID-19 patients with underlying CVD are more likely to have elevated CRP, elevated leucocytes and decreased lymphocytes, reflecting a more powerful and lethal inflammatory response. Previous studies have shown that patients with COVID-19 had decreased number of lymphocytes and increased level of serum inflammatory factors (interleukin (IL)-9, IL-1β, interferon (IFN)-γ, tumour necrosis factor (TNF)-α and

Table 4 Comparison of factors associated with ordinary/severe versus critical and ordinary versus severe/critical disease in logistic regression analysis

Variable	Ordinary/severe vs critical			Ordinary vs severe/critical		
	OR	95% CI	P value	OR	95% CI	P value
Male	1.490	0.857 to 2.592	0.157	1.315	0.878 to 1.970	0.184
Age	1.019	0.998 to 1.041	0.083	1.042	1.027 to 1.057	<0.001
Respiratory system disease	2.000	0.881 to 4.544	0.098	0.715	0.333 to 1.536	0.390
Malignant tumour	1.296	0.232 to 7.244	0.768	4.044	0.493 to 33.153	0.193
Endocrine system disease	0.865	0.391 to 1.914	0.721	1.331	0.657 to 2.696	0.428
Urinary system disease	1.372	0.427 to 4.413	0.596	0.377	0.124 to 1.149	0.086
Cardiovascular diseases	2.735	1.495 to 5.003	0.001	1.114	0.649 to 1.910	0.696
Haemoglobin <115.0 g/L	0.621	0.344 to 1.121	0.114	1.833	1.166 to 2.882	0.009
Albumin <40 g/L	2.891	1.228 to 6.803	0.015	1.072	0.685 to 1.678	0.762
Serum creatinine >81 μmol/L	2.656	1.355 to 5.203	0.004	1.624	0.744 to 3.546	0.223
Aspartate aminotransferase >35 U/L	1.783	1.061 to 3.128	0.044	1.716	1.063 to 2.769	0.027

Table 5 Association between cardiovascular diseases and recovery during follow-up in logistic regression analysis

Variable	OR	95% CI	P value
Male	1.264	0.852 to 1.876	0.244
Age	1.010	0.996 to 1.025	0.157
Respiratory system disease	0.877	0.419 to 1.836	0.727
Urinary system disease	0.940	0.321 to 2.751	0.910
Endocrine system disease	2.228	1.208 to 4.106	0.010
Malignant tumour	1.096	0.306 to 3.929	0.888
Haemoglobin <115.0 g/L	1.407	0.918 to 2.155	0.117
Albumin <40 g/L	0.512	0.329 to 0.797	0.003
Serum creatinine >81 µmol/L	0.529	0.259 to 1.078	0.079
Aspartate aminotransferase >35 U/L	0.884	0.560 to 1.395	0.596
Hypertension	0.846	0.500 to 1.433	0.535
Coronary heart disease	0.331	0.125 to 0.880	0.027
Abnormal heart rhythms	0.639	0.127 to 3.203	0.586
Cerebrovascular disease	0.304	0.031 to 2.931	0.303

granulocyte colony-stimulating factor (G-CSF)), especially in those who were critically ill, which was consistent with our findings.^{6–11} It is well known that inflammatory and biomarkers, such as CRP, are a typical hallmark of cardiac disease and play a critical role in the development and prognosis of CVD.^{12–13} For instance, IFN- γ and IL-17 are involved in blood pressure elevation and target organ damage, while IL-6, TNF- α and transforming growth factor- β are significantly associated with the odds of treatment-resistant hypertension.^{13–14} As independent predictors of cardiovascular events, elevated leucocytes and decreased lymphocytes have been demonstrated to be implicated in the progression and destabilisation of atherosclerosis.¹² Coronary plaque instability has been reported in patients with severe acute respiratory syndrome and HIV.^{15–16} Furthermore, SARS-CoV has also been found to mediate myocardial inflammation and damage associated with downregulation of the myocardial ACE2 system.¹⁷ We also found that hypertension is an independent risk factor for critical patients, but the mechanism is yet to be proven. The interaction effects between the cytokine storm caused by SARS-CoV-2 and CVD patients with chronic inflammation may be contributing factors to the deterioration of patients' conditions.

In addition, COVID-19 patients with underlying CVD had higher prevalence of liver function abnormality (albumin was decreased, AST was increased), and abnormalities in AST and albumin were more common in the critically ill group. In times of cardiovascular compromise, severe hypoxaemia or increased metabolic activity/demand, the regulatory functions of the liver can be overwhelmed, leading to liver function abnormality.¹⁸ Serum aminotransferase levels are used for prognostic evaluation of cardiovascular surgery, particularly in the elderly.¹⁹ Based on the pathological manifestations of COVID-19 patient's liver tissue, which showed moderate microvesicular steatosis and mild lobular activity,²⁰ we speculate that, in addition to adverse drug reactions, severe hypoxaemia, increased metabolic activity/demand and passive congestion of the liver might contribute to the more abnormal liver function in COVID-19 patients with CVD, but the significance of these needs to be studied further.

Meanwhile, symptoms of sputum production and increased leucocytes are more common in patients with CVD. In our study, COVID-19 patients with underlying CVD had higher prevalence of albumin and haemoglobin below the normal range, influencing an individual's susceptibility to superinfection, which may be one

of the contributors to sputum production.⁴ An autopsy report of COVID-19 patients with CVD showed a huge amount of grey-white viscous liquid in the lung with pulmonary congestion, which seemed to be consistent with our study.²¹ As the cardiodepressant factors, the increasing inflammatory markers (TNF- α , IL-1 β) in COVID-19 might influence heart function (right heart dilation, ventricular systolic dysfunction), which might also increase the risk of pulmonary congestion and superinfection.^{22–24}

Moreover, as a highly infectious disease with high possibility of familial clustering, COVID-19 may cause psychological stress, which could influence progress of CVD. All in all, although it is yet unknown whether COVID-19 causes myocardial inflammation, the more critically ill patients and death in the CVD group might be the result of a persistent combination of more powerful inflammatory response, systemic organ damage and susceptibility to superinfection. CVD as an independent risk factor of the critical type of COVID-19 may lead to exacerbations in patients.

Therefore, a thorough CVD assessment at diagnosis is recommended in patients with COVID-19. At the same time, timely intervention and early multiorgan conservation therapy in COVID-19 patients with underlying CVD are important in disease progression and prognosis.

Limitations

There were several limitations to this study. First, this was a single-centre study from our hospital that did not include mild patients and did not reflect the true denominator of the disease. The findings need to be confirmed in larger prospective studies. Second, although we excluded patients with incomplete information, more detailed information (such as smoking, drug information, pre-existing heart failure) and dynamic changes in data were not investigated. Third, we collected the data on admission to analyse the progression and prognosis at an early stage; however, the complications (myocardial infarction, heart failure, ARDS) in the present study population were not evaluated. We need to investigate

Key messages

What is already known on this subject?

- ▶ Cardiovascular disease (CVD) which is prevalent in the general population is also the most common chronic disease in patients with COVID-19.
- ▶ Organ dysfunction caused by COVID-19 is the major cause of early deterioration and death in patients, especially in those with many concomitant diseases.

What might this study add?

- ▶ We identified that 26.6% of hospitalised patients with COVID-19 had a history of CVD, and nearly one-third simultaneously had different types of cardiovascular diseases.
- ▶ The mortality of patients with CVD reached 22.2%, which was higher than that of the overall population of this study (9.8%).
- ▶ We further found that CVD is an independent risk factor for the critical type of COVID-19, while coronary artery disease and cerebrovascular disease were strongly associated with adverse outcomes within the CVD category.

How might this impact on clinical practice?

- ▶ Our findings highlight a thorough CVD assessment at diagnosis and timely intervention in COVID-19 patients with underlying CVD to avoid uncontrolled progress.

further to elucidate the interaction between COVID-19 and CVD in order to guide early treatment. Despite the shortcomings described previously, data from this study provide an early assessment of patients with COVID-19, especially those with CVD, to assist in the early management of at-risk populations. Further investigations are warranted to elucidate the interaction between COVID-19 and CVD in order to guide early treatment.

In conclusion, COVID-19 patients with CVD are more likely to become worse and need early intervention and timely monitoring.

Author affiliations

- ¹Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China
- ²Department of Plastic Surgery, Renmin Hospital of Wuhan University, Wuhan, Hubei, China
- ³Department of Oncology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China
- ⁴Department of Geriatrics, Renmin Hospital of Wuhan University, Wuhan, Hubei, China
- ⁵Department of Respiriology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China
- ⁶Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China
- ⁷Department of Otorhinolaryngology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Contributors JZ and SL shared first authorship. WD and YX contributed equally to this article. Concept and design: JZ, SL, WD and YX. Acquisition, analysis or interpretation of data: XJ, SL, JL, HL, MJ, JJM, SL, DW and WD. Drafting of the manuscript: JZ, SL and YX. Statistical analysis: XJ, ST, SL, ZL, XL, LF, JK, YG and WD. Supervision: WD and YX. All authors have been personally and actively involved in the substantive work leading to the report and will hold themselves jointly and individually responsible for its content.

Funding This research was supported by a grant from the Nature Science Foundation of China (grant 81870392).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by the Wuhan University Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data generated or analysed during this study are included in this article.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD

Weiguo Dong <http://orcid.org/0000-0002-4228-6508>

REFERENCES

- 1 Phelan AL, Katz R, Gostin LO, *et al.* The novel coronavirus originating in Wuhan, China: challenges for global health governance. *JAMA* 2020. doi:10.1001/jama.2020.1097. [Epub ahead of print: 30 Jan 2020].

- 2 Wu JT, Leung K, Leung GM, *et al.* Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet* 2020;395:689–97.
- 3 Patel A, Jernigan DB, 2019-nCoV CDC Response Team. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak - United States, December 31, 2019-February 4, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:140–6.
- 4 Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- 5 Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061.
- 6 Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- 7 Shi S, Qin M, Shen B, *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020. doi:10.1001/jamacardio.2020.0950. [Epub ahead of print: 25 Mar 2020].
- 8 World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Interim guidance, 2020. Available: <https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf> [Accessed 4 Feb 2020].
- 9 National Health Commission of China. *New coronavirus pneumonia prevention and control program*. 6th edn, 2020. http://www.gov.cn/zhengce/zhengceku/2020-02/19/content_5480948.htm.pdf. Chinese
- 10 World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. interim guidance, 2020. Available: <https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117> [Accessed 4 Feb 2020].
- 11 Chen H, Guo J, Wang C, *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020;395:809–15.
- 12 Wada H, Dohi T, Miyauchi K, *et al.* Pre-procedural neutrophil-to-lymphocyte ratio and long-term cardiac outcomes after percutaneous coronary intervention for stable coronary artery disease. *Atherosclerosis* 2017;265:35–40.
- 13 Fioranelli M, Bottaccioli AG, Bottaccioli F, *et al.* Stress and inflammation in coronary artery disease: a review Psychoneuroendocrinology-Based. *Front Immunol* 2018;9:9.
- 14 Ruan C-C, Gao P-J. Role of complement-related inflammation and vascular dysfunction in hypertension. *Hypertension* 2019;73:965–71.
- 15 Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. *Nat Rev Cardiol* 2019;16:745–59.
- 16 Tsui K-L, Leung T-C, Yam LY-C, *et al.* Coronary plaque instability in severe acute respiratory syndrome. *Int J Cardiol* 2005;99:471–2.
- 17 Kuba K, Imai Y, Rao S, *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;11:875–9.
- 18 Weisberg IS, Jacobson IM. Cardiovascular diseases and the liver. *Clin Liver Dis* 2011;15:1–20.
- 19 Nam J-S, Kim W-J, An S-M, *et al.* Age-dependent relationship between preoperative serum aminotransferase and mortality after cardiovascular surgery. *Aging* 2019;11:9060–74.
- 20 Xu Z, Shi L, Wang Y, *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420–2.
- 21 Liu X, Wang RS, GQ Q, *et al.* General anatomy report of novel coronavirus pneumonia death corpse. *J Forensic Med* 2020;36:1–3. Chinese.
- 22 Boissier F, Razazi K, Seemann A, *et al.* Left ventricular systolic dysfunction during septic shock: the role of loading conditions. *Intensive Care Med* 2017;43:633–42.
- 23 Hackam DG, Mamdani M, Li P, *et al.* Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. *Lancet* 2006;367:413–8.
- 24 Zochios V, Parhar K, Tunnicliffe W, *et al.* The right ventricle in ARDS. *Chest* 2017;152:181–93.