

# World Journal of *Clinical Cases*

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## Retrospective Study

## Increased levels of lactate dehydrogenase and hypertension are associated with severe illness of COVID-19

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## Abstract

**BACKGROUND**

Coronavirus disease 2019 (COVID-19) is amid an ongoing pandemic. It has been shown that patients with cardiovascular comorbidities are at higher risk of severe illness of COVID-19.

**AIM**

To find out the relationship between cardiovascular comorbidities and severe illness of COVID-19.

**METHODS**

The clinical data of 140 COVID-19 patients treated from January 22, 2020 to March 3, 2020 at our hospital were retrospectively collected. The clinical characteristics were compared between patients with mild illness and those with severe illness.

**RESULTS**

There were 75 male patients and 65 female patients (53.6% vs 46.4%). The mean age was  $45.4 \pm 14.6$  years (range, 2-85 years). Most of the patients had mild illness ( $n = 114$ , 81.4%) and 26 patients had severe illness (18.6%). The most common symptom was fever ( $n = 110$ , 78.6%), followed by cough ( $n = 82$ , 58.6%) and



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expectoration ( $n = 51, 36.4\%$ ). Eight patients were asymptomatic but were positive for severe acute respiratory syndrome coronavirus 2 RNA. Patients with severe illness were significantly more likely to be hypertensive than those with mild illness [(10/26, 38.4%) *vs* (22/114, 19.3%),  $P = 0.036$ ]. The levels of lactate dehydrogenase were significantly higher in the severe illness group than in the mild illness group ( $299.35 \pm 68.82$  *vs*  $202.94 \pm 63.87$ ,  $P < 0.001$ ). No patient died in either the severe illness or the mild illness group.

## CONCLUSION

Hypertension and elevated levels of lactate dehydrogenase may be associated with severe illness of COVID-19.

**Key Words:** Pneumonia; Virus; COVID-19; Hypertension; Lactate dehydrogenase; Radiology

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**Core Tip:** Coronavirus disease 2019 (COVID-19) is amid an ongoing pandemic. It has been shown that patients with cardiovascular comorbidities are at higher risk of severe illness of COVID-19. Although most COVID-19 patients have mild symptoms and generally good outcomes, some of them still show severe illness. Patients with hypertension and elevated levels of lactate dehydrogenase may be at high risk of severe illness of COVID-19.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has rapidly evolved into a pandemic since its first outbreak in Wuhan, China in December 2019. However, there is still no effective drugs for this disease[1,2]. In addition, the symptoms and signs and pathological mechanisms of COVID-19 are very complex, posing great challenges in treating patients. Our hospital is a dedicated hospital for treating patients with COVID-19 in Wenzhou, China, which is 680 km from Wuhan. There is strong economic connectivity and mass migrations between the two cities. The present study aimed to analyze the clinical characteristics of COVID-19 patients from a hospital in Wenzhou, China.

## MATERIALS AND METHODS

### Patients

The clinical data of COVID-19 patients treated from January 22, 2020 to March 3, 2020 at our hospital were retrospectively collected. The diagnostic criteria for COVID-19 at our hospital were: (1) Potential exposure to COVID-19; (2) Had fever, respiratory symptoms, radiological abnormalities in the lungs, or leukocytopenia/lymphocytopenia; and (3) Presence of viral RNA in nasopharyngeal specimens. The inclusion criteria were: (1) With laboratory-confirmed COVID-19; (2) With specific outcomes of discharge or death; and (3) Had been examined by chest computed tomography (CT) during hospitalization. Our study was approved by the ethics committee of our hospital.

### Data collection

All data were retrospectively collected from electronic records of the patients, including sex, age, symptoms, radiological findings, laboratory test results, treatment



methods, and patient outcomes. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was tested using quantitative real-time polymerase chain reaction. Blood samples were collected at 7 am after fasting overnight. Disease severity was classified as mild illness (respiratory symptoms and/or radiological findings of pneumonia) and severe illness (respiratory distress and/or need of mechanical ventilation).

### Statistical analysis

Continuous data are presented as the mean and standard deviation and were compared using the independent student's *t*-test. Categorical data are presented as counts or percentages and were compared using the Chi-square test. All statistical analyses were performed using SPSS 24.0 (IBM, United States). A *P* value less than 0.05 was considered statistical significance.

## RESULTS

### Patient general information

A total of 140 laboratory-confirmed COVID-19 patients were included in our study (Table 1). There were 75 male patients and 65 female patients (53.6% *vs* 46.4%). The mean age was  $45.4 \pm 14.6$  years (range, 2-85 years). Most of the patients had potential exposure to COVID-19 ( $n = 92$ , 65.7%).

### Clinical characteristics

The most common symptom was fever ( $n = 110$ , 78.6%), followed by cough ( $n = 82$ , 58.6%), expectoration ( $n = 51$ , 36.4%), fatigue ( $n = 20$ , 14.3%), shortness of breath ( $n = 15$ , 10.7%), diarrhea ( $n = 14$ , 10%), and headache ( $n = 4$ , 2.9%) (Table 1). Eight patients (5.6%) were asymptomatic but were positive for SARS-CoV-2 RNA. These patients were family members or neighbors of other symptomatic patients and thus were tested for COVID-19.

The most common comorbidity was hypertension ( $n = 32$ , 22.9%). Other comorbidities included diabetes ( $n = 6$ ), coronary heart disease ( $n = 3$ ), and malignant tumor ( $n = 4$ ). Most of the patients had mild illness ( $n = 114$ , 81.4%) and 26 had severe illness (18.6%) (Table 1). Patients with severe illness were significantly more likely to be hypertensive than those with mild illness [ $(10/26, 38.5\%)$  *vs*  $(22/114, 19.3\%)$ ,  $P = 0.036$ ].

The results of laboratory tests are shown in Table 2. The leukocyte count was lower than  $3.5 \times 10^9/L$  in 26 patients (18.6%). The lymphocyte count was lower than  $1.1 \times 10^9/L$  in 54 patients (38.6%). Low levels of hemoglobin were present in 16 patients (11.4%). Thrombocytopenia ( $< 100 \times 10^9/L$ ) was present in three patients. Elevated serum levels of creatinine  $> 94 \mu\text{mol/L}$  were noticed in 18 patients. Elevated serum levels of creatine kinase  $> 200 \text{ U/L}$  were noticed in 12 patients, and  $> 500 \text{ U/L}$  in three patients. Elevated serum levels of lactate dehydrogenase were noticed in 37 patients. The level of lactate dehydrogenase was significantly higher in the severe illness group than in the mild illness group ( $299.35 \pm 68.82$  *vs*  $202.94 \pm 63.87$ ,  $P < 0.001$ ). There were significant differences in lymphocyte count, platelet count, levels of total serum protein, prealbumin, blood uric acid, lactate dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, arterial partial pressure of oxygen, and oxygenation index between patients with mild illness and those with severe illness (Table 2).

### Radiologic characteristics in computed tomography

Only 3 patients showed no significant radiologic findings (3/140, 2.1%). The radiologic characteristics are shown in Table 3. There was no significant difference in the frequency of affected lung sites between patients with mild illness and those with severe illness. However, significantly more patients with mild illness had ground-glass opacity than those with severe illness (78.9% *vs* 23.1%,  $P < 0.0001$ ). On the contrary, there were significantly more patients with consolidation (100% *vs* 25.4%,  $P < 0.0001$ ) and pleural effusion (30.8% *vs* 2.6%,  $P < 0.0001$ ) in the severe illness group than in the mild illness group.

### Treatment outcomes

High-flow nasal oxygen therapy was used in 22 patients with mild illness (22/114, 19.3%), while all the 26 patients with severe illness used this treatment. Non-invasive mechanical ventilation was used in 4/26 (15.4%) patients with severe illness, while

**Table 1 Characteristics of the patients (n = 140)**

Characteristic	Mild illness (n = 114)	Severe illness (n = 26)	P value
Age (yr, %)	43.2 ± 14.0	54.7 ± 13.8	0.98
Female (n, %)	56 (49.1)	9 (34.6)	0.20
Comorbidities (n)			
Hypertension	22 (19.3)	10 (38.5)	0.07
Diabetes	5 (4.4)	1 (3.8)	1.0
Chronic obstructive pulmonary disease	3 (2.6)	0	1.0
Chronic renal failure	0	2 (7.7)	1.0
Coronary heart disease	1 (0.9)	2 (7.7)	0.09
Malignant tumor	2 (1.8)	2 (7.7)	0.16
Hepatitis B	10 (8.8)	3 (11.5)	0.71
Connective tissue disease	1 (0.9)	0	0.08
Gout	2 (1.8)	1 (3.8)	0.46
Symptoms (n, %)			
Fever	86 (75.4)	24 (92.3)	0.06
Cough	61 (53.5)	21 (80.8)	0.01
Expectoration	34 (29.8)	17 (65.4)	< 0.01
Fatigue	15 (13.2)	5 (19.2)	0.53
Chest pain	2 (1.8)	2 (7.7)	0.16
Myalgia	8 (7.0)	2 (7.7)	1.0
Headache	5 (4.4)	1 (3.8)	1.0
Sore throat	14 (12.3)	2 (7.7)	0.74
Shortness of breath	7 (6.1)	8 (30.8)	< 0.01
Diarrhea	12 (10.5)	2 (7.7)	1.0

none of the patients with mild illness used this treatment. No tracheal intubation was required in our patients. All patients were cured and discharged as of March 3, 2020.

## DISCUSSION

Our study retrospectively analyzed 140 patients with laboratory-confirmed COVID-19 and found that patients with severe illness were more likely to have hypertension than those with mild illness. In addition, the level of lactate dehydrogenase was significantly higher in the severe illness group than in the mild illness group.

Fever (78.6%) and cough (58.6%) were the most common symptoms in our patients. This finding is consistent with previous reports[3,4]. However, these symptoms are not specific and many of the patients had early on-set symptoms of fatigue, diarrhea, and myalgia. In addition, eight patients (5.6%) were asymptomatic but were positive for SARS-CoV-2 RNA. Most recent research showed that the rate of asymptomatic infection in the general population may be as high as 80.9%[5,6]. Due to the criteria for diagnosis and patient admission for COVID-19 at our hospital, asymptomatic patients were not tested for viral RNA and thus were not confirmed with the diagnosis of COVID-19.

The existence of comorbidities can increase the risk of more severe illness and mortality in COVID-19 patients[7,8]. The most common comorbidity in our patients was hypertension (22.9%), and patients with severe illness were significantly more likely to be hypertensive than those with mild illness (38.4% *vs* 19.3%). A previous study with 1099 COVID-19 patients also found that hypertension was associated with severe disease[3]. In addition, we found that the levels of lactate dehydrogenase were

**Table 2 Laboratory test results of the patients (n = 140)**

	Mild illness (n = 114)	Severe illness (n = 26)	P value
Leukocyte count ( $\times 10^9/L$ )	5.01 $\pm$ 1.85	4.67 $\pm$ 1.84	0.398
Neutrophil count ( $\times 10^9/L$ )	3.15 $\pm$ 1.41	3.55 $\pm$ 1.88	0.308
Lymphocyte count ( $\times 10^9/L$ )	1.4 $\pm$ 0.59	0.74 $\pm$ 0.31	< 0.001
Hemoglobin (g/L)	136.13 $\pm$ 14.43	130.73 $\pm$ 15.18	0.09
Platelet count ( $\times 10^9/L$ )	201.48 $\pm$ 72.45	164.35 $\pm$ 62.69	0.017
Alanine aminotransferase (U/L)	29.26 $\pm$ 29.67	35.69 $\pm$ 25.43	0.309
Aspartate transaminase (U/L)	27.97 $\pm$ 17.45	41.54 $\pm$ 26.22	0.017
Total serum protein (g/L)	70.27 $\pm$ 5.08	65.38 $\pm$ 5.19	< 0.001
Albumin (g/L)	45.71 $\pm$ 33.39	37.42 $\pm$ 3.55	0.209
Prealbumin (g/L)	198.66 $\pm$ 50.55	123.13 $\pm$ 47.11	< 0.001
Blood urea nitrogen (mmol/L)	3.71 $\pm$ 5.96	5.96 $\pm$ 10.91	0.303
Blood creatinine ( $\mu$ mol/L)	172.63 $\pm$ 34.15	159.24 $\pm$ 433.95	0.319
Blood uric acid ( $\mu$ mol/L)	241.84 $\pm$ 89.51	194.92 $\pm$ 96.27	0.019
Creatine kinase (U/L)	103.54 $\pm$ 180.73	211.49 $\pm$ 379.39	0.168
Lactate dehydrogenase (U/L)	202.94 $\pm$ 63.87	299.35 $\pm$ 68.82	< 0.001
C-reactive protein (mg/L)	14.61 $\pm$ 19.35	52.48 $\pm$ 29.63	< 0.001
Erythrocyte sedimentation rate (mm/h)	23.68 $\pm$ 14.36	33.25 $\pm$ 15.00	0.003
Arterial partial pressure of oxygen (kPa)	13.23 $\pm$ 4.00	11.06 $\pm$ 2.91	0.01
Oxygenation index (mmHg)	460.80 $\pm$ 138.71	324.62 $\pm$ 61.52	< 0.001

**Table 3 Radiologic characteristics of the patients (n = 140)**

	Mild illness (n = 114)	Severe illness (n = 26)	P value
Affected sites (n, %)			
Left upper lobe	90 (78.9)	16 (61.5)	0.08
Left lower lobe	107 (93.9)	23 (88.5)	0.39
Right upper lobe	86 (75.4)	14 (53.8)	0.052
Right middle lobe	73 (64.0)	19 (73.1)	0.49
Right lower lobe	105 (92.1)	22 (84.6)	0.26
Bilateral lungs	109 (95.6)	26 (100.0)	0.58
Features (n, %)			
Irregular patches	110 (96.5)	23 (88.5)	0.12
Ground-glass opacity	90 (78.9)	6 (23.1)	< 0.0001
Consolidation	29 (25.4)	26 (100.0)	< 0.0001
Nodules	12 (10.5)	0	0.12
Wedge-shaped opacity	1 (0.9)	4 (15.4)	0.004
Pleural effusion	3 (2.6)	8 (30.8)	< 0.0001

significantly elevated in patients with severe illness compared to those with mild illness. Lactate dehydrogenase is a biomarker for myocardial injury[9,10]. All these findings suggest that hypertension and the resulting myocardial injury may lead to a poor prognosis in COVID-19. There have been concerns and debates on the roles of the renin-angiotensin system, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in COVID-19 and poor prognosis[11-15]. However, there is no con-

crete evidence at present suggesting that these anti-hypertensive drugs should be discontinued in hypertensive COVID-19 patients[16,17].

All our patients were examined by CT and only three showed no significant radiologic findings in the lungs. Most patients had signs of involvement of bilateral lungs, especially the lower lobes. Patients with severe illness of COVID-19 had features of involvement of multiple lobes, irregular patches, and consolidations. Significant radiological progression was seen in 32 patients (22.9%) even after 3 to 7 d. Consistent with previous studies[18,19], our findings suggest that COVID-19 patients with mild or no symptoms may be negative in chest CT examinations. Although CT should not be relied on as a method for screening or diagnosing COVID-19, we recommend repeated chest CT for suspected patients in case of symptoms onset or disease progression.

Our study has limitations. First, most of our patients were only diagnosed with COVID-19 and admitted to the hospital when they showed symptoms. This criterion for diagnosis may underestimate the true population of COVID-19 patients. Second, patients with mild symptoms may not visit the clinics and just stay at home. This may potentially increase the proportion of patients with severe illness in our study. Third, the relationship between hypertension and elevated levels of lactate dehydrogenase in COVID-19 patients was not addressed due to the retrospective nature of our study.

## CONCLUSION

Our study found that most of the laboratory-confirmed COVID-19 patients in Wenzhou, China had mild illness and generally good outcomes. Hypertension and elevated levels of lactate dehydrogenase may be associated with severe illness of COVID-19. Targeting hypertension-associated myocardial injury may be a potential option in the treatment of COVID-19.

## ARTICLE HIGHLIGHTS

### **Research background**

The coronavirus disease 2019 (COVID-19) pandemic is still evolving.

### **Research motivation**

Older people are at increased risk of cardiovascular diseases and COVID-19. The relationship between COVID-19 and cardiovascular diseases is poorly understood.

### **Research objectives**

Our study aimed to find out the relationship between COVID-19 and cardiovascular diseases.

### **Research methods**

The clinical data of 140 COVID-19 patients were retrospectively analyzed. The clinical characteristics were compared between patients with mild illness and those with severe illness.

### **Research results**

Patients with severe illness of COVID-19 were more likely to be hypertensive and had significantly higher levels of lactate dehydrogenase than those with mild illness.

### **Research conclusions**

The coexistence of hypertension and higher levels of lactate dehydrogenase in patients with severe illness of COVID-19 suggests a close relationship between COVID-19 and cardiovascular diseases.

### **Research perspectives**

The relationship between hypertension and elevated levels of lactate dehydrogenase in COVID-19 patients should be addressed in future investigations.

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