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## Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study --Manuscript Draft--

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<b>Manuscript Region of Origin:</b>	CHINA
<b>Abstract:</b>	<p>Summary</p> <p>Background</p> <p>Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Apart from respiratory complications, acute cerebrovascular disease (CVD) has been observed in some patients with COVID-19. Therefore, we described the clinical characteristics, laboratory features, treatment, and outcomes of CVD complicating SARS-CoV-2 infection.</p> <p>Methods</p> <p>We conducted a single center, retrospective, observational analysis of consecutive COVID-19 patients admitted to Union Hospital, Wuhan, China from 16 January 2020 to 29 February 2020. Demographic and clinical characteristics, laboratory findings, treatments, and clinical outcomes were extracted from electronic medical records and compared between COVID-19 patients with and without new onset of CVD.</p> <p>Results</p> <p>Of 221 patients with COVID-19, 11 (5%) developed acute ischemic stroke, 1 (0.5%) cerebral venous sinus thrombosis (CVST), and 1 (0.5%) cerebral hemorrhage. COVID-19 with new onset of CVD were significantly older (<math>71.6 \pm 15.7</math> years vs <math>52.1 \pm 15.3</math> years; <math>p &lt; 0.05</math>), more likely to present with severe COVID-19 (84.6% vs. 39.9%, <math>p &lt; 0.01</math>) and were more likely to have cardiovascular risk factors, including</p>

hypertension, diabetes, and previous medical history of cerebrovascular disease (all  $p < 0.05$ ). In addition, they were more likely to have increased inflammatory response and hypercoagulable state as reflected in C-reaction protein (51.1 [1.3-127.9] vs 12.1 [0.1-212.0] mg/L,  $p < 0.01$ ) and D-dimer (6.9 [0.3-20.0] vs 0.5 [0.1-20.0] mg/L,  $p < 0.001$ ). Of 11 patients with ischemic stroke, 6 received antiplatelet treatment with Aspirin or Clopidogrel and 3 of them died. The other 5 patients received anticoagulant treatment with Clexane and one of them died. As of Feb 29, 2020, 5 patients with CVD died (38%).

#### Conclusions

Acute cerebrovascular disease is not uncommon in COVID-19. Our findings suggest that older patients with risk factors are more likely to develop CVD. The development of CVD is an important negative prognostic factor, which require further study to identify optimal management strategy to combat the COVID-19 outbreak.

## **Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study**

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**Key word:** Cerebrovascular disease, COVID-19, Anticoagulation therapy, Thromboembolic events

## Summary

**Background:** Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Apart from respiratory complications, acute cerebrovascular disease (CVD) has been observed in some patients with COVID-19. Therefore, we described the clinical characteristics, laboratory features, treatment, and outcomes of CVD complicating SARS-CoV-2 infection.

**Methods:** We conducted a single center, retrospective, observational analysis of consecutive COVID-19 patients admitted to Union Hospital, Wuhan, China from 16 January 2020 to 29 February 2020. Demographic and clinical characteristics, laboratory findings, treatments, and clinical outcomes were extracted from electronic medical records and compared between COVID-19 patients with and without new onset of CVD.

**Results:** Of 221 patients with COVID-19, 11 (5%) developed acute ischemic stroke, 1 (0.5%) cerebral venous sinus thrombosis (CVST), and 1 (0.5%) cerebral hemorrhage. COVID-19 with new onset of CVD were significantly older ( $71.6 \pm 15.7$  years vs  $52.1 \pm 15.3$  years;  $p < 0.05$ ), more likely to present with severe COVID-19 (84.6% vs. 39.9%,  $p < 0.01$ ) and were more likely to have cardiovascular risk factors, including hypertension, diabetes, and previous medical history of cerebrovascular disease (all  $p < 0.05$ ). In addition, they were more likely to have increased inflammatory response and hypercoagulable state as reflected in C-reaction protein ( $51.1 [1.3-127.9]$  vs  $12.1 [0.1-212.0]$  mg/L,  $p < 0.01$ ) and D-dimer ( $6.9 [0.3-20.0]$  vs  $0.5 [0.1-20.0]$  mg/L,  $p < 0.001$ ). Of 11 patients with ischemic stroke, 6 received antiplatelet treatment with Aspirin or Clopidogrel and 3 of them died. The other 5

patients received anticoagulant treatment with Clexane and one of them died. As of Feb 29, 2020, 5

patients with CVD died (38%).

**Conclusions:** Acute cerebrovascular disease is not uncommon in COVID-19. Our findings suggest that older patients with risk factors are more likely to develop CVD. The development of CVD is an important negative prognostic factor, which require further study to identify optimal management strategy to combat the COVID-19 outbreak.

**Funding:** None.

## **Introduction**

Since the identification of the first case of SARS-CoV-2 infection in Wuhan in December 2019,<sup>1</sup> As of 29 Feb. 2020, the number of laboratory-confirmed COVID-19 cases has exceeded 85403 cases globally, of which 79394 in China.<sup>2</sup> The spectrum of the clinical presentation of COVID-19 patients very considerably, ranging from asymptomatic infection, to severe pneumonia that may lead to respiratory failure and death.<sup>3</sup>

We recently reported the clinical manifestations and outcome in 214 patients with COVID-19 infection and found severe patients commonly had neurologic symptoms including consciousness impairment (14.8%) and skeletal muscle symptoms (19.3%).<sup>4</sup> Previous study has suggested that bacterial and/or viral infection may be a trigger for acute ischemic stroke, probably related to the prothrombotic effect of the inflammatory response.<sup>5</sup> However, there is sparse information regarding acute cerebrovascular disease (CVD) following COVID-19 infection. Accordingly, here we reported 13 cases who suffered from a SARS-CoV-2 infection and developed a sudden-onset of cerebrovascular diseases. We described clinical characteristics, treatment strategy, and outcomes between COVID-19 with and without new onset with cerebrovascular disease.

## **Methods**

This was a single-center retrospective study. A total of 221 consecutive patients with confirmed COVID-19 admitted to the Union Hospital of Huazhong University of Science and Technology between January 16 and February 29, 2020 were included in this analysis. Union Hospital, located in the endemic areas of COVID-19 in Wuhan, Hubei Province, is one of the major tertiary healthcare system and teaching hospitals in the region and has been designated by the government as a COVID-19 care hospital since

the outbreak, responsible for the treatments for SARS-CoV-2 infection as designated. All patients with COVID-19 in this study were diagnosed according to the WHO interim guideline,<sup>6</sup> with respiratory symptom, SARS-CoV-2 RT-PCR positive in throat swab, and viral-like pneumonia in chest CT.<sup>7</sup> The date of 214 patients with COVID-19 had been published in our previous paper.<sup>4</sup> The study was performed in accordance to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Verbal consent was obtained from patients before the enrollment.

The demographic characteristics, medical history, symptoms, clinical signs, laboratory findings, chest computed tomographic (CT) scan findings were extracted from electronic medical records. The data were reviewed by a trained team of physicians. Each cases of stroke diagnose was confirmed by brain CT and CVST diagnose was made by CT venography (CTV). All neurological symptoms were reviewed and confirmed by two trained neurologists. The date of disease onset was defined as the day when the symptom was noticed. The severity of COVID-19 was defined by the international guidelines for community-acquired pneumonia.<sup>8</sup> Throat swab samples were collected and placed into a collection tube containing preservation solution for the virus.<sup>7</sup> SARS-CoV-2 infection was confirmed by real-time RT-PCR assay using a SARS-CoV-2 nucleic acid detection kit according to the manufacturer's protocol (Shanghai bio-germ Medical Technology Co Ltd). The types of stroke were classified by the TOAST classification, including largeartery stenosis, small vessel occlusion, cardioembolic, unknown and other stroke cause.

### **Statistical Analysis**

Continuous variables were described as means and standard deviations, or medians and interquartile range (IQR) values between patients with or without new onset of CVD. Categorical variables were expressed as counts and percentages. Continuous variables were compared by using the unpaired Wilcoxon rank-sum test. Proportions for categorical variables were compared using the  $\chi^2$  test. All statistical analyses were performed using R (version 3.3.0) software, with  $p < 0.05$  considered as statistically significant.

## Results

Of 221 patients with confirmed SARS-CoV-2, 13 (5.9%) developed new onset of CVD following COVID infection. Their demographic and clinical characteristics were shown in Table 1. Of these patients, 11 (84.6%) were diagnosed as ischemic stroke, 1 (7.7%) cerebral venous sinus thrombosis and 1 (7.7%) cerebral hemorrhage. Representative brain and chest images of number 2 patient with ischemic stroke, number 12 patient with cerebral venous sinus thrombosis and number 13 patient with cerebral hemorrhage were shown in Figure 1. Except for one patient with cerebral venous sinus thrombosis (age 32 years), age ranged from 57 to 91 years (median 73.5 [IQR 57-91]). Six (46.2%) were female. Five (38.5%) patients had smoking history and 2 (15.4%) patients had drinking history, respectively. Seven (53.8%) patients had increased blood pressure ( $\geq 130/80$  mmHg) and 10 (76.9%) had elevated fasting blood glucose levels ( $> 6.1$  mmol/L) at admission of CVD. The median durations from first symptoms of SARS-CoV-2 infection to CVD were 10 days (IQR 1-29). Of the 11 patients with ischemic stroke, five were large vessel stenosis, 3 were small vessel occlusion and 3 were cardioembolic type according to TOAST classification. All of these patients were combined with increased inflammatory response and hypercoagulable state. The choice of treatment for ischemic

stroke (Antiplatelet/Anticoagulant) was determined by physicians according to the comprehensive judgment of TOAST classification, clinical syndrome and laboratory findings.

Table 2 shows the clinical characteristics between COVID-19 patients with CVD and those without CVD. COVID-19 with new onset of CVD were significantly older ( $71.6 \pm 15.7$  years vs  $52.1 \pm 15.3$  years;  $p < 0.05$ ) and were more likely to present with severe COVID-19 (84.6% vs. 39.9%,  $p < 0.01$ ). Moreover, patients with CVD were more likely to have other underlying disorders, including hypertension (69.2% vs 22.1%,  $p < 0.001$ ), and diabetes mellitus (46.2% vs 12.0%, all  $p < 0.01$ ), which were the common risk factors of CVD.

Table 3 showed the laboratory findings in COVID-19 patients with or without CVD. Patients with CVD had more increased inflammatory response, including higher white blood cell (median 7.7 [IQR 3.9-17.5] vs 4.9 [0.1-20.4]  $\times 10^9/L$ ,  $p < 0.001$ ), neutrophil counts (6.8 [0.0-15.3] vs 3.0 [0.0-18.7]  $\times 10^9/L$ ,  $p < 0.001$ ), and C-reaction protein levels (51.1 [1.3-127.9] vs 12.1 [0.1-212.0] mg/L,  $p < 0.01$ ), but lower lymphocyte counts (0.6 [0.3-1.2] vs 1.1 [0.1-2.6]  $\times 10^9/L$ ,  $p < 0.001$ ), suggesting presence of immunosuppression. Patients with CVD also had higher D-dimer levels (6.9 [0.3-20.0] vs 0.5 [0.1-20.0] mg/L,  $p < 0.001$ ), indicating the hypercoagulable state. In addition, patients with CVD were more likely to have multiple organ involvement, including liver injury (increased aspartate aminotransferase levels: 37.0 [19.0-271.0] vs 26.0 [8.0-8191.0] U/L,  $p < 0.05$ ) and kidney injury, with elevated blood urea nitrogen (7.4 [4.0-43.2] vs 4.1 [1.5-48.1],  $p < 0.001$ ) and creatinine levels (75.5 [42.7-261.3] vs 68.2 [35.9-9435.0],  $p < 0.01$ ).

Of 11 patients with ischemic stroke, six received antiplatelet treatment with Aspirin or Clopidogrel and 5 received anticoagulant treatment with Clexane. As of Feb 29, 2020, the overall mortality rate was 38.5% (5/13) and 7 patients remained hospitalized. Among those treated with antiplatelet, 3 died (50%) as compared with 20% in those treated with anticoagulant. One patient with cerebral venous sinus thrombosis received anticoagulant treatment and remained hospitalized. One patient with cerebral hemorrhage died 22 days after stroke.

## **Discussion**

This is the case series of COVID-19 with new onset of CVD. 13 patients with COVID-19 developed CVD following infection. Patients with CVD were older and were more likely to have cardiovascular and cerebrovascular risk factors. These findings suggested that elder patients with COVID-19 may be more likely to develop CVD and more attention should be paid to older patient with cerebrovascular risk factors.

Importantly, 11 out of 13 patients with CVD were severe SARS-CoV-2 infection patients, suggesting severe infection may be a indicator of CVD, especially acute ischemic stroke. Our past work also showed that severe patients were more likely to develop neurological symptoms.<sup>4</sup> Inflammation has been increasingly recognized as a key contributor to the pathophysiology of cerebrovascular diseases<sup>9</sup> and involved in the acute intravascular events triggered by the interruption of the blood supply.

Meanwhile blood inflammatory factors (e.g. Interleukin and c-reactive protein) is responsible for early molecular events triggered by coagulation abnormalities.<sup>10-12</sup> We found that compared with the patients without CVD, patients with CVD was found a rise in blood C-reactive protein level. 12 out of 13 patients with both CVD and COVID-19 had extremely high level of D-dimer (average level of 6.9), by

contrast, D-dimer of patients without CVD was at a lower level (average level of 0.5). According to the laboratory test index of blood, patients with COVID-19 with CVD had more severe inflammatory infection and in a state of high coagulation. The inflammatory response increased significantly could be the causes of abnormal blood coagulation function in early stage and could be one of the main reasons of onset CVD.

The average of time from SARS-CoV-2 infection to onset of CVD was about 12 days. Neurological injury has been confirmed in the infection of other coronavirus such as in SARS-CoV and Middle East respiratory syndrome corona virus (MER-CoV).<sup>13,14</sup> A study reported that 28 days after onset of SARS-CoV infection patient experienced central nervous symptoms.<sup>15</sup> A 4-patient case report showed patients developed neuromuscular diseases approximately 3 weeks after the onset of SARS.<sup>16</sup> Another 3-patient case report showed brain MRI revealed significant changes characterized by widespread, bilateral hyperintense lesions on T2-weighted imaging within the white matter and subcortical areas of the frontal, temporal, and parietal lobes after 25-28 days onset of MER-CoV.<sup>13</sup> Thus, in early stages, to make diagnosis according to clinical symptoms and lab tests and take measures for anti-inflammatory treatment as early as possible may arrested the growth of the COVID-19. It may be one way to reduce the risk of CVD.

This study has several limitations. First, this is a single center report. While it may not be generalizable, our study represent the first report of COVID-19 patients with new onset of CVD following infection. . Second, xxx patients were still hospitalized as of Feb 29, 2020 and information regarding their outcomes was unavailable at the time of analysis. Further evaluation of the natural history of disease are needed.

In conclusion, CVD is not uncommon with patients with COVID-19. Patients developed CVD were older, had multiple risk factors (hypertension and diabetes), more severe SARS-CoV-2 infection, inflammatory response in the state of blood hypercoagulable. Physicians should pay more attention to control risk factors of cerebrovascular diseases while treating the patients with COVID-19.

### **Contributors**

YL and HJ did the literature search. BH was responsible for the concept of the study and was responsible for its design. Data were collected by MW, YZ, LM, SC, YW, HJ, YL and ML; analyzed by JC; and interpreted by BH and YX. YX, YL, HJ and HW wrote the manuscript.

### **Declaration of interests**

We declare no competing interests.

### **Data sharing**

After publication, the data will be made available to others on reasonable requests to the corresponding author. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the corresponding author and Union hospital, Tongji medical college, Huazhong university of science and technology.

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### Declaration of interests

We declare no competing interests.

### Reference

1. China NHCotPsRo. Update on the outbreak of Coronavirus disease 2019 as of 24:00 on February 28, 2020. <http://www.nhc.gov.cn/xcs/yqtb/202002/4ef8b5221b4d4740bda3145ac37e68ed.shtml> (accessed February 29, 2020).
2. WHO. Coronavirus disease 2019 (COVID-19) Situation Report-40. 2020. [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200229-sitrep-40-covid-19.pdf?sfvrsn=849d0665\\_2](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200229-sitrep-40-covid-19.pdf?sfvrsn=849d0665_2) (accessed Feb 29, 2020).
3. 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.
4. Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. *medRxiv* 2020: 2020.02.22.20026500.
5. Grau AJ, Bugge F, Becher H, et al. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: clinical and biochemical studies. *Neurology* 1998; **50**(1): 196-203.
6. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. January, 2020. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) (accessed February 28, 2020).
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020; **395**(10223): 497-506.
8. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200**(7): e45-e67.
9. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nat Med* 2011; **17**(7): 796-808.
10. Ding P, Zhang S, Yu M, et al. IL-17A promotes the formation of deep vein thrombosis in a mouse model. *Int Immunopharmacol* 2018; **57**: 132-8.
11. Ji Y, Fish PM, Strawn TL, et al. C-reactive protein induces expression of tissue factor and plasminogen activator inhibitor-1 and promotes fibrin accumulation in vein grafts. *J Thromb Haemost* 2014; **12**(10): 1667-77.
12. Horvei LD, Grimnes G, Hindberg K, et al. C-reactive protein, obesity, and the risk of arterial and venous thrombosis. *J Thromb Haemost* 2016; **14**(8): 1561-71.
13. Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 2015; **43**(4): 495-501.
14. Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol* 2004; **251**(10): 1227-31.

15. Xu J, Zhong S, Liu J, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis* 2005; **41**(8): 1089-96.
16. Tsai LK, Hsieh ST, Chao CC, et al. Neuromuscular disorders in severe acute respiratory syndrome. *Arch Neurol* 2004; **61**(11): 1669-73.

**Table 1. Baseline characteristics of COVID-19 patients with new onset of CVD during infection**

	Type of CVD	Subtype of AIS	Age, y	Sex	Smoking History	Drinking History	Blood pressure (mm Hg)	Fasting Blood-glucose (mmol/L)	Type of COVID-19 Patients (Severe/Non-Severe)	Onset Time of SARS-CoV-2 Infection	Onset Time of CVD	Treatment of CVD	Outcome Event
1	AIS	Small vessel	70	M	No	No	110/70	5.44	Severe	01/26/20	02/23/20	Antiplatelet	Survival
2	AIS	Large vessel stenosis	75	F	No	No	110/67	6.03	Severe	01/24/20	02/15/20	Antiplatelet	Survival
3	AIS	Cardioembolic	89	F	No	No	97/64	6.77	Non-severe	02/19/20	02/19/20	Anticoagulant	Survival
4	AIS	Large vessel stenosis	91	F	No	No	192/97	6.7	Severe	02/01/20	02/10/20	Anticoagulant	Survival
5	AIS	Large vessel stenosis	72	F	No	No	155/89	7.93	Severe	02/01/20	02/12/20	Anticoagulant	Survival
6	AIS	Cardioembolic	71	M	Yes	No	142/67	16.25	Severe	01/31/20	02/07/20	Anticoagulant	Death
7	AIS	Cardioembolic	86	M	Yes	No	110/72	13.81	Severe	01/24/20	02/11/20	Antiplatelet	Death
8	AIS	Large vessel stenosis	82	F	No	No	140/83	24.2	Severe	02/02/20	02/16/20	Antiplatelet	Death
9	AIS	Small vessel	78	M	Yes	No	156/82	11.0	Severe	01/17/20	01/17/20	Antiplatelet	Death
10	AIS	Large vessel stenosis	57	M	No	No	127/83	13.24	Non-severe	02/06/20	02/07/20	Antiplatelet	Survival
11	AIS	Small vessel	66	F	No	No	98/62	8.67	Severe	02/11/20	02/17/20	Anticoagulant	Survival
12	CVST		32	M	Yes	Yes	130/80	8.23	Severe	02/09/20	02/23/20	Anticoagulant	Survival
13	CH		62	M	Yes	Yes	150/80	5.81	Severe	01/23/20	02/01/20		Death

\* The patients of COVID-19 were confirmed by SARS-CoV-2 RT-PCR positive in throat swab and viral-like pneumonia in chest CT.

Abbreviations: COVID-19, Coronavirus disease 2019; CVD, Cerebrovascular disease; AIS, Acute ischemia stroke; CH, Cerebral hemorrhage; CVST, Cerebral Venous Sinus Thrombosis; F, Female; M, Male

**Table 2. Clinical characteristics of COVID-19 patients with or without new onset CVD**

	<b>Total (N=221)</b>	<b>COVID-19 with CVD (n=13)</b>	<b>COVID-19 without CVD (n=208)</b>	<b>P*</b>
<b>Age (y), mean±SD</b>	53.3±15.9	71.6±15.7	52.1±15.3	
<b>Age, n (%)</b>				0.02
<50 y	91 (41.2)	1 (7.7)	90 (43.3)	
≥50 y	130 (58.8)	12 (92.3)	118 (56.7)	
<b>Sex, n (%)</b>				0.39
Female	90 (40.7)	7 (53.8)	83 (39.9)	
<b>COVID-19</b>				0.002
Severe	94 (42.5)	11 (84.6)	83 (39.9)	
Non-Severe	127 (57.5)	2 (15.4)	125 (60.1)	
<b>Medical history, n (%)</b>				
Any	85 (38.5)	10 (76.9)	75 (36.1)	0.006
Hypertension	55 (24.9)	9 (69.2)	46 (22.1)	<0.001
Diabetes	31 (14.0)	6 (46.2)	25 (12.0)	0.004
<b>Cardio cerebrovascular disease</b>	17 (7.7)	3 (23.1)	14 (6.7)	0.07
Malignancy	14 (6.3)	1 (7.7)	13 (6.3)	0.58

Data are presented as mean ± standard deviation (SD) and n/N (%).

Abbreviations: COVID-19, Coronavirus disease 2019; CVD, Cerebrovascular disease.

P values indicate differences between COVID-19 patients with and without new onset CVD. P<0.05 was considered statistically significant.

\*fisher exact test

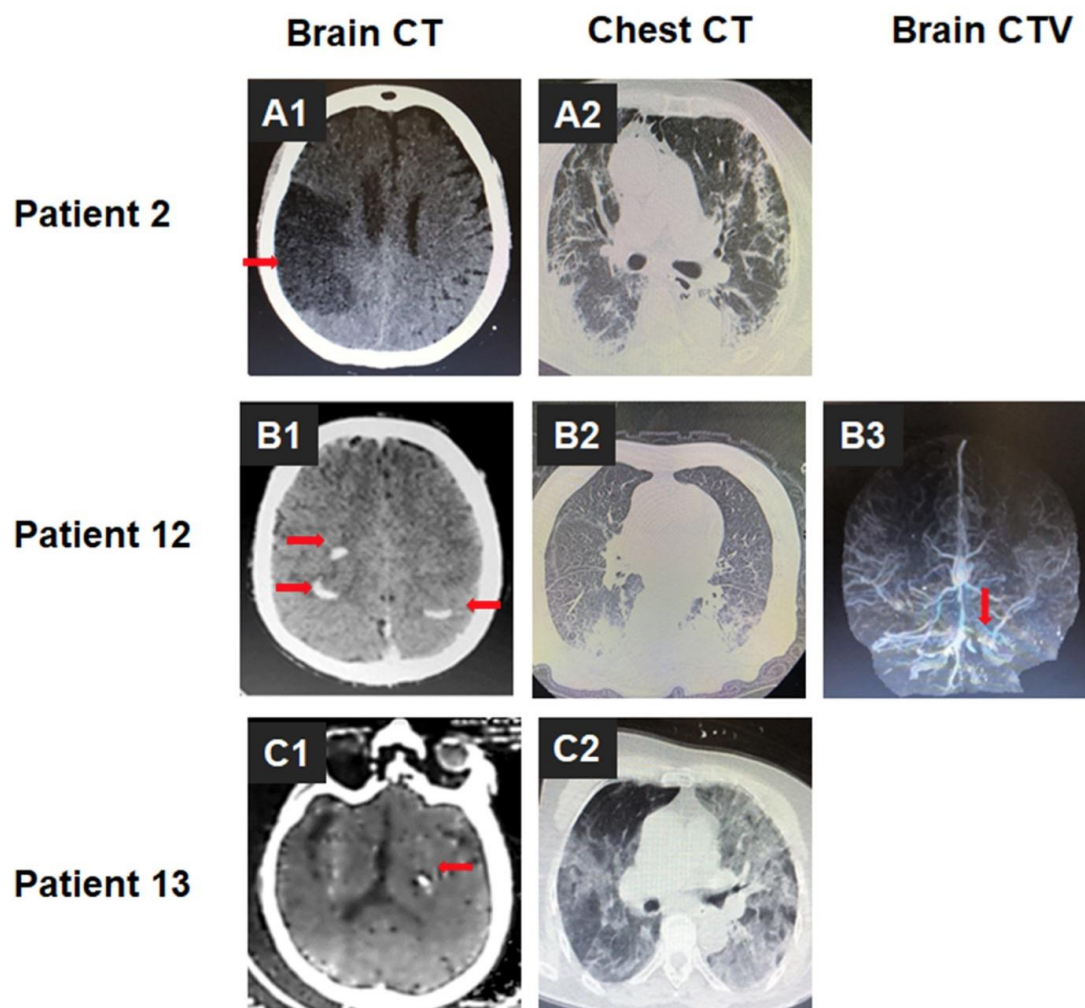
**Table 3. Laboratory findings of COVID-19 patients with or without new onset CVD**

	<b>Total (n=221)</b>	<b>COVID-19 with CVD (n=13)</b>	<b>COVID-19 without CVD (n=208)</b>	<b><i>P</i>*</b>
<b>White blood cell count, ×10<sup>9</sup>/L</b>	5.0 (0.1-20.4)	7.7 (3.9-17.5)	4.9 (0.1-20.4)	<0.001
<b>Neutrophil, ×10<sup>9</sup>/L</b>	3.1 (0.0-18.7)	6.8 (0.0-15.3)	3.0 (0.0-18.7)	<0.001
<b>Lymphocyte count, ×10<sup>9</sup>/L</b>	1.1 (0.1-2.6)	0.6 (0.3-1.2)	1.1 (0.1-2.6)	<0.001
<b>Platelet count, ×10<sup>9</sup>/L</b>	205.0 (18.0-583.0)	142.0 (90.0-564.0)	211.0 (18.0-583.0)	0.04
<b>C-reactive protein, mg/L</b>	12.9 (0.1-212.0)	51.1 (1.3-127.9)	12.1 (0.1-212.0)	0.008
<b>D-dimer, mg/L</b>	0.5 (0.1-20.0)	6.9 (0.3-20.0)	0.5 (0.1-20.0)	<0.001
<b>Alanine aminotransferase, U/L</b>	27.0 (5.0-1933.0)	28.0 (13.0-163.0)	26.5 (5.0-1933.0)	0.75
<b>Aspartate aminotransferase, U/L</b>	26.5 (8.0-8191.0)	37.0 (19.0-271.0)	26.0 (8.0-8191.0)	0.02
<b>Blood urea nitrogen, mmol/L</b>	4.2 (1.5-48.1)	7.4 (4.0-43.2)	4.1 (1.5-48.1)	<0.001
<b>Creatinine, μmol/L</b>	68.4 (35.9-9435.0)	75.5 (42.7-261.3)	68.2 (35.9-9435.0)	0.01

Abbreviations: COVID-19, Coronavirus disease 2019; CVD, Cerebrovascular disease.

*P* values indicate differences between COVID-19 patients with and without new onset CVD. *P*<0.05 was considered statistically significant.

\* Wilcoxon non-parameter test



**Figure 1. Representative brain and chest images of COVID-19 patients with CVD.** (A) Representative brain (A1) and chest (A2) CT images of the Patient 2 with new onset of ischemic stroke. (B) Representative brain (B1), chest (B2) CT images and brain CTV images (B3) of the Patient 12 with new onset of cerebral venous sinus thrombosis. (C) Representative brain (C1) and chest (C2) CT images of the Patient 13 with new onset of left basal ganglia hemorrhage.

March 3, 2020

Dear Editor:

Please find enclosed manuscript for consideration of expedited publication as an original article in *The Lancet*: "Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study."

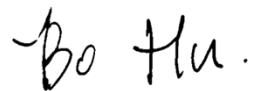
The outbreak of COVID-19 from Wuhan China is serious and has the potential to become epidemic unfortunately worldwide. As of 1 March, 2020, the number of laboratory-confirmed COVID-19 cases has exceeded 87137 cases globally, of which 79968 in China, and 2873 death in China. Several studies have described clinical manifestations of patients with COVID-19 including the typical symptoms, such as fever, cough, pharyngalgia, diarrhea. Previous study has suggested that bacterial and/or viral infection may be a trigger for acute ischemic stroke, probably related to the prothrombotic effect of the inflammatory response. However, there is sparse information regarding acute cerebrovascular disease (CVD) following COVID-19 infection. To our knowledge, this is the first report which described clinical characteristics, treatment strategy, and outcomes between COVID-19 with and without new onset with cerebrovascular disease. We reported 13 patients with COVID-19 developed CVD following infection. Result suggesting that CVD is not uncommon with patients with COVID-19. Patients developed CVD were older, had multiple risk factors (hypertension and diabetes), more severe SARS-CoV-2 infection, inflammatory response in the state of blood hypercoagulable. Therefore, physicians should pay more attention to control risk factors of cerebrovascular diseases while treating the patients with COVID-19, especially for elder patients with multiple risk factors.

Due to the urgency of this epidemic, our results could be important clinical findings to warn the healthcare providers not to delay the recognition clinically and begin treatment of COVID-19 combining with CVD, especially for severe patients. It is especially meaningful to all to learn that for those with severe COVID-19, rapid clinical deterioration or worsening could be related to CVD, which would contribute to its high mortality rate.

We would appreciate that *The Lancet* Editors would know the urgent nature of getting this new finding out so that the world can learn more about COVID-9 and apply to its diagnosis and management.

Again thank you for paying attention to this urgent matter. It would be deeply appreciated if *The Lancet* could expedite the review and inform us early of your decisions.

Sincerely,

A handwritten signature in black ink that reads "Bo Hu." The signature is written in a cursive, flowing style.

Bo Hu, Ph.D. (Corresponding author)

Professor

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