

# The clinical characteristics and prognosis of COVID-19 patients with cerebral stroke—a retrospective cohort study

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# Abstract

**Objective:** To explore the clinical characteristics and prognosis of COVID-19 patients with cerebral stroke.

**Methods:** In this retrospective study, 2474 patients with COVID-19 were admitted and treated in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in Wuhan from February 10, 2020, to March 24, 2020. Data on the clinical characteristics, laboratory parameters and prognosis of COVID-19 patients with or without cerebral stroke were collected and comparatively analyzed.

**Results:** Of 2474 COVID-19 patients ( $61.0 \pm 15.7$  years; 1235 males [49.9%]), 113 (4.7%) patients had cerebral stroke, and 25 (1.0%) patients had a new onset of stroke. Eighty-eight (77.9%) patients in the previous stroke group had cerebral ischemia, while 25 (22.1%) patients in the new-onset stroke group had cerebral ischemia. Most COVID-19 patients with stroke were elderly with more complicated disorders, such as hypertension, diabetes and heart diseases. Laboratory examinations showed a hypercoagulation status and elevated serum parameters such as IL-6, cTnI, NT pro-BNP and BUN. Of note, stroke patients revealed a nearly double mortality (12.4% vs 6.9%) to that of patients without stroke. Additionally, age ( $\geq 60$  years), fingertip oxygen saturation ( $< 93\%$ ) and consciousness disorder were independent predictors for new cerebral stroke in COVID-19 patients.

**Interpretation:** The high risk of new-onset stroke in COVID-19 patients was older age combined with fingertip oxygen saturation ( $< 93\%$ ) and consciousness disorder. These patients are more vulnerable to multiple organ dysfunction and an overactivated inflammatory response, in turn leading to a deteriorated outcome and mortality.

## Key Points

### Question

What are the clinical characteristics and prognosis of COVID-19 patients with cerebral stroke?

### Findings

Based on the data from 2474 cases, the presence of cerebral stroke in COVID-19 patients was 5.9% (113/2474), and the incidence of new-onset stroke was 1.6% (25/2474). COVID-19 patients with stroke showed older age, multiple symptoms and complicated previous medical history. In addition, they were more likely to have abnormalities in heart, kidney, liver and immune function. Age ( $\geq 60$  years), fingertip oxygen saturation ( $< 93\%$ ) and consciousness disorder were independent predictors for new stroke occurrence under SARS-CoV-2 infection.

### Meaning

COVID-19 patients with stroke were elderly with complicated fingertip oxygen saturation (<93%) and consciousness disorder, more likely to have multiorgan dysfunction and an overactivated inflammatory response, resulting in poor prognosis and higher mortality. Closer observation and early intervention should be given to COVID-19 patients with a history or high-risk factor for stroke to avoid serious complications and high mortality.

## Introduction

From late December 2019, viral pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and caused a global pandemic outbreak world over the next few months. Although the source of this virus is still unclear, it has led to the death of a large number of infected patients, especially elderly patients with underlying disease. Multiple studies have confirmed that hypertension, diabetes and cardiovascular disease are the main risk factors associated with acute respiratory distress syndrome and death in coronavirus disease 2019 (COVID-19) patients<sup>1</sup>. However, little is known about the impact of cerebral stroke as a common senile disease on its clinical characteristics and prognosis.

Stroke, also known as an acute cerebrovascular disease, is caused by various vascular causes (including ischemic and hemorrhagic stroke) with neurological dysfunction. COVID-19 patients with stroke can present disturbance of consciousness and difficulty in physical activity, which may result in central respiratory depression and exacerbate lung infection<sup>2</sup>. On the other hand, severe COVID-19 cases are often accompanied by hypoxia, impaired cardiac function and abnormal blood coagulation, which are high-risk factors for stroke<sup>3</sup>. Considering the different clinical characteristics and prognosis of ischemic and hemorrhagic stroke and the higher incidence of ischemic stroke, we explored the interacting effects between ischemic stroke and SARS-CoV-2 infection, which will be of great benefit for better prevention and treatment of stroke-related clinical symptoms in COVID-19 patients.

In the present study, we reported the clinical characteristics and prognosis of COVID-19 patients with previous or new-onset stroke separately. The risk factors for new-onset stroke were also investigated. Our study revealed the effects of cerebral stroke on the clinical features and prognosis of COVID-19 patients and provided novel insights into the spectrum of this disease. We hope our study may provide a reference for better treatment of COVID-19 patients with stroke.

## Methods

### Study design and participants

All patients were admitted and treated in two branches (Optic valley branch and Sino-French new city branch) of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in Wuhan. These two comprehensive clinic centers are designated hospitals for the treatment of severely and critically ill patients with COVID-19. Clinical data of 2474 patients who were diagnosed with COVID-

19 according to World Health Organization interim guidance were retrospectively collected from February 10, 2020, to March 24, 2020<sup>3</sup>. Laboratory confirmation of SARS-CoV-2 infection was performed in all patients on admission in our hospitals. This study was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in accordance with the Helsinki Criteria. Written informed consent was waived in line with the urgent need to collect data.

## Data collection

The clinical data, including basic information (age and gender), past medical history (hypertension, diabetes, heart disease and others), typical symptoms (fever, cough, shortness of breath, muscle ache and diarrhea), neurological symptoms (headache, dizziness and consciousness disorder), medical course, laboratory findings (blood cell count, serum inflammation factor testing, serum biochemical analysis, serum electrolyte testing and blood coagulation factor testing), chest and brain computed tomography (CT) scan, treatment and outcomes, were retrospectively collected by careful review of medical records of patients with laboratory-confirmed SARS-CoV-2 infection. Symptoms were acquired by direct communication with conscious patients or with relatives of unconscious persons. Additionally, consciousness disorder was exclusively evaluated by experienced neurological doctors. Laboratory examination was performed on admission and when necessary in our hospital. The highest value of each laboratory testing parameter of patients during hospitalization was collected for statistical analysis. We defined a composite end point as the date of patient discharge, death or date of March 24, 2020. Accordingly, we evaluated two medical courses for each patient, including days from onset to the end point of observation as well as days from hospital admission to the end point of observation.

Stroke is a severe cerebrovascular disease and is divided into two types: cerebral ischemic infarction and cerebral hemorrhage<sup>4-5</sup>. In the present study, we only enrolled all ischemic infarction patients. In accordance with the period of stroke occurrence, we further categorized COVID-19 patients with stroke into two groups. One group was the previous stroke group, in which the patients had a stroke at least one month prior to confirmation of COVID-19; the other group was the new stroke group, in which stroke occurred after COVID-19 diagnosis. Previous stroke was identified from personal medical records. New stroke in COVID-19 patients was identified by brain CT scan or MRI. The diagnosis of stroke was carefully confirmed by at least two trained neurological doctors.

All patients received personal systematic treatments in accordance with WHO interim guidelines<sup>3</sup> including antiviral therapy, oxygen support, secondary infection control, multiple organ function monitoring and support. Oxygen support is one of the most important approaches and is consistently achieved by normal or high-flow nasal cannula application, noninvasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)<sup>2</sup>{Organization, 2020 #1069}. For patients with ischemic stroke, anti-coagulation, high brain perfusion and brain protection therapy were performed. To treat patients with hemorrhagic stroke, hemostatic drugs, brain edema and swelling control and brain protection agents were used. In our patient series, none of the stroke patients underwent neurosurgical

interventions. In light of the end point of observation, the outcomes of COVID-19 patients included discharge, hospitalization and death.

## Statistical analyses

All statistical analyses were performed using SPSS 17.0 statistical software. For continuous data, the mean  $\pm$  standard deviation (SD) and median with range were used for normal and abnormal distribution data, respectively. The differences were statistically analyzed using unpaired t-test. Qualitative data were expressed as counts and percentages, and the chi-square test was used. A multivariate regression analysis was performed to determine the risk factors for new-onset stroke in COVID-19 patients. The distribution of overall survival of patients was estimated by using the Kaplan-Meier method and compared with each other by using the log-rank test.  $P < 0.05$  was considered statistically significant.

## Results

### Clinical characteristics of COVID-19 patients with or without stroke

The essential clinical information of COVID-19 patients is summarized in Table 1. A total of 2474 cases were included in this study, with a mean age of  $61.0 \pm 15.7$  years. The mean age of patients in the stroke group was significantly older than that in the nonstroke group ( $P < .001$ ). Specifically, patients older than 60 years were more frequently observed in the stroke group than in the nonstroke group ( $P < .001$ ). However, there was no difference in sex among groups ( $P = .558$ ). The presence of comorbidities (hypertension, diabetes and heart disease) was more common among patients with stroke (all  $P < .001$ ). Moreover, the stroke patients showed a higher incidence of consciousness disorder than nonstroke patients ( $P < .001$ ), while the other common symptoms, such as cough, shortness of breath, and diarrhea, were similar. Stroke patients were more likely to have low fingertip oxygen saturation than nonstroke patients ( $P < .001$ ).

The stroke patients were further divided into two subgroups according to the time point of stroke onset: patients with previous stroke and new stroke. The detailed clinical characteristics for patients in different subgroups are listed in Table 1. Generally, there were 88 patients with previous stroke and 25 cases with newly identified stroke. In comparison to nonstroke patients, both previous and new stroke patients showed similar incidences of common symptoms, such as cough, shortness of breath, diarrhea and fever, but a higher incidence of consciousness disorder than nonstroke patients (all  $P < .001$ ). The proportion of patients with headache or dizziness (44.4% vs 18.0%,  $P = .01$ ) was higher for new stroke patients than nonstroke patients. Previous stroke patients were more likely to have low fingertip oxygen saturation (<93%) than nonstroke patients (23.1% vs 11.5%,  $P < .001$ ).

Figure 1 shows representative radiological images of COVID-19 patients with new-onset and previous stroke.

### Laboratory parameters of COVID-19 patients with and without stroke

Table 2 shows the laboratory findings of patients with and without stroke. Previous and new stroke patients exhibited more prevalent neutrophilia (33.0% and 48.0% vs 21.1%,  $P<.001$ , respectively), lymphocytopenia (58% and 76% vs 31.2%,  $P<.001$ , respectively) and anemia (25% and 28% vs 8.5%,  $P<.001$ , respectively) than the nonstroke group. Blood levels of cytokines and infection-related factors were detected in a certain proportion of patients with or without stroke, including IL-1 $\beta$ , TNF- $\alpha$ , IL-8, IL-2R, IL-10 and hsCRP. An abnormal concentration of IL-6 was more frequently found in previous and new stroke patients (68.3% and 87.0% vs 42.4%,  $P<.001$ , respectively). More previous and new stroke cases had markedly higher concentrations of myohemoglobin (MG, 30.4% and 45% vs 12.7%,  $P<.001$ , respectively), N terminal pro-brain natriuretic peptide (NT pro-BNP, 78.2% and 91.3% vs 50.5%,  $P<.001$ , respectively), blood urea nitrogen (BUN, 44.8% and 44% vs 16.5%,  $P<.001$ , respectively) and creatinine (Cr, 44.8% and 44% vs 13%,  $P<.001$ , respectively) than nonstroke patients. In addition, elevated concentrations of cardiac troponin I (cTnI, 26.4% vs 11.3%,  $P<.001$ ), creatine kinase-myoglobin (CK-MB, 10.1% vs 4.7%,  $P=.028$ ) and decreased levels of albumin (42.5% vs 19.8%,  $P<.001$ ) were more frequently found in previous stroke patients than in nonstroke patients. Disturbance of electrolytes, including potassium and sodium, was more likely to occur in both previous- and new stroke patients. In terms of coagulation-related indexes, significantly increased D-dimer (80.5% and 84% vs 58.8%,  $P<.001$ , respectively) and fibrinogen (Fgb, 75.6% and 80.8% vs 60.6%,  $P=.005$  and  $P=.001$ ) were more prevalent in previous- and new stroke patients. Additionally, prolonged activated partial thromboplastin time (APTT, 47.7% vs 33.8%,  $P=.008$ ), fibrinogen degradation products (FDP, 58.9% vs 32.6%,  $P<.001$ ) and the incidences of decreased prothrombin activity (PTA, 1.1% vs 11.6%,  $P<.001$ ) and thrombocytopenia (39.8% vs 19.4%,  $P<.001$ ) were higher in previous stroke cases than in nonstroke cases.

### **Prognosis and survival analysis of COVID-19 patients with and without stroke**

The stroke patients had a significantly worse outcome than patients in the nonstroke group ( $P<.001$ ), including a higher mortality and longer disease course. Furthermore, the mean duration from symptom onset to the end point of observation was longer in the stroke group than in the nonstroke group ( $P<.05$ ) (Table 1). However, the mean duration from admission to the end point of observation between the two groups was similar (Table 1). Kaplan–Meier survival curves showed an improved overall survival (OS) for patients without stroke compared to those with previous stroke and new stroke (all  $P<.001$ ) (Figure 2). However, no significant difference was established regarding the OS between patients with previous stroke and those with new stroke (Figure 2).

### **Analysis of predictors for new stroke onset in COVID-19 patients**

Data on clinical variables and log-rank regression analysis are listed in Table 3. As a result, age $\geq$ 60 years, fingertip oxygen saturation ( $<93\%$ ) and consciousness disorder were independent predictors for new stroke occurrence in COVID-19 patients ( $P<.001$ ). However, heart disease and diabetes were not independent predictors for new stroke occurrence under SARS-CoV-2 infection.

## **Discussion**

In the present study, we retrospectively analyzed the effect of cerebral ischemic stroke on the clinical features and prognosis of COVID-19 patients, providing novel insights into the spectrum of this disease. The prevalence of stroke (4.7%) in COVID-19 patients was markedly higher than that of the population (1.79%) without infection<sup>5</sup>. One possible reason is that this cohort was predominantly from the designated hospital for severely and critically ill patients. Additionally, SARS-CoV-2 infection might also promote attack of ischemic stroke since a certain portion of cases were newly onset<sup>6</sup>. If so, treating patients with viral infection and concurrent stroke will be a great burden for the public health system.

COVID-19 patients share some common characteristics with the normal population in stroke prevalence, including older age<sup>7</sup>, as well as more prevalent comorbidities in stroke patients<sup>8</sup>, such as hypertension, diabetes and heart disease. However, none of them was an independent predictor for new stroke in this study.

From the robustly increased levels of biomarkers (e.g., cTnl, CK-MB, NT pro-BNP, Cr, BUN and IL-6) predicting extrapulmonary organ injuries, the presence of multiple organ dysfunction and overactivated systematic inflammation were more common in COVID-19 patients with stroke than in those without stroke<sup>9-10</sup>. These changes are important factors contributing to the impaired outcome of patients with stroke, as they were also widely observed in severe<sup>11-13</sup> and deceased cases<sup>1</sup>. In addition, due to impaired locomotor function and insufficient nutrition<sup>14</sup>, patients with stroke have poor immunity and cardiac function, bearing a considerable risk of suffering from hospital-acquired pneumonia caused by organisms other than viruses<sup>15-16</sup>. This is especially critical for stroke patients who lose consciousness and spontaneous respiration, while mechanical ventilation is required<sup>17</sup>. Coinfection will in turn aggravate the illness condition of COVID-19 patients<sup>1,18</sup>. In this study, a higher incidence of consciousness disorder in stroke patients might be an early sign related to their poor outcome.

Although the exact mechanisms underlying ischemic stroke in COVID-19 patients are still unknown, we can speculate the potential links between stroke and SARS-CoV-2 infection from its clinical features and cases caused by other coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), since these viruses share some common characteristics<sup>2</sup> and are involved in stroke<sup>19</sup>. For instance, ischemic stroke was found to occur in SARS<sup>19</sup> and MERS<sup>20</sup> at high incidences, and SARS-CoV could even be found in the cerebrum<sup>21</sup>.

Cytokine storms are widely considered to be a factor leading to aggravation of pneumonia and extrapulmonary injuries such as cardiac and renal failure<sup>11,12</sup>. There might be correlations between cytokines and stroke. Associated with cerebrovascular risks, cytokines and systemic inflammation-related factors such as IL-6, C reaction protein and monocyte chemoattractant protein 1 increase in acute respiratory tract infections were triggers for stroke<sup>22,23</sup>. Since inflammatory responses mediated by cytokines were found to disturb the stability of coronary plaque, which leads to cardiac ischemia<sup>24</sup>, we speculate that they might also affect the stability of carotid and cerebrovascular atherosclerosis, resulting in abnormal occlusive thrombus and cerebral infarction. Markedly elevated levels of IL-6 in new stroke patients in this

study could help to support this hypothesis. However, other cytokines were not found to differ between stroke and nonstroke patients. In addition, viral infection of the vascular endothelium is another possible mechanism. The genome of SARS-CoV-2 is highly homologous to SARS-CoV<sup>2</sup> and may also have high affinity for the host angiotensin-converting enzyme 2 receptor<sup>19,25</sup>. This mechanism needs further investigation even though vasculitis caused by viral infection is a risk factor for stroke<sup>25</sup>. Additionally, dysfunction of blood coagulation that leads to microthrombosis is another potential mechanism leading to ischemic stroke. Therefore, the administration of hemostatic drugs for COVID-19 cases should be rigorously considered.

As mentioned above, COVID-19 patients with stroke were more vulnerable to multiple organ dysfunction and an overactivated inflammatory response, which in turn resulted in significantly impaired outcomes. In this study, patients with stroke had a nearly double mortality to those patients without stroke. The discharge rate in patients with stroke was only half of that in patients without stroke. In comparison to patients without stroke, a significantly decreased OS was observed not only in patients with previous stroke but also in those with new stroke.

## **Limitations**

Our study has a few limitations. First, because the outbreak of SARS-CoV-2 occurred in a short time and the public health resources were seriously occupied, some patients could not be hospitalized in time, leading to the deviation between the observation point of disease course and the length of stay in hospital. This also results in the absence of initial values of laboratory parameters at symptom onset. Second, some tests (for example, cTnl, NT pro-BNP, and arterial blood gas tests) were not performed in all patients, and absent data might lead to bias of clinical characteristics. Additionally, considering that this is a single-center retrospective study, further study is warranted to gain a better understanding of risk factors for and outcome of COVID-19 patients combined with stroke.

## **Conclusion**

To summarize, elderly COVID-19 patients with lower fingertip oxygen saturation (<93%) and consciousness disorder are more likely to develop cerebral stroke, which results in severe neurological symptoms, multiple organ injuries, coagulation dysfunction and an overactivated inflammatory response. All these factors will contribute to impaired outcomes, including a prolonged course, decreased OS and high mortality. Therefore, intensive treatments for both COVID-19 and stroke must be taken into consideration for patients with risk factors for stroke.

## **Declarations**

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## Conflict-of-interest :

The authors declare that they have no competing interests.

## Author Contributions:

Huaqiu Zhang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Xiaolong Yao, Shengwen Liu, Junwen Wang, Kai Zhao, Xiaobing Long, Xuejun He contributed equally and share first authorship. Concept and design: Jihong Liu, Wei Wang, Huaqiu Zhang . Acquisition, analysis, or interpretation of data: Xiaolong Yao, Xiaobing Long, Xuejun He. Drafting of the manuscript: Xiaolong Yao, Shengwen Liu, Junwen Wang, Kai Zhao, Xiaobing Long. Critical revision of the manuscript for important intellectual content: Huicong Kang, Kai Shu, Zhouping Tang, Ting Lei. Statistical analysis: Xiaobing Long, Xuejun He, Yiping Yang, Xiaopeng Ma, Pengjie Yue. Obtained funding: Huaqiu Zhang.

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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## Tables

**Table 1. Demographic features and clinical characteristics of COVID-19 patients.**

| Variables   | Total<br>(n=2474) | Non-stroke<br>(n=2361) | Stroke                   |                        | <i>p</i> <sup>b</sup> | <i>P</i> <sup>c</sup> |
|---|-------------------|------------------------|--------------------------|------------------------|-----------------------|-----------------------|
|   |                   |                        | Previous<br>(n=88)       | New<br>(n=25)          |                       |                       |
| Mean age (years, mean ± SD)                                       | 61.0±15.7         | 57.8±15.6              | 70.69±10.85 <sup>a</sup> | 74.2±10.6 <sup>a</sup> | .150                  | <.001                 |
| <b>Age subgroups</b>  |                   |                        | a                        | a                      |                       |                       |
| <40 yr  | 359 (14.5)        | 359 (15.2)             | 0(0)                     | 0(0)                   | .515                  | <.001                 |
| 40-60 yr  | 775 (31.3)        | 760 (32.2)             | 13(14.77)                | 2(8.0)                 |                       |                       |
| ≥60 yr  | 1340 (54.2)       | 1242 (52.6)            | 75(85.23)                | 23(92.0)               |                       |                       |
| <b>Sex, n (%)</b>   |                   |                        |                          |                        |                       |                       |
| Male  | 1235 (49.9)       | 1172 (49.6)            | 47(53.41)                | 16(64.0)               | .260                  | .558                  |
| Female  | 1239 (50.1)       | 1189 (50.4)            | 41(46.59)                | 9(36.0)                |                       |                       |
| <b>Comorbidities, n (%)</b>                                       |                   |                        |                          |                        |                       |                       |
| Hypertension  | 745 (30.1)        | 665 (28.2)             | 63 (71.59) <sup>a</sup>  | 17 (68.0) <sup>a</sup> | .728                  | <.001                 |
| Diabetes  | 355 (14.3)        | 321 (13.6)             | 27 (30.68) <sup>a</sup>  | 7 (28.0) <sup>a</sup>  | .796                  | <.001                 |
| Heart disease   | 202 (8.2)         | 173 (7.3)              | 22 (25.00) <sup>a</sup>  | 7 (28.0) <sup>a</sup>  | .762                  | <.001                 |
| Others disease  | 931(37.1)         | 879(37.2)              | 32 (29.6)                | 20 (51.3)              | .019                  | .725                  |
| <b>Prognosis, n (%)</b>   |                   |                        | a                        | a                      |                       |                       |
| Discharge   | 1744 (70.5)       | 1687 (71.5)            | 49 (82.95)               | 8 (32.0)               | .111                  | <.001                 |
| Hospitalisation   | 551 (22.3)        | 509 (21.5)             | 29 (5.68)                | 13 (52.0)              |                       |                       |
| Death   | 179 (7.2)         | 165 (6.9)              | 10 (11.36)               | 4 (16.0)               |                       |                       |
| Days from onset to end point of observation (days, mean ± SD)     | 39.6±14.0         | 39.5±14.0              | 44.16±13.06 <sup>a</sup> | 46.2±14.4              | <.001                 | .002                  |
| Days from admission to end point of observation (days, mean ± SD) | 21.2±12.2         | 21.2±12.1              | 23.69±13.42              | 18.7±8.4 <sup>a</sup>  | <.001                 | .699                  |
| <b>Symptoms and signs at onset of COVID-19</b>                    |                   |                        |                          |                        |                       |                       |
| Cough   | 1680 (67.9)       | 1601 (67.8)            | 63(71.59)                | 16(64.0)               | .465                  | .640                  |
| Shortness of breath   | 983 (39.7)        | 933 (39.5)             | 44(50.00)                | 6(24.0)                | .021                  | .315                  |
| Diarrhea  | 540 (21.8)        | 519 (22.0)             | 16(18.18)                | 5(20.0)                | .837                  | .393                  |
| Headache or dizziness   | 545 (22.0)        | 518 (21.9)             | 16(18.18)                | 11(44.0) <sup>a</sup>  | .008                  | .624                  |
| Muscle ache   | 511 (20.7)        | 483 (20.4)             | 19(21.59)                | 9(36.0)                | .141                  | .268                  |
| consciousness disorder  | 66 (2.7)          | 50 (2.1)               | 7(8.14) <sup>a</sup>     | 9(36.0) <sup>a</sup>   | <.001                 | <.001                 |
| <b>Fever, (°C)</b>  |                   |                        |                          |                        |                       |                       |
| <37.3   | 656 (26.5)        | 614 (26.0)             | 32(36.36)                | 10(40.0)               | .980                  | .030                  |
| 37.3-38   | 617 (24.9)        | 589 (24.9)             | 22(25.00)                | 6(24.0)                |                       |                       |
| 38.1-39   | 645 (26.1)        | 618 (26.2)             | 21(23.86)                | 6(24.0)                |                       |                       |
| ≥39   | 556 (22.5)        | 540 (22.9)             | 13(14.77)                | 3(12.0)                |                       |                       |
| Fingertip oxygen saturation (¶93%)                                | 251 (10.1)        | 229 (11.5)             | 18(23.07) <sup>a</sup>   | 4(3.5)                 | .620                  | .012                  |

Note: Values are numbers (%) unless stated otherwise

<sup>a</sup> Compared to the non-stroke subjects, *P* < .05; <sup>b</sup> Previous vs new; <sup>c</sup> Stroke vs. non-stroke.

Table 2. Laboratory findings of patients with COVID-19.

|  | Total (n=2474)      | Non-stroke<br>(n=2361) | Stroke              |                     | P <sup>a</sup> | P <sup>b</sup> | P <sup>c</sup> |
|--|---------------------|------------------------|---------------------|---------------------|----------------|----------------|----------------|
|  |                     |                        | Previous (n=88)     | New (n=25)          |                |                |                |
| <b>Blood routine examination</b>               |                     |                        |                     |                     |                |                |                |
| WBC, ×10 <sup>9</sup> /L (3.5-9.5)             | 6.9(5.4-9.6)        | 8.34(5.3-9.3)          | 8.12(5.1-11.8)      | 9.84(6.6-13.6)      |                |                |                |
| <4   | 227/2454 (9.3)      | 216/2341 (9.2)         | 10/88(11.3)         | 1/25 (4.0)          | .016           | .005           | .285           |
| 4-10   | 1691/2454<br>(68.9) | 1630/2341 (69.6)       | 49/88(55.7)         | 12/25 (48.0)        |                |                |                |
| >10  | 536/2454 (21.8)     | 495/2341 (21.1)        | 29/88(33.0)         | 12/25 (48.0)        |                |                |                |
| Neutrophils,×10 <sup>9</sup> /L (1.8-6.3)      | 4.6 (3.3-7.3)       | 6.2(3.2-7.1)           | 5.2(3.3-8.4)        | 7.0 (4.7-10.8)      |                |                |                |
| ≥6.3   | 748/2454 (30.5)     | 696/2341 (29.7)        | 38/88(43.2)         | 14/25 (56.0)        | .007           | .004           | .256           |
| Lymphocytes,×10 <sup>9</sup> /L(1.1-3.2)       | 1.7(0.9-2.4)        | 4.6(0.9-2.5)           | 1.0(0.5-1.5)        | 0.7 (0.5-1.0)       |                |                |                |
| ≥1.1   | 799/2452 (32.6)     | 729/2339 (31.2)        | 51/88 (58.0)        | 19/25 (76.0)        | <.001          | <.001          | .101           |
| Hgb, g/L (120-150)                             | 121(106.0-135.0)    | 119.35(107.0-135.0)    | 105.0(88.0-130.0)   | 98.0(87.5-125.0)    |                |                |                |
| ≥120   | 1315/2457<br>(53.3) | 1281/2344(54.7)        | 28/88(31.8)         | 6/25 (24.0)         | <.001          | <.001          | .735           |
| 90-120   | 912/2457 (37.1)     | 863/2344(36.8)         | 37/88(42.0)         | 12/25 (48.0)        |                |                |                |
| <90  | 229/2457 (9.3)      | 200/2344(8.5)          | 22/88(25.0)         | 7/25 (28.0)         |                |                |                |
| <b>Cytokines and infection related factors</b> |                     |                        |                     |                     |                |                |                |
| IL-1β (≥5pg/mL)                                | 469/2078 (22.6)     | 452/1974 (22.9)        | 13/81(16.0)         | 4/23 (17.4)         | .149           | .532           | .878           |
| TNF-α, pg/mL (<8.1)                            | 8.4(6.3-11.4)       | 11.2(6.3-11.4)         | 8.5(6.1-10.8)       | 10.7 (8.6-12.8)     |                |                |                |
| ≥8.1   | 1151/2075<br>(54.7) | 1072/1971 (54.4)       | 44/81(54.3)         | 20/23 (87.0)        | 0.99           | .002           | .005           |
| IL-6, pg/mL (<7)                               | 5.4(2.0-23.3)       | 74.4(1.9-21.3)         | 19.4(4.7-71.5)      | 18.1(7.6-31.7)      |                |                |                |
| ≥7   | 917/2078 (44.1)     | 841/1982 (42.4)        | 56/82(68.3)         | 20/23 (87.0)        | <.001          | <.001          | .077           |
| IL-8, pg/mL (<62)                              | 11.2(6.5-21.8)      | 60.9(6.4-21.7)         | 11.1(7.0-23.0)      | 15.3(11.9-25.2)     |                |                |                |
| ≥62  | 162/2078 (7.8)      | 158/1974(8.0)          | 2/81(2.5)           | 2/23 (8.7)          | .068           | .903           | .171           |
| IL-2R, U/mL (223-710)                          | 521.0(329.0-820.3)  | 676.4(321.0-808.0)     | 588.5(384.0-913.3)  | 642.0(473.5-861.0)  |                |                |                |
| ≥710   | 670/2071 (32.4)     | 619/1964 (31.5)        | 32/84(38.1)         | 19/23 (39.1)        | .130           | <.001          | .928           |
| IL-10, pg/mL (<9.1)                            | 5.0(5.0-6.6)        | 12.7(5.0-6.7)          | 5.0(5.0-5.1)        | 5.0 (5.0-6.3)       |                |                |                |
| ≥9.1   | 367/2067 (17.8)     | 353/1963 (18.0)        | 11/81(13.6)         | 3/23 (13.0)         | .310           | .539           | .947           |
| hsCRP, mg/L (<1)                               | 18.2(2.2-73.5)      | 47.5(2.1-70.5)         | 49.4(9.3-125.4)     | 33.8(11.8-94.6)     |                |                |                |
| ≥1   | 2055/2393(85.9)     | 1953/2281(85.6)        | 78/87(90.0)         | 24/25 (96.0)        | .290           | .140           | .327           |
| <b>Serum biochemical index</b>                 |                     |                        |                     |                     |                |                |                |
| Albumin, g/L (≥35)                             | 35.9(30.8-40.2)     | 35.6(31.1-40.3)        | 30.8(27.9-38.0)     | 35.0(28.0-37.5)     |                |                |                |
| ≥35  | 1357/2451(55.3)     | 1305/2339(55.8)        | 38/87(43.7)         | 14/25 (56.0)        | <.001          | .179           | .544           |
| ≥30, <35                                       | 587/2451(23.9)      | 572/2339(24.5)         | 12/87(13.8)         | 3/25 (12.0)         |                |                |                |
| <30g/L   | 507/2451(20.7)      | 462/2339(19.8)         | 37/87(42.5)         | 8/25 (32.0)         |                |                |                |
| cTnI, pg/mL (<34.2)                            | 4.1(1.9-12.3)       | 198.8(1.9-12.3)        | 9.8(4.1-36.6)       | 10.3(4.3-31.9)      |                |                |                |
| ≥34.2  | 264/2202 (12.0)     | 236/2091 (11.3)        | 23/87 (26.4)        | 5/24 (20.8)         | <.001          | .143           | .576           |
| MG, ng/mL (<154.9)                             | 39.0(27.7-74.4)     | 113.5(27.4-66.1)       | 76.6(42.5-200.6)    | 133.9(58.7-246.0)   |                |                |                |
| ≥154.9   | 251/1812(13.9)      | 218/1713 (12.7)        | 24/79(30.4)         | 9/20 (45.0)         | <.001          | <.001          | .215           |
| CK-MB, ng/mL (<7.2)                            | 0.8(0.5-1.4)        | 2.1(0.4-1.3)           | 1.5(0.7-2.9)        | 1.3(0.7-2.9)        |                |                |                |
| ≥7.2   | 88/1793 (4.9)       | 79/1694 (4.7)          | 8/79(10.1)          | 1/20 (5.0)          | .028           | .943           | .476           |
| NT pro-BNP, pg/mL (<116)                       | 126.0(44.0-470.0)   | 1.8(41.0-421.8)        | 707.5(128.0-2806.8) | 595.0(290.0-2055.0) |                |                |                |
| ≥116   | 1071/2059(52.0)     | 989/1958 (50.5)        | 61/78(78.2)         | 21/23 (91.3)        | <.001          | <.001          | .158           |
| BUN, mmol/L (3.1-8.0)                          | 5.0(3.7-6.7)        | 6.6(3.7-8.6)           | 7.2(5.0-12.5)       | 6.7(4.6-10.7)       |                |                |                |
| ≥8.0   | 436/2455 (17.8)     | 386/2343 (16.5)        | 39/87(44.8)         | 11/25 (44.0)        | <.001          | <.001          | .942           |

|                                    |                    |                    |                    |                    |       |       |      |
|------------------------------------|--------------------|--------------------|--------------------|--------------------|-------|-------|------|
| Cr, umol/L (59-104)                | 73.0(56.0-89.0)    | 90.5(57.0-88.3)    | 79.0(60.0-100.0)   | 68.0(43.0-88.0)    |       |       |      |
| □104                               | 354/2455(14.4)     | 304/2343 (13.0)    | 39/87 (44.8)       | 11/25 (44.0)       | .007  | <.001 | .942 |
| ALT, U/L (<41)                     | 31.0(19.0-57.0)    | 54.6(19.0-57.0)    | 24.0(15.0-59.0)    | 24.0 (15.5-35.0)   |       |       |      |
| ≥41                                | 928/2455 (37.8)    | 894/2343(38.2)     | 30/87(34.5)        | 4/25 (16.0)        | .488  | .023  | .076 |
| AST, U/L (<40)                     | 28.0(20.0-44.0)    | 51.2(20.0-44.0)    | 29.0(20.0-61.0)    | 29.5 (21.0-45.8)   |       |       |      |
| ≥40                                | 740/2451 (30.2)    | 698/2340 (29.8)    | 32/87(36.8)        | 10/24 (41.7)       | .165  | .208  | .662 |
| <b>Electrolyte disturbance</b>     |                    |                    |                    |                    |       |       |      |
| potassium, mmol/L (3.5-5.1)        | 4.5(4.2-4.9)       | 4.5(4.2-4.9)       | 4.7(4.1-5.3)       | 4.6(3.5-5.1)       |       |       |      |
| <3.5                               | 188/2452(7.7)      | 166/2339(7.1)      | 15/88(17.0)        | 7/25(28.0)         | <.001 | <.001 | .277 |
| 3.5-5.1                            | 1853/2452(75.6)    | 1792/2339(76.6)    | 47/88(53.4)        | 14/25(56.0)        |       |       |      |
| >5.1                               | 411/2452(16.7)     | 381/2339(16.3)     | 26/88(29.6)        | 4/25(16.0)         |       |       |      |
| sodium, mmol/L (136-145)           | 140.6(138.1-142.3) | 140.6(138.2-142.3) | 141.4(135.3-143.9) | 141.4(135.9-144.5) |       |       |      |
| <136                               | 421/2451(17.2)     | 389/2338(16.6)     | 27/88(30.7)        | 5/25(20.0)         | <.001 | .401  | .514 |
| 136-145                            | 1872/2451(76.4)    | 1806/2338(77.3)    | 49/88(55.7)        | 17/25(68.0)        |       |       |      |
| >145                               | 158/2451(6.9)      | 143/2338(6.1)      | 12/88(13.6)        | 3/25(12.0)         |       |       |      |
| <b>Blood coagulation factor</b>    |                    |                    |                    |                    |       |       |      |
| TT, s (14-19)                      | 16.7(15.5-17.6)    | 18.6(15.4-17.8)    | 17.0(16.2-19.5)    | 16.7 (15.5-17.6)   |       |       |      |
| □19                                | 528/2351 (22.5)    | 503/2240 (22.5)    | 23/86(26.8)        | 2/25 (8.0)         | .351  | .084  | .048 |
| PT, s (11.5-14.5)                  | 14.1(13.4-15.6)    | 15.0(13.4-15.5)    | 14.4(13.4-16.3)    | 14.4 (14.0-15.4)   |       |       |      |
| □14.5                              | 924/2401 (38.5)    | 871/2289 (38.1)    | 41/87 (47.1)       | 12/25 (48.0)       | .088  | .308  | .939 |
| APTT, s (29-42)                    | 39.5(36.7-43.9)    | 41.1(36.5-43.6)    | 41.5(37.8-49.0)    | 41.3 (39.3-47.3)   |       |       |      |
| □42                                | 802/2325 (34.5)    | 749/2214 (33.8)    | 41/86 (47.7)       | 12/25 (48.0)       | .008  | .137  | .939 |
| AT: A, % (80-120)                  | 96.0(85.0-105.0)   | 94.5(86.0-105.0)   | 91.0(72.0-100.0)   | 87.0 (64.0-98.0)   |       |       |      |
| □120                               | 360/1823 (19.7)    | 355/1727 (20.6)    | 4/75(5.3)          | 1/21 (4.8)         | .001  | .074  | .917 |
| D-Dimer, mg/L (<0.5)               | 0.7(0.3-2.2)       | 2.8(0.3-2.0)       | 2.3(0.8-6.5)       | 1.8(0.8-3.9)       |       |       |      |
| ≥0.5                               | 1441/2408 (59.8)   | 1350/2296 (58.8)   | 70/87(80.5)        | 21/25 (84.0)       | <.001 | .011  | .689 |
| FDP, mg/L (<5)                     | 4.0(4.0-7.7)       | 15.4(4.0-6.8)      | 8.5(4.0-25.5)      | 4.9 (4.0-17.4)     |       |       |      |
| ≥5                                 | 616/1822 (33.8)    | 562/1725 (32.6)    | 44/76(58.9)        | 10/21 (47.6)       | <.001 | .144  | .401 |
| Fgb, mg/L (2-4)                    | 4.5(3.4-5.8)       | 4.6(3.4-5.7)       | 5.5(4.1-6.6)       | 5.0 (4.1-5.7)      |       |       |      |
| □4                                 | 1433/2334 (61.4)   | 1348/2223 (60.6)   | 65/86 (75.6)       | 20/25 (80.0)       | .005  | .001  | .646 |
| PTA, % (75-125)                    | 96.0(87.0-104.0)   | 94.3(88.0-104.0)   | 94.0(70.0-103.0)   | 91.0 (79.0-97.5)   |       |       |      |
| □125                               | 269/2420 (11.1)    | 268/2308 (11.6)    | 1/87(1.1)          | 0/25 (0)           | <.001 | .070  | .590 |
| Plt, ×10 <sup>9</sup> /L (150-350) | 239(170.8-319.0)   | 251.4(174.0-319.0) | 229.5(104.8-346.8) | 241(130.0-303.0)   |       |       |      |
| □150                               | 496/2446 (20.3)    | 453/2333 (19.4)    | 35/88 (39.8)       | 8/25 (32.0)        | <.001 | .115  | .480 |

Continuous variables are presented as median (interquartile range) and categorical variables are numbers (percentages) unless stated otherwise; *P<sup>a</sup>*: Previous vs non-stroke, *P<sup>b</sup>*: New vs non-stroke, *P<sup>c</sup>*: Previous vs new. WBC: white blood cell count; Hgb: hemoglobin; IL: interleukin; TNF: tumor necrosis factor; hs-CRP: hypersensitive c-reactive protein; cTnI: cardiac troponin I; MG: myohemoglobin; CK-MB: creatine kinase-mb isoenzymes; NT pro-BNP: N terminal pro-brain natriuretic peptide; BUN: blood urea nitrogen; Cr: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TT: thrombin time; PT: prothrombin time; APTT: activated partial thromboplastin time; AT: A: thrombin activity; FDP: fibrinogen degradation products; Fgb: fibrinogen; PTA: prothrombin activity; Plt: platelet.

Table 3 Regression analysis for incident risk of new-onset stroke among COVID-19 patients.

| Variable                           | Controls (n=2361) | New stroke(n=25) | Logistic regression |         |        |
|------------------------------------|-------------------|------------------|---------------------|---------|--------|
|                                    |                   |                  | Adjusted OR         | 95% CI  | Pvalue |
| Age (≥60 years)                    | 1242(52.6)        | 24(96.0)         | 0.3                 | 0.2-0.5 | <.001  |
| Fingertip oxygen saturation (≤93%) | 228(9.7)          | 4(16.0)          | 3.8                 | 2.5-5.7 | <.001  |
| consciousness disorder             | 50(2.1)           | 9(36.0)          | 0.1                 | 0.1-0.2 | <.001  |

Abbreviations: OR, odd ratio; CI, confidence interval.

## Figures

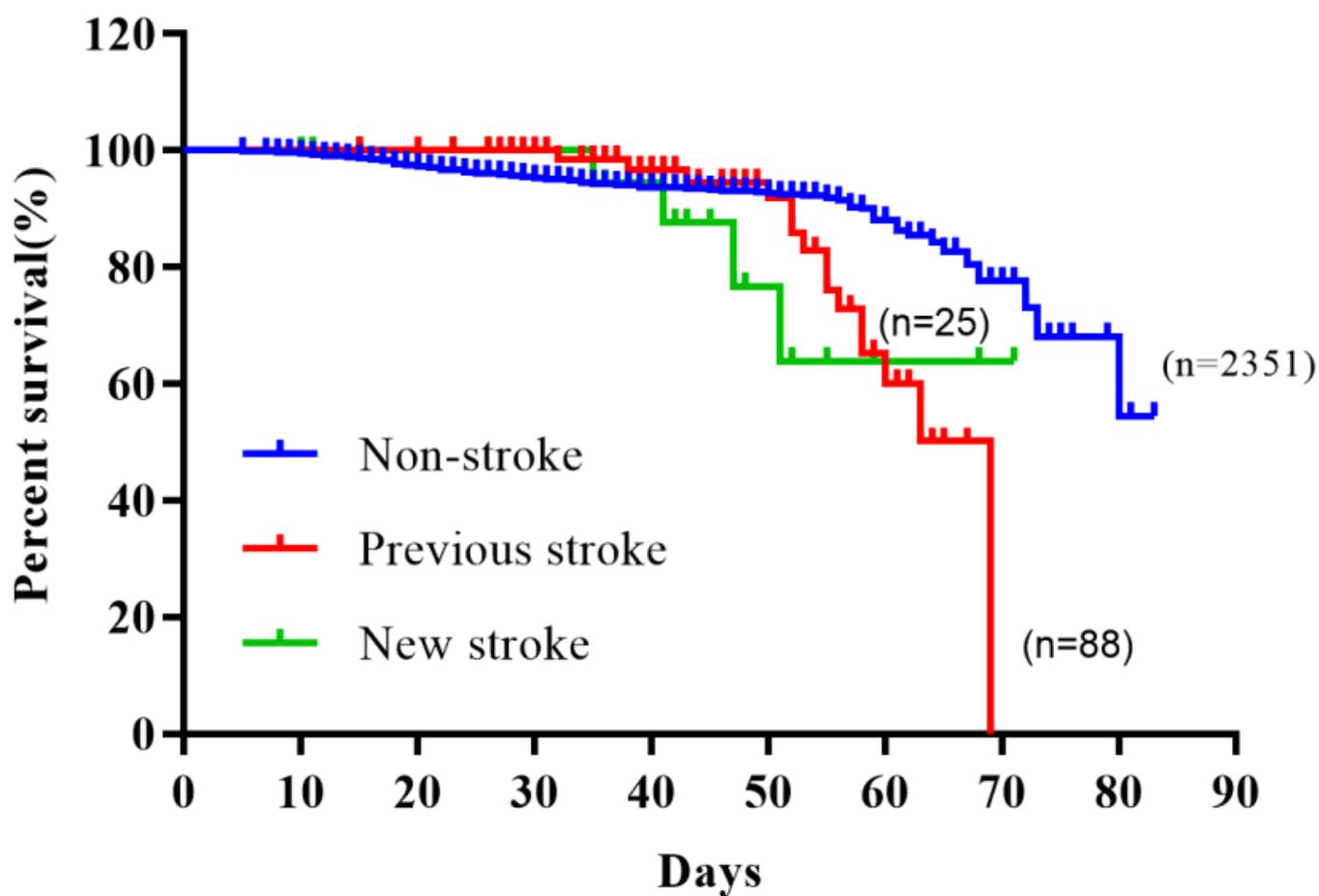
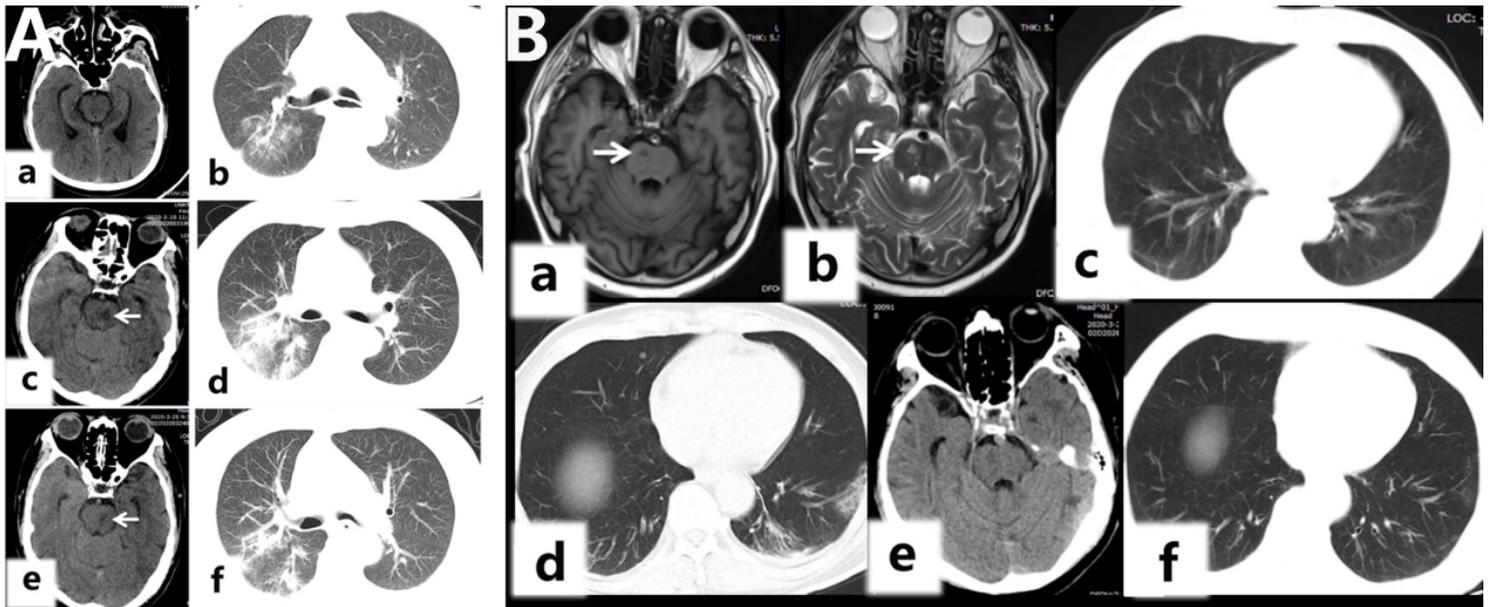


Figure 1

Kaplan–Meier survival curves showing previous and new stroke-related overall survival (OS) of COVID-19 patients. Nonstroke vs previous stroke,  $P=.006$ ; nonstroke vs new stroke,  $P<.001$ ; previous stroke vs new stroke,  $P=.76$



**Figure 2**

Representative cardiological images of COVID-19 patients with new-onset (A) and previous ischemia (B). A: Brain (a, c, e) and chest CT images (b, d, f) before hospitalization, the day of new onset and after treatment, respectively. B: The T1WI (a) T2WI (b) and CT images displayed an ischemic infarction, chest CT scan (b, d, f) during cerebral infarction treatment, viral pneumonia and the day before discharge. The right arrow shows the ischemic infarction.