Association Between Ischemic Stroke and COVID-19 in China: A Population-Based Retrospective Study

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Background and Purpose: To investigate the effect of prior ischemic stroke on the outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19), and to describe the incidence, clinical features, and risk factors of acute ischemic stroke (AIS) following COVID-19.

Methods: In this population-based retrospective study, we included all the hospitalized positive patients with COVID-19 at Wuhan City from December 29, 2019 to April 15, 2020. Clinical data were extracted from administrative datasets coordinated by the Wuhan Health Commission. The propensity score matching and multivariate logistic regression analyses were used to adjust the confounding factors.

Results: There are 36,358 patients in the final cohort, in which 1,160 (3.2%) had a prior stroke. After adjusting for available baseline characteristics, patients with prior stroke had a higher proportion of severe and critical illness and mortality. We found for the first time that the premorbid modified Rankin Scale (MRS) grouping (odds ratio [OR] = 1.796 [95% CI 1.334–2.435], p < 0.001) and older age (OR = 1.905 [95% CI 1.211–3.046], p = 0.006) imparted increased risk of death. AIS following COVID-19 occurred in 124 (0.34%) cases, and patients with prior stroke had a much higher incidence of AIS (3.4%). Logistic regression analyses confirmed an association between the severity of COVID-19 with the incidence of AIS. COVID-19 patients with AIS had a significantly higher mortality compared with COVID-19 patients without stroke and AIS patients without COVID-19.

Conclusions: Coronavirus disease 2019 patients with prior stroke, especially those with the higher premorbid MRS or aged, have worse clinical outcomes. Furthermore, COVID-19 increases the incidence of AIS, and the incidence is positively associated with the severity of COVID-19.

Keywords: COVID-19, risk factors, prior stroke, acute ischemic stroke, MRS

INTRODUCTION

At present, with more than 80 million survivors (1), the global burden of ischemic stroke (IS) is high (2). Prior IS is a suggested risk factor contributing to the severity and mortality of coronavirus disease 2019 (COVID-19) (3, 4), but this association is indicated by studies of limited sample size (5). Patients with prior stroke are particularly vulnerable toward pulmonary and inflammatory complications due to their frequent disability (6), greater age, and higher prevalence of smoking, hypertension, and cardiovascular disease, all of which were important predictors of poor COVID-19 outcomes (7). As such, patients with prior stroke are a special population, and their specific risk factors for severe disease and death after COVID-19 infection need to be further studied.

Moreover, a temporal relationship between various respiratory viral infections and increased risk of stroke has been reported (8), and COVID-19 had been reported to increase the incidence of acute ischemic stroke (AIS) in several case series and meta-analyses (9, 10). However, the reported incidence of AIS varied widely between studies (11), and the predictors, clinical characteristics, and outcomes of AIS in patients with COVID-19 need further study.

Wuhan city is the capital of Hubei province in China, which emerged as the original epicenter of COVID-19, with some 50,000 individuals infected and nearly 4,000 deaths recorded during the early phase of this pandemic. Having access to detailed medical records for the entire cohort, we undertook to investigate the effect of prior stroke on the severity of COVID-19 and the risk of in-hospital death among hospitalized patients. We furthermore describe the incidence, clinical features, risk factors, and outcomes of patients with AIS following their COVID-19 hospitalization.

METHODS

Study Design and Participants

This is a retrospective cohort study using data collected from all inpatients in Wuhan with positive COVID-19 test results recorded from Dec 29, 2019, when patients were admitted to hospital for the first time, and extending to April 15, 2020, which was the first day with no new cases declared in Wuhan city. The compilation of data was coordinated by the Wuhan Health Commission, which mandated the reporting of clinical information from every designated hospital in Wuhan that had admitted patients with laboratory confirmed COVID-19 (**Figure 1**). Patient follow-up continued through July 1, 2020. This study was designed by the authors and approved with provision of a waiver of authorization and informed consent by the Ethics Committee of Tongji Hospital (IRB ID: TJ-C20200121).

Data Collection and Data Extraction

The demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records of 61 Wuhan hospitals and mobile cabin hospitals using a standardized data collection and processing method (detail in

Supplementary Materials). The laboratory data were collected upon patient admission. Systolic blood pressure (SBP) was recorded on admission. We excluded patient records with incomplete clinic data. All data were checked by two physicians (HZ and YH), and a third researcher (MW) adjudicated any difference in the interpretation between the two primary reviewers. Patients with COVID-19 were divided into four categories according to the severity as Mild, Moderate, Severe, and Critical according to Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 6) released by the National Health Commission (detail in **Supplementary Materials**). Prior stroke was determined according to the electronic medical record. The COVID-19-associated AIS was defined as the AIS that occurred during hospitalization of patients with COVID-19 or COVID-19 was found at the same time as the hospital visit due to AIS. We excluded patients who were infected after the onset of AIS. The diagnosis of AIS required the validation by brain CT or MRI. Neurological recovery in patients with prior stroke and patients with AIS was determined using the modified Rankin Scale (MRS). MRS score of prior stroke patients before the onset of COVID-19 was obtained from the electronic medical record system or by follow-up on telephone. For AIS patients with or without COVID-19, MRS score was obtained at discharge.

Propensity Scores Match Methods

The propensity score match (PSM) method was used to reduce the confounding factor among patients with stroke at baseline. The propensity scores were analyzed using a logistic regression model. The baseline matching variables included age, gender, smoking status, blood pressure, alcohol consumption, and complications, such as diabetes, hypertension, hyperlipidemia, heart disease, cancer, chronic obstructive pulmonary disease (COPD), tuberculosis, chronic kidney disease, liver disease, intracerebral hemorrhage, and asthma. The PSM was established by a nearest-neighbor strategy with ratio 2:1, and caliper 0.02 (12). After matching, a standardized difference was generated and the value <0.1 was taken as an indication of the covariates which were well balanced between the two groups (**Supplementary Table S1**). Blood pressure at admission was missing in 15.3% of patients, a multivariate imputation by chained equations (MICE) was used to impute SBP and diastolic blood pressure (DBP) (13).

Statistical Analysis

Continuous variables with non-normal distributions were described as median [interquartile range, IQR]. Categorical variables were described as number and percentage (%). Comparison between two groups was performed with Wilcoxon test for nonparametric variables, Fisher's exact test or chi-square test was performed for categorical variables. Multivariate logistic regression models were developed to explore the relative contribution of risk factors. Variables with $p < 0.1$ in univariate regression were included in multiple regression. No significant interaction was found between variables enrolled in multivariate analyses. The $p < 0.05$ was considered statistically significant. Data preprocessing and statistical analysis were calculated with

FIGURE 1 | Flowchart of patient inclusion and exclusion.
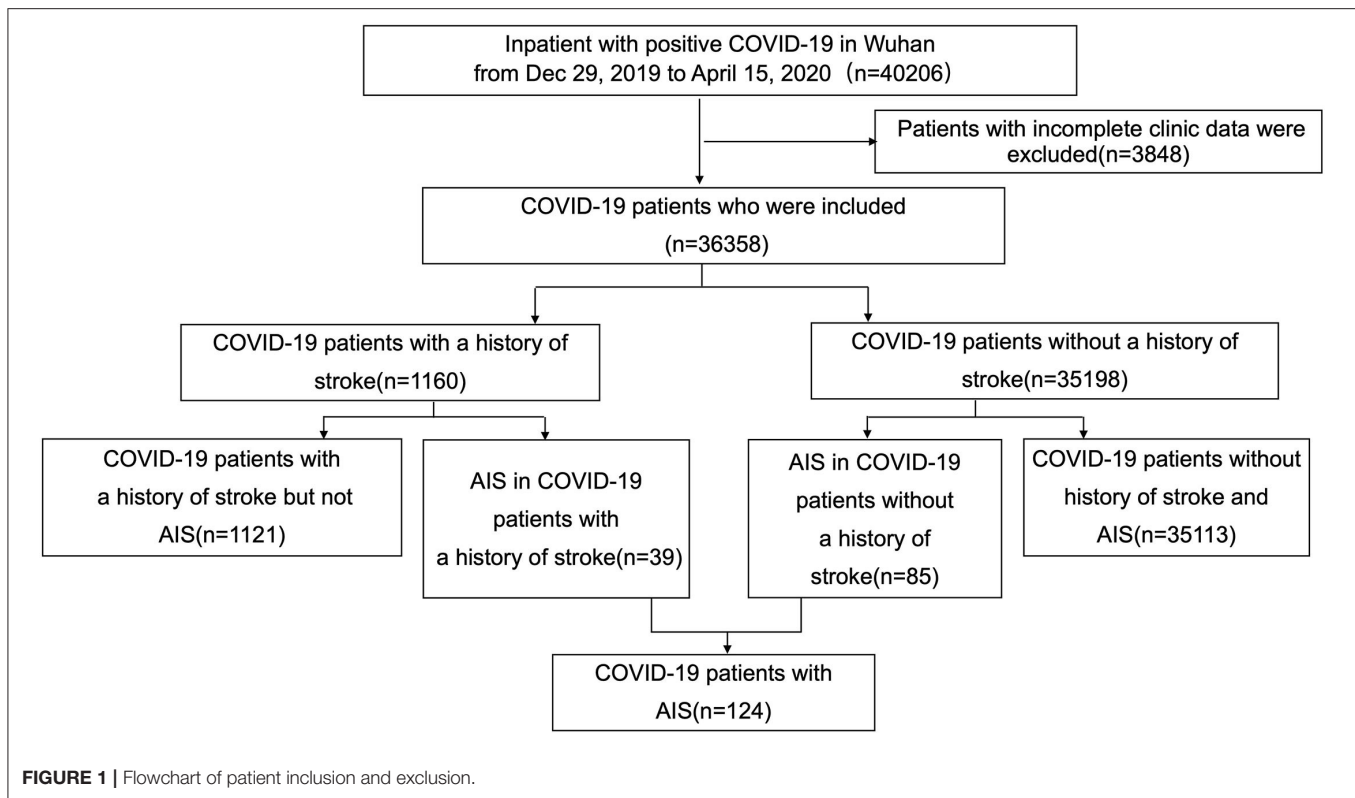
Ubuntu 16.04.6 and a Rstudio server (R-4.0.3 R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics and Outcomes of Patients With COVID-19 and Patients With or Without Prior Stroke

In total, 40,206 patients were found positive for COVID-19 and received in-hospital treatment in Wuhan Province. After excluding patients with missing critical data, the final cohort consisted of 36,358 patients, of whom 1,160 of the patients (3.19%) had prior stroke (**Table 1**). Patients with prior stroke were significantly older, most of them were male patients (55.4 vs. 48.4%, $p < 0.001$), and had higher SBP (130.00 [114.00, 143.00] vs. 125.00 [114.00, 138.00], $p < 0.001$), with a greater prevalence of smoking (5.1 vs. 2.1%, $p < 0.001$) and alcohol consumption (10.6 vs. 7.3%, $p < 0.001$). COVID-19 patients with prior stroke had more comorbidities, such as hypertension (62.3 vs. 22.1%, $p < 0.001$), diabetes (25.7 vs. 10.3%, $p < 0.001$), hyperlipidemia (5.3 vs. 1.1%, $p < 0.001$), heart disease (23 vs. 6.2%, $p < 0.001$), COPD (9.1 vs. 2.1%, $p < 0.001$), tuberculosis (3 vs. 1.3%, $p < 0.001$), chronic kidney disease (6.6 vs. 2.4%, $p < 0.001$), and cerebral hemorrhage (4 vs. 0.4%, $p < 0.001$). Compared with patients without prior stroke, patients with a positive history had significant leukocytosis, increased neutrophils, lymphopenia, prothrombin time and

D-dimer, lower platelet count, hemoglobin, albumin, and alanine aminotransferase (**Table 1**).

Prior stroke did not increase the length of hospital stay but did increase the requirement for mechanical ventilation (4 vs. 2.4%, $p < 0.001$). In the cohort of patients with prior stroke, 356 (30.7%) patients were diagnosed as being severely and critically ill with COVID-19, and 202 (17.4%) died during their hospitalization. The mortality was 11.6% in the general and mild patients with COVID-19, and 30.6% in the severe and critical patients with COVID-19. Patients with prior history had a higher proportion of severe and critical COVID-19 illness (24.1 and 6.6% vs. 17 and 3.7%, $p < 0.001$), and were significantly more likely to die during their hospitalization (17.4 vs 6.5%, $p < 0.001$), compared with patients without COVID-19 (**Table 1**).

Propensity-matched analysis was used to adjust for differences in available baseline characteristics and comorbidities. The results showed that 2,170 suitable propensity matches were found for 1,106 (95.3%) of 1,160 COVID-19 patients with prior stroke. After propensity matching, patients with prior stroke still had a higher proportion of severe and critical COVID-19 illness (22.4 and 5.8% vs. 24.2 and 5.8%, $p = 0.042$), and had significantly higher mortality during their hospitalization (16.5 vs. 12.5%, $p = 0.002$) (**Supplementary Table S2**).

To investigate the effect of MRS scores after IS on the prognosis of COVID-19, we compared the outcomes of patients with COVID-19 in different MRS scores group. We found that patients in MRS score 2–3 and 4–5 have a much higher proportion of severe illness (38.6 and 32.7 vs. 26.5%)
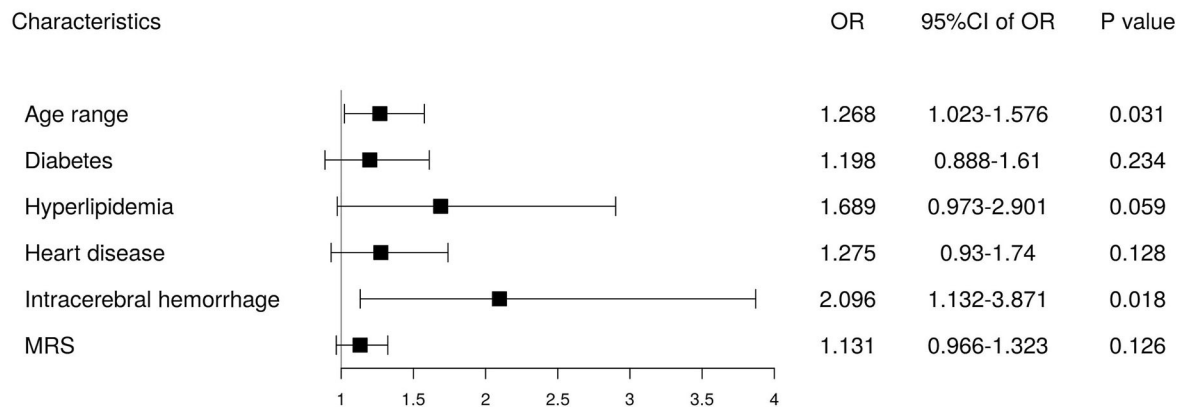
TABLE 1 | Baseline characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and patient with or without prior stroke.

Characteristic	Overall COVID-19 patient	COVID-19 patient without history of stroke	COVID-19 patient with history of stroke	P-value
n	36,358	35,198	1,160	
Age ranges				
<40	6,106 (16.8)	6,098 (17.3)	8 (0.7)	<0.001
40–60	12,950 (35.6)	12,814 (36.4)	136 (11.7)	
60–80	14,805 (40.7)	14,137 (40.2)	668 (57.6)	
>80	2,497 (6.9)	2,149 (6.1)	348 (30.0)	
Sex				
Female	18,696 (51.4)	18,179 (51.6)	517 (44.6)	<0.001
Male	17,662 (48.6)	17,019 (48.4)	643 (55.4)	
Systolic pressure	126.00 [114.00, 138.00]	125.00 [114.00, 138.00]	130.00 [114.00, 143.00]	<0.001
Diastolic pressure	80.00 [72.00, 90.00]	80.00 [73.00, 90.00]	80.00 [71.00, 91.25]	0.472
Smoking	794 (2.2%)	735 (2.1%)	59 (5.1%)	<0.001
Drinking	2,697 (7.4)	2,574 (7.3)	123 (10.6)	<0.001
Diabetes	3,931 (10.8)	3,633 (10.3)	298 (25.7)	<0.001
Hypertension	8,498 (23.4)	7,775 (22.1)	723 (62.3)	<0.001
Hyperlipidemia	459 (1.3)	397 (1.1)	62 (5.3)	<0.001
Heart disease	2,452 (6.7)	2,185 (6.2)	267 (23.0)	<0.001
Cancer	824 (2.3)	799 (2.3)	25 (2.2)	0.796
COPD	850 (2.3)	744 (2.1)	106 (9.1)	<0.001
Tuberculosis	506 (1.4)	471 (1.3)	35 (3.0)	<0.001
Chronic kidney disease	924 (2.5)	847 (2.4)	77 (6.6)	<0.001
Liver disease	1,189 (3.3)	1,138 (3.2)	51 (4.4)	0.028
Intracerebral hemorrhage	178 (0.5)	132 (0.4)	46 (4.0)	<0.001
Asthma	386 (1.1)	374 (1.1)	12 (1.0)	0.927
History of stroke	1,160 (3.2)	0 (0.0)	1,160 (100.0)	<0.001
Disturbance of consciousness	404 (1.1)	339 (1.0)	65 (5.6)	<0.001
White blood cells, × 109 cells/L	5.60 [4.40, 7.10]	5.57 [4.40, 7.06]	6.00 [4.70, 8.14]	<0.001
Neutrophils, × 109 cells/L	3.51 [2.59, 4.90]	3.50 [2.58, 4.86]	4.16 [2.99, 6.03]	<0.001
Lymphocytes,× 109 cells/L	1.30 [0.88, 1.77]	1.31 [0.89, 1.77]	1.09 [0.73, 1.54]	<0.001
Eosnophils, × 109 cells/L	0.06 [0.01, 0.13]	0.07 [0.01, 0.13]	0.06 [0.01, 0.13]	0.083
Monocyte, × 109 cells/L	0.41 [0.30, 0.53]	0.41 [0.30, 0.53]	0.42 [0.31, 0.57]	0.095
Platelets, × 109 cells/L	212.00 [166.00, 267.00]	212.60 [166.00, 267.00]	203.00 [153.00, 257.00]	<0.001
Hemoglobin, g/L	126.00 [115.00, 138.00]	127.00 [116.00, 138.00]	119.00 [106.00, 132.30]	<0.001
Albumin, g/L	38.00 [34.20, 41.40]	38.10 [34.30, 41.50]	35.60 [31.80, 39.20]	<0.001
Alanine aminotransferase, U/L	23.00 [14.90, 38.00]	23.00 [15.00, 38.00]	19.55 [12.83, 31.92]	<0.001
Prothrombin time, s	12.50 [11.50, 13.64]	12.50 [11.50, 13.60]	12.60 [11.60, 13.90]	0.043
D-dimer, μg/L	0.49 [0.23, 1.11]	0.48 [0.22, 1.07]	0.91 [0.45, 2.17]	<0.001
Duration of hospital stay, days	15.00 [9.00, 22.00]	15.00 [9.00, 22.00]	15.00 [9.00, 23.00]	0.440
Non-invasive mechanical ventilation	1,188 (3.3)	1,111 (3.2)	77 (6.6)	<0.001
Invasive mechanical ventilation	818 (2.2)	772 (2.2)	46 (4.0)	<0.001
Disease severity of COVID-19				
Mild	11,921 (32.8)	11,641 (33.1)	280 (24.1)	<0.001
Moderate	16,823 (46.3)	16,299 (46.3)	524 (45.2)	
Severe	6,247 (17.2)	5,967 (17.0)	280 (24.1)	
Critical	1,367 (3.8)	1,291 (3.7)	76 (6.6)	
Died during hospitalization	2,492 (6.9)	2,290 (6.5)	202 (17.4)	<0.001

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; Data are reported as number and percentage (%) for categorical variables and median (interquartile range, IQR) for continuous variables..
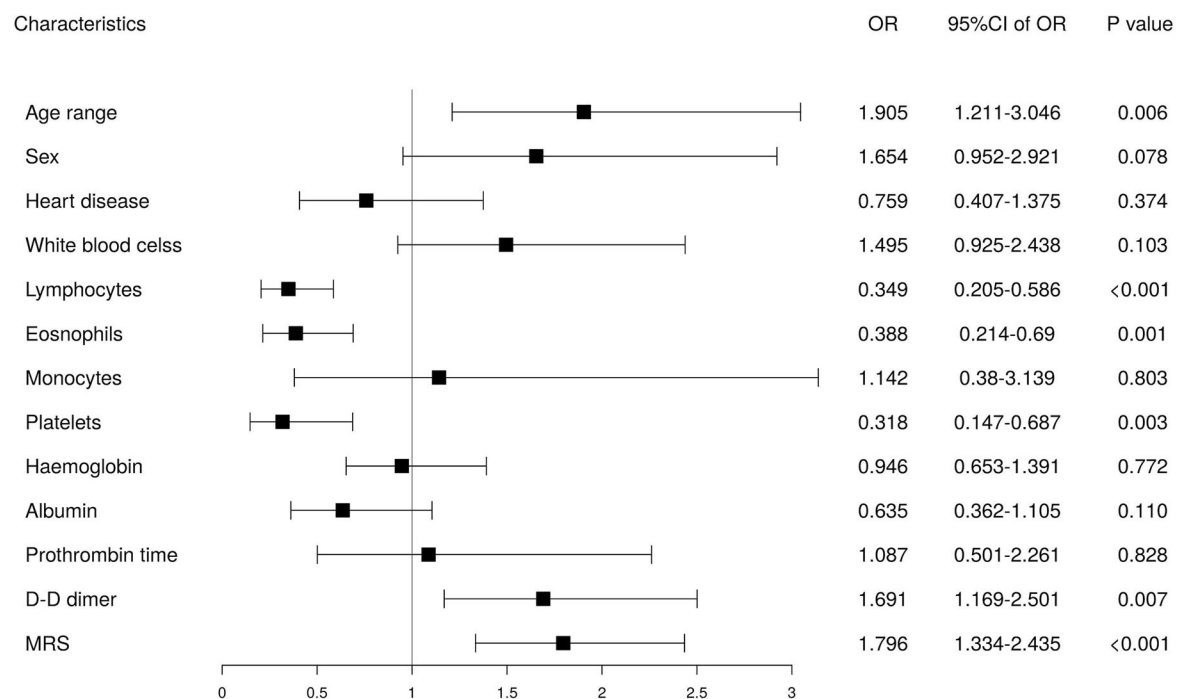
FIGURE 2 | Multivariable logistic regression analysis for risk factors of clinical outcomes in patients with a history of stroke ($n = 1,160$). **(A)** Multivariable logistic regression analysis for risk factors of severe or critical illness in patients with a history of stroke. **(B)** Multivariable logistic regression analysis for risk factors of death in patients with a history of stroke.

and a much higher mortality (20.1 and 26.8 vs. 10.8%) (**Supplementary Table S3**).

Analysis of Risk Factors for the Clinical Outcome of Patients With Prior Stroke

To investigate the risk factors for the development of COVID-19 with severe and critical illness and death in patients with prior stroke, we performed a bilateral logistic regression analysis. A univariable logistic regression analysis showed that greater age, hyperlipidemia, heart disease, cerebral hemorrhage, and premorbid MRS grouping were associated with the severe and critical COVID-19 illness (**Supplementary Figure 1**). Multivariable regression analysis which adjusted for above factors showed that greater age (odds ratio [OR] = 1.268 [95% CI 1.023–1.576], $p = 0.031$) and cerebral hemorrhage (OR = 2.096 [95% CI 1.132–3.871], $p = 0.018$) were independent

TABLE 2 | Incidence of acute ischemic stroke (AIS) in different disease severity of COVID-19.

Disease severity of COVID-19	Incidence of AIS in total COVID-19 patients	P-value	Incidence of AIS in COVID-19 patients with prior ischemic stroke	P-value
Mild	13/11,921 (0.11)	<0.001	3/280 (1.07)	<0.001
Moderate	60/16,823 (0.37)		16/624 (2.56)	
Severe	39/6,247 (0.62)		15/280 (5.36)	
Critical	12/1,367 (0.88)		5/76 (6.58)	
Total	124/36,358 (0.342)		39/1,160 (3.36)	

AIS, acute ischemic stroke; COVID-19, coronavirus disease 2019; Data are reported as number and percentage (%) for categorical variables.

risk factors for the severe and critical COVID-19 illness (**Figure 2A**).

Higher odds of death were associated with greater age ($OR = 1.905$ [95% CI 1.211–3.046], $p = 0.006$), premorbid MRS grouping ($OR = 1.796$ [95% CI 1.334–2.435], $p < 0.001$), and laboratory test indices, such as lymphopenia ($OR = 0.349$ [95% CI 0.205–0.586], $p < 0.001$), eosinophilopenia ($OR = 0.388$ [95% CI 0.214–0.69], $p = 0.001$), and lower platelet count ($OR = 0.318$ [95% CI 0.147–0.687], $p = 0.003$) in multivariable regression analysis (**Figure 2B**). There was no interaction effect between the selected variables.

The Clinical Characteristics and Outcomes of Patients With AIS

Among a total of 36,358 patients, we identified 124 cases of AIS during their hospitalization, for an incidence of 0.342%. Patients with severe or critical COVID-19 were more likely to have an AIS compared with non-severe groups (0.62 and 0.88% vs. 0.11 and 0.37%, $p < 0.001$), and those with prior stroke had a much higher incidence of AIS (3.36%), with an incidence of 6.58% in the critically ill group ($p < 0.001$) (**Table 2**).

Compared with COVID-19 patients without AIS, the patients with AIS were older ($p < 0.001$) and had higher SBP (131.50 [115.75, 145.75] vs. 126.00 [114.00, 138.00], $p = 0.013$), male gender (58.1 vs. 48.5%, $p = 0.034$), greater prevalence of smoking (7.3 vs. 2.2%, $p < 0.001$), and had a greater rate of comorbidities, such as hypertension (53.2 vs. 23.3%, $p < 0.001$), diabetes (30.6 vs. 10.7%, $p < 0.001$), hyperlipidemia (4.0 vs. 1.3%, $p = 0.006$), heart disease (25 vs. 6.7%, $p < 0.001$), COPD (5.6 vs. 2.3%, $p = 0.015$), chronic kidney disease (6.5 vs. 2.5%, $p = 0.006$), intracerebral hemorrhage (4.0 vs. 0.5%, $p < 0.001$), and prior IS (31.5 vs. 3.1%, $p < 0.001$). In terms of clinical outcomes, COVID-19 patients with AIS had a significantly higher mortality rate (27.4 vs. 6.8%, $p < 0.001$) (**Table 3**).

Analysis of Risk Factors for AIS in Patients With COVID-19

In a univariable logistic regression analysis on all 36,358 patients with COVID-19 to study risk factors for AIS, we found greater age, male gender, smoking, hypertension, diabetes, hyperlipidemia, heart disease, COPD, kidney disease, intracerebral hemorrhage, history of stroke, and disease severity of COVID-19 were associated with AIS

(**Supplementary Figure 2A**). A multivariable regression analysis adjusted for factors in the univariable logistic regression analysis revealed that higher odds of AIS were associated with greater age ($OR = 2.696$ [95% CI 2.046–3.58], $p < 0.001$), smoking ($OR = 2.151$ [95% CI 0.975–4.218], $p = 0.038$), diabetes ($OR = 1.86$ [95% CI 1.217–2.795], $p = 0.003$), prior IS ($OR = 4.962$ [95% CI 3.179–7.628], $p < 0.001$) and disease severity of COVID-19 ($OR = 1.499$ [95% CI 1.224–1.832], $p < 0.001$) (**Figure 3A**).

In the cohort of 1,160 COVID-19 patients with prior IS, a univariable logistic regression analysis showed only greater age and disease severity of COVID-19 to be associated with AIS (**Supplementary Figure 2B**). Furthermore, multivariable regression analysis indicated greater age ($OR = 2.76$ [95% CI 1.531–5.198], $p < 0.001$) and disease severity of COVID-19 ($OR = 1.61$ [95% CI 1.114–2.328], $p = 0.011$) to be independent risk factors (**Figure 3B**).

DISCUSSIONS

In this study, we included the whole dataset of hospitalized patients with COVID-19 in Wuhan city. By mid-April 2020, when the first wave of COVID-19 was over, a total of 50,333 patients were diagnosed with COVID-19, in which 40,206 had been hospitalized. This unique cohort may facilitate to draw more reliable conclusions regarding the relationship between IS and COVID-19. We found COVID-19 patients with prior stroke experienced worse clinical outcomes than those without. After propensity matching for age, sex, and all significant co-morbidities, history of stroke retained its strong association with the severity of disease and death from COVID-19. Our results suggested that prior stroke may have an adverse effect on the prognosis of COVID-19. In addition to other reported risk factors, we found that the risk of death from COVID-19 in patients with prior stroke were associated with premorbid MRS grouping for the first time. MRS is a widely used scale that has been proven to be a valid and reliable instrument for defining the impairment of neurological function in patients with stroke (14). In our patients with MRS scores of 4–5, the mortality was as high as 26.8%. Patients with more severe neurological deficit experienced worse clinical outcomes after the infection may be due to impaired mechanism for delivery secretions in respiratory tract and host immune responses (6, 15). Our results indicated that the hospitalized COVID-19 patients with prior stroke,

TABLE 3 | Clinical characteristics of COVID-19 patients with and without AIS.

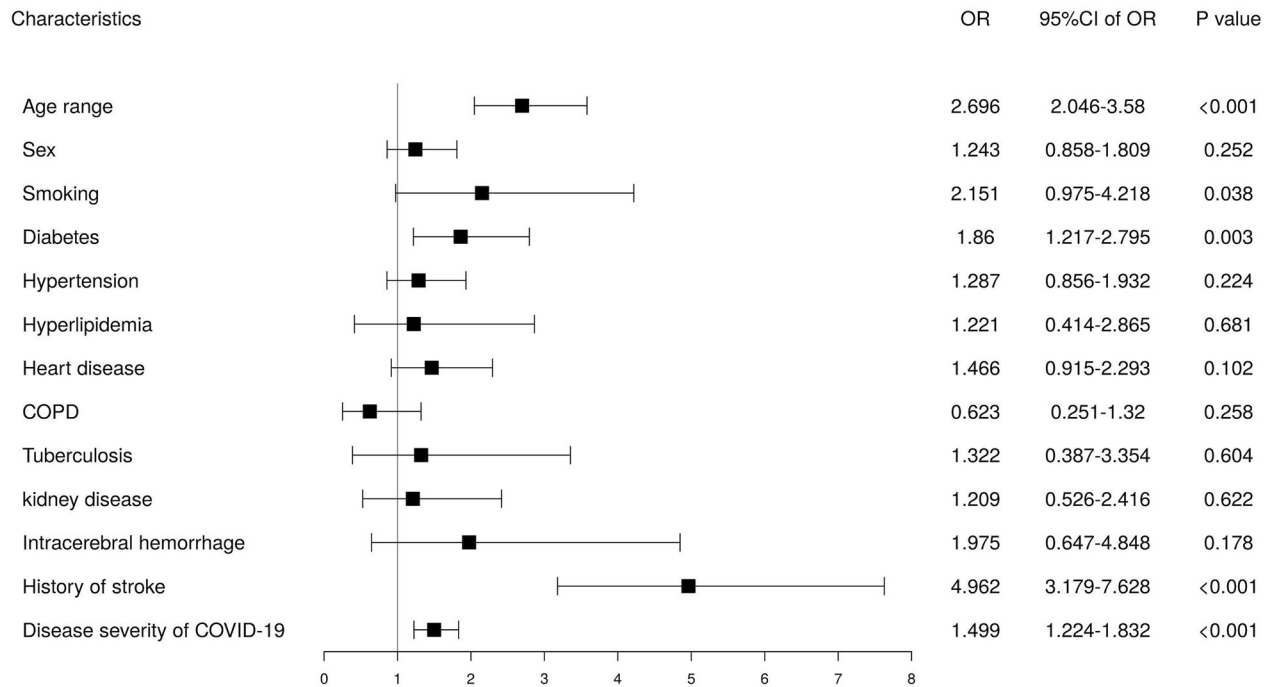| Characteristic	Overall	COVID-19 patients without acute ischemic stroke	COVID-19 patients with acute ischemic stroke	P-value
N	36,358	36,234	124	
Age ranges				
<40	6,106 (16.8)	6,105 (16.8)	1 (0.8)	<0.001
40–60	12,950 (35.6)	12,933 (35.7)	17 (13.7)	
60–80	14,805 (40.7)	14,744 (40.7)	61 (49.2)	
>80	2,497 (6.9)	2,452 (6.8)	45 (36.3)	
Sex				
Female	18,696 (51.4)	18,644 (51.5)	52 (41.9)	0.034
Male	17,662 (48.6)	17,590 (48.5)	72 (58.1)	
Systolic pressure	126.00 [114.00, 138.00]	126.00 [114.00, 138.00]	131.50 [115.75, 145.75]	0.013
Diastolic pressure	80.00 [72.00, 90.00]	80.00 [72.00, 90.00]	80.50 [70.00, 96.00]	0.630
Smoking	794 (2.2)	785 (2.2)	9 (7.3)	<0.001
Drinking	2,697 (7.4)	2,686 (7.4)	11 (8.9)	0.536
Diabetes	3,931 (10.8)	3,893 (10.7)	38 (30.6)	<0.001
Hypertension	8,498 (23.4)	8,432 (23.3)	66 (53.2)	<0.001
Hyperlipidemia	459 (1.3)	454 (1.3)	5 (4.0)	0.006
Heart disease	2,452 (6.7)	2,421 (6.7)	31 (25.0)	<0.001
Cancer	824 (2.3)	820 (2.3)	4 (3.2)	0.472
COPD	850 (2.3)	843 (2.3)	7 (5.6)	0.015
Tuberculosis	506 (1.4)	502 (1.4)	4 (3.2)	0.081
Chronic kidney disease	924 (2.5)	916 (2.5)	8 (6.5)	0.006
Liver disease	1,189 (3.3)	1,184 (3.3)	5 (4.0)	0.633
Intracerebral hemorrhage	178 (0.5)	173 (0.5)	5 (4.0)	<0.001
Asthma	386 (1.1)	385 (1.1)	1 (0.8)	0.781
History of stroke	1,160 (3.2)	1,121 (3.1)	39 (31.5)	<0.001
White blood cells, $\times 10^9$ cells/L	5.60 [4.40, 7.10]	5.59 [4.40, 7.10]	7.04 [5.50, 9.31]	<0.001
Neutrophils, $\times 10^9$ cells/L	3.51 [2.59, 4.90]	3.51 [2.59, 4.89]	4.98 [3.51, 7.42]	<0.001
Lymphocytes, $\times 10^9$ cells/L	1.30 [0.88, 1.77]	1.30 [0.88, 1.77]	1.17 [0.78, 1.53]	0.020
Eosnophils, $\times 10^9$ cells/L	0.06 [0.01, 0.13]	0.06 [0.01, 0.13]	0.06 [0.02, 0.13]	0.569
Monocytes, $\times 10^9$ cells/L	0.41 [0.30, 0.53]	0.41 [0.30, 0.53]	0.49 [0.37, 0.63]	<0.001
Platelets, $\times 10^9$ cells/L	212.00 [166.00, 267.00]	212.00 [166.00, 267.00]	199.00 [146.75, 248.00]	0.057
Hemoglobin, g/L	126.00 [115.00, 138.00]	126.00 [115.00, 138.00]	125.50 [111.00, 137.25]	0.562
Albumin, g/L	38.00 [34.20, 41.40]	38.00 [34.20, 41.40]	36.50 [32.90, 40.38]	0.017
Alanine aminotransferase, U/L	23.00 [14.90, 38.00]	23.00 [14.90, 38.00]	18.00 [11.93, 27.75]	0.002
Prothrombin time, s	12.50 [11.50, 13.64]	12.50 [11.50, 13.64]	12.15 [11.17, 13.10]	0.021
D-dimer, μg/L	0.49 [0.23, 1.11]	0.49 [0.23, 1.10]	0.95 [0.43, 2.12]	<0.001
Duration of hospital stay, days	15.00 [9.00, 22.00]	15.00 [9.00, 22.00]	13.00 [7.00, 21.25]	0.134
Non-invasive mechanical ventilation	1,188 (3.3)	1,176 (3.2)	12 (9.7)	<0.001
Invasive mechanical ventilation	818 (2.2)	810 (2.2)	8 (6.5)	0.002
Disease severity of COVID-19				
Mild	11,921 (32.8)	11,908 (32.9)	13 (10.5)	<0.001
Moderate	16,823 (46.3)	16,763 (46.3)	60 (48.4)	
Severe	6,247 (17.2)	6,208 (17.1)	39 (31.5)	
Critical	1,367 (3.8)	1,355 (3.7)	12 (9.7)	
Died during hospitalization	2,492 (6.9)	2,458 (6.8)	34 (27.4)	<0.001

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; Data are reported as number and percentage (%) for categorical variables and median (IQR) for continuous variables.

and particularly those with high MRS scores, have a markedly increased risk of death, such that these vulnerable patients need very close monitoring and aggressive treatment measures.

While the exact relationship between AIS and COVID-19 is still not fully clarified (16, 17), in the early days of the epidemic, some small sample studies found COVID-19 infection

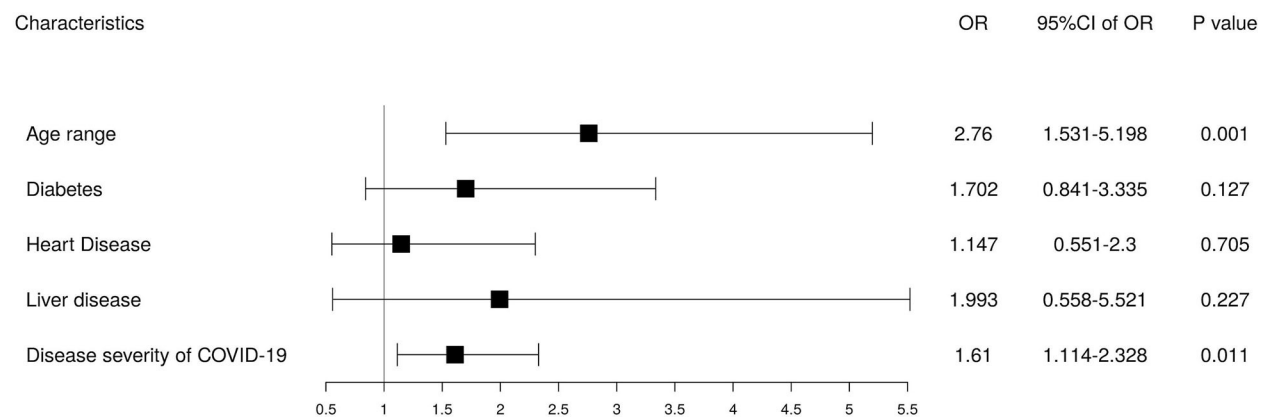## Multivariable logistic regression analysis for risk factors of AIS

A

Characteristics		OR	95%CI of OR	P value
Age range		2.696	2.046-3.58	<0.001
Sex		1.243	0.858-1.809	0.252
Smoking		2.151	0.975-4.218	0.038
Diabetes		1.86	1.217-2.795	0.003
Hypertension		1.287	0.856-1.932	0.224
Hyperlipidemia		1.221	0.414-2.865	0.681
Heart disease		1.466	0.915-2.293	0.102
COPD		0.623	0.251-1.32	0.258
Tuberculosis		1.322	0.387-3.354	0.604
kidney disease		1.209	0.526-2.416	0.622
Intracerebral hemorrhage		1.975	0.647-4.848	0.178
History of stroke		4.962	3.179-7.628	<0.001
Disease severity of COVID-19		1.499	1.224-1.832	<0.001

B

Characteristics		OR	95%CI of OR	P value
Age range		2.76	1.531-5.198	0.001
Diabetes		1.702	0.841-3.335	0.127
Heart Disease		1.147	0.551-2.3	0.705
Liver disease		1.993	0.558-5.521	0.227
Disease severity of COVID-19		1.61	1.114-2.328	0.011

FIGURE 3 | Multivariable logistic regression analysis for risk factors of acute ischemic stroke (AIS) in patients with coronavirus disease 2019 (COVID-19) and COVID-19 patients with a history of stroke. **(A)** Multivariable logistic regression analysis for risk factors of AIS in patients with COVID-19 (n = 36,358). **(B)** Multivariable logistic regression analysis for risk factors of AIS in COVID-19 patients with a history of stroke (n = 1,160).

is significantly associated with AIS compared with control subjects with an OR of 3.9 (18), and later evidence indicated that the infection can trigger IS or worsen an existing stroke (19, 20). In this study, we reported a stroke incidence of 0.342% in Wuhan city, which corresponds to an annual incidence of 345/100,000 person-years for IS (21) within an average course of ~20 days following admission, and was higher than the in-hospital stroke rate of 0.11% (22). The stroke incidence we

reported was lower than that in some previous reports. Other studies from heavily affected regions have suggested a stroke risk among patients hospitalized with COVID-19 in the range of 0.5–5% (23–25), with the most recent single center, multi-center studies or meta-analysis reporting a stroke rate of 1–2% among hospitalized patients (26, 27). However, the stroke incidence in this study was comparable with that in a multinational study, which reported an overall stroke risk of 0.5 and 0.3% in Asia

(11). In addition, we note that the recurrence of IS is a particular problem which has not been examined in previous studies in the context of the COVID-19 pandemic. In this study, we found that patients with COVID-19 with prior stroke had a 3.36% risk of AIS, which is compared with a 5% annual recurrence rate for patients with stroke in the general population (28), it indicated that a patient with COVID-19 during infection has a much higher rate of AIS. The disease severity of COVID-19 was suspected to associate with the occurrence of AIS (29, 30), since AIS has been reported to occur more frequently in severe ill patients (31). In this study, we first found that the occurrence of AIS was independently associated with the greater disease severity of COVID-19 in the patients after adjusting for age, sex, and comorbidities. The independent association between AIS and the disease severity of COVID-19 may further explain why the stroke incidence rate varies greatly across different regions, centers, and levels of hospitals, since some centers have relaxed criteria for admission, while the other centers with excessive disease burden have adopted strict criteria. Other possible reasons for differences between centers include ethnicity differences, small sample size, and publication bias. As a whole region study, we have included all inpatients in Wuhan, which should have reduced the influence of differing admission criteria between hospitals. However, the rate of AIS in our study may be underestimated, as the detection of AIS symptoms is challenging in those critically ill with COVID-19, especially those typically intubated and sedated. In addition, our study suggests that when reporting AIS caused by COVID-19, the severity or diagnostic criteria of COVID-19 in patients enrolled should be specified, or there may be a lack of comparability between groups of data.

To get a better understanding of the risk factors and clinical outcomes of patients with AIS following COVID-19, we selected AIS patients without COVID-19 who were hospitalized in Tongji Hospital over the same period as a control group. We found that AIS among patients with COVID-19 occurred more commonly in elderly patients, and showed a lesser association with hypertension, hyperlipidemia, smoking, and alcohol consumption, but more association with comorbidities, such as heart disease, COPD, kidney disease, liver disease, and prior IS (**Supplementary Table S4**). These differences in demographic characteristics and risk factors suggested that AIS occurred following the COVID-19 hospitalization may differ in its etiology from conventional stroke. Unfortunately, we failed to do TOAST classification due to the incompleteness of examinations during the epidemic. We did not study the mechanisms of stroke following COVID-19, the key proposed mechanisms include the development of cytokine storm and activation of the innate immune system, embolic events propagated by pre-existing or new-onset arrhythmias, hypoxia-induced ischemia secondary to severe pulmonary disease, thrombotic microangiopathy, endotheliopathy/endothelialitis, and multifactorial activation of coagulation (32). AIS patients with COVID-19 had a higher ratio of MRS 4–5 at discharge, and a much higher mortality, this is consistent with previous studies (19, 33). Given that COVID-19 is prone to coagulation disorders, such as pulmonary embolism and venous thrombosis

(34), patients at high risk might benefit from an anticoagulant or antiplatelet therapy, but further research is needed.

A notable strength of our study is that we included all patients with COVID-19 from hospitals across Wuhan State, such that our results should be more representative than existing studies from a single hospital system or multi-centers (24, 25). We thus provided a more reliable assessment of the incidence of AIS after COVID-19 and illustrated its correlation with the severity of COVID-19. Although there are many multi-center studies and meta-analyses on the incidence of AIS in patients with COVID-19, but the majority of studies included are either case series or case reports, with only a few being observational cohort studies, thus, many of these studies are considered relatively lower in the quality with publication and reporting bias, and stratification of patients' AIS risk based on the COVID-19 severity may be of more interest to clinicians. To the best of our knowledge, this is the largest retrospective cohort study among COVID-19 patients with prior stroke who have experienced a definite outcome, which, as such, enabled us to have identified severe illness and other mortality associated risk factors, notably premorbid MRS in those patients with prior stroke.

LIMITATIONS

The main limitation of this study arises from the retrospective study design, and the necessity of identifying the primary exposure and outcome, as well as confounding factors, using hospital electronic records from administrative datasets, which may vary in assessment criteria between hospitals. Second, this study took place in a severely challenged health system during the local peak of the COVID-19 pandemic, such that some reports or test results were simply unavailable, which could have introduced reporting or indication biases. In addition, we cannot address the possibility that treatment protocols may have varied based on local experience.

CONCLUSIONS

The major finding of our regional study is that the prior stroke is associated with an increased risk of developing severe course of COVID-19 and death. In patients hospitalized with COVID-19 with prior stroke, with high premorbid MRS scores have a markedly increased risk of death. COVID-19 increased the incidence of AIS, especially in patients with a prior IS, and the incidence is independently correlated with the severity of COVID-19. Nevertheless, these results will hopefully provide guidance for clinicians to understand the interactions between COVID-19 and IS, and are conducive to the management of patients with prior stroke who are at a high risk for COVID-19.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

AUTHOR CONTRIBUTIONS

MW, HZ, GL, SX, and WW: concept and design. MW, HZ, YH, CQ, XinL, and YuT: acquisition, analysis, and interpretation of data. MW, HZ, SX, and WW: drafting of the manuscript and critical revision of the manuscript for important intellectual content. ML, YuT, XiaL, and GY: statistical analysis. SX and WW: obtained funding. YH, CQ, XinL, and YiT: administrative, technical, and material support. SX and WW: supervision.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.792487/full#supplementary-material

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