Manifestations and outcomes of intracerebral hemorrhage during COVID-19 pandemic in China: a multicenter, longitudinal cohort study

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April 05, 2024

Abstract

Background: We just right were carrying out a multicenter cohort study about ICH when COVID-19 broke out in Wuhan,and we wondered whether COVID-19 pandemic was associated with the manifestations and outcomes of intracerebral hemorrhage (ICH). **Methods:** Acute ICH patients before (1/12/2018-30/11/2019) and during COVID-19(1/12/2019-30/11/2020) pandemic at 31 centers in China, were entered into the analysis. Demographic information, clinical manifestations and outcomes were collected and compared between the two groups. **Results:** From December 1, 2018 to November 30, 2020, a total of 3460 patients with ICH were enrolled and eventually analyzed. Results showed that patients with ICH were more likely to be older, have higher systolic blood pressure (BP) (P<0.001), diastolic-BP (P=0.002), higher admission NIHSS score (P=0.039) and higher fasting blood glucose (P=0.003) during COVID-19 pandemic compared with before. After adjusting age, gender, COVID-19 pandemic was associated with 3-month poor outcome ($OR_{adjusted}$ = 1.206, 95%CI: 1.043-1.395) and 3-month mortality ($OR_{adjusted}$ = 1.711, 95%CI: 1.428-2.050) after ICH onset. **Conclusions:** COVID-19 pandemic deteriorated the manifestations and outcomes of ICH.

Introduction

As a global health crisis, COVID-19 pandemic has been the most serious challenge to deliver timely care to patients with other conditions[1]. Intracerebral hemorrhage (ICH), as a neurological emergency, is one of the most devastating diseases worldwide and would require emergency medical care in specialized neurological intensive care unit (NICU)[2]. However, it is difficult to balance between ICH treatment and COVID prevention during COVID-19 pandemic.

Moreover, hypertension management may be a problem. An unproven notion before that ACE-1 inhibitors and ARBs might increase the risk of COVID-19 infection theoretically since increased ACE-2 activity led to practical medicine restriction. Recently there have been reports that discontinuation of ACEI/ARB in COVID-19 patients is not related to severity of COVID-19[3, 4]. However, discontinuation of ACEI/ARB once was not an uncommon phenomenon. Besides during COVID-19 pandemic the public may also suffered from social pressure, anxiety, depressed economy, lack of public health resources and so on.

Herein, we compared the differences of ICH manifestations, major interventions and outcomes between before and during COVID-19 pandemic at 31 centers in China, from the CHEERY study: Chinese cerebral hemorrhage: mechanism and intervention study.

Methods Study design The underlying data for this analysis was collected prospectively of two groups of patients with ICH before (1/12/2018-30/11/2019) and during COVID-19 (1/12/2019-30/11/2020) pandemic at 31 centers in China. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Participants

All ICH patients enrolled must meet the following criteria: (1) eligible patients were > 18 years of age; (2) acute ICH, duration from onset to admission[?]7 days, (3) received either a CT or MRI of brain to confirm the diagnosis of ICH.

Data collected and analyzed

The demographic information collected include age, sex, residence, smoke and alcohol history, medical history from the medical record. Vehicle to hospital, duration from onset to admission were collected shortly after admission from patients or escorts. SBP/DBP, hematoma location, hematoma volume, and laboratory data were copied from medical record. SMASH-U flow-chart was adopted to classify the most likely cause for each ICH event, including structural vascular lesions (S), medication (M), amyloid angiopathy (A), systemic disease (S), hypertension (H), undetermined (U)[5]. Modified ranking scale (mRS) score was assessed centrally by face-to-face interview if the patient survive at 3 months.

Definitions

ICH was defined as hemorrhage into the cerebral parenchyma that may also extend into ventricles and rarely, subarachnoid spaces. Poor outcome was defined as mRS more than 3 points (mRS>3).

Statistical analysis

Data were presented as means±SD, No. (%), M (P25, P75). Continuous variables were compared by using the t-test or Mann–Whitney U test. Categorical variables were compared using the $\chi 2$ test. All statistical analyses were done with the SPSS statistical software (version 26.0, SPSS Corporation, Chicago). The significance threshold was set at $P<0.05$. We used conditional logistic regression models to compute odds ratios (OR) and 95% confidence intervals (CI).

Ethics statement and consent to participate

The study protocol and data collection were conducted strictly following the Declaration of Helsinki and approved by the Research Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (ethical approval number:2018-S485). Protocol training was conducted for all researchers prior to the implementation of the project. All participants signed a written informed consent prior to the enrollment.

Results

From December 1, 2018 to November 30, 2020, there were 3460 patients with acute ICH enrolled in the CHEERY study and 3260 patients were included in the final analysis (figure 1). The demographic data were listed in table 1.

Patients' average age was 61.9±12.3 during COVID-19 pandemic and 60.5±12.5 before COVID-19 breakout (P=0.001), respectively. COVID-19 pandemic was associated with lower percentage of the male (P=0.002), history of smoking (P=0.001) and drinking (P=0.017) (table 1).

During COVID-19 pandemic, patients more likely went to hospital directly by themselves (P<0.001), and took less time from the onset to admission (4(2,12) vs. 6(2,24) h, P<0.001) compared with before COVID-19. COVID-19 pandemic was also associated with increase of systolic blood pressure (BP) (171.3±29.2 vs. 164.3±28.7 mmHg, P<0.001), diastolic-BP (97.6±16.9 vs. 95.7±17.6 mmHg, P=0.002), NIHSS score (11.6±10.5 vs. 10.8±10.0, P=0.039), deep ICH (81% vs. 77%, P=0.010), hematoma volume (11.0(5.0,27.0) vs. 10.0(4.6,20.9)ml, P=0.009), IVH (16% vs. 14%, P=0.021) and fasting blood glucose (6.2(5.2,7.8) vs.

6.1(5.3,7.3) mmol/L, P=0.003) on admission (table 1). At 3 month, mRS score distribution was shown in figure 2. The three-month mortality was 23%, much higher than that of last year (14%) (P¡0.001).

We then comparatively evaluated the outcomes. Table 2 shows COVID-19 pandemic was associated with increased risk of 3-month poor outcome ($OR_{unadjusted}$ = 1.244, 95%CI: 1.078-1.436; $OR_{adjusted}$ = 1.206, 95%CI: 1.043-1.395) and 3-month mortality ($OR_{unadjusted}$ = 1.772, 95%CI: 1.481-2.120; $OR_{adjusted}$ = 1.711, 95%CI: 1.428-2.050).

Discussion

From December, 2019, outbreak of COVID-19 infection has had a major impact on the occurrence, development and treatment of cerebrovascular diseases[1].Currently, Delta and other variants are driving some countries to reinstate strict public health social. Our study has found that during COVID-19 pandemic, patients with ICH were more likely to be older, and have higher blood pressure, bigger hematoma volume, and increased risk of 3-month poor outcome and mortality.

The global burden of ICH is related to the inadequate management of chronic hypertension and other modifiable risk factors[6]. In China, nearly half of the adults aged between 35-75 have hypertension, but only 30.1% of hypertensive patients are being treated while about 7.2% are under control[7]. During COVID-19 pandemic, the situation was worse, and the higher blood pressure in ICH patients could be attributed to the social pressure, anxiety, depressed economy, lack of public health resources, inadequate control of risk factors and people's unwillingness to seek medical treatment during this special period. Furthermore, the use of ACEI/ARBs might increase the risk of COVID-19 infection theoretically, though recent reports did not find any correlation between the discontinuation of ACEI/ARB in COVID-19 patients and severity of COVID-19[3, 4]. For the fear of infection of COVID-19, patents may discontinue the use of ACEI/ARB.

Our study found that more ICH people went to hospitals directly without calling an ambulance. We speculated that this phenomenon was related to limited public medical resources, and anxiety.

Most important of all, our study found that ICH patients demonstrated higher NIHSS score on admission and larger hemorrhage volume. They also needed more ICU intervention and had more poor outcomes and mortality at 3 months. This finding indicated that ICH was more severe during COVID-19 pandemic, which could be related to their higher blood pressure on admission that may lead to a larger hematoma and poor prognosis. Our results were consistent with the studies reported there poor predictors of mortality: older age, larger ICH volume[8].

One main limitation of our study was that we only included hospitalized patients. Those who were treated in the outpatient setting and died before reaching the hospital were not included. In addition, this study did not contain COVID-19 infected patients.

A major strength of this study is the use of CHEERY study and its consecutive enrollment of patients within a defined study time including the year before and after COVID-19 outbreak. This excludes relevant selection bias and ensures that results from this cohort are fairly representative.

Our study indicated that the cloud of COVID-19 has adversely impacted the presentation and outcomes of ICH. The medical workers may pay more attention on patients with ICH, while the public should pay more attention on hypertension control and ICH prevention.

Author Contributions

Bo Hu was responsible for the concept and design of the study. Yan Wan, Quanwei He did the literature search and wrote the manuscript. Man Li, Yuanpeng Xia, Lei Zhang, Zhou Sun, Xiaolu Chen acquired and interpreted data. Shaoli Chen analyzed the data. David Wang revised the manuscript. Xingquan Zhao and Yongjun Wang did the administrative, technical, or statistical support.

Acknowledgments

The authors would like to express their gratitude to all the participants and investigators in the 31 centers of the CHEERY study.

Sources of Funding

This work was supported by the National Key Research and Development Program of China (No. 2018YFC1312200 to BH), the National Natural Science Foundation of China (No. 81820108010 to BH, NO. 81901214 to YW, NO. 82071335 to QWH).

Disclosures of conflict of interest

None.

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Table 1. Baseline and admission characteristics of patients admitted to hospital in the year during COVID-19 pandemic and the year before COVID-19 outbreak. Values are numbers (percentages) unless stated otherwise

Characteristics	during COVID-19 pandemic (2019.12.1-2020.11.30)	before COVID-19 pandemic (2018.12.1-2019.11.30)	*P* value
Total No.	1510	1750	
Age(y), mean±SD	61.9±12.3	60.5±12.5	0.001
Age			<0.001
¡60	625(41)	828(47)	
[?]60	885(59)	922(53)	
Gender			0.002
Male	868(57)	1098(63)	
Female	642(43)	652(37)	

Characteristics	during COVID-19 pandemic (2019.12.1-2020.11.30)	before COVID-19 pandemic (2018.12.1-2019.11.30)	*P* value
Residence			
Rural	850(56)	930(53)	0.066
Urban	639(42)	797(46)	
Unknow	21(1)	23(1)	
Smoke history			0.001
Yes	424(28)	584(34)	
No	1081(72)	1159(66)	
Unknown	5(0)	7(0)	
Alcohol history			0.017
Yes	346(23)	464(27)	
No	1159(77)	1279(73)	
Unknown	5(0)	7(0)	
Comorbidities			
Ischemic heart disease	62(4)	53(3)	0.096
Ischemic stroke	156(10)	150(9)	0.086
Hypertension	970(64)	1141(65)	0.567
Diabetes	137(9)	143(8)	0.360
Pre-ICH anti-hypertension+	281/970(29)	299/1141(26)	0.156
Pre ACEI/ARB usage	49/281(17)	45/299(15)	0.436
Vehicle to hospital			<0.001
Ambulance	660(44)	1012(58)	
Self-admission	838(55)	686(39)	
Unknown	12(1)	52(3)	
Duration from onset to admission(h), M (P_{25}, P_{75})	4(2,12)	6(2,24)	<0.001
Systolic-BP on admission (mm Hg), M(P_{25}, P_{75})	171.3±29.2	164.3±28.7	<0.001
Diastolic-BP on admission (mm Hg), mean±SD	97.6±16.9	95.7±17.6	0.002
NIHSS on admission, M(P_{25}, P_{75})	11.6±10.5	10.8±10.0	0.039
Location of hematoma, n(%)			0.010*
Lobe	292(19)	403(23)	
Deep	1218(81)	1347(77)	
Hematoma volume(ml), M(P_{25}, P_{75}) ++	11.0(5.0,27.0)	10.0(4.6,20.9)	0.009*
IVH, n (%)	249(16)	238(14)	0.021*
ICU treatment, n(%)	960(64)	938(54)	¡0.001*
Surgical intervention, n(%)	271(18)	358(20)	0.269
SMASH-U classification			
Structural lesion	26(2)	31(2)	0.914

Characteristics	during COVID-19 pandemic (2019.12.1-2020.11.30)	before COVID-19 pandemic (2018.12.1-2019.11.30)	*P* value
Medication	7(0)	4(0)	0.365
Amyloid angiopathy	196(13)	235(13)	0.706
Systemic Diseases	16(1)	18(1)	0.931
Hypertension	775(51)	919(53)	0.498
Undetermined	411(27)	478(27)	0.951
Laboratory measurements on admission			
TC (mmol/L), mean±SD	4.6±1.5	4.7±3.0	0.577
Triglycerides(mmol/L), mean±SD	1.7±2.7	1.7±3.9	0.851
LDL-C(mmol/L), mean±SD	2.6±0.8	2.6±0.9	0.833
PT(s), M(P_{25}, P_{75})	12.4±4.8	12.8±6.2	0.068
INR, mean±SD	1.0±0.2	1.1±0.6	0.136
APTT(s), mean±SD	29.1±11.4	30.1±11.7	0.013
FIB(g/L), M(P_{25}, P_{75})	2.9(2.4,3.6)	3.0(2.4,3.8)	0.001
Platelet count ($\times 10^9$/L), mean±SD	196.3±65.6	195.8±68.7	0.826
Fasting blood glucose (mmol/L), M(P_{25}, P_{75})	6.2(5.2,7.8)	6.1(5.3,7.3)	0.003

No., number; SD, standard deviation; M, median; P_{25}, 25% quartile; P_{75}, 75% quartile; BP, blood pressure; ICH: intracerebral hemorrhage; SMASH-U: structural vascular lesions (S), medication (M), amyloid angiopathy (A), systemic disease (S), hypertension (H), undetermined (U); NIHSS, National Institute of Health Stroke Scale; IVH, intraventricular hemorrhage; ICU, Intensive Care Unit; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; PT, prothrombin Time; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen.

+Percentage of pre-ICH anti-hypertension treatment in patients with hypertension.

++Excluding those patients with IVH.

Table 2 outcomes in patients admitted to hospital during and COVID-19 pandemic. Values are numbers (percentages)

Characteristics	**during COVID-19 pandemic (2019.12.1-2020.11.30)**	**before COVID-19 outbreak (2018.12.1-2019.11.30)**	**Unadjusted Analysis**	**Unadjusted Analysis**	**Adjusted Analysis+**	**Adjusted Analysis+**
			OR (95% CI)	*P* value	OR (95% CI)	*P* value

Characteristics	during COVID-19 pandemic (2019.12.1-2020.11.30)	before COVID-19 outbreak (2018.12.1-2019.11.30)	Unadjusted Analysis	Unadjusted Analysis	Adjusted Analysis+	Adjusted Analysis+
3-month poor outcome (mRS 4-6), n(%)	587(39)	592(34)	1.244(1.078-1.436)	0.003	1.206(1.043-1.395)	0.011
3-month mortality, n(%)	348(23)	253(14)	1.772(1.481-2.120)	<0.001	1.711(1.428-2.050)	<0.001

OR: Odds ratio; mRS, modified ranking scale.

+adjusted for age,gender

Figure legends

Figure 1 Flow chart of patients screened, included and excluded from the study.

Figure 2 The distribution of 3 month modified Rankin scale score.

Shown are the results of the ordinal analysis of the modified Rankin scale scores at 3 months among ICH patients of the year before COVID-19 outbreak and the year during COVID-19 pandemic. Scores range from 0 to 6, with 0 indicating no neurological deficit, 1 no clinically significant disability, 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (eg, with shopping, cleaning and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention) and 6 death.