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Mitigating the impact of coronavirus disease 2019 on emergency stroke care: an original study and meta-analysis

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Abstract: The coronavirus disease 2019 is still continuing and may affect stroke emergency care. We aim to investigate the impact of pandemic on stroke treatment in tertiary stroke centers in western China, and to quantitatively evaluate the worldwide influence with a meta-analysis. The original part was conducted in three tertiary stroke centers in Sichuan province. We compared emergency visits and efficiency of stroke treatment pre-, early, peak and late pandemic. Single-center analysis was further conducted in the largest local hospital and one hospital located close to the epicenter respectively. Relevant studies were searched in PubMed, Ovid Embase and Cochrane Library for English publications from December 2019 to July 2020 for systematic review. Fixed-and random-effect meta-analysis was performed to calculate the overall rates. Totally current original study showed fewer time of hospital admission and significantly higher rates of mechanical thrombectomy during the early and peak epidemic periods, compared with pre-epidemic time. The

largest local hospital had significantly higher mechanical thrombectomy rates during the whole crisis and less daily admission during early and peak epidemic periods. The hospital located close to the epicenter presented higher proportions of intravenous thrombolysis since outbreak, and more favorable outcomes after reperfusion therapies than later (all P values <0.05). In meta-analysis, studies reported differences in reperfusion therapies and stroke severity but pooled results were non-significant. Overall, comprehensive measures should be implemented to keep hospital's capacity to deliver high-quality stroke emergency care during the global pandemic. Some key messages were provided for medical practice in the crisis.

Keywords: coronavirus disease 2019 (COVID-19); emergency care; management strategies; meta-analysis; stroke.

Introduction

The 2019 novel coronavirus disease (COVID-19) has posed a considerable threat to international public health (Du et al. 2020; Wang et al. 2020). The coronavirus has spread to numerous countries across the globe with over 18 million confirmed cases and 700 thousand deaths. All healthcare systems worldwide have suffered a heavy backlash. Scientists have confirmed that the pathogen is highly contagious via human-to-human transmission, and can cause multisystem impairments (Chan et al. 2020; Huang et al. 2020; Li et al. 2020; National Health Commission of China 2020; Zhu et al. 2020). Complications of COVID-19 and cerebrovascular disease were associated with an increased disease severity (Aggarwal et al. 2020). The infection with this coronavirus might result in a worse outcome in patients with stroke, through direct damage on the nervous system or an activation of inflammation and coagulation disorders (Siniscalchi and Gallelli 2020). Furthermore, medical services, especially acute stroke care, could be affected adversely. Public perceive hospitals as sites of potential exposure and feel anxious seeking medical help. People prefer to stay at home rather than visit hospitals unless they are severely ill. Some stroke patients with

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needing intensive care may not arrive at hospital early enough. Preliminary data from a large city demonstrated a 40% decline in timely presentation of stroke emergencies during the pandemic, compared with the same period last year according to the national TV news (Beijing Stroke Quality Control Center 2020). Moreover, several studies conducted in China and European countries respectively showed a significant drop in the rates of thrombolysis and thrombectomy, which demonstrated the reduction in the capacity for stroke care during the crisis (Frisullo et al. 2020; Pop et al. 2020; Zhao et al. 2020a, 2020b).

When the COVID-19 became paramount, in order to mitigate the impact on stroke emergency management, comprehensive measures were mandated in China during the pandemic. Several expert recommendations were issued by the China National Health Commission and Chinese Medical Association (National Health Commission Stroke Expert Committee of China 2020a, 2020b, 2020c; COVID-19 Neurologists Consensus Collaborators 2020). In Sichuan province, there are over 2000 medical establishments with 400 thousand beds. The intensive care unit beds are more than 280 thousand. A provincial health emergency was declared with over 200 hospitals and 5490 beds dedicated for COVID-19 treatment. Potential solutions were also widely shared (Zhao et al. 2020a, 2020b). Hospitals also prepared a series of contingency plans to deal with the crisis.

Furthermore, more and more health systems have gradually taken different steps and tried to mitigate the pandemic effect on emergency treatment based on their specific circumstances. However, the crisis is still string and the impact on stroke emergency care hasn't been settled. There are little data informing how the pandemic can affect the time-dependent emergency medical care for stroke patients. Published data of pooled samples of individuals from different regions make it possible to determine the impact of COVID-19 pandemic on stroke emergency care worldwide. It will also help to better understand the current situation and develop more effective global strategies for stroke care during crisis period.

To date, no systematic critical evaluation of literatures with purpose of confirming the impact of COVID-19 pandemic on stroke medical care has been performed. This study used the database of an original study performed in multiple tertiary stroke centers with different characteristics in Sichuan province of China in addition to a systematic review and meta-analysis of previously published studies reporting the pandemic effects. The paper describes the measures taken to mitigate the effect of the pandemic on emergency stroke care in western China, providing a framework for other health systems

and comparable medical establishments to follow during the current and probable future COVID-like pandemic emergencies in the future.

Methods – original study

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the ethical review board in West China Hospital of Sichuan University (2019/319).

Study design

This retrospective, multi-center study was conducted at three designated hospitals for COVID-19 including West China Hospital of Sichuan University, Chengdu Fifth People's Hospital, and West China-Guang'An Hospital of Sichuan University. The West China Hospital of Sichuan University is the largest hospital with around 4300 beds and 6700 healthcare workers in the southwest of China. The hospital annual census has exceeded five million patients. The Chengdu Fifth People's Hospital served the majority of patients in the satellite towns of Chengdu, with over 2400 staffs. The West China-Guang'An Hospital of Sichuan University is located in Guang'An, a big city which is nearest to Hubei Province, the epicenter in China. Under the city lockdown, people in Guang'An could be in great fear of affection and paid more attention on keep social distance than others.

During the pandemic, medical practice strictly followed hospitals contingency plans, and the recently developed expert consensus on the stroke treatment announced by China National Health Commission and Chinese Medical Association (COVID-19 Neurologists Consensus Collaborators 2020; National Health Commission Stroke Expert Committee of China 2020a, 2020b, 2020c). Experience from other cities in China were also used (Zhao et al. 2020a, 2020b). Figures 1 and 2 summarized the changes in the process of emergency stroke treatment before and during the crisis period. These included:

- I. All staff were equipped with standardized personal protection including goggles, protective gowns, surgical masks, and gloves when practicing in emergency department;
- II. All patients had temperature screening at the entrance to the hospital and checked again before treatment was started. Epidemiological investigation

- (questionnaires about whether they had been to epicenter of the outbreak, or in contact with infected patients) was conducted at entrance;
- III. Patients were all required to take computed tomography (CT) test for chest to screen viral pneumonia and identify suspected case;
 - IV. Before conducting endovascular thrombectomy, the attending doctor checked the temperature again. A negative pressure operation room was established for patients suspected or positive for COVID-19;
 - V. Suspected patients were kept in an isolation room for medical observation. After the confirmation by quantitative real-time polymerase chain reaction (qRT-PCR) and/or CT test of chest, negative patients would be admitted to the normal neurology ward. The temperature was taken again before entering the ward;

- VI. For the hospital located nearest to the epicenter, the qRT-PCR test was required for all patients.
- VII. One-caregiver demand. Each patient could only have one caregiver for company. Everyone in the ward had to wear a mask.

Participants

The most suspenseful COVID-19 period in Sichuan was defined from Dec 1, 2019 to Mar 11, 2020, 102 days in total. According to the governmental announcement, the first COVID-19 case in Sichuan was reported on Jan 21, 2020, so we further divided the COVID-19 period into early epidemic stage (Dec 1, 2019 to Jan 20, 2020) and peak epidemic stage (Jan 21 to Mar 11, 2020). Moreover, we also explored the late epidemic (Mar 12 to May 1, 2020) and pre-epidemic stages

Figure 1: The protocol of stroke emergency treatment during the pre-epidemic stage. AIS, acute ischemic stroke; ED, emergency department; CT, computer tomography.

Figure 2: The protocol of stroke emergency treatment during the peak-epidemic stage. T, temperature; AIS, acute ischemic stroke; ED, emergency department; CT, computer tomography; qRT-PCR, quantitative real-time polymerase chain reaction; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

(Jan 21 to Mar 11, 2019). All stages last 51 days. We consecutively registered patients visiting emergency department of stroke center diagnosed with acute ischemic stroke during the four stages according to the criteria of World Health Organization (Recommendations on stroke prevention, diagnosis, and therapy 1989). Patients who presented with hemorrhagic stroke or other neurological diseases were excluded from the study.

Study variables and outcomes

Information about the stroke emergency visits, demographics and processes of care including patient volume, reperfusion

therapy rates, delays in visits and outcome after recanalization were obtained from the database of these three stroke centers. The National Institutes of Health Stroke Scale (NIHSS) score was used to assess severity of neurologic deficit. Both NIHSS at admission and discharge were collected to compare the neurological improvements after treatments including reperfusion therapies. We calculated admission rates for acute ischemic stroke, rates of reperfusion therapies [including intravenous thrombolysis (IVT) and mechanical thrombectomy (MT), onset to admission time, door to needle time (DNT), door to puncture time (DPT), and neurological improvements during the baseline and COVID-19 periods as primary outcomes. Changes in the stroke

care in two representative hospitals during peak-epidemic stage were set as secondary outcomes.

Statistical analyses

Comparisons were performed using SPSS, Version 20.0 (IBM, Armonk, New York). The increase and decrease in percentages were presented to show the changes during the whole crisis period. Continuous variables including age and patient volume were reported as mean $\pm$ standard deviation and compared by Kruskal–Wallis H-test or ANOVA after Normal distribution test and homogeneity test of variance. Categorical variables including sex distribution, time from onset to admission, disease severity, rates of reperfusion therapies, and neurological improvements were presented as frequency (percentage), using Chi-Square test or Fisher exact test. Bonferroni correction was performed to adjust for multiple tests ($\alpha = 0.05/6 = 0.0083$). Missing data within 5% of all cases were allowed, and the missing parts would be deleted when analyzing. All *P*-values are two-sided, with $P < 0.05$ considered statistically significant.

Systematic literature search and meta-analysis

We strictly followed the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines throughout the design, implementation, analysis and reporting processes in this study (Stroup et al. 2000).

Search strategy and data extraction

A systematic literature search was conducted in PubMed, Ovid Embase and Cochrane online scientific publication databases for English language publications from Dec 2019 to July 2020 to identify potentially relevant observational studies. The following medical subject heading (MeSH) terms and/or text words were used “stroke or ischemic stroke or cerebrovascular incident or cerebrovascular diseases” and “COVID-19 or the 2019 novel coronavirus disease or 2019-nCoV or SARS-Cov-2 or severe acute respiratory syndrome coronavirus 2”.

Study selection

Two qualified investigators independently screened the titles and abstracts from the initial search to assess potential relevance (JW and YH). Discrepancies were resolved by discussion. Furthermore, full-text articles were obtained to reevaluate the eligibility and determine the final inclusion. Included studies should: 1) report data from an original, peer-reviewed observational human study of all designs, 2) present the change in stroke care quantitatively before and during the COVID-19 pandemic. We excluded studies that with duplicate citations or unavailable data. When studies had been published more than one time on the same topic and theme, only the most recent study was selected to extract data, others were listed and analyzed as similar studies. References of the included studies were also reviewed.

Study quality assessment

Two investigators (JW and YH) independently assessed the quality of each study using the Agency for Healthcare Research and Quality (AHRQ) including following items: source of information, inclusion and exclusion criteria, study period indication, consecutive subjects or not, evaluators of subjective components of study were masked to other aspects of the status of the participants, assessments undertaken for quality assurance purposes, patients exclusion from analysis, confounding assessment, missing data, patients response rates and completeness of data collection, follow-up related (Rostom et al. 2004). An item would be scored 0 if it was answered no or unclear; inversely the item would be scored 1 with a yes answer. Total score was 11. High quality was defined as 8–11. Discrepancies were resolved by consensus with input from a third investigator (MM).

Data extraction and outcome variables

The following information was extracted from the included studies: authors' name, publication year, study countries (regions), participants' ages and sex ratios, number of participants, study periods and quality scores. Outcome parameters included the change in the rates of reperfusion therapies during pandemic.

Statistical analysis

The pooled outcomes were meta-analyzed if sources were available from a minimum of three studies using a random or fixed effect model according to the heterogeneity. The 95% CI of the odds ratio (OR) and their 95% CIs were calculated and presented by forest plot. Heterogeneity was quantified with the I^2 test (values of 0–40%: not important, 30–60%: moderate heterogeneity, 50–90%: substantial heterogeneity). Once substantial heterogeneity was assessed, analyses predefined by stratifying original estimate (countries/regions) would be conducted to further investigate the sources of heterogeneity between studies. Qualitative analyses using funnel plots were performed to assess publication bias (10 studies at least). We extracted data from specific studies using Chi-Square test or Fisher exact test to compare percentage change. Bonferroni correction was used to adjust for multiple tests ($\alpha = 0.05/3 = 0.00167$). The analyses were performed using the metaphor package for Review Manager software version 5.3 and SPSS, Version 20.0 (IBM, Armonk, New York). $P < 0.05$ was considered statistically significant.

Data availability

All extracted data could be made available upon request from qualified investigators to corresponding authors.

Results – original study

Participant characteristics

The mean age (and standard deviation) of the patients seen in the stroke center for emergencies during the pre-, early, peak and late epidemic stages were comparable with 69.2 (13.2), 70.2 (12.6), 69.6 (12.4) and 71.2 (11.5) years respectively (Bonferroni adjusted $P > 0.05$). Male patients accounted for 55.7% in pre-epidemic stages, 55.8% in early epidemic stage, 56.9% male patients in peak epidemic stage and 53.9% in late epidemic stage (Bonferroni adjusted $P > 0.05$). None of stroke patients were diagnosed with COVID-19.

Comparison between four epidemic stages

Details of the comparison between four epidemic stages appear in Table 1. There were no significant changes in patient volume, stroke severity, rate of intravenous

thrombolysis rate (IVT) and neurological improvements in the whole COVID-19 period. However, rates of mechanical thrombectomy (MT) in early and peak epidemic stages were significantly higher than pre-epidemic period and more patients came to hospital within 6 h after stroke onset during peak pandemic (all Bonferroni adjusted $P < 0.05$). Descriptive data especially on early and peak epidemic stages are depicted in Figure 3.

Single-center analysis based on different characteristics

Changes in stroke care in a large and elite hospital

The comparison conducted in West China Hospital of Sichuan University, which is the largest and elite hospital in southwest of China between epidemic stages, is presented in Table 2. The admission severity, the rate of IVT, time ranges of DNT and DPT, and neurological improvements were comparable across the various stages of the COVID-19 pandemic. Meanwhile, compared with pre-epidemic time, the increase in the rate of MT during the whole crisis and reduction in daily hospital visits during the peak and late epidemic stages were significantly occurred (all Bonferroni adjusted $P < 0.05$).

Changes in stroke care in a hospital located close to epicenter

We further dug the information about medical care in the largest stroke center in Guang'An city during this crisis (Table 3). We witnessed statistically higher proportion of IVT during the whole crisis compared with pre-epidemic time and more favorable outcomes after reperfusion therapies during early and peak-epidemic stages compared with later period (all Bonferroni adjusted $P < 0.05$). No significant changes were found in the patient visits, rate of MT, and stroke severity.

Results – meta-analysis

Literature search

Based on the pre-specified selection criteria, 583 studies were excluded after the initial screen of title. 276 studies were excluded after reading the abstracts. 43 studies were excluded after a review of the full text review for several major reasons including: studies were presented as case reports, reviews or editorial articles; no pre-pandemic data

Table 1: Changes in stroke care in multiple centers.

Items	Pre-epidemic	Early epidemic	Peak epidemic	Late epidemic
Demographics				
Age (y)	69.2 ± 13.2	70.2 ± 12.6	69.6 ± 12.4	71.2 ± 11 0.5
Male, <i>n</i> (%)	108 (55.7%)	111 (55.8%)	95 (56.9%)	110 (53.9%)
Patient volume, <i>n</i>				
Total visits	194	199	167	204
Daily visits, mean	3.9 ± 1.8	3.9 ± 2.1	3.3 ± 2.1	4.0 ± 2.1
Onset to admission (≤6 h)	149 (76.8%)	169 (84.9%)	153 (91.6%)*	173 (84.8%)
Neurological deficit at admission, <i>n</i> (%)				
NIHSS 0–4	78 (40.2%)	79 (39.7%)	59 (35.3%)	97 (47.5%)
NIHSS 5–15	77 (39.3%)	75 (37.7%)	72 (43.1%)	74 (36.3%)
NIHSS >15	39 (20.1%)	45 (22.6%)	36 (21.6%)	33 (16.2%)
Reperfusion therapy				
Rate of IVT, <i>n</i> (%)	48 (24.7%)	49 (24.6%)	50 (29.9%)	47 (23.0%)
Rate of MT, <i>n</i> (%)	23 (11.9%)	44 (22.1%)*	39 (23.4%)*	31 (15.2%)
DNT, range, min	48–104	37–138	38–145	50–150
DPT, range, min	29–300	40–219	58–247	34–195
Neurological improvements after IVT/MT, <i>n</i> (%)				
Favorable outcome	28 (39.4%)	36 (38.7%)	38 (42.7%)	44 (56.4%)
Excellent outcome	18 (25.4%)	26 (28.0%)	21 (23.6 %)	30 (38.5%)
Death	12 (16.9%)	8 (8.6%)	7 (7.9%)	11 (14.1%)

* $P < 0.05$ compared with pre-epidemic period in 2019 after Bonferroni adjusted. Favorable outcome was defined as NIHSS score decreased 0–4 and excellent outcome was defined as NIHSS score decreased >4. IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

Figure 3: Numbers of patient visits in stroke emergencies during the whole COVID-19 period. The x-axis represents time weekly started from Dec 7 the first week to Mar 11 the last week in COVID-19 period. The y-axis represents number of patients visit multiple stroke centers for emergency care.

or no separate analysis on ischemic stroke care. In total, 11 published articles, together with our current study were included for meta-analysis (Ahmad et al. 2020; Diegoli et al. 2020; Frisullo et al. 2020; Kristoffersen et al. 2020; Pop et al. 2020; Rudilosso et al. 2020; Siegler et al. 2020; Meza et al. 2020a,b; Silva et al. 2020). All data were successfully extracted from the published studies. The selection process is provided in Figure 4.

Study characteristics of eligible studies

The meta-analysis was performed on 12 studies (i.e., 11 previously published studies identified by literature search as described in the methods section as well as the current original study) with a total of 4,789 patients (3,149 patients in pre-pandemic and 1,640 patients during pandemic). The number of participants ranged from 57 (Silva et al. 2020) to

Table 2: Changes in stroke care in a large and elite hospital.

Items	Pre-epidemic	Early epidemic	Peak epidemic	Late epidemic
Total visits	94	66	51	57
Daily visits, mean	1.9 ± 1.4	1.3 ± 1.2	1.0 ± 1.0*	1.1 ± 1.1*
NIHSS 0–4	37 (39.4%)	17 (25.8%)	10 (19.6%)	15 (26.3%)
NIHSS 5–15	35 (37.2%)	25 (37.9%)	26 (51.0%)	24 (42.1%)
NIHSS >15	22 (23.4%)	24 (36.4%)	15 (29.4%)	18 (31.6%)
Rate of IVT, n (%)	35 (37.2%)	12 (18.2%)	18 (35.3%)	13 (22.8%)
Rate of MT, n (%)	17 (18.1%)	34 (51.5%)*	27 (52.9%)*	29 (50.9%)*
DNT, range, min	48–104	45–119	57–109	53–140
DPT, range, min	44–178	40–185	58–247	34–174
Favorable outcome	17 (32.7%)	10 (21.7%)	12 (26.7%)	16 (38.1%)
Excellent outcome	16 (30.8%)	18 (39.1%)	16 (35.6%)	15 (35.7%)
Death	11 (21.2%)	6 (13.0%)	6 (13.3%)	4 (9.5%)

* $P < 0.05$ compared with pre-epidemic period in 2019 after Bonferroni adjusted. Favorable outcome was defined as NIHSS score decreased 0–4 and excellent outcome was defined as NIHSS score decreased >4. CI, confidence interval; NIHSS, The National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; DNT, door to needle time; DPT, door to puncture time.

2737 (Meza et al. 2020a). Six studies were performed in European countries (Frisullo et al. 2020; Kristoffersen et al. 2020; Pop et al. 2020; Rudilosso et al. 2020; Meza et al. 2020a,b), two were conducted in the United States (Ahmad et al. 2020; Siegler et al. 2020), two were in Brazil (Diegoli et al. 2020; Silva et al. 2020), and another 2 in the China mainland (current original study) and Hong Kong respectively (Teo et al. 2020). Data collection was all based on cross-sectional design. A significant reduction in thrombolysis occurred in one study (Frisullo et al. 2020), total reperfusion therapies in another study (Pop et al. 2020). Others reported no significant association (Ahmad et al. 2020; Diegoli et al. 2020; Kristoffersen et al. 2020; Rudilosso et al. 2020; Siegler et al. 2020; Meza et al. 2020a,b; Teo et al. 2020; Silva et al. 2020) and current original study. A total of three studies had a low risk of bias (Diegoli et al. 2020; Siegler et al. 2020; and current original study), and nine had a moderate of bias (Ahmad et al. 2020; Frisullo et al. 2020; Kristoffersen et al. 2020; Pop et al. 2020; Rudilosso et al. 2020; Meza et al. 2020a,b; Teo et al. 2020; Silva et al. 2020). The characteristics of included studies are summarized in Table 4.

Table 3: Changes in stroke care in a hospital located close to the epicenter.

Items	Pre-epidemic	Early epidemic	Peak epidemic	Late epidemic
Patient volume, <i>n</i>				
Total visits	70	65	61	65
Daily visits, mean	1.4 ± 1.2	1.3 ± 1.2	1.2 ± 1.0	1.3 ± 1.2
Neurological deficit at admission, <i>n</i> (%)				
NIHSS 0–4	30 (42.9%)	29 (44.6%)	19 (31.1%)	24 (36.9%)
NIHSS 5–15	34 (48.6%)	24 (36.9%)	28 (45.9%)	31 (47.7%)
NIHSS >15	6 (8.6%)	12 (18.5%)	14 (23.0%)	10 (15.4%)
Reperfusion therapy				
Rate of IVT, <i>n</i> (%)	5 (7.1%)	25 (38.5%)*	17 (27.9%)*	18 (27.7%)*
Rate of MT, <i>n</i> (%)	1 (1.4%)	1 (1.5%)	1 (1.6%)	2 (3.1%)
DNT, range, min	51–85	37–138	38–145	50–150
DPT, range, min	300	130	100	100–135
Neurological improvements after IVT/MT, <i>n</i> (%)				
Favorable outcome	3 (50%)	19 (73.1%)†	14 (77.8%)†	6 (30%)
Excellent outcome	1 (16.7%)	7 (26.9%)	4 (22.2%)	8 (40%)
Death	1 (16.7%)	0	0	4 (20%)

* $P < 0.05$ compared with pre-epidemic period in 2019 after Bonferroni adjusted. † $P < 0.005$ compared with late epidemic period after Bonferroni adjusted. Favorable outcome was defined as NIHSS score decreased 0–4, excellent outcome was defined as NIHSS score decreased >4. CI, confidence interval; NIHSS, The National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; DNT, door to needle time; DPT, door to puncture time.

Change in the rates of IVT and MT treatments

The summarized characteristics of reperfusion therapies and stroke severity were reported in Table 5. There were significantly more severe stroke cases (OR = 1.49, 95%CI 1.01, 2.19; $P = 0.044$) and less minor stroke admission (OR = 0.75, 95%CI 0.58, 0.96; $P = 0.025$) after the outbreak as reported. While we found an increase in the number of MT treatment, the reductions in IVT and total reperfusion therapies were presented. However, none of them showed statistical difference. Moreover, as conducted in different countries/regions with completely different epidemiologic situation and health services, included studies with IVT/

Figure 4: Study screening flow diagram.

MT changes were further divided into three major parts (Europe, Asia and the United States) to compare data before and during the epidemic. In Table 6, the rate of IVT was significantly higher in Europe (32.6%) than in Asia (22.7%) and the United States (12.0%) before the epidemic. After COVID-19 outbreak, Asia started to show the highest rate of IVT (26.6%) among these three parts (13.2% for Europe and 5.7% for the United States) of world (Bonferroni adjusted $P < 0.05$). The United States presented lowest IVT rates in both periods. However, things changed when it came to the rate of MT. The highest rate of MT was significantly showed in Asia (20.3%) before the epidemic while the United States (34.1%) during the crisis (Bonferroni adjusted $P < 0.05$).

Investigators in totally 11 studies respectively reported on the change in the rates of IVT or MT treatments during the epidemic (Figure 5). Results showed the forest plot of the pooled OR for the effect of the crisis on stroke emergency care. With an OR of 0.87 (95% CI 0.74, 1.02), it showed a trend toward great impact on thrombolysis treatment, but not significantly ($P = 0.09$). Similarly, analysis was conducted by fixed-effect model among studies focused on MT treatment during the crisis, with an OR of 1.11 (95% CI 0.96, 1.29; $P = 0.17$), presenting no statistical significance either. Heterogeneities were mild ($I^2 = 21\%$ for IVT and 36% for MT) between studies.

Change in the rates of total reperfusion therapies

Ten studies that explored change in the rates of total reperfusion therapies caused by the COVID-19 pandemic were included in the meta-analysis, as shown in Figure 6. The pooled data under random-effect model showed an OR of 0.89 (95% CI 0.68, 1.15; $P = 0.36$), with substantial heterogeneity ($I^2 = 51\%$, $P = 0.03$). Thus, a stratified analyses restricted to European studies were conducted to investigate potential source of heterogeneity (Figure 7). With the strict inclusion of only European studies, the heterogeneity between studies was reduced to $I^2 = 34\%$ ($P = 0.20$), with an OR = 0.92 ($P = 0.27$).

Publication bias

Publication bias assessments were carried out on studies focused on IVT and MT treatments separately. Funnel plots suggested possible publication bias as asymmetric graph was observed (Figure 8). We aimed for a comprehensive search, thus published and unpublished studies were all included. Moreover, we noticed that six of our included studies had small sample sizes (<200), which could somewhat reduce the statistical power of analyses and increase the publication bias. However, the limited number of studies did not permit many of our planned subgroup analyses to furthermore detect potential biases.

Discussion

The original study as well as the systematic review and meta-analysis showed no significant changes in the number of patients presenting to the hospital with stroke, mild and severe stroke emergencies, and neurological improvements after medical intervention amid the whole COVID-19 period either. Compared with pre-epidemic time, more patients came to hospital within 6 h after stroke onset during the whole crisis and rates of MT were significantly higher in early and peak epidemic stages. Moreover, in one-center analysis, we observed significantly higher rates of MT during the whole crisis and less daily visits during early and peak epidemic periods in a large and elite tertiary stroke center. We also noticed that the hospital located close to the epicenter presented higher proportions of intravenous thrombolysis since outbreak, and more favorable outcomes after reperfusion therapies in early and peak epidemic stages than later.

Table 4: Characteristics of included studies.

Study ID	Country/ Region	Mean age/Male gender (%)>	N of study popula- tion with AIS (pre-pandemic)	N of study population with AIS (pandemic)	Quality score	Study period	Study design
Silva (2020)	Brazil	76.9 (44.3%)	36	21	5	March–May 2019 & 2020	Cross- sectional
Meza (2020)	Spain	79.0 (52.3%)	275	79	7	Dec 30th, 2019– Apr 19th, 2020	Cross- sectional
Pop (2020)	France	NR	160	159	5	Mar 2019 & 2020	Cross- sectional
Teo (2020)	Hong Kong, China	72.0 (47.5%)	52	47	7	Jan 23rd, 2019– mar 24th, 2020	Cross- sectional
Kristoffersen (2020)	Norway	74.0 (54.0%)	143	76	7	Jan 1st –Apr 30th, 2020	Cross- sectional
Meza (2020)	Spain (North-west)	73.5 (53.5%)	1756	981	7	Dec 30th, 2019– May 3rd, 2020	Cross- sectional
Siegler (2020)	The United States	68.0 (58.0%)	275	53	8	Oct 1st, 2019–Apr 15th, 2020	Cross- sectional
Diegoli (2020)	Brazil	67.3 (49.2%)	121	75	8	Feb 16th–Apr 15th, 2020	Cross- sectional
Sweid (2020)	The United States	NR	91	70	6	Mar 15th–Apr 30th, 2017–2020	Cross- sectional
Rudilosso (2020)	Spain	NR (55.6%)	53	42	6	Mar 2019 & 2020	Cross- sectional
Frisullo (2020)	Italy	72.5 (53.8%)	41	52	7	Mar 11th–Apr 11th, 2019 & 2020	Cross- sectional
Wang 2020 (current study)	China	69.9 (56.3%)	199	167	8	Dec 1st, 2019– mar 12th, 2020	Cross- sectional

NR, not reported; N, number; AIS, acute ischemic stroke.

Table 5: Changes in reperfusion therapies and stroke severity by report.

Variable (n/sum)	Number of included studies	Pre- epidemic	Peak epidemic	OR/ 95%CI	P value
Only IVT	10	538/2990	274/1677	0.89, (0.76, 1.04)	0.153
Only MT	10	571/2938	359/1671	1.13, (0.98, 1.32)	0.096
Both IVT and MT	10	1083/2968	599/1676	0.97, (0.85, 1.10)	0.610
Severe stroke	2	77/474	55/246	1.49, (1.01, 2.19)	0.044*
Minor stroke	3	384/692	169/351	0.75, (0.58, 0.96)	0.025*

* $P < 0.05$. IVT, intravenous thrombolysis; MT, mechanical thrombectomy; OR, odds ratio; CI, confidence interval.**Table 6:** Changes in reperfusion therapies in different regions by report.

Variables (n/sum)	Europe	Asia	The United States
IVT			
Pre-epidemic	32.6%* (219/672)	22.7%† (57/251)	12.0%* (33/275)
Peak epidemic	13.2%* (54/408)	26.6%† (57/214)	5.7%* (3/53)
MT			
Pre-epidemic	19.7%† (451/2285)	20.3%† (51/251)	18.0%* (66/366)
Peak epidemic	20.7%† (272/1313)	20.1%† (43/214)	34.1%* (42/123)

* $P < 0.0167$ compared with Asia after Bonferroni adjusted. † $P < 0.0167$ compared with the United States after Bonferroni adjusted. IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

The meta-analysis underscored that the emergency stroke care in Europe, America and China were not greatly affected by the COVID-19 pandemic. But most of included

Figure 5: Pooled estimate of change in the rates of IVT and MT treatments.

Figure 6: Pooled estimate of change in the rates of total reperfusion therapies.

Figure 7: Pooled estimate of analyses stratified by nation.

Figure 8: Funnel plot for publication bias.

studies reported a decline in the rates of IVT and reperfusion therapies. Some studies presented a bit higher MT rates in the crisis. It should be noted that limited sample size might cause the non-significant association. Moreover, we still found that the summarized plots showed a trend toward decreased IVT and total reperfusion therapies rates, and an increased MT rate during the pandemic. After restricting the analysis of total reperfusion therapies to European studies, the between-study heterogeneity reduced obviously. However, we should aware that the analysis showed an increase in patients presented with severe stroke and a reduction in mild stroke, which could affect the proportion of patients receive reperfusion therapies. Besides, there was an important issue that, the articles were conducted in different countries and the epidemiologic situations were not the same. As our analysis showed, the rates of reperfusion therapies varied across different regions during the pre-and peak epidemic periods. While COVID-19 cases were increasing rapidly in some countries, the outbreak had not reached its peak at the time of publication in some places. Together, these results suggested that the massive spread of COVID-19 and some relevant strategies in different countries have impacted the time-dependent stroke management to some extent. The “lock-down” demand and social restrictions would make it harder for families and friends to recognize a stroke patient. Public education about stroke should be reinforced continuously. The global crisis has been last for over 11 months till now. Some countries even faced a second outbreak. Results from this article force us to stay alert and make the emergency stroke treatment better.

Similar to previous studies, our original study has provided preliminary evidence showing that the consequences of epidemic and the effect of timely, necessary management plans on the stroke emergency treatment

during the COVID-19 period can be mitigated though the implementation of careful, comprehensive planning. The patient volumes, disease severity, rates of IVT and MT, and neurological outcomes during early, peak, and late epidemic stages were comparable, which indicated that stroke emergency treatment remained essential even at the peak of epidemic. Furthermore, after the COVID-19 outbreak, rates of MT were higher than pre-epidemic time in 2019. More stroke patients with a definite requirement for intensive care still arrived in a timely way for treatment. This was achieved by taking comprehensive measures to alleviate public anxiety about infection among patients with critical conditions for needing hospital care. Methods for stroke fast recognition (mouth deviated, body weakness, speech disorder) and 4.5-h golden time for stroke treatment were constantly popularized both online and offline. The minor increases in DPT and DNT seen initially were possibly due to health personnel shortages during the early days of outbreak. Of note, amid the COVID-19 reality, changes in two different stroke centers were also thoughtful. We observed significant rise in the rate of MT in the largest local hospital and the rate of IVT in the hospital located close to the epicenter, compared with pre-epidemic stage in early 2019. The higher rates of reperfusion therapies during the global crisis suggested that high-quality care for stroke emergency was maintained during the pandemic. Also, we found less daily admission visit to the largest and elite hospital during the peak and late epidemic periods, and better outcomes after reperfusion therapies in the hospital located close to the epicenter. In general, we believed the phenomenon was not an accident, but a result of multiple factors. First of all, with the development of technological progress and constant education for health-care workers, the improvement of stroke emergency care becomes apparently necessary. More and more local hospitals, such as the hospital located close to the epicenter, are able to develop reperfusion therapies (intravenous thrombolysis in particular). Patients don't have to go to the largest hospital for medical seeking. They can choose the nearest stroke center for timely standardized treatment, especially during the pandemic. Patients with specific indications and strong wills for MT were then promptly transferred to the largest and elite hospital for further treatment. This could result in the higher rates of IVT/MT during the whole crisis. Besides, during this global public health emergency, several contingency strategies played their roles in the stroke emergency care. The measures including provision of expert guidance on how to continue to deliver emergency care, general hospital preparedness for the management of a pandemic and having a green channel in the emergency department to identify those

patients with time critical conditions, made professional health-care workers pay more attention on the critical diseases treatment, such as acute ischemic stroke. And since the “lock down” demand asked people to stay home and refrain from going outdoors, the raising of public awareness for seek medical help through non-stopped stroke education made people focus on their health conditions, so that they could come to the hospital in time for treatment. All these strategies made it possible for patients to have a better outcome. Moreover, as the meta-analysis showed, we should be aware of the fact that the pandemic itself may also have increased the proportion of patients treated with IVT and MT, since it may have provoked cases of severe stroke. In this special period, patients who came to a comprehensive hospital with severe conditions were under great panic, and would be more eager to take best medical treatment than usual. Thus, the rate of IVT and MT might experience an increase after the outbreak in the tertiary stroke centers.

Our results have confirmed the positive effect of comprehensive measures taken for stroke emergency treatment during the epidemic. The multiple plans required action by governmental, academic and hospital components. In western China, the government of Sichuan province declared a provincial health emergency on Jan 24, 2020. Over 200 hospitals and 5490 beds were dedicated for confirmed and suspected cases treatment. Academically, national expert consensus documents were regularly issued for the safety of stroke treatment (COVID-19 Neurologists Consensus Collaborators 2020; National Health Commission Stroke Expert Committee of China 2020a, 2020b, 2020c). Hospitals also invested great effort and adopted strict measures, including a separate passage to limit personnel access, standardized personal protection, temperatures taken repeatedly, questionnaires about whether they had been to epicenter of the outbreak or in contact with infected patients, CT examination of chest before starting stroke treatment, a temporary visit triage to identify suspected cases, specific routines for suspected patients, a green channel to reduce in-hospital delays for stroke patients and restricting access to just one care-giver per patient after admission (Cao et al. 2020; Liao et al. 2020). Meanwhile, research group conducted publicity through a website to give instructions for stroke prevention, and encourage patients to seek appropriate medical help. Experience from the severe acute respiratory syndrome (SARS) epidemic had previously demonstrated how badly emergency medical care can be affected (Schull et al. 2007). Our study proved that high-quality routine emergency care can be maintained during such an epidemic through timely and comprehensive planning.

The study has several limitations. First, the original part was a multi-center study conducted in three tertiary stroke centers, thus the generalizability of our findings may be limited to comparable medical establishments. Moreover, administrative data were lacking on patients who were transferred to other hospitals, so the impact of epidemic on the transfers could not be analyzed. Future studies are needed to examine the longer term effects of the pandemic and examine the quality of care and outcomes on larger groups of patients in more hospitals. Second, the limited sample size and study regions of literatures included in the systematic review and meta-analysis, may limit the generalization of the present findings. Stroke care in low-income countries during the COVID-19 pandemic should also be better investigated. In relation to this point, it is important for researchers to pay more attention to the situation in other part of the world such as the Africa and South Asia.

Conclusions

This is the first-ever combined scientific original study and systematic-review demonstrating that emergency stroke treatment need not be compromised during a pandemic if timely and comprehensive management strategies are implemented. The results give insight into the impact of epidemic and effect of necessary measures on the stroke emergency treatment during this special period.

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