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Impact of COVID-19 pandemic on haemorrhagic stroke admissions: a systematic review and meta-analysis

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ABSTRACT

Background and purpose COVID-19 pandemic, a global health crisis, is disrupting the present medical environment. This systematic review and meta-analysis aimed to evaluate the impact of the COVID-19 pandemic on stroke hospitalisations, especially haemorrhagic stroke.

Methods The EMBASE, PubMed, Web of Science, Elsevier, Medline, Cochrane Library and Google Scholar electronic databases were searched for all relevant studies. Two researchers independently screened the studies, extracted data and assessed the quality of the included studies. Odds ratio (OR), total events, OR and 95% CI were considered as the effect size. A fixed-effects model was used to pool the study-specific estimate. The present study was performed by using Review Manager (V.5.3.0) software. We assessed the risk of bias using the Newcastle–Ottawa Scale.

Results A total of 17 studies with 14 445 cases were included. Overall, the number of stroke admissions is lower in the pandemic period versus the control period (6252 vs 8193). The difference of haemorrhagic stroke is significant, with 1233 of 6252 cases in the pandemic group and 1621 of 8193 cases in the control group. Intracerebral haemorrhage is present in 461 of 1948 cases in the pandemic group and 618 of 2734 cases in the control group. As for subarachnoid haemorrhage, the difference between the two groups is significant, with 70 of 985 cases in the pandemic group and 202 of 1493 cases in the control group.

Conclusions The number of stroke admissions is lower in the pandemic period compared with the control period. There is a higher rate of haemorrhagic stroke in the pandemic period. Subgroup analysis identifies a significant increase in the occurrence of intracerebral haemorrhage in the pandemic period. Due to limited data and the impact of a single article, the impact of COVID-19 pandemic on subarachnoid haemorrhage is unclear.

Strengths and limitations of this study

- Because we collected results from different regions, the meaning of our study is wide and important.
- The result of this study is credible by meta-analysis, which could further explain disputes between different articles.
- This study lacks information about stroke severity and prognoses, which might have to some extent underestimated impacts of the pandemic on stroke.
- The total number of inpatients in the pandemic was not reported, so the prevalence of stroke is inconclusive.
- Although our meta-analysis indicates higher morbidity of intracerebral haemorrhage, the reliability needs to be verified by further researches because of the small sample size.

INTRODUCTION

In December 2019, COVID-19 or SARS-CoV-2 was first reported in Wuhan, China.[1] On 30 January 2020, the WHO declared COVID-19 as a Public Health Emergency of International Concern.[2] As of 16 August 2021, there have been over 206.69 million confirmed cases and 4 352 488 deaths globally, resulting in serious social and economic implications.[3 4]

Stroke is the second leading cause of death and functional inability worldwide, and one of the main contributors of disability-adjusted life years among neurological disorders.[5 6] The burden of stroke is projected to increase via absolute numbers of incident strokes and deaths.[7] The main contributor to stroke burden is ischaemic stroke, followed by intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).[7 8] To prevent and treat stroke, most countries try to establish major and emerging strategies, including activities that reinforce the local healthcare system through the establishment of a social, economic, environmental and cultural combination.[9 10]

Unfortunately, the COVID-19 outbreak affected acute stroke services, both direct and indirect. During the pandemic, a lot of people refuse to visit the hospital due to nosocomial infection, and some studies indicate that the incidence of acute conditions such as myocardial infarction and ischaemic stroke has reduced.[11 12] The World Stroke Organizatiton (WSO) survey showed that the number of acute stroke admissions was reduced in multiple countries, including Chile, Colombia, Iran, Greece, the UK, Belgium and Italy.[13] In addition, concerns have been raised about the impact of COVID-19 pandemic on haemorrhagic stroke (HS), including ICH and SAH.[14–16] For example, Balestrino *et al*,[17] John *et al*[18] and Schwarz *et al*[19] reported that the HS admission has increased in the pandemic period compared with the control period. However, reports of Rameez *et al*,[16] Zini *et al*[20] and Sacco *et al* showed that the HS admission was reduced in the pandemic period. It makes the impact remain controversial. Moreover, most of these reports are limited to regional or country-specific analysis, and thus, there is no systematic review and meta-analysis on the impact of the COVID-19 pandemic on the HS admission. To further examine whether this pandemic influenced the HS admission, we reviewed recent studies that compared rates of HS admissions

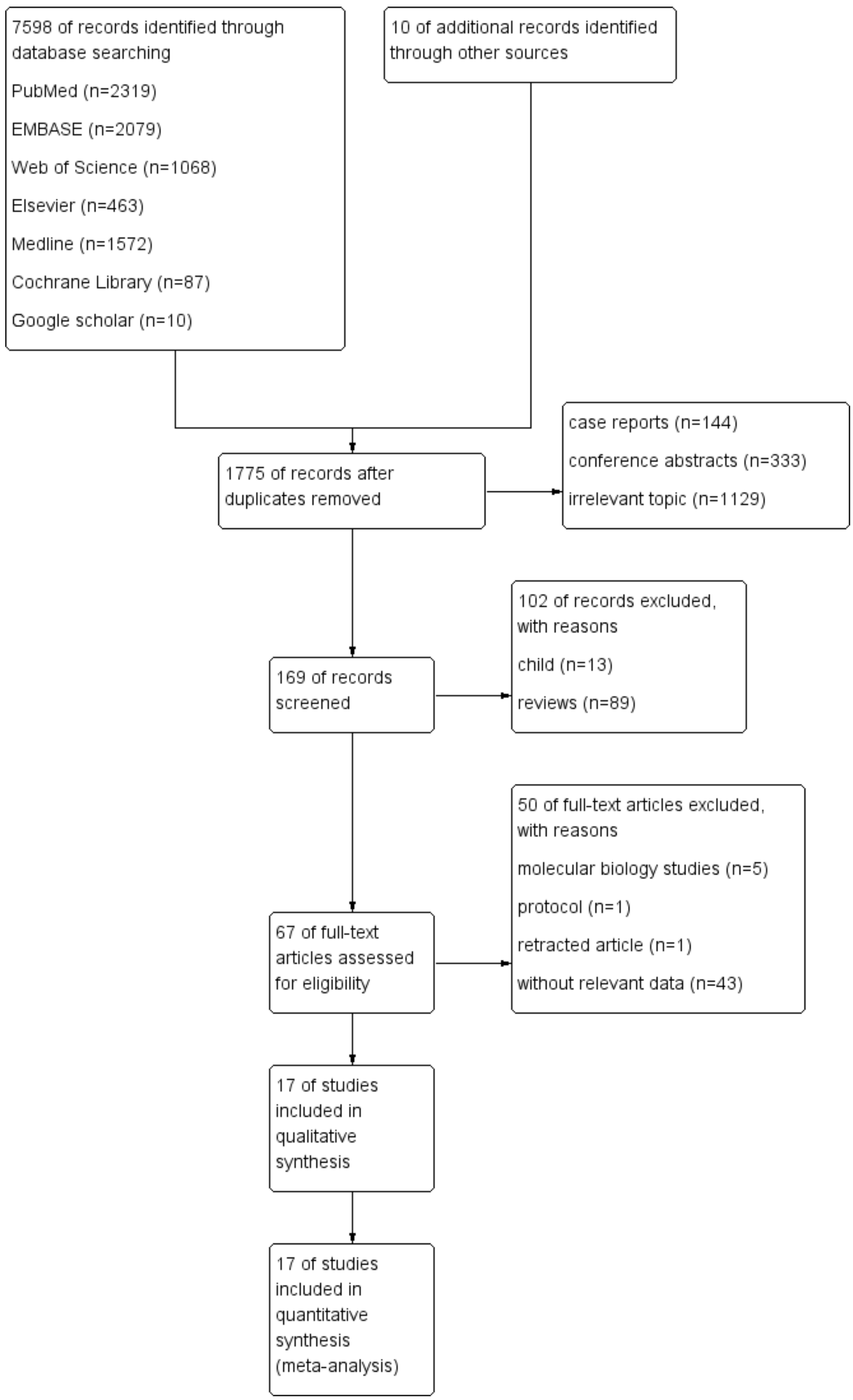

Figure 1 Flow chart of study selection process.

Table 1 Summary of characteristics of included studies

Author	Study design	Region	Age (years)	Male (%)	Pandemic period	Control period	Total number of intracerebral haemorrhage admissions (pandemic vs control)	Total number of subarachnoid haemorrhage admissions (pandemic vs control)	Total number of haemorrhagic stroke admissions (pandemic vs control)	Total number of stroke admissions (pandemic vs control)
Balestrino *et al*[17]	Single centre; retrospective observational	Italy	N/A	N/A	8 March 2020–2 May 2020	8 March 2019–2 May 2019	N/A	N/A	20 vs 17	124 vs 165
John *et al*[18]	Single centre; retrospective observational	UAE	48.9 (±14.7) vs 49.3 (±14.1)	66.7 vs 80.8	1 March 2020 –10 May 2020	1 March 2019 –10 May 2019	24 vs 12	13 vs 13	42 vs 26	210 vs 148
Rameez *et al*[16]	Single centre; retrospective observational	USA	65.6 vs 72.4	61.7 vs 51.3	24 March 2020–23 April 2020	24 March 2019–23 April 2019	9 vs 12	0 vs 0	9 vs 12	47 vs 80
Zini *et al*[20]	Single centre; retrospective observational	Italy	71.7 (±18) vs 75.2 (±13.8)	53.8 vs 50.7	1 March 2020–30 April 2020	1 March 2019–30 April 2019	17 vs 21	N/A	17 vs 21	145 vs 138
Schwarz *et al*[19]	Single centre; retrospective observational	Germany	N/A	N/A	Calendar weeks 1–16 in 2020	Calendar weeks 1–16 in 2019	32 vs 24	N/A	32 vs 24	286 vs 386
Sarfo *et al*[22]	Single centre; retrospective observational	Ghana	60.6 (±14.8) vs 59.7 (±15.4)	57.1 vs 53.4	19 January 2020–20 June 2020	19 January 2019–20 June 2019	N/A	N/A	118 vs 111	431 vs 401
Sacco *et al*[15]	Multicentre; prospective and retrospective	Italy	73.5 (±12.9) vs 73.6 (±13.3)	53 vs 53.4	1 March 2020–31 March 2020	1 March 2019–31 March 2019	N/A	N/A	322 vs 400	2379 vs 3145
Roushdy *et al*[23]	Single centre; retrospective observational	Egypt	63.2 (±12.7) vs 63 (±13.8)	61.3 vs 57	15 February 2020–5 April 2020	15 February 2019–5 April 2019	7 vs 5	1 vs 3	8 vs 8	93 vs 151
Altunisik and Arık[26]	Single centre; retrospective observational	Turkey	71.95 (±12.37) vs 70.96 (±13.52)	61.36 vs 53.93	1 April 2020–31 May 2020	1 April 2019–31 May 2019	3 vs 8	N/A	3 vs 8	40 vs 72
Luke *et al*[27]	Single centre; retrospective observational	Switzerland	N/A	N/A	11 March 2020–26 May 2020	11 March 2019–26 May 2019	26 vs 19	N/A	26 vs 19	200 vs 223
Thomas *et al*[28]	Multicentre; retrospective observational	Austria	N/A	N/A	1 March 2020–31 May 2020	1 March 2019–31 May 2019	N/A	N/A	188 vs 219	1014 vs 1185
Abdoreza *et al*[29]	Single centre; retrospective observational	Iran	69.21 (±13.88) vs 68.74 (±14.49)	55.17 vs 55.21	18 February 2020–18 July 2020	18 February 2019–18 July 2019	48 vs 50	N/A	48 vs 50	229 vs 352

Continued

Table 1 Continued

Author	Study design	Region	Age (years)	Male (%)	Pandemic period	Control period	Total number of intracerebral haemorrhage admissions (pandemic vs control)	Total number of subarachnoid haemorrhage admissions (pandemic vs control)	Total number of haemorrhagic stroke admissions (pandemic vs control)	Total number of stroke admissions (pandemic vs control)
Hasan *et al*[30]	Single centre; retrospective observational	Bangladesh	N/A	N/A	1 April 2020–30 June 2020	1 January 2020 –31 March 2020	282 vs 449	52 vs 182	334 vs 631	487 vs 907
Robin *et al*[24]	Single centre; retrospective observational	Germany	77 (64–82) vs 79 (69–85)	47.6 vs 45.7	16 March 2020–12 April 2020	16 March 2019–12 April 2019	6 vs 6	N/A	6 vs 6	63 vs 70
Ramírez-Moreno *et al*[31]	Multicentre; retrospective observational	Spain	70.9 (±2.9)	N/A	1 January 2020–31 May 2020	1 January 2019 –31 May 2019	N/A	N/A	44 vs 48	273 vs 451
Timo *et al*[25]	Single centre; retrospective observational	Germany	72.9 (±12.5) vs 72.6 (±13.4)	46.6 vs 54.3	March/April 2020	March/April 2019	7 vs 12	4 vs 4	9 vs 13	148 vs 207
Gabriel *et al*[32]	Single centre; retrospective observational	Spain	68 (53–79) vs 76 (60.2–83)	51.8 vs 55.4	14 March 2020–14 May 2020	14 March 2019–14 May 2019	N/A	N/A	7 vs 8	83 vs 112

N/A: No data.

between corresponding periods of pandemic and pre-pandemic.

MATERIALS AND METHODS

Research strategy and selection criteria

Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors (YY and YN) independently identified studies published until 22 August 2021 through systematically searching EMBASE, PubMed, Web of Science, Elsevier, Medline, Cochrane Library and Google Scholar. The following search key terms were used: stroke, subarachnoid hemorrhage, hemorrhagic stroke, cerebral hemorrhage, COVID-19, SARS-CoV-2, pandemic. We used Boolean operators 'AND' or 'OR' to combine the literature searches (online supplemental appendix 1). No language restrictions were applied. Every eligible publication was selected based on the articles' title and abstract by two authors (YY and YN). If there was any disagreement during study screening for relevance, we discussed it with a senior author (PD). This systematic review and meta-analysis was not registered in the International Prospective Register of Systematic Reviews Database.

The inclusion criteria for this review were original articles, retrospective observational studies, prospective and retrospective studies, and research letters. The data of interest were the ICH, SAH, HS and stroke admissions during the COVID-19 pandemic versus the comparator period. Only studies involving adults were eligible for inclusion. The exclusion criteria included protocols, retracted articles, conference abstracts, preprints, case reports, review articles, biochemical trials, no appropriate outcomes or trials without proper treatment groups and control groups.

Data extraction and quality assessment

The following data were extracted from each article by two independent researchers (YY and YN): author name, publication year, study type and design, source and region of study, patient demographics (age, gender), number of ICH admissions, number of SAH admissions, number of HS admissions and number of stroke admissions. Any conflicts between the researchers were resolved by discussion or decision of a third senior researcher. If there were incomplete data, we attempted to contact the corresponding authors for complete data. We also calculated the necessary information which was not reported in the articles.

The Newcastle–Ottawa Scale was used to evaluate the risk of bias of the included retrospective observational studies. The score consisted of eight items, including adequate case definition, representativeness of cases, selection of controls, definition of controls, comparability, ascertainment of exposure, same method and non-response rate. The total quality score ranged between 0 and 9. Studies assessed with ≥5 points were regarded

Table 2 Newcastle–Ottawa quality assessment scale and total score of each study

	Newcastle–Ottawa quality assessment scale								Score
Included studies	1	2	3	4	5	6	7	8	Total of number of stars
Balestrino *et al*[17]	B	A*	B	A*	A*	A*	A*	A*	6
John *et al*[18]	A*	A*	B	A*	A*	A*	A*	A*	7
Rameez *et al*[16]	B	A*	B	A*	A*	A*	A*	A*	6
Zini *et al*[20]	A*	A*	B	A*	A*	A*	A*	A*	7
Schwarz *et al*[19]	B	A*	B	A*	A*	A*	A*	A*	6
Sarfo *et al*[22]	B	A*	B	A*	A*	A*	A*	A*	6
Sacco *et al*[15]	A*	A*	A*	A*	A**	A*	A*	A*	9
Roushdy *et al*[23]	B	B	B	A*	A*	A*	A*	A*	5
Altunisik and Arık[26]	A*	A*	B	A*	A*	A*	A*	A*	7
Luke *et al*[27]	A*	A*	B	A*	A*	A*	A*	A*	7
Thomas *et al*[28]	A*	A*	A*	A*	A*	A*	A*	A*	8
Abdoreza *et al*[29]	B	A*	B	A*	A*	A*	A*	A*	6
Hasan *et al*[30]	A*	B	A*	A*	B	A*	A*	A*	6
Robin *et al*[24]	A*	A*	A*	A*	A*	A*	A*	A*	8
Ramírez-Moreno *et al*[31]	A*	A*	B	A*	A*	A*	A*	A*	7
Timo *et al*[25]	A*	A*	A*	A*	A*	A*	A*	A*	8
Gabriel *et al*[32]	A*	A*	A*	A*	A**	A*	A*	A*	9

A*, one star; A**, two stars; B, no star; 1, adequate case definition; 2, representativeness of cases; 3, selection of controls; 4, definition of controls; 5, comparability; 6, ascertainment of exposure; 7, same method; 8, non-response rate.

as low risk of bias, compared with the studies scoring <5 points that were regarded as high risk of bias.

Data synthesis and analysis

Meta-analysis of proportion was used to determine ICH, SAH, HS and stroke admissions during the pandemic compared with that during the historical pre-pandemic control period. The present study was performed by using Review Manager (V.5.3.0) software. Heterogeneity was calculated by using Q test and I^2, in which p<0.1, I^2 >50% meant significant heterogeneity. A fixed-effects model was used when statistically indicated heterogeneity was not found (p>0.1, I^2 <50%). Sensitivity analysis was used to assess the impact of individual articles. If there were a limited number of studies (<10), an assessment for publication bias was not performed. Conversely, publication bias was analysed and represented by a funnel plot that allowed evaluation of publication bias by presenting the study's log OR as a function of its SE.

Patient and public involvement

This is a meta-analysis based on study-level data and no individual-level data were involved in the study or in defining the research question or outcome measures.

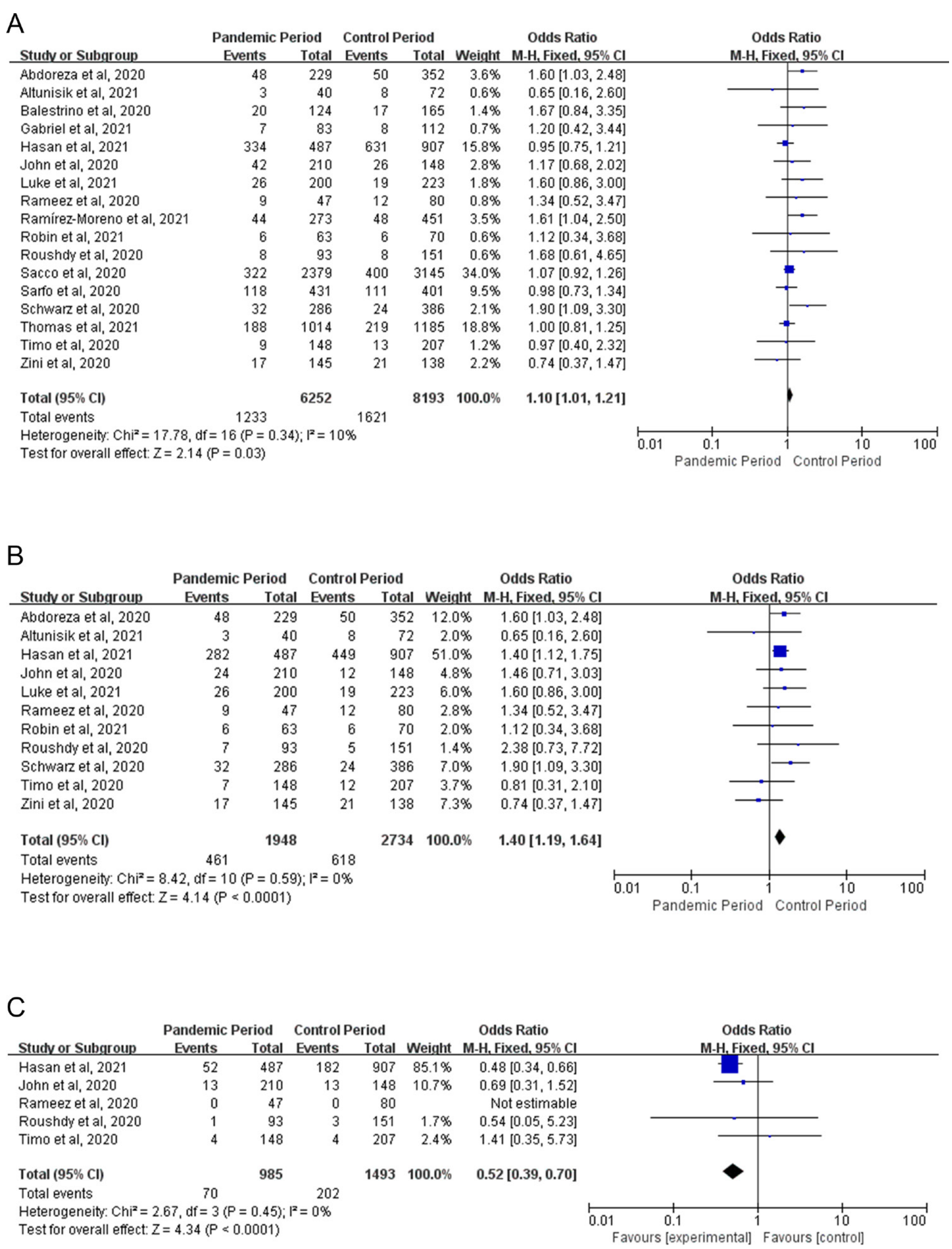

Figure 2 (A) Forest plot showing the HS admission during the pandemic compared with the control period. (B) Forest plot showing the ICH admission during the pandemic compared with the control period. (C) Forest plot showing the SAH admission during the pandemic compared with the control period. HS, haemorrhagic stroke; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage.

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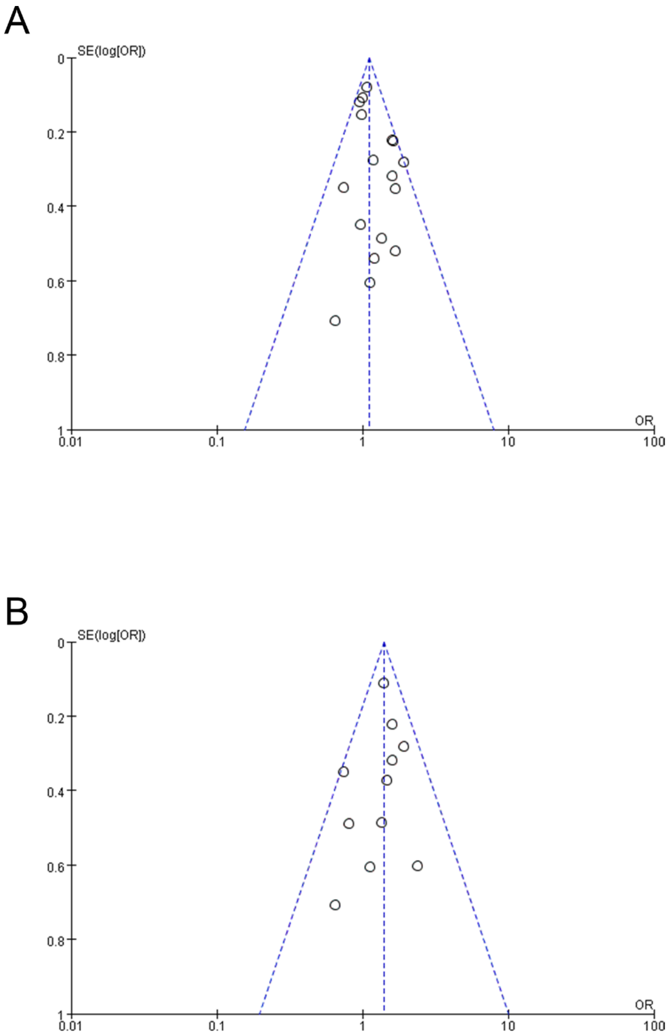

Figure 3 Funnel plot with the pooled estimate of the fixed-effects model. (A) The funnel plot of HS group. (B) The funnel plot of ICH group. HS, haemorrhagic stroke; ICH, intracerebral haemorrhage

RESULTS

Study selection

By using the key phrases mentioned above, the literature search yielded 7608 articles from the following databases: 2319 from PubMed, 2079 from EMBASE, 1068 from Web of Science, 463 from Elsevier, 1572 from Medline, 87 from Cochrane Library, 10 from Google Scholar and 10 from other sources. A total of 1775 articles were retained after removal of duplicates. A total of 1708 records were excluded after screening the titles and abstracts, leaving 67 eligible studies. After the full texts were assessed for eligibility, we excluded 50 articles for the following reasons: (1) molecular biology studies (n=5), (2) protocol (n=1), (3) retracted article (n=1), (4) without relevant data (n=43). Finally, 17 studies were eligible and included in our systematic review.[15–23] A PRISMA diagram detailing the study selection process is shown in figure 1.

Characteristics of included studies

The main characteristics of included studies, including author, the design of study, country or region, age, male to female ratio, pandemic period, control period and each disease admission are summarised in table 1.

A total sample of 14 445 subjects from 17 studies was included in the systematic review. The studies were conducted in many countries worldwide including Italy,[15 17 20] United Arab Emirates,[18] the USA,[16] Germany,[19 24 25] Ghana,[22] Turkey,[26] Switzerland,[27] Austria,[28] Iran,[29] Bangladesh,[30] Spain[31 32] and Egypt.[23] These studies included retrospective-observational studies and prospective and retrospective studies. All studies were reported on the number of ICH, SAH, HS and stroke admissions during the COVID-19 pandemic compared with the control period.

Risk of bias within studies

The Newcastle–Ottawa score results for each study were shown in table 2. All of these studies were assessed as having a low risk of bias.

Synthesis of results

Haemorrhagic stroke

The HS admission was reported in 17 articles.[15–20 22–28 30–32] In HS, the pandemic group has 1233 of 6252 cases and the control group has 1621 of 8193 cases. The proportion of HS admissions is higher at stroke admissions in the pandemic period than the proportion of HS admissions in the control period. The difference is significant (OR 1.10, 95% CI 1.01 to 1.21, I^2=10%, p=0.03) (figure 2A). Figure 3A shows a funnel plot for the visual inspection of publication bias. The plot shows there is no significant publication bias.

Subgroup analysis

To explore the reason for the increased proportion of HS admissions in the pandemic, we conducted a subgroup analysis based on disease categories. In ICH, the admission was reported in 11 articles.[16 18–20 23–27 29 30] It was present in 461 of 1948 cases in the pandemic group and 618 of 2734 cases in the control group, with statistically significant differences between two groups (OR 1.40, 95% CI 1.19 to 1.64, I^2=0%, p<0.0001) (figure 2B). The funnel plot shows there is no significant publication bias (figure 3B). In SAH, only five articles showed the SAH admission.[16 18 23] Seventy of 985 cases in the pandemic group and 202 of 1493 cases in the control group suffered from SAH. The difference is significant (OR 0.52, 95% CI 0.39 to 0.70, I^2=0%, p<0.0001) (figure 2C).

Sensitivity analysis

Sensitivity analysis shows that the study of Hasan *et al*[30] has a significant impact on the outcomes of SAH. As for the outcomes of HS and ICH, there is no individual study that has a significant impact on the outcomes.

DISCUSSION

In this review, the result shows that the number of stroke admissions is reduced in the COVID-19 pandemic. Although the HS admissions are less during the pandemic period than during the pre-pandemic period, the proportion of HS hospitalisations in stroke hospitalisations is significantly increased. Our results further indicate that the number of ICH admissions reduces from 618 in the pandemic group to 461 in the control group, with a corresponding rate raised. As for SAH, the number of SAH admissions and the proportion of SAH admissions are less during the pandemic period than during the control period, but sensitivity analysis indicates that exclusion of an article (Hasan *et al*) influences the pooled estimates.

The WSO survey indicated that the COVID-19 pandemic had a momentous impact on stroke care with delayed presentation and reduced hospital admissions. Our results further support the decreased trend in stroke admissions during the pandemic period by analysing 14445 cases from 17 studies. However, our results on overall strokes might not be comprehensive, because we only considered studies that reported data on HS separately. Although different search strategies are used to weaken the study selection bias, we think that the bias is an objective existence. At all events, the phenomenon of reduced stroke admissions is certain. We find three possible reasons to explain this phenomenon. First, patients who had a stroke and mild symptoms preferred to stay at home and rejected the emergency department for treatment in the pandemic period. Second, increased social isolation decreased the discovery rate of patients who had a stroke, because their friends or family members could not recognise who was suffering from a stroke. Third, under city lockdown, limited transportation made some patients hardly acquire ambulances and drivers, which delayed the treatment for stroke. So we appeal that local government should carry out focused education and intervention for high-risk groups, and provide a green channel for the treatment of strokes. On the other hand, people should strengthen their connection with relatives and friends by phone or online video.

Additionally, we document a numerically higher proportion of HS admissions in stroke admissions and notice that ICH has a significant increase in occurrence during the epidemic. In a previous review and meta-analysis of the risk factors for spontaneous ICH, we identified hypertension and alcohol intake as important risk factors.[33] We further found some studies reported that the pandemic led to an increase in alcohol consumption and alcohol abuse which may be attributed to the stress and isolation experienced with the current pandemic.[34–44] Therefore, we think that the significant increase of ICH is related to alcohol abuse and stress during the pandemic. But the authenticity needs further validation by special studies. In addition, the data variability is small, because patients with ICH kept seeking hospital care in emergency medical services in the pandemic as they had done in pre-pandemic (eg, the emergency was way heavily avoided that some patients with mild symptoms choose to keep away from hospitals). In summary, in this particular period, the quarantine and social isolation just like some degree of grouping exclude other potentially confounding risk factors. It makes us have gained a deeper appreciation of obvious risk factors for ICH. In view of the above-mentioned facts, we wish to make the following proposals: (1) people should pay more attention to modifiable risk factors such as alcohol intake and hypertension to reduce the risk of ICH in the COVID-19 pandemic period; (2) various health organisations and clinicians should develop recommendations for people on how to have a healthy lifestyle to cope with physical distancing and social isolation; (3) governments should explore effective prevention and intervention measures to prevent crises. As for SAH, we think it is hard to acquire any important conclusions due to too little data and a huge impact of a single article. It needs more authoritative studies to explore the impact of COVID-19 pandemic on SAH.

Limitations

Limitations to this study are the lack of information about stroke severity and prognoses, which might have to some extent underestimated the impact of the pandemic on stroke. Moreover, the total number of admissions in the pandemic is not reported, so the prevalence of stroke is inconclusive. Although our meta-analysis indicates higher morbidity of HS and ICH, the reliability needs to be verified by further researches because of the small sample size. Despite this, this study still has notable clinical and public health implications. For example, our data may encourage people to conduct further research to prove the potential pathogenesis of ICH. On the other hand, our results could attract more attention to the influence of COVID-19, thus people can perfect isolation approaches and prevention measures.

Conclusions

The study identifies moderate reductions in stroke admissions during the COVID-19 pandemic. Studies have shown that alcohol abuse and stress are important causes of increased ICH hospitalisations during the pandemic. All governments, healthcare institutions, clinicians and academics should aim at preventing potential crisis in the COVID-19 pandemic, exploring more effective policies for prevention and intervention.

Contributors YY conceived and designed the study and drafted the manuscript. YY and YN acquired the data and performed data extraction. YY interpreted the data and performed extensive research on the topic. YY performed the statistical analysis and made all tables and figures. FS, JZ and SH checked the data. PD funded the project. PD and XW supervised the project. YY is the guarantor. All authors contributed to the accomplishment of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data are available from the corresponding author (cematianya@foxmail.com) upon request.

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