COVID-19

The relationship between COVID-19's severity and ischemic stroke: a systematic review and meta-analysis

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Abstract

Objective We aim to determine the risk of acute ischemic stroke in patients with severe and non-severe coronavirus disease 2019 (COVID-19).

Methods A literature search was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases until October 28, 2020. Studies covering COVID-19's severity classification data and COVID-19 patients with acute ischemic stroke were included. Two independent evaluators extracted data, and the random effects model was used to calculate the risk ratios (RR) and 95% confidence interval (95% CI) of acute ischemic stroke associated with COVID-19's severity.

Results A total of 8 studies were included, involving 5266 patients. Among all COVID-19 patients, the total incidence of ischemic stroke was 1.76% (95% CI: 0.82–3.01). Severe patients have an increased risk of acute ischemic stroke compared with non-severe patients (RR = 3.53, 95% CI: 2.06–6.07, $P < 0.0001$; $I^2 = 12\%$). This association was also observed when COVID-19's severity was defined by clinical parameters (RR 2.91, 95% CI: 1.17–7.26, $P = 0.02$; $I^2 = 29\%$) and the need for intensive care (RR 4.47, 95% CI: 2.40–8.31, $P < 0.0001$; $I^2 = 0\%$).

Conclusions This meta-analysis shows that the severe course of COVID-19 is associated with an increased risk of acute ischemic stroke.

Keywords Meta-analysis · COVID-19 · Severity · Ischemic stroke

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with changes in blood coagulation, and it increases the risk of thromboembolism (including arterial and venous embolism). These complications may be mediated by systemic inflammatory injury of vascular endothelial cells, platelet activation, and stasis [1, 2]. Although the incidence of deep venous thrombosis and pulmonary embolism is high in many coronavirus disease 2019 (COVID-19) cohorts, it is not clear how acute ischemic stroke occurs in this disease [3, 4]. Recent reviews or meta-analysis about the neurological manifestations of COVID-19 suggest that a majority of COVID-19 patients with stroke show ischemic stroke, while a few patients show hemorrhagic stroke or cerebral venous thrombosis [5–7]. Almost all patients have potential risk

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factors for stroke, including diabetes, hyperlipidemia, hypertension, and previous history of cerebrovascular disease [5].

Recently, some articles about COVID-19 have expounded the relationship between acute ischemic stroke and COVID-19 [8, 9]. Siepmann et al. [10] recently conducted a multicenter study and meta-analysis of 741 patients with COVID-19. They found that the total stroke rate was 2.9% and that patients with severe COVID-19 had an increased risk of acute ischemic stroke compared with patients with non-severe COVID. However, this meta-analysis included only three studies, which is too few. Therefore, we conducted a systematic review and meta-analysis to explore the possible association between SARS-CoV-2 infection and acute ischemic stroke.

Methods

Literature search strategy

A literature search was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases until October 28, 2020. Studies covering COVID-19's severity classification data and COVID-19 patients with acute ischemic stroke were included. The search terms were as follows: "Coronavirus," "COVID 19," "2019-nCoV," "SARS-CoV-2," "stroke," "cerebrovascular," "transient ischemic attack," "cerebral infarction," "brain infarction," "cerebral ischemia."

Selection criteria

The studies were included according to the following criteria: (1) randomized or non-randomized observational study of at least five adult patients diagnosed with COVID-19 by molecular RT-PCR; (2) available data on the incidence of ischemic stroke in COVID-19 patients; and (3) classification of the severity of COVID-19 patients mentioned. We excluded all case series, case reports, letters, editorial, comments, conference abstracts, and studies including only cerebral hemorrhage and cerebral venous thrombosis.

Data extraction and quality assessment

Two reviewers independently accessed all retrieved articles according to screening titles, abstracts, and full texts. If there were differences between the two reviewers on the results of literature retrieval, the opinions of other co-authors would be consulted and resolved through consensus. We obtained data from each study including authors, publication year, study types, countries, sample size, age, sex, observational period, definition of COVID-19 severity, and acute ischemic stroke incidence in COVID-19 patients. The Newcastle-Ottawa scale (NOS) was used to assess the quality of the included studies [11]. The NOS

scores of 1 to 3, 4 to 6, and 7 to 9 were judged for low, moderate, and high quality of studies, respectively. Two investigators independently conducted the quality assessment, and the differences were resolved by consensus.

Statistical analysis

A comprehensive dichotomy of severity was used in our main analysis, which included all severity results reported in each study comprising severity based on clinical parameters [12–16] and the need for intensive care (ICU) and non-ICU. If the included studies divide the severity outcomes into two or more categories based on clinical parameters (e.g., mild, moderate, severe, critical), these are classified as non-severe (including mild and moderate) and severe (including severe and critical) categories. Therefore, in our main analysis, we divided all patients into severe or non-severe COVID-19 according to the classification used in each study included.

We performed this meta-analysis using R software. The variance-stabilizing double arcsine transformation was used in all proportion analyses. The random effects model was used to calculate the outcomes through pooled proportion meta-analysis. The Mantel-Haenszel formula is used to calculate the binary variable to calculate the risk ratio (RR) and report it with its 95% confidence interval (CI). $P<0.05$ indicated statistical significance. I^2 statistics were used to record and evaluate statistical heterogeneity (I^2 value of 0–40% indicated no or low heterogeneity, 30–60% indicated moderate heterogeneity, 50–90% indicated substantial heterogeneity, and 75–100% indicated considerable heterogeneity). Publication bias was evaluated using a funnel plot.

Results

Characteristics of included studies

The database search identified 2391 relevant studies: 890 from PubMed, 20 from the Cochrane library, 880 from Embase, and 601 from Web of Science. Among these studies, 1339 studies were excluded due to repetition, and 958 studies were excluded after preliminary screening of titles and abstracts. After reading the full text, 86 articles were excluded. Finally, 5266 patients from 8 studies were included in the final review and meta-analysis [9, 10, 12, 17–21]. The systematic screening and selection process are depicted in Fig. 1. The characteristics of the included studies are shown in Table 1. The included studies consisted of cohorts from China, Italy, Germany, the USA, Spain, and Pakistan and were designed for descriptive observations.

In these studies, the severity of COVID-19 was clinically defined according to the necessity of intensive care, the

Table 1 Study characteristics of included published studies

Study	Location	Study design	Severity outcomes	Study size (n)	Acute stroke, n (%)	Observational period
Li et al., 2020 [17]	Wuhan, China	Single center, retrospective	Severe vs. non-severe[a]	92 vs. 127	8 (8.7) vs. 2 (1.6)	16 January 2020–19 February 2020
Lodigiani et al., 2020 [21]	Milan, Italy	Single center, retrospective	ICU vs. non-ICU	61 vs. 327	3 (4.9) vs. 6 (1.8)	13 February 2020–10 April 2020
Siepmann et al., 2020 [10]	Saxony, Germany	Multicenter, retrospective	Severe vs. non-severe[b]	119 vs. 46	6 (5.0) vs. 1 (2.2)	1 March 2020–30 April 2020
Romero-Sánchez et al., 2020 [9]	Castilla-La Mancha, Spain	Multicenter, retrospective	Severe vs. non-severe[c]	329 vs. 512	4 (1.2) vs. 7 (1.4)	1 March 2020–1 April 2020
Merkler et al., 2020 [20, 22]	New York, USA	Multicenter, retrospective	ICU vs. non-ICU	474 vs. 1442	19 (4.0) vs. 12 (0.8)	4 March 2020–2 May 2020
Liotta et al., 2020 [12]	Chicago, USA	Multicenter, retrospective	Severe vs. non-severe[d]	134 vs. 375	5 (3.7) vs. 2 (0.5)	5 March 2020–6 April 2020
Piazza et al., 2020 [19]	Boston, USA	Multicenter, retrospective	ICU vs. non-ICU	170 vs. 944	1 (0.6) vs. 0	13 March 2020–03 April 2020
Makda et al., 2020 [18]	Karachi, Pakistan	Single center, retrospective	Severe vs. non-severe[e]	62 vs. 52	3 (4.8) vs. 0	April 2020–July 2020

USA the United States, ICU intensive care unit. Results are expressed as number (column %), mean ± SD, or median (interquartile range)

[a] According to the American Thoracic Society guidelines for community-acquired pneumonia

[b] According to National Health Commission of the People's Republic of China. Chinese Management Guideline for COVID-19 (version 7.0)

[c] According to the 2007 Infectious Diseases Society of America/American Thoracic Society criteria

[d] According to the need for mechanical ventilation during hospitalization

[e] According to the Pakistan's national guidelines for the management of COVID-19

American Thoracic Society guidelines for community-acquired pneumonia[13], the Chinese Management Guidance for COVID-19 Diagnosis and Treatment (7th version) [14], the 2007 Infectious Diseases Society of America/American Thoracic Society criteria [15], the need for mechanical ventilation during hospitalization [12], and the Pakistan's national guidelines for the management of COVID-19 [16].

Quantitative data synthesis

Among all COVID-19 patients, the total incidence of ischemic stroke was 1.76% (95% CI: 0.82–3.01). According to the severity of the disease, the total stroke rate of patients with severe COVID-19 was 3.37% (95% CI: 1.74–5.44), and that of patients with non-severe COVID-19 was 0.61% (95% CI: 0.08–1.45).

Severe patients had an increased risk of acute ischemic stroke than non-severe patients when using a compound dichotomy that included all severity results included in each study report (RR = 3.53, 95% CI: 2.06–6.07, $P < 0.0001$; I^2 = 12%; Fig. 2a). This association was also observed when COVID-19's severity was defined by clinical parameters (RR 2.91, 95% CI: 1.17–7.26, $P = 0.02$; $I^2 = 29\%$; Fig. 2b) and the need for intensive care (RR 4.47, 95% CI: 2.40–8.31, $P < 0.0001$; $I^2 = 0\%$; Fig. 2c).

Quality analysis of studies and assessment of publication bias

As shown in Table 2, the quality of the eight included studies according to the NOS was moderate to high with NOS scores ranging from 5 to 7. Through the visual observation of the funnel plot (Fig. 3), both the studies plotted near the average, and the studies more distant from the average showed symmetry, so the distribution does not imply publication bias.

Discussion

Through a systematic review and meta-analysis of 8 studies, 5266 COVID-19 patients with ischemic stroke were identified. The main findings of this study are as follows: (1) the total incidence of ischemic stroke was 1.76% in COVID-19 patients; and (2) the severe course of COVID-19's disease is associated with an increased risk of acute ischemic stroke.

For acute ischemic stroke, infection is an important risk factor, especially systemic upper respiratory disease [23, 24]. It is reported that patients with COVID-19 are about 7 times more likely to suffer from acute ischemic stroke during emergency department visits or hospitalization than patients with influenza [22]. Thus, SARS-CoV-2 may be a higher risk factor for acute ischemic stroke than other classic respiratory infections such as influenza [21].
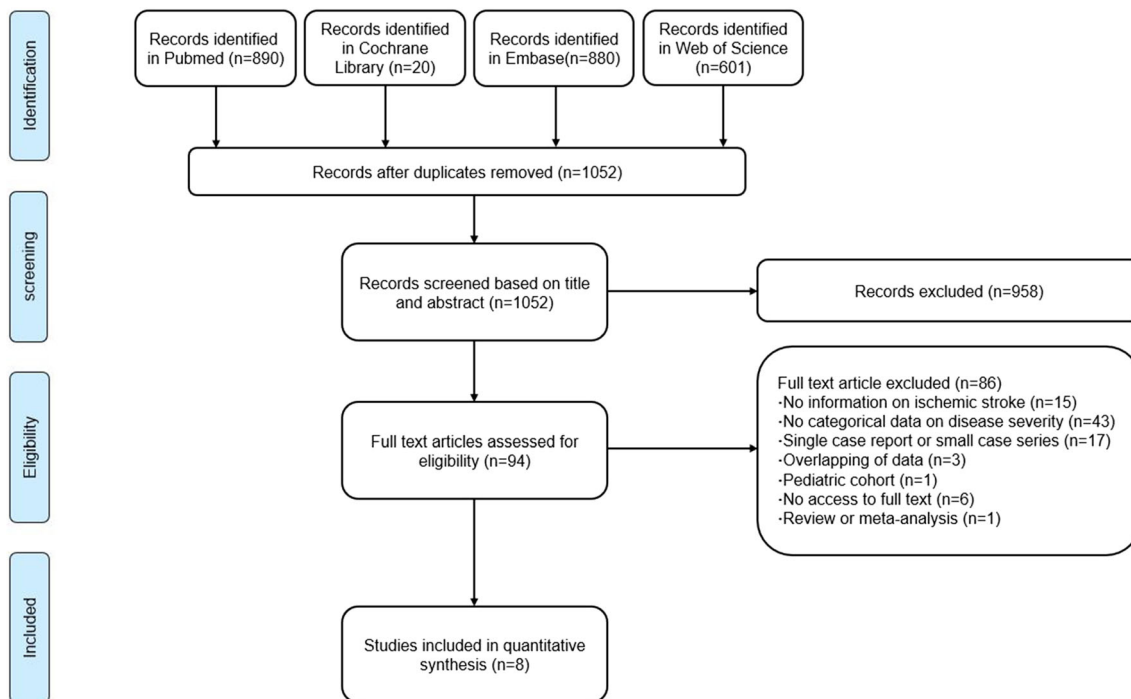
Fig. 1 Flow diagram of the publication search and selection process.

Fig. 2 Forest plots illustrating associations of ischemic stroke and COVID-19's severity among included studies: (**a**) composite severity outcome subsuming all definitions of severity as reported by included studies; (**b**) severity by grading of clinical parameters; (**c**) severity by whether patients required intensive care.
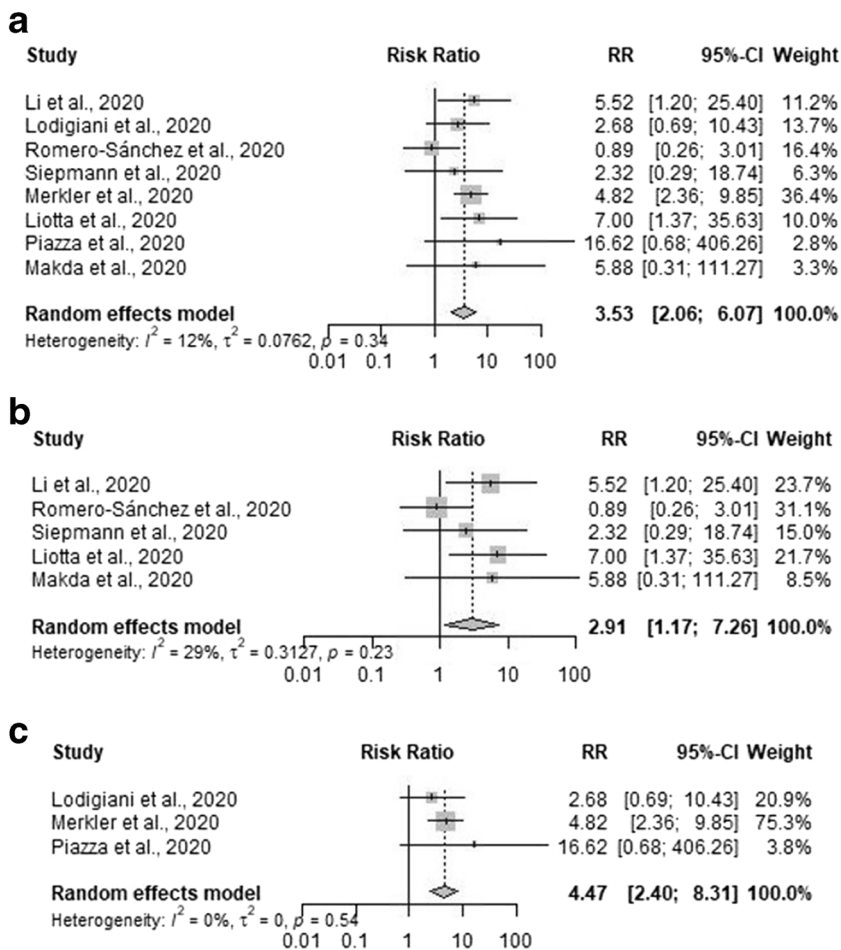
Table 2 Quality assessment of included studies

| Study	Selection	Comparability	Outcome	Overall
Li et al., 2020 [17]	4*	0	2*	6*
Lodigiani et al., 2020 [21]	3*	0	2*	5*
Siepmann et al., 2020 [10]	3*	0	2*	5*
Romero-Sánchez et al., 2020 [9]	4*	0	2*	6*
Merkler et al., 2020 [20, 22]	3*	0	2*	5*
Liotta et al., 2020 [12]	4*	0	2*	6*
Piazza et al., 2020 [19]	4*	0	2*	6*
Makda et al., 2020 [18]	3*	2*	2*	7*

*Number of stars awarded for each category

The exact mechanism by which COVID-19 increases the risk of acute stroke is not known. Previous studies have shown that the hypercoagulable state caused by COVID-19 is mediated by the increase of prethrombotic factors, immobilization-related stagnation and endothelial injury, or through direct viral invasion of endothelial cells by acute systemic inflammatory mediators such as interleukin-6 [25, 26]. COVID-19 has been reported to increase D-dimer levels and to produce antiphospholipid antibodies and other markers of hypercoagulability [27, 28]. In one of the first published cohort studies, compared with non-ICU patients, 41 patients admitted to a hospital in Wuhan with COVID-19 had elevated D-dimer levels in ICU patients [29]. Guan et al. analyzed the data of 1099 patients in 552 hospitals in China, of which 59.6% of the

severe patients had higher levels of D-dimer, while fewer (43.2%) of the non-severe patients had elevated levels of D-dimer [30]. It was previously reported that D-dimer > 1mg/mL was a risk factor for death and severe COVID-19 [31, 32]. Other reports show that C-reactive protein > 200 mg/L and D-dimer > 2.5 mg/mL are related to COVID-19's critical illness, which may be related to high inflammatory state and hypercoagulable state [33]. In addition, critically ill patients may be in a particularly dangerous state due to systemic inflammatory response syndrome accompanied by thrombosis (thrombotic inflammation), hypoxia, and hypotension.

It will be challenging to determine the true incidence of ischemic stroke in COVID-19 patients. Firstly, it is difficult to detect signs of ischemic stroke in severe COVID-19

Fig. 3 Assessment of publication bias. Visual inspection of funnel plot is not indicative of publication bias.
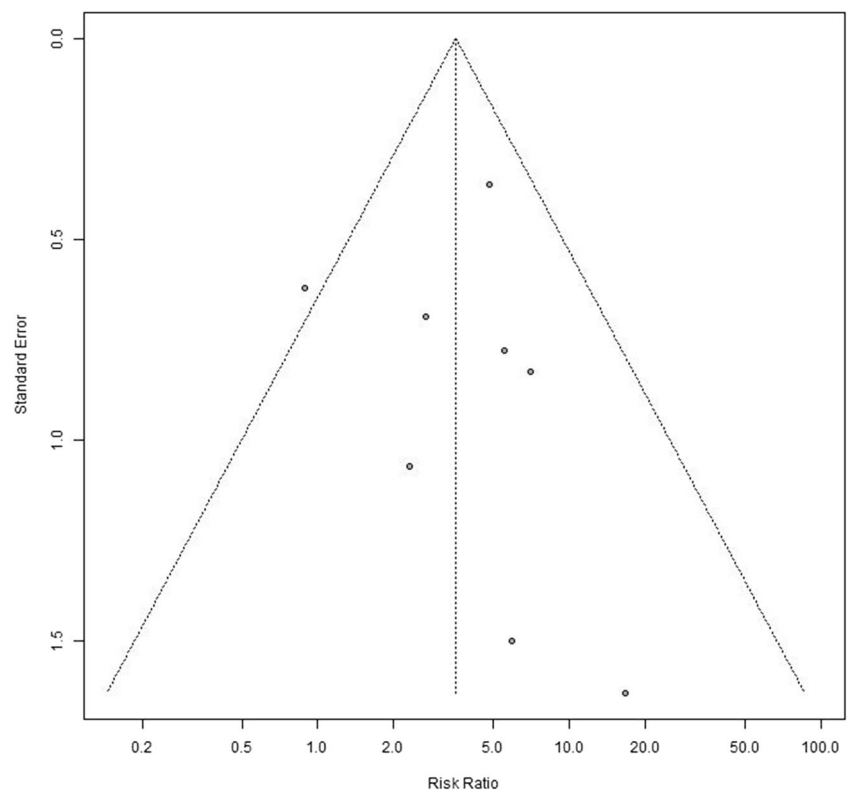
patients with frequent intubation and severe sedation. Decreased awareness is reported to be a risk factor for missing stroke in the emergency room [34]. Secondly, the role of different demographics and ethnicity of patients with COVID-19 in affecting the incidence of acute ischemic stroke remains uncertain. Thirdly, certain countries may also be limited by detection capacity, leading to underreporting of new coronary pneumonia cases, thereby overestimating the incidence of acute ischemic stroke [35]. Fourthly, reluctance to go to the hospital and social distancing policies can also lead to underreporting of mild strokes in mild or asymptomatic COVID-19 patients [36]. It is challenging to determine the true incidence of ischemic stroke in COVID-19 patients, so more research is needed to prove it.

There are still some important limitations in our research. First, our study is limited by the differences in the definition of COVID-19's severity in different studies. However, the result of the analysis using a composite dichotomized outcome is consistent with the results of the application of clinical parameters and the need for intensive care. Second, the sample size of the systematic review may still be limited because it covered a short period of time, and more research is needed.

Conclusion

The data we have collected from the published literature show that the severe course of COVID-19 is associated with an increased risk of acute ischemic stroke, which highlights the need for clinical neuromonitoring in COVID-19 patients. What is more, further research on its potential pathophysiology is also in demand.

Declarations

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