



# Ischemic stroke associated with COVID-19: a systematic review and meta-analysis

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## Abstract

**Background** Coronavirus disease 2019 (COVID-19), a contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across the world. Apart from respiratory complications, an increasing number of patients with ischemic stroke have been reporting.

**Objective** This systematic review and meta-analysis aims to explore the characteristics of ischemic stroke after SARS-CoV-2 infection, and provides valuable reference materials for subsequent clinical treatment.

**Materials and methods** PubMed, Web of Science, and Ovid-Embase databases were searched up to 24th March 2021. We utilized the search strategy of medical subject headings combined with entry terms to search all related literatures. All studies identified with the electronic and manual searches were listed by citation, title, authors, and abstract. Only studies involving patients with COVID-19-related stroke were eligible. The references of included studies were also manually screened.

**Results** The meta-analysis was conducted following the PRISMA and MOOSE reporting guidelines. Bias risk was assessed using the Newcastle–Ottawa Scale (NOS). Ten articles, including 26,691 participants and 280 patients with ischemic stroke and COVID-19, were selected. The pooled prevalence of ischemic stroke in COVID-19 was 2% (95% CI 1–2%;  $p < 0.01$ ). The pooled proportions of hypertension, hyperlipidemia and diabetes in COVID-19-related ischemic stroke was 66% (95% CI 51–81%;  $p < 0.01$ ), 48% (95% CI 19–76%;  $p < 0.01$ ) and 40% (95% CI 29–51%;  $p < 0.01$ ), respectively. Notably, the pooled proportions of female was 36% (95% CI 21–50%;  $p < 0.01$ ) in patients with COVID-19 and stroke. In addition, in TOAST classification, cryptogenic stroke subtype was associated with a high trend, and its pooled proportion was 35% (95% CI 12–59%;  $p < 0.01$ ).

**Conclusion** Ischemic stroke caused by COVID-19 has its own unique clinical features. Although common high-risk factors can also be observed, its importance may have changed. The major inflammatory storm of COVID-19 is more likely to occur in male patients. The increase in the proportion of cryptogenic stroke has also made stroke related to COVID-19 complicated.

**Keywords** Ischemic stroke · COVID-19 · SARS-CoV-2 · Clinical characteristics

## Introduction

The clinical manifestations of patients with new coronary pneumonia vary greatly from asymptomatic infection to severe pneumonia that may cause respiratory failure and death [1]. In an early study in Wuhan, China, 2.3% of 214 patients hospitalized with COVID-19 suffered an ischemic stroke [2]. Several other studies had also reported that they have found ischemic stroke in patients with COVID-19, which was comparable to the rate found in Wuhan, China in the early stages of the pandemic [3–5]. However, more recently, a large cohort study from New York reported ischemic stroke only in 0.9% of 3556 hospitalized patients

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with COVID-19 [6]. The incidence rates vary greatly among different research cohorts.

Although the cause of ischemic stroke associated with COVID-19 is unclear, previous studies have hypothesized that inflammatory cytokine storms may be a trigger for hypercoagulable state or endothelial damage [7]. At the same time, several studies have described the different mechanisms by which SARS-CoV-2 can cause neurological disorders and stroke. Many of these mechanisms focus on angiotensin-converting enzyme-2 (ACE-2), the binding site of SARS-CoV-2, and its function as a trigger for a series of events leading to vasoconstriction, hypertension, or thrombosis imbalance. Other studies have suggested that immune-mediated mechanisms and over expression of cytokines, hypercoagulable state and thromboembolism are potential causes of stroke [8–11]. It can be observed that the COVID-19 is closely related to ischemic stroke, because it has potential factors leading to stroke.

There is imperative to understand stroke demographic and clinical features since stroke remains an emergency. This article serves as a systematic review and meta-analysis of relevant literatures to summarize the characteristics of ischemic stroke associated with COVID-19 and discusses its value for clinical treatment.

## Methods

This systematic review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines statement [12, 13]. The PRISMA flow diagram of the selection process and the MOOSE checklist are provided in Fig. 1.

### Data source and strategy

We searched PubMed, Web of Science, and Ovid-Embase to identify relevant studies. We used search terms related to COVID-19 and stroke. Detailed search strategies are presented in supplemental document 1.

### Eligibility criteria and study selection

For the selection of the papers, the following inclusion criteria were defined: (1) articles focused on ischemic stroke associated with COVID-19, (2) articles with original data (e.g., cohort, retrospective, case–control studies), (3) diagnosis of all patients with COVID-19 was based on positive real-time polymerase chain reaction (PCR) assay for severe acute respiratory syndrome coronavirus 2, (4) diagnosis of all patients with stroke was based on imaging and clinical symptoms, (5) articles published in English, and (6) objects of research > 10 patients. We excluded studies

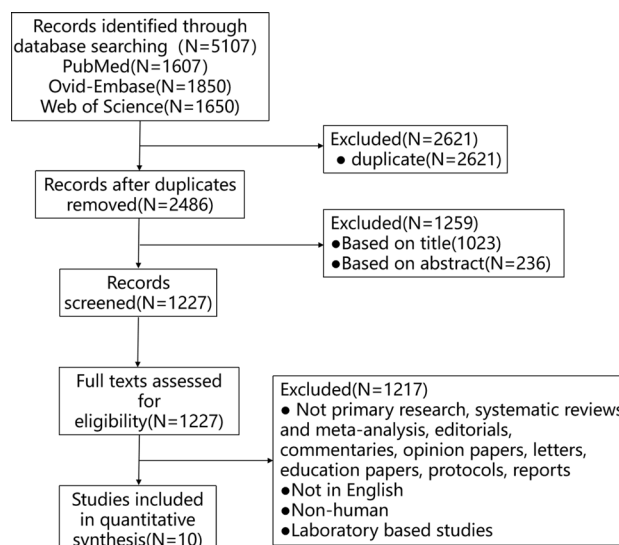


Fig. 1 Flow diagram

such as not primary research, systematic reviews and meta-analysis, editorials, commentaries, opinion papers, letters, education papers, protocols, reports, not in English, non-human and laboratory-based studies.

### Data extraction

Two independent reviewers (Wenzhang Luo and Xiang Liu) screened the titles and abstracts according to the selection criteria. Three independent reviewers (Wenzhang Luo, Xiang Liu, and Kunyang Bao) screened the full texts. Data were extracted independently by two reviewers (Wenzhang Luo and Kunyang Bao), and any disagreements were resolved through consensus. We performed data extraction using a predefined form including the following data: first author name, country, journal, sample size, number of ischemic stroke in the study, mean age and list of the outcomes of interest.

During the data extraction, the outcomes of interest were classified into five groups: gender, number of patients with hypertension, number of patients with hyperlipidemia, number of patients with diabetes and TOAST classification (Supplemental Document 2).

### Assessment of risk of bias

The bias risk assessment was carried out using the Newcastle–Ottawa Scale (NOS) by two authors (Wenzhang Luo and Kunyang Bao) [14]. Another author (Changren Huang) adjudicated in case consensus was not reached.

## Data analysis

The meta-analysis was performed with R×64 4.0.3 and RStudio using the ‘Matrix’, ‘Meta’ and ‘Metafor’ packages and led to pooled proportions with 95% confidence intervals (95% CIs).

The  $I^2$  was used to assess heterogeneity. Low, moderate and high levels of heterogeneity were defined by  $I^2$  values of 25%, 50%, and 75%, respectively. The data which had low heterogeneity chose the fixed-effects meta-analysis and others chose random-effects meta-analysis [15]. All analyses were done using 2-tailed tests with a  $p$  value <0.05 considered statistically significant.

## Results

### Study selection and characteristics

The searches in PubMed, Web of Science, and Ovid-Embase retrieved 5107 citations. Following removal of duplicates and screening of titles and abstracts, 1227 articles were selected for full-text evaluation. Ten articles were retained after full-text assessment. The included studies were from China, United States of America, United Arab Emirates, Switzerland, Canada, Brazil, Greece, Italy, Finland, Turkey, Lebanon, Iran, India, and New Zealand. The studies involved a total of 26,691 patients.

In one paper, it only included COVID-19 patients with stroke, and did not mention the overall number of COVID-19 infection [16]. In addition, in another paper, though it included 17,799 participants, 6200 patients without stroke

were received in details. Other centers provided summary data that could not be used for comparison [17].

The reported mean age ranged from 48.1 to 75.7 years, and 35.1% (52 of 148; 8 studies) of the patients were females (Table 1).

### Risk of bias of included study

The bias risk assessment showed that, among the included papers, nine respected the criteria for a fair-quality study, only one is poor quality (Supplemental Document 3).

### Synthesis of results

#### Gender

The forest plot of gender shows that the pooled proportions of female were 36% (95% CI 21–50%;  $p < 0.01$ ;  $I^2 = 77%$ ; random-effects model; Fig. 2). It suggests that stroke related to COVID-19 is more common in men. Especially in John et al. study, male accounted for 95% (18 of 19) [18].

#### Hypertension

We identified 280 hospitalized patients with ischemic stroke associated with COVID-19. 165 of those had hypertension. The reported prevalence of hypertension ranged from 37 to 95%, and the pooled prevalence was 66% (95% CI 51–81%;  $p < 0.01$ ;  $I^2 = 88%$ ; random-effects model; Fig. 3). Hypertension continues to be a risk factor for stroke. However, patients with COVID-19 and stroke were less likely to have hypertension when compared with historical stroke controls in Yaghi et al. study [6].

**Table 1** Characteristics of included studies

Reference, year	Countries	Journal	Sample size	Ischemic stroke, n (%)	Ischemic stroke	
					Mean age (SD)	Female, n (%)
Li et al. 27	China	Stroke Vasc Neurol	219	10 (4.6)	75.7 (10.8)	5 (50)
Rothstein et al. 3	USA	Stroke	844	20 (2.4)	64 (12)	8 (40)
Grewal et al. 2020	USA	Front Neurol	650	13 (2.0)	61.6 (NR)	7 (53.8)
John et al. 18	UAE	Clin Neurol Neurosurg	591	19 (3.2)	48.1 (10.8)	1 (5.3)
Chen et al. 21	China	Aging	2037	10 (0.5)	74.1 (12.8)	5 (50)
Mendes et al. 18	Switzerland	BMC Geriatr	265	9 (3.4)	NR	NR
Shahjouei et al. 17	USA, Canada, Brazil, Greece, Italy, Finland, Turkey, Lebanon, Iran, India, New Zealand	EBioMedicine	17,799	123 (0.7)	NR	NR
Yaghi et al. 6	USA	Stroke	3556	32 (0.9)	NR	9 (28.1)
Bach et al. 2020	USA	Stroke Vasc Neurol	683	20 (2.9)	63.1 (10.7)	6 (30)
Behzadnia et al. 16	Iran	Ro J Neurol	47*	24 (51.1)	73.1 (11.8)	11 (45.8)

USA United States of America, UAE United Arab Emirates, NR not reported

\*This study only included COVID-19 patients with stroke, and did not mention the overall number of COVID-19 infection

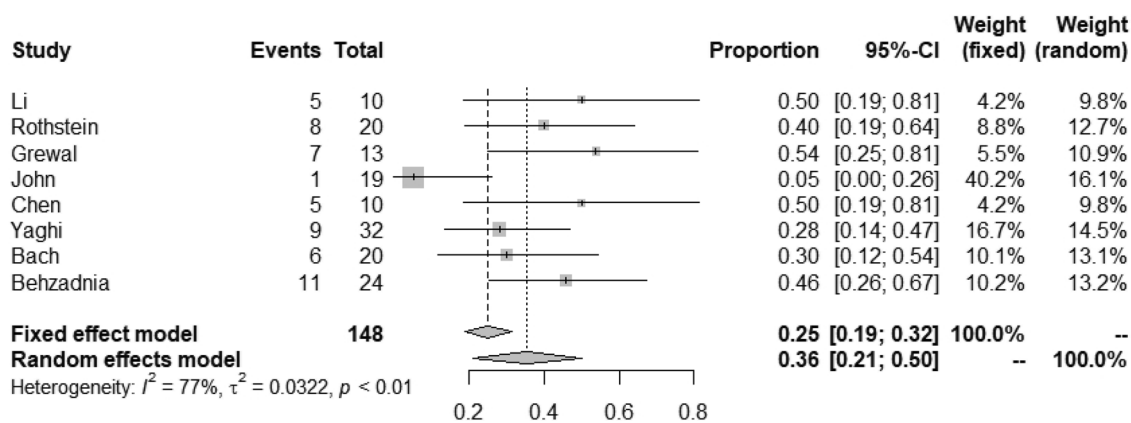


Fig. 2 Forest plot of gender proportion among hospitalized patients with ischemic stroke and COVID-19

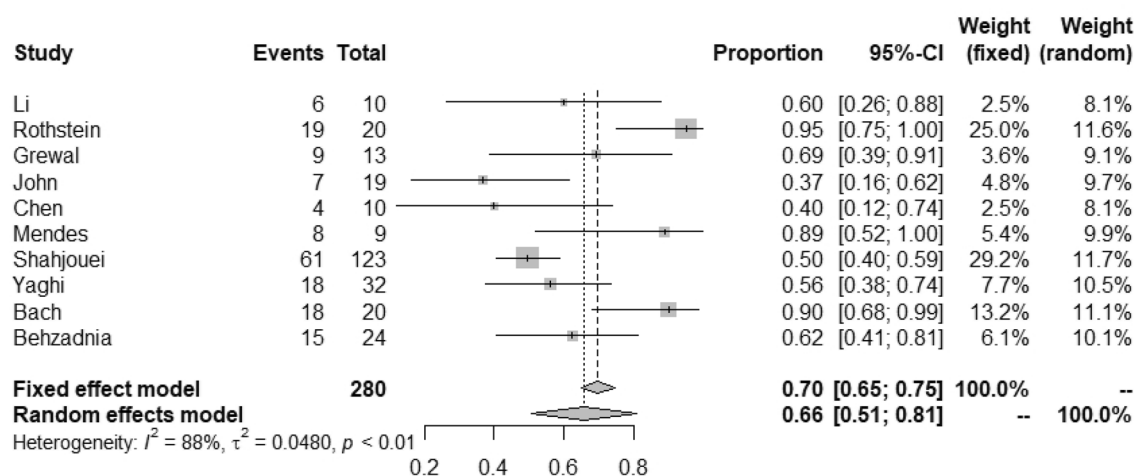


Fig. 3 Forest plot of hypertension prevalence among hospitalized patients with ischemic stroke and COVID-19

**Diabetes**

The reported prevalence of hypertension ranged from 20 to 65%, and the pooled prevalence was 40% (95% CI 29–51%;  $p < 0.01$ ;  $I^2 = 69\%$ ; random-effects model; Fig. 4). Patients with diabetes mellitus in COVID-19-related stroke still account for a considerable proportion.

**Hyperlipidemia**

The reported prevalence of hyperlipidemia ranged from 5 to 80%, and the pooled prevalence was 48% (95% CI 19–76%;  $p < 0.01$ ;  $I^2 = 93\%$ ; random-effects model; Fig. 5). In Mendes et al. study, there were no differences regarding other cerebrovascular risk factors, except for dyslipidemia, which was more frequent in stroke patients [19].

**TOAST classification for COVID-19-related stroke patients**

The TOAST classification denotes five subtypes of ischemic stroke: (1) large vessel disease, (2) small vessel disease, (3) cardioembolic, (4) cryptogenic, and (5) other defined mechanisms [20, 21]. The Table 2 shows the TOAST classification of our included studies. In our study, we found that the proportion of cryptogenic stroke was prominent. Its pooled prevalence was 35% (95% CI 12–59%;  $p < 0.01$ ;  $I^2 = 89\%$ ; random-effects model; Fig. 6). When compared with historical stroke controls, patients with COVID-19-related stroke were more likely to have a cryptogenic stroke subtype in Yaghi et al. study (66%; 95% CI 47–81%;  $p < 0.01$ ) [6]. However, the incidence of stroke due to small vessel disease was low. Its pooled prevalence was 2% (95% CI 0–5%;  $p = 0.44$ ;  $I^2 = 0\%$ ; random-effects model; Fig. 7).

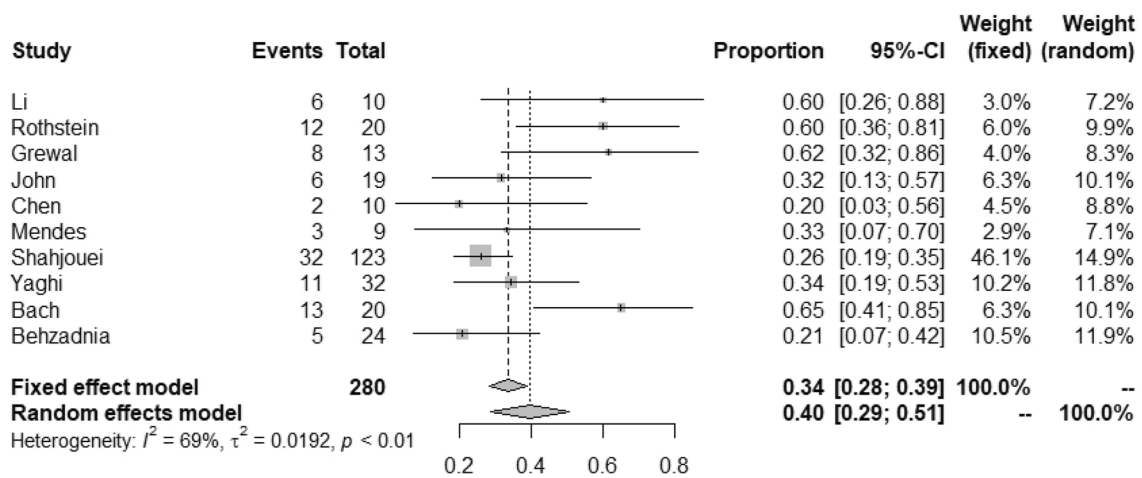


Fig. 4 Forest plot of diabetes prevalence among hospitalized patients with ischemic stroke and COVID-19

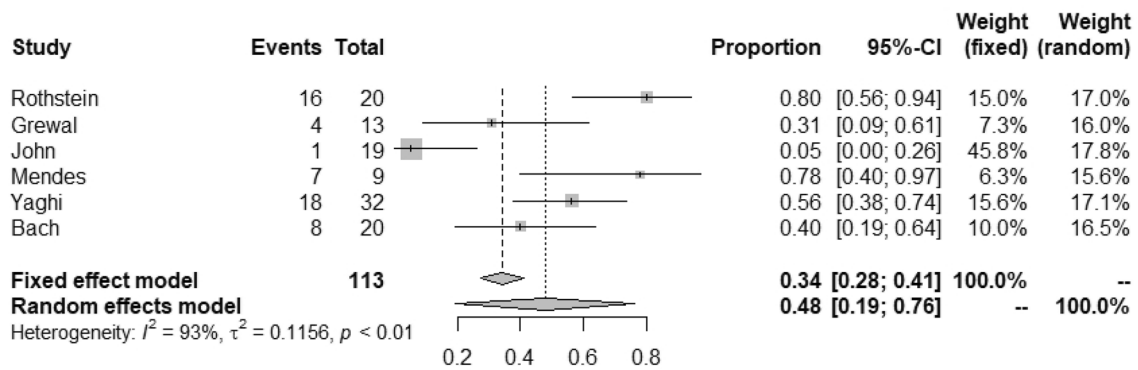


Fig. 5 Forest plot of hyperlipidemia prevalence among hospitalized patients with ischemic stroke and COVID-19

Table 2 TOAST classification of included studies

Study	Large vessel disease	Small vessel disease	Cardioembolic	Cryptogenic	Other defined mechanisms
Li et al. 27	5	2	3	0	0
Rothstein et al. 3	0	1	8	7	4
Grewal et al. 2020	2	1	3	7	0
John et al. 18	6	0	4	8	1
Chen et al. 21	NR	NR	NR	NR	NR
Mendes et al. 18	NR	NR	NR	NR	NR
Shahjouei et al. 17	NR	NR	NR	NR	NR
Yaghi et al. 6	2	0	7	21	2
Bach et al. 2020	5	1	2	2	1
Behzadnia et al. 16	NR	NR	NR	NR	NR

NR not reported

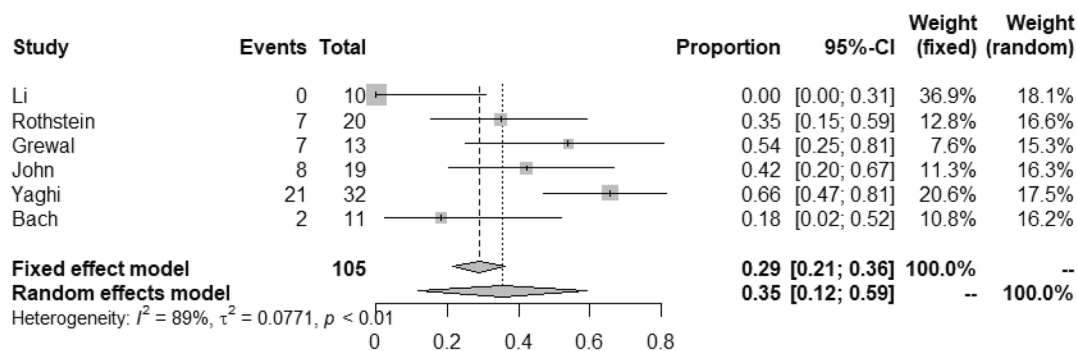


Fig. 6 Forest plot of cryptogenic stroke prevalence among hospitalized patients with ischemic stroke and COVID-19

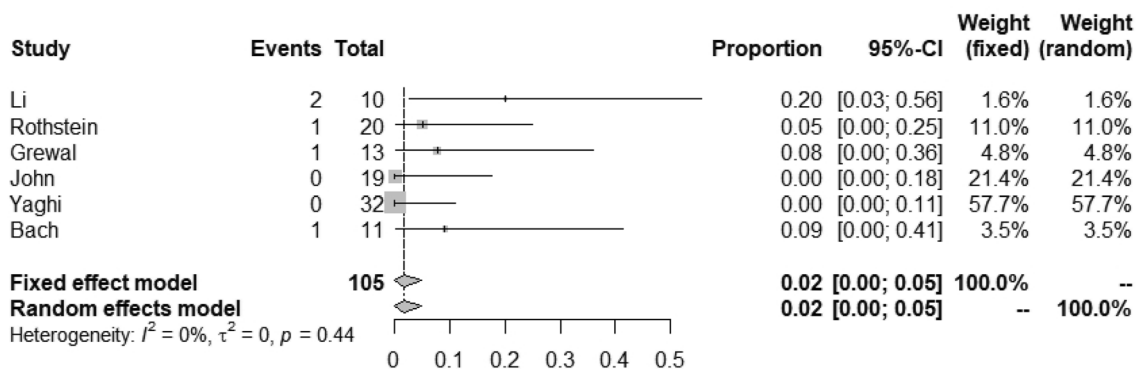


Fig. 7 Forest plot of small vessel disease stroke prevalence among hospitalized patients with ischemic stroke and COVID-19

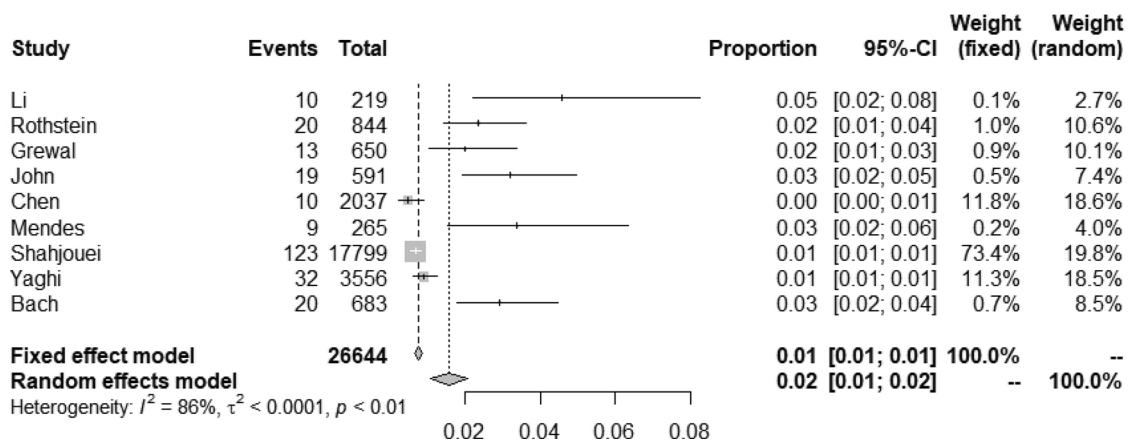


Fig. 8 Forest plot of the morbidity of stroke in COVID-19

**The morbidity of stroke in COVID-19 patient**

In our included studies, the morbidity of stroke in COVID-19 patient ranged from 0 to 5%. The pooled prevalence

of ischemic stroke in COVID-19 was 2% (95% CI 1–2%;  $p < 0.01$ ;  $I^2 = 86\%$ ; random-effects model; Fig. 8). Similarly, a recent systematic review polled 135 cases of ischemic

stroke in patients with COVID-19, showing a stroke incidence varying from 0.9 to 2.7% [22].

## Discussion

In this systematic review and meta-analysis, based on data from 10 relevant literature and 26,691 COVID-19 patients across all ages, we found that approximately 2% patients with COVID-19 infection could present with ischemic stroke. These data are similar to previous studies [2–5]. However, a study from a multinational cohort showed that hospitalized patients with SARS-CoV-2 infection indicated an overall stroke risk of 0.5% (pooled risk: 0.9%) [17]. Coincidentally, a large cohort study from New York reported ischemic stroke only in 0.9% of 3556 hospitalized patients with COVID-19 [6]. The incidence rate varies greatly between different research cohorts. Reasons for the difference are unknown, possibly be related to COVID-19 infection severity of hospitalized patients, prevalence of vascular risk factors in the population, ability to accurately diagnose all strokes in a situation of medical services being overwhelmed, and methodological differences. For instance, the ischemic stroke cohort in Mendes et al. study was all old patients whereas in John et al. study the ischemic stroke cohort mean age was 48.1 years.

Previous studies have shown that recent bacterial and/or viral infections may be triggers of acute ischemic stroke and may be related to the prothrombotic effects of inflammatory reactions [23]. SARS-CoV-2 has a spike protein surface unit that highly binds to human ACE-2 receptor. It may cause endothelial cell apoptosis and neuronal damage [24]. Viral infection may promote endothelial cell dysfunction, leading to excessive thrombin production and fibrinolysis inhibition [25]. At present, numerous studies have reported the potential development of the hypercoagulable state of COVID-19: triggering a strong inflammatory response, leading to hypercoagulable state and thromboembolism [26–30]. In addition, hypoxemia is related to the increase in blood viscosity and the activation of hypoxia-related genes. Hypoxia-related genes mediate coagulation and fibrinolysis, which is conducive to the occurrence of thrombotic events [31]. The COVID-19 often causes hypoxemia, especially severe pneumonia, which promotes the occurrence of embolic events. Acute inflammation caused by COVID-19 is prone to hypercoagulable state, which is due to the early molecular events caused by abnormal coagulation due to the increased concentration of pro-inflammatory cytokines and serum inflammatory factors (such as interleukin and C-reactive protein) [32–34]. Depending on the blood laboratory test indicators, patients with COVID-19 and cerebrovascular disease have severe inflammation and infection, and are in a hypercoagulable state. Significantly enhanced inflammation may be one

of the reasons for the abnormal coagulation function in the initial stage, and it may also be one of the reasons for the onset of cerebrovascular disease [27]. In short, the mechanism of stroke caused by COVID-19 is currently unclear. At present, most opinions are still focused on the hypercoagulable state brought about by inflammation [7, 26, 27, 30, 32–36]. Severe Acute Respiratory Syndrome Coronavirus 2 directly infects endothelial cells, causing diffuse endothelial inflammation [7, 24, 25, 30, 37, 38]. This may be the mechanism leading to ischemic stroke or cerebral hemorrhage. Other mechanisms linked to new coronary pneumonia in ischemic stroke include infection-induced hypercoagulable state, viral cardiomyopathy, and diffuse hyperinflammatory state. Therefore, in clinical practice, active control of inflammatory reactions and anticoagulation may be a powerful measure to preventing stroke caused by COVID-19. Nonetheless, this relies on further powerful randomized controlled trials to verify.

It is also worth noting that the vast majority of ischemic stroke patients associated with COVID-19 in our study had common vascular risk factors such as hypertension, hyperlipidemia, and diabetes [39–45]. A study from Lebanon showed that a total of 284 cases were included with a mean age of 72 years, and 58% male gender [46]. The most commonly identified risk factors were hypertension, dyslipidemia, and diabetes mellitus [42, 47–50]. We found that hypertension pooled prevalence was 66% (95% CI 51–81%;  $p < 0.01$ ), in keeping with other modern stroke cohorts [51]. In our study, hyperlipidemia occupies a prominent position. In Pawelczyk M et al. study, they reported that hyperlipidemia could promote the activation of platelets [52]. Active control of these high-risk factors, especially hyperlipidemia, is of positive significance for reducing ischemic stroke caused by COVID-19.

As we all know, gender is a significant factor in ischemic stroke [53–55]. Women differ from men in the distribution of risk factors and stroke subtype, stroke severity, and outcome. In the study of Arboix et al. [56], 2318 women and 2274 men with first-ever stroke were included. Vascular risk factors such as high blood pressure, atrial fibrillation, heart failure, valvular heart disease, and obesity are more common in women. Men are more likely to suffer from lacunar infarction (21.5% vs. 16.2%,  $p = 0.0003$ ), while women are more likely to suffer from cardiogenic stroke (26% vs. 15.6%,  $p = 0.0001$ ). It should be noted that cardioembolic infarctions are the most severe ischemic stroke subtype, with a high early mortality rate and degree of disability. Early outcome is worse in women with a higher in-hospital mortality, longer hospital stay and more disabled. However, in our research, we found that ischemic stroke caused by COVID-19 is more likely to occur in men. The reason may be related to the gender imbalance in the detection of COVID-19 cases and fatality rates [57–59]. In addition, male patients may

have more severe new coronary pneumonia and may lead to more severe inflammation [60]. Other form of strokes associated with other viral diseases was also learned in the research field. For examples, in the study of Helmuth, they found that men accounted for 67% in post-varicella arterial ischemic stroke [61]. This was consistent with our research that viral infection-related strokes are more likely to occur in men.

In our review, we also found that the proportion of cryptogenic stroke has increased. This may be linked to the unknown mechanism of ischemic stroke caused by COVID-19. In addition, the frequency of acute strokes due to small vessel disease was much lower than the approximately 20% mentioned in most stroke databanks [62]. The cause of this phenomenon, however, was not clearly known. Perhaps it was related to the small amount of sample data we included in the study. Cerebral small vessel disease would be a crucial role in the field of stroke, especially lacunar stroke.

### Limitation

Our study also has some limitations, most importantly, our research is limited by the fact that the selected literatures are all retrospective observational studies, and the different sample sizes of each study lead to inherent selection bias. Another limitation is that the variables we discussed are limited, such as some laboratory indicators, imaging characteristics, related treatment methods and prognosis are not included in the analysis of our article.

### Conclusions

Ischemic stroke caused by COVID-19 has its own unique clinical features. Although common high-risk factors can also be observed, its importance may have changed. The major inflammatory storm of COVID-19 is more likely to occur in male patients. The increase in the proportion of cryptogenic stroke also made stroke related to COVID-19 complicated. Therefore, the risk of ischemic stroke must be taken into consideration when the patient was admitted with COVID-19. Patients may benefit from the early initiation of anti-inflammatory and anticoagulant therapy. However, further clinical trials are needed to be done for verified evidences.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00415-021-10837-7>.

**Author contributions** WL made substantial contributions to conception and design of the study, analysis and interpretation of data, and to the drafting of the manuscript. XL made substantial contributions to the analysis and interpretation of the data and to the drafting of the manuscript. KB made substantial contributions to the conception and

design of the study, analysis and interpretation of the data, and to the drafting of the manuscript. CH made substantial contributions to the conception and design of the study, and to drafting and revising the manuscript. All the authors have given final approval of the version of the manuscript to be published.

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**Availability of data and materials** Most of analyzed data were included in this manuscript and supplemental materials. The relevant data can also be obtained with the request from any qualified investigator for purposes of replicating procedures and results.

**Code availability** Not applicable.

### Declarations

**Conflicts of interest** On behalf of all the authors, the corresponding author states that there is no conflict of interest.

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

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