Archives of Academic Emergency Medicine. 2024; 12(1): e65

OPEN ACCESS

REVIEW ARTICLE

Stroke and COVID-19: An Umbrella Review

Kavous Shahsavarinia[1], Nasim Hajipoor Kashgsaray[2], Morteza Ghojazadeh[1], Zahra Falaki[3], Maryam Soleimanpour[4], Hassan Soleimanpour[2]*

1. Research Center for Evidence-based Medicine, Iranian EBM Centre: AJBI Centre of Excellence, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
2. Emergency and trauma care research center, Tabriz University of Medical Sciences, Tabriz, Iran
3. Student Research Committee, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
4. Clinical Research Development Unit of Tabriz Valiasr hospital, Tabriz University of Medical Sciences, Tabriz, Iran

Received: June 2024; Accepted: July 2024; Published online: 25 August 2024

Abstract: **Introduction:** Acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) are among the acute cerebrovascular diseases (CVDs) that have been reported as a result of COVID-19. It will be a significant step forward if our research helps improve the compilation and analysis of existing data from other studies. **Methods:** The study is registered on PROSPERO with an ID of CRD42023464058. It encompasses articles published until December 2023 and involves searching databases such as PubMed, Scopus, Web of Knowledge, Embase, and Cochrane. Additionally, we conducted manual searches in respected publications within this discipline, utilized the Google Scholar search engine, and conducted reference checks, citation checks, and study of gray literature. The publications' reporting quality was assessed using the "Assessment of Multiple Systematic Reviews" (AMSTAR) checklist. The meta-analysis was conducted using Stata software (StataCorp, version 16). **Results:** We analyzed the findings of 23 meta-analyses, which included 795 articles and encompassed 5,937 patients who had previously experienced a stroke. The average age of these patients was 62.3 years, and 68.3% were male. The findings indicated that the collective incidence of stroke among individuals with COVID-19 is roughly 1.75% [95% confidence interval (CI): 0.4%-3.03], with 1.59% for ischemic strokes and 0.3% for hemorrhagic strokes. 32.3% (95% CI: 27.8%-36.9%) of COVID-19 patients with stroke passed away, approximately 27% were discharged from the hospital with very mild or no complications, and around 28.1% (95% CI: 14.1%-42.1%) were referred for rehabilitation. **Conclusions:** The overall rate of stroke in COVID-19 patients was approximately 1.75%, with a higher incidence in males and those with an average age of 62.3 years. Almost 80% of the strokes were ischemic, and the mortality rate was approximately 32%. Finally, 27% of the patients were discharged without complications, and 28% required rehabilitation.

Keywords: COVID-19; Ischemic stroke; Hemorrhagic stroke; Systematic review; Meta-analysis

Cite this article as: Shahsavarinia K, Hajipoor Kashgsaray N, Ghojazadeh M, et al. Stroke and COVID-19: An Umbrella Review. Arch Acad Emerg Med. 2024; 12(1): e65. https://doi.org/10.22037/aaem.v12i1.2385.

1. Introduction

The widespread COVID-19 disease, which ranges from mild symptoms resembling a common cold to a severe respiratory illness similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), quickly escalated to a global emergency (1-4).

Even before the COVID-19 pandemic, researchers recognized respiratory infections as short-term risk factors for ischemic stroke (5, 6).

Early reports from China reveal neurological symptoms in nearly 36% of hospitalized COVID-19 patients. Poor outcomes with COVID-19 infection are associated with vascular risk factors such as hypertension, coronary artery disease, and diabetes (7). Various have been proposed for ischemic stroke during COVID-19 infection. Main proposed mechanisms include cytokine storm induction and activation of the innate immune system, embolic events precipitated by pre-existing or new-onset arrhythmias, ischemia induced by secondary hypoxia to severe respiratory illness, thrombotic microangiopathy, epitheliopathy, or endothelialitis, and activation of the multifactorial coagulation cascade (8). One unifying factor that seems to exist among published articles is the increase in D-dimer levels in COVID-19 patients experiencing acute ischemic stroke, indicating activation of the coagulation and innate immune system. Other considerations include a cytokine storm leading to increased levels of IL-6 and C-reactive protein, associated with an increased risk of stroke and myocardial infarction in healthy individuals (9-11). The ACE-2 receptor's expression and binding to the virus may represent a dual mechanism by which COVID-

***Corresponding Author:** Hassan Soleimanpour, Emergency and trauma care research center, Tabriz University of Medical Sciences, Tabriz, Iran. Email: h.soleimanpour@gmail.com or soleimanpourh@tbzmed.ac.ir, Tel:+989141164134, ORCID: https://orcid.org/0000-0002-1311-4096.

19 increases the risk of stroke. First, direct infection of the brain endothelium expressing the ACE-2 receptor can create a risk of viral-induced vasculitis. Finally, hypoxia resulting from a severe respiratory infection with COVID-19 can also contribute to increased stroke risk by decreasing oxygen delivery (12). Several studies have investigated the association between stroke and COVID-19, with reports of a significant incidence of acute cerebrovascular disease (CVD), including acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH), attributable to COVID-19. Previous investigations have demonstrated an association between a history of CVD and the increased severity and mortality of COVID-19. Other studies have examined the spectrum of neurological manifestations in COVID-19 (13).

Given the existence of systematic reviews on the relationship between stroke and COVID-19, conducting an umbrella review study is essential. This type of study can aid in aggregating and analyzing the existing information from previous studies more accurately and comprehensively, highlighting common patterns and differences among various findings. By meticulously analyzing these data, researchers can arrive at more general and conclusive results regarding the relationship between stroke and COVID-19, thereby improving the treatment, prevention, and management of both diseases. Such studies can expand our knowledge of the neurological consequences of COVID-19 and its effects on the nervous system, as well as enhance diagnostic and therapeutic methods for stroke patients during emergencies such as epidemics and pandemics.

2. Methods

2.1. Study design and setting

This study is an umbrella review designed and conducted in 2023 to determine the relationship between COVID-19 and stroke. The study utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14) and the Joanna Briggs Institute (JBI) methodology for umbrella reviews (15). Furthermore, the protocol for this study has been registered in the PROSPERO registry with the code CRD42023464058.

2.2. Search strategy

An experienced librarian, under the guidance of a field expert, developed and implemented the search strategy in the present study (Appendix 1). We gathered the data using keyword searches and MeSH terms in PubMed, Scopus, Cochrane, Embase, and Web of Science databases. We searched for articles published up until December 2023. After excluding irrelevant articles and selecting primary papers, a further check was conducted to ensure the identification and review of existing literature through a reference check, a citation check, and an exploration of gray literature.

2.3. Inclusion and exclusion criteria

Inclusion criteria:

• This study included all systematic reviews and reports published in English worldwide that examined laboratory and diagnostic findings and stroke outcomes in COVID-19 patients using meta-analysis.

Exclusion criteria:

• Narrative reviews, and scoping reviews

• Studies that specifically addressed the effects of interventions and medications

• Studies and reports lacking complete text or inaccessible full-text articles

• Articles targeting only deceased patients as their study population

• Meta-analyses lacking appropriate reporting methods

2.4. Assessment of quality of articles

Two assessors independently used the A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) tool (16) to assess the reporting quality of all articles during the full-text screening stage. According to the standards outlined by AMSTAR-2, research studies were classified into one of four levels of methodological quality: high, moderate, low, or critically low. A study was considered to be of high quality if it had no flaws or only a minor issue. Conversely, studies with multiple minor issues were categorized as moderate quality.

Consideration of an issue as minor or major was determined using the criteria provided by the AMSTAR-2 tool. The final assessment score for each article was determined through agreement between the two assessors. A third assessor resolved any discrepancies between the two assessors.

2.5. Data extraction

A data extraction form was manually designed in Microsoft Word 2013 to extract the data. Initially, the research team extracted data from five articles as a trial for filling out the forms and addressed any deficiencies or issues. If the articles did not contain the necessary information, the research team computed it based on the article specifications and included it in the meta-analysis. In certain cases, the researchers contacted the corresponding authors of the articles through email. In certain studies, the number of articles entered into the systematic review differed from those entered into the meta-analysis, with the latter being the researchers' focus.

2.6. Data analysis

The random-effects model was used to estimate the outcomes of stroke in COVID-19 patients. We used Stata software (Stata Corp., version 16) for the meta-analysis [StataCorp L: Stata statistical software: release 15. 2017]. The I^2 index and Galbraith plot were employed to assess the heterogeneity of the study results. In this study, I^2 values less than 50% were considered low heterogeneity, I^2 values between 50 and 74% were considered moderate heterogeneity,

and values above 75% were considered high heterogeneity (17). We conducted a regression analysis based on the mean age (years), the percentage of males, and the last date of source search (month). Additionally, subgroup analyses were performed based on the previous date of the article search (month).

Funnel plot diagrams and Egger's regression test were used at a significance level of 0.1% to assess publication bias (18).

Assessing the percentage of the overlap of primary studies was done using corrected covered area (CCA), and covered area (CA) published by Pieper et al. (2014) (19). In this study, overlap was defined as primary articles that were repeated in more than one meta-analysis.

Covered Area (CA) = N/rc

Corrected Covered Area (CCA) = N-r/rc-r

N: The sum of primary published studies and repeated studies are counted to calculate N

r: Number of rows

c: Number of columns

3. Results

3.1. General characteristics of the studies

Among the 23 studies included in the present umbrella review (20-42), in terms of publication years, eight were published in 2020, ten in 2021, four in 2022, and two in 2023. The studies examining stroke history reported a total of 5,937 individuals. We estimated the average age of the patients to be 62.3 years. The majority of participants in the studies were male, comprising 68.3%. The affiliation (country) of the first authors of the articles was China in five, the United States in four, and Singapore in three. Italy, India, Saudi Arabia, and the United Kingdom each had two articles. Iran, Australia, Indonesia, Bangladesh, Georgia, France, Germany, Greece, Hungary, Mexico, Sri Lanka, and Malaysia each had one article. The 24 reviewed articles included 795 articles, with an average of 33.1 articles per systematic review and meta-analysis (Figure 1, table 1). In most studies, the authors used the PRISMA guideline for study design and reporting. The overlap results show a slight percent of overlap (CA: 3.84% and CCA: 2.14%).

3.2. Quality Assessment

The AMSTAR-2 criteria were used to assess the quality of these meta-analyses. Out of the meta-analyses reviewed, five were deemed to be of high quality, seven received a moderate quality rating, seven were rated as low quality, indicating potential methodological limitations, and four were classified as having critically low quality, suggesting significant concerns about their methods and the trustworthiness of their results (Table 2).

3.3. Classification of strokes

Figure 2 shows the average rates. As depicted in the figure, ischemic stroke had the highest average rate, close to 80%. Hemorrhagic stroke was next, with approximately 16.5%. Also, according to the TOAST criteria, the results indicated that the most common type of stroke is cryptogenic stroke, with an average rate of 37% (Figure 3).

3.4. Incidence of stroke

The results indicated that the overall incidence of stroke among COVID-19 patients is approximately 1.75% [95% confidence interval (CI): 0.4%–3.03], with ischemic strokes accounting for 1.59% and hemorrhagic strokes for approximately 0.3%. Additionally, studies that did not specify the type of stroke estimated the incidence at 1.83% (Figure 4, forest plot). Heterogeneity assessment results showed very low heterogeneity among the study results (I^2 = 0.03%, p >0.99) (Figure 5, Galbraith plot). Furthermore, the probability of publication bias was very low (z = -0.27, Prob > |z | = 0.7849; Figure 6).

3.5. Outcomes

3.5.1 Mortality

The meta-analysis results from 15 studies with a sample size of 8,731 showed that approximately 32% of COVID-19 patients with stroke lost their lives (32.3% [95% CI: 27.8-36.9]) (Figure 7, Forest plot). Heterogeneity was very low among the study results (I^2 = 0, P = 0.92) (Figure 8, Galbraith plot). Additionally, the probability of publication bias was very low (z = 1.60, Prob > |z| = 0.1086; Figure 9).

3.5.2 Mild complications/discharge to home

The meta-analysis results from five studies with a sample size of 5,685 indicated that approximately 27% of COVID-19 patients with stroke experienced very mild or asymptomatic complications and were discharged from the hospital (27.3% [95% CI: 21-33.6]) (Figure 10, Forest plot). Heterogeneity was very low among the study results (I^2 = 2.4%, P = 0.61) (Figure 11, Galbraith plot). Additionally, the probability of publication bias was very low (z = -0.03, Prob > |z| = 0.9780; Figure 12).

3.5.3 Referral to rehabilitation

The meta-analysis results from three studies with a sample size of 1,036 showed that approximately 28% of COVID-19 patients with stroke were referred to rehabilitation (28.1% [95% CI: 14.1%-42.1%]) (Figure 13, Forest plot). Heterogeneity was very low among the study results (I^2 = 0%, P = 0.54) (Figure 14, Galbraith plot). Additionally, the probability of publication bias was very low (z = -0.08, Prob > |z| = 0.9369; Figure 15).

4. Discussion

In this umbrella review, we investigated the relationship between COVID-19 and the characteristics and outcomes of stroke. A total of 24 systematic reviews and meta-analyses, which included 795 articles, were studied. Several studies indicated that the occurrence of stroke in COVID-19 patients is approximately 1.75% (which is equivalent to 1.59% for ischemic strokes and almost 0.3% for hemorrhagic strokes).

Additionally, in other studies where the type of stroke was not specified, the occurrence of stroke was estimated to be 1.83%. Stefania Nannoni et al. (30) found that the occurrence of stroke in COVID-19 patients is 1.4%, with ischemic stroke being the most common subtype of stroke. Ischemic strokes often involve multiple brain infarctions and have a cryptogenic cause. In comparison to strokes not associated with COVID-19, individuals affected by ischemic stroke tend to be younger and experience more severe strokes, primarily due to large artery occlusion.

Previous studies have indicated that the risk of stroke occurrence in COVID-19 patients is more than twice as high compared to healthy individuals of the same age, gender, and ethnicity. Perry RJ observed that ischemic stroke is more frequent and severe in Asian COVID-19 patients (with an average National Institute of Health Stroke Score (NIHSS) of 8 compared to 5) and is associated with higher mortality rates. Additionally, D-dimer levels are higher in this group of individuals. However, recurrence of stroke during the hospitalization of COVID-19 and non-COVID-19 patients is rare (43). Isabel Siow et al. found that the occurrence of stroke in COVID-19 patients is relatively low, but it increases in some instances. However, COVID-19 patients who experienced stroke and were hospitalized in the intensive care unit (ICU) for a prolonged period had a high mortality rate (33).

In another study, although the incidence of stroke among COVID-19 patients was low (1.1%), it was found that strokes occur in severe cases of COVID-19 and are associated with poorer prognosis. Severe COVID-19 and bad prognosis are more often found in older men with one or more underlying diseases (26). In our study, the average age of patients was estimated to be 63.3 years, with the majority being male (63.3%). The meta-analysis showed a positive association between ischemic stroke risk and COVID-19, increasing the risk by 1.4 times (35, 38, 42).

The risk of ischemic stroke should be considered when a patient with COVID-19 is hospitalized, as they may benefit from early anti-inflammatory and anticoagulant therapies (25, 27-29, 31, 34). Laboratory studies have revealed an increase in D-dimer, fibrinogen, anti-phospholipid antibodies, ferritin, C-reactive protein (CRP), and Erythrocyte sedimentation rate (ESR) levels, with D-dimer being a reliable marker in these patients. Elevated levels of these markers are associated with a poorer prognosis in patients with COVID-19 (21, 30, 35-37, 40). In general, patients with severe COVID-19 are at increased risk of acute stroke, emphasizing the necessity for neurological clinical monitoring in patients with SARS-CoV-2 infection and further investigation into the underlying pathophysiology (32). In most studies, common clinical symptoms of stroke have been reported in patients who developed stroke following COVID-19. The most common symptoms include unilateral hemiparesis or hemiplegia, loss of consciousness or decreased consciousness levels, slurred speech/aphasia, face drooping, visual disturbances, and headaches (22, 33, 39, 40). Additionally, a significant association between the cause of stroke and age was observed in COVID-19 patients, with cryptogenic strokes predominantly seen in younger patients (average age: 62 years). In contrast, cardioembolic strokes are observed in older individuals (38). In hospitalized COVID-19 patients, intracranial hemorrhage rates ranging from 0.1% to 3.3% have been reported, with higher occurrences in patients over 80 years old. These patients often experience more complications, require more extended hospital stays, especially in the ICU, and need ventilator support and vasopressors. Moreover, they have an extraordinarily high mortality rate, ranging from 42 to 84% (23). Advanced age, underlying conditions (such as hypertension and diabetes), and the severity of respiratory symptoms in COVID-19 are strongly associated with high mortality rates (20, 24).

Our meta-analysis results in this umbrella study show that ischemic stroke, with an average rate close to 80%, had the highest average rate, followed by hemorrhagic stroke with approximately 16.5%. Additionally, based on TOAST criteria, the majority of strokes were cryptogenic, accounting for 37%. Regarding the outcomes of stroke in COVID-19, the meta-analysis of 15 studies with a sample size of 8,731 patients showed that about 32% of COVID-19 patients with stroke lost their lives. The meta-analysis of five studies with a sample size of 5,685 indicated that around 27% of COVID-19 patients with stroke were discharged from the hospital with very mild symptoms or no complications and returned home. Furthermore, the meta-analysis of three studies with a sample size of 1,036 showed that approximately 28% of COVID-19 patients with stroke were referred to rehabilitation.

5. Limitations

The present umbrella review synthesizes systematically reviewed studies on stroke and COVID-19 but has limitations. One of the most significant limitations is the type of studies included in the previous systematic reviews, which mainly consisted of retrospective studies, including various case-control or case-series studies. Additionally, the limitation in accessing data from other studies was another constraint of the current study, which may have hindered the ability to access all previous studies and collect data accurately, potentially leading to reduced accuracy and reliability of the results. Another limitation of this study was that according to the information reported in the articles, subgroup analyses could only be performed based on the type of stroke. Variations in data collection methods and reporting across different studies and the data overlaps in the included articles may disrupt the analysis and interpretation of the results. In this regard, conducting prospective studies on stroke patients affected by COVID-19 to investigate the causes, related risk factors, and long-term outcomes of this comorbidity is recommended. Future clinical studies are suggested to evaluate the best diagnostic, preventive, and treatment methods for COVID-19 patients with stroke, as well as to gain a better understanding of the patterns of occurrence and outcomes of

this comorbidity in different communities.

6. Conclusions

In our study, the incidence of stroke in COVID-19 patients was approximately 1.75%, with a higher occurrence in men and those with an average age of 62.3 years. Approximately, 80% of strokes were ischemic, with a mortality rate of around 32%. Additionally, 27% of patients were discharged from the hospital without complications and 28% of COVID-19 patients with stroke required rehabilitation.

7. Declarations

7.1. Acknowledgments

We would like to thank the cooperation of the Clinical Research Development Unit, Imam Reza General Hospital, Tabriz, Iran, for their support for conducting this research. This article is based on a dataset forming part of Zahra Falaki's M.D thesis, entitled "Stroke and COVID-19: An Umbrella Review ". It was registered at Tabriz University of Medical Sciences (IR.TBZMED.REC.1402.853).

7.2. Authors contributions

HS and KS supervised the whole study. MG and ZF conducted a systematic search and meta-analysis. MS, NHK, and ZF screened the articles, extracted the data, and assessed the methodological quality of the studies. ZF prepared the early draft of the manuscript. All authors confirmed the final manuscript.

7.3. Availability of data

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

7.4. Using artificial intelligence chatbots

For preparing this manuscript artificial intelligence (AI) has not been applied either in the search process or drafting.

7.5. Funding

None was requested.

7.6. Competing Interests

The authors declare no competing interests.

References

1. Bagi HM, Soleimanpour M, Abdollahi F, Soleimanpour H. Evaluation of clinical outcomes of patients with mild symptoms of coronavirus disease 2019 (COVID-19) discharged from the emergency department. PLoS One. 2021;16(10):e0258697.
2. Shahsavarinia K, Ghojazadeh M, Ghabousian A, Hatefnia F, Soleimanpour M, Soleimanpour H. An Umbrella Review of Clinical Efficacy and Adverse Cardiac Events Associated with Hydroxychloroquine or Chloroquine with or Without Azithromycin in Patients with COVID-19. Anesth Pain Med. 2021 Aug 15;11(4):e115827.
3. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. Viruses. 2020;12(2).
4. Iyengar K, Bahl S, Raju V, Vaish A. Challenges and solutions in meeting up the urgent requirement of ventilators for COVID-19 patients. Diabetes Metab Syndr. 2020;14(4):499-501.
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-90.
6. Zurrú MC, Alonzo C, Brescacín L, Romano M, Cámera LA, Waisman G, et al. Recent respiratory infection predicts atherothrombotic stroke: case-control study in a Buenos Aires healthcare system. Stroke. 2009;40(6):1986-90.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
8. Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, et al. Mechanisms of Stroke in COVID-19. Cerebrovasc Dis. 2020;49(4):451-8.
9. Ayromlou H, Soleimanpour H, Farhoudi M, Sadeghi-Hokmabadi E, Rajaei Ghafouri R, Sharifipour E, et al. What are the most important barriers for thrombolytic therapy in ischemic stroke patients? Int J Stroke. 2013;8(4):E7.
10. Nikbakht H-A, Shojaie L, Niknejad N, Hassanipour S, Soleimanpour H, Heidari S, et al. Mortality rate of acute stroke in Iran: a systematic review and meta-analysis. Caspian Journal of Neurological Sciences. 2022;8(4):252-67.
11. Soleimanpour H, Pashapour A, Mohammadi N, Golzari SE, Khodaverdizadeh H. Juvenile ischemic stroke secondary to cardiogenic embolism: a rare case report. Int J Prev Med. 2014;5(1):117-22.
12. Zakeri A, Jadhav AP, Sullenger BA, Nimjee SM. Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. J Neurointerv Surg. 2021;13(3):202-6.
13. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun. 2020;87:115-9.
14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
15. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015;13(3):132-40.
16. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N,

Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.
19. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.
20. Athanasios A, Daley I, Patel A, Oyesanmi O, Desai P, Frunzi J. Cerebrovascular Accident and SARS-CoV-19 (COVID-19): A Systematic Review. Eur Neurol. 2021;84(6):418-25.
21. Bhatia R, Pedapati R, Komakula S, Srivastava MVP, Vishnubhatla S, Khurana D. Stroke in Coronavirus Disease 2019: A Systematic Review. J Stroke. 2020;22(3):324-35.
22. Castro-Varela A, Martinez-Magallanes DM, Reyes-Chavez MF, Gonzalez-Rayas JM, Paredes-Vazquez JG, Vazquez-Garza E, et al. Risk Factors, Clinical Presentation, Therapeutic Trends, and Outcomes in Arterial Thrombosis Complicating Unvaccinated COVID-19 Patients: A Systematic Review. Angiology. 2024;75(7):625-34.
23. Daly SR, Nguyen AV, Zhang Y, Feng D, Huang JH. The relationship between COVID-19 infection and intracranial hemorrhage: A systematic review. Brain Hemorrhages. 2021;2(4):141-50.
24. Fridman S, Bres Bullrich M, Jimenez-Ruiz A, Costantini P, Shah P, Just C, et al. Stroke risk, phenotypes, and death in COVID-19: Systematic review and newly reported cases. Neurology. 2020;95(24):e3373-e85.
25. Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, et al. The Impact of SARS-CoV-2 on Stroke Epidemiology and Care: A Meta-Analysis. Ann Neurol. 2021;89(2):380-8.
26. Lee KW, Yusof Khan AHK, Ching SM, Chia PK, Loh WC, Abdul Rashid AM, et al. Stroke and Novel Coronavirus Infection in Humans: A Systematic Review and Meta-Analysis. Front Neurol. 2020;11:579070.
27. Li S, Ren J, Hou H, Han X, Xu J, Duan G, et al. The association between stroke and COVID-19-related mortality: a systematic review and meta-analysis based on adjusted effect estimates. Neurol Sci. 2022;43(7):4049-59.
28. Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. J Neurol. 2022;269(4):1731-40.
29. Menezes RG, Alabduladhem TO, Siddiqi AK, Maniya MT, Al Dahlawi AM, Almulhim MWA, et al. Cerebrovascular disease in COVID-19: a systematic review and meta-analysis. Infez Med. 2023;31(2):140-50.
30. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021;16(2):137-49.
31. Parsay S, Vosoughi A, Khabbaz A, Sadigh-Eteghad S. The Incidence and Mortality Ratio of Ischemic Cerebrovascular Accidents in COVID-19 Cases: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis. 2021;30(3):105552.
32. Siepmann T, Sedghi A, Simon E, Winzer S, Barlinn J, de With K, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. Eur J Neurol. 2021;28(1):238-47.
33. Siow I, Lee KS, Zhang JJY, Saffari SE, Ng A, Young B. Stroke as a Neurological Complication of COVID-19: A Systematic Review and Meta-Analysis of Incidence, Outcomes and Predictors. J Stroke Cerebrovasc Dis. 2021;30(3):105549.
34. Syahrul S, Maliga HA, Ilmawan M, Fahriani M, Mamada SS, Fajar JK, et al. Hemorrhagic and ischemic stroke in patients with coronavirus disease 2019: incidence, risk factors, and pathogenesis - a systematic review and meta-analysis. F1000Res. 2021;10:34.
35. Szegedi I, Orbán-Kálmándi R, Csiba L, Bagoly Z. Stroke as a Potential Complication of COVID-19-Associated Coagulopathy: A Narrative and Systematic Review of the Literature. J Clin Med. 2020;9(10).
36. Tan YK, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis. 2020;50(3):587-95.
37. Trepet G, Radzikhovska N. Ischemic Stroke in COVID-19: A Systematic Review. Journal of Pharmaceutical Research International. 2021;33(60B):2412-20.
38. Vidale S. Risk Factors, and Clinical and Etiological Characteristics of Ischemic Strokes in COVID-19-Infected Patients: A Systematic Review of Literature. Cerebrovasc Dis. 2021;50(4):371-4.
39. Yamakawa M, Kuno T, Mikami T, Takagi H, Gronseth G. Clinical Characteristics of Stroke with COVID-19: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis. 2020;29(12):105288.
40. Yao Z, Huang L, Cheng Y, Qi R, Xu B, Zhang Q, et al. Clinical characteristics and outcomes of acute ischemic stroke in patients with COVID-19: A systematic review and meta-analysis of global data. Advanced Neurology. 2022;1(1):28.
41. Yu T, Wang H, Zheng S, Huo L. SARS-CoV-2-associated cerebrovascular disease amid the COVID-19 pandemic: A systematic review. Infection and Drug Resistance. 2021:4967-75.
42. Cui Y, Zhao B, Li T, Yang Z, Li S, Le W. Risk of ischemic stroke in patients with COVID-19 infection: A systematic review and meta-analysis. Brain Res Bull. 2022;180:31-7.

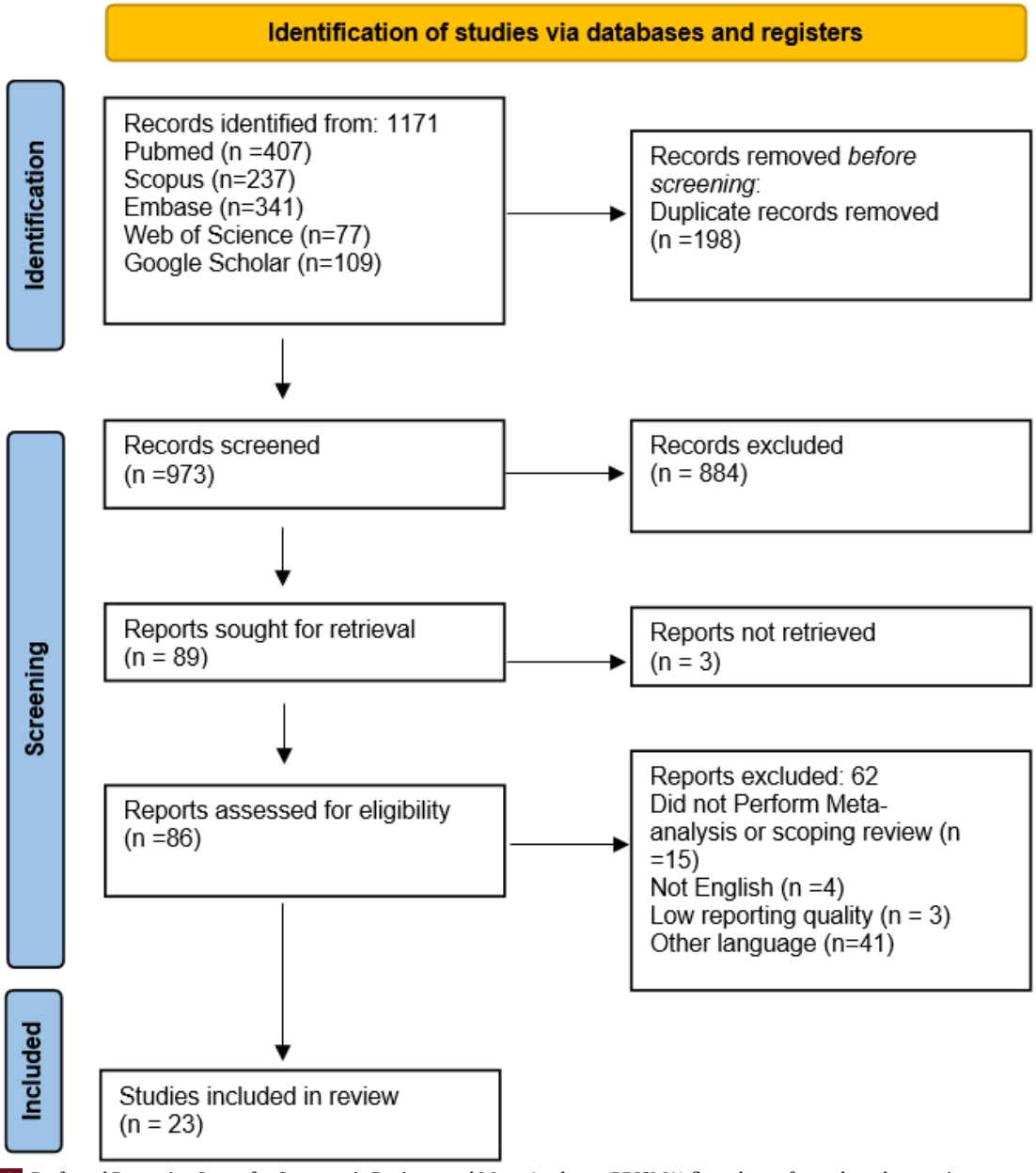

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of search and screening process.

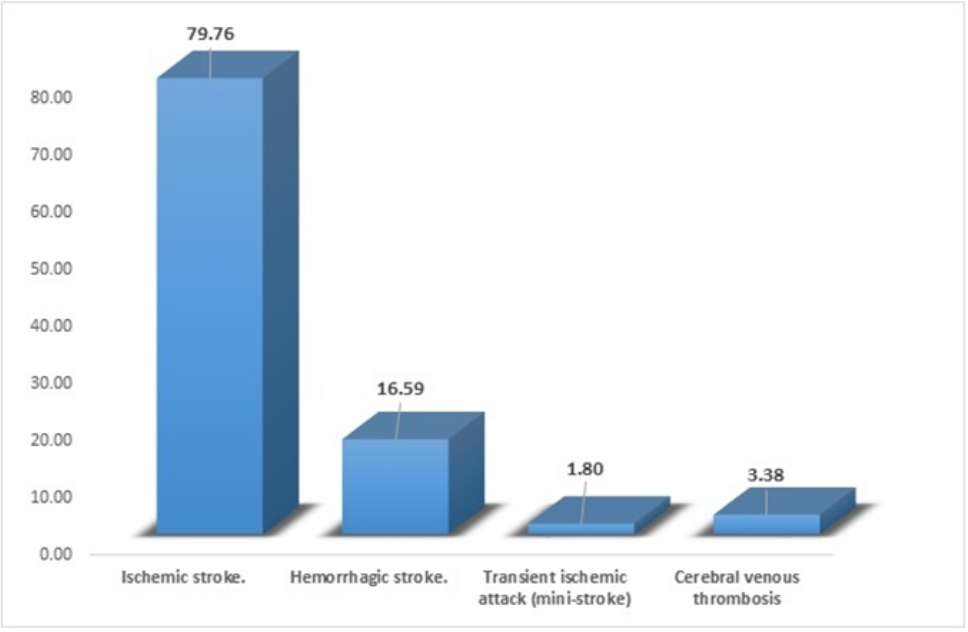

Figure 2: Average percentages of reported stroke types in studies.

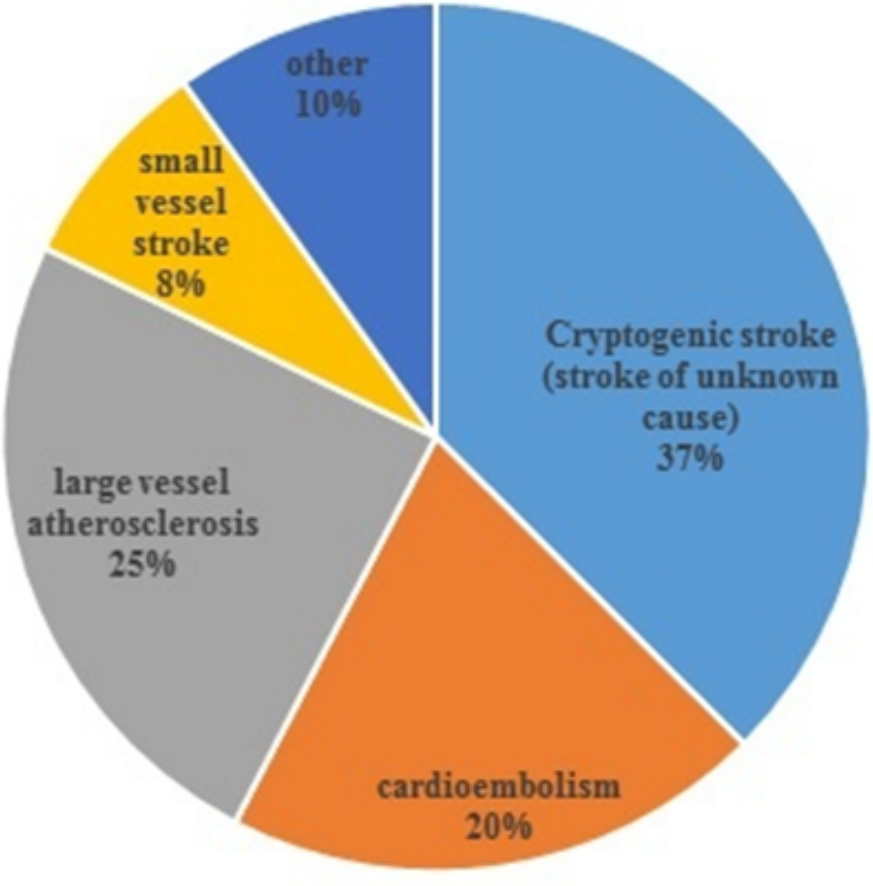

Figure 3: Prevalence of types of stroke.

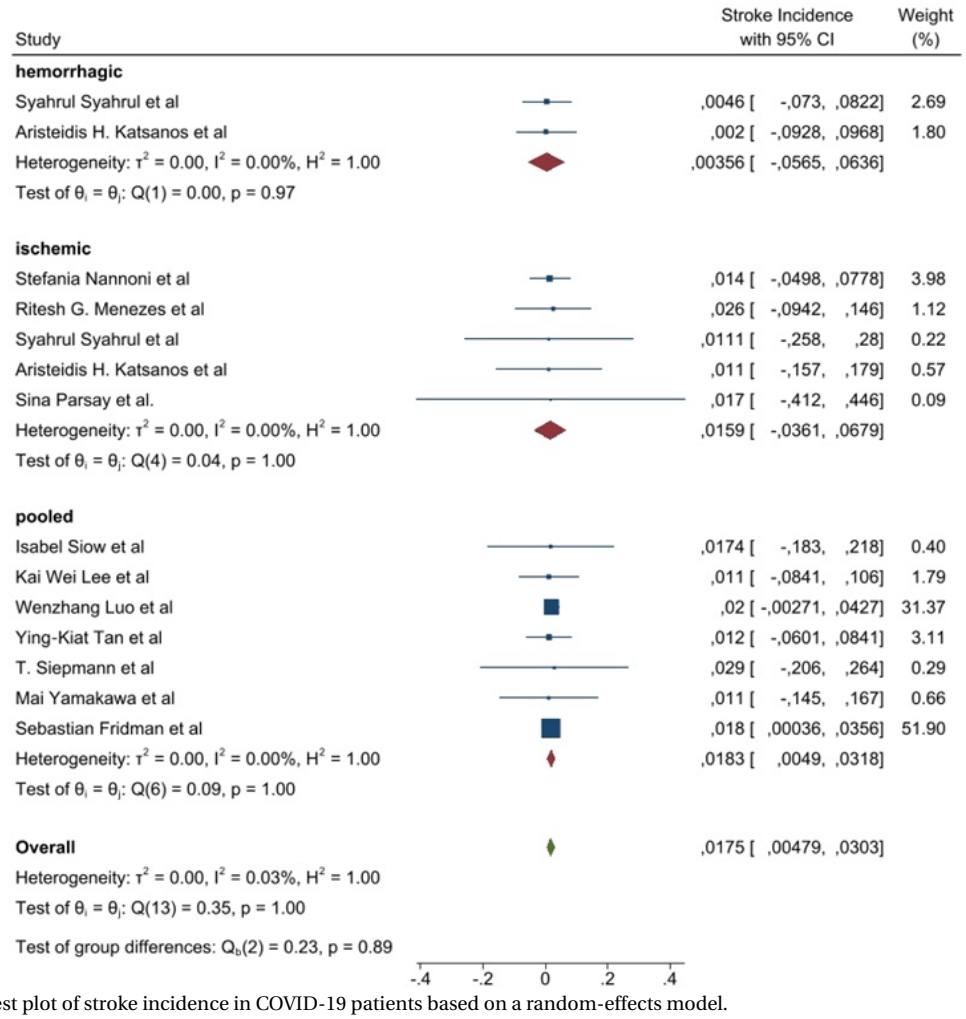

Figure 4: Forest plot of stroke incidence in COVID-19 patients based on a random-effects model.

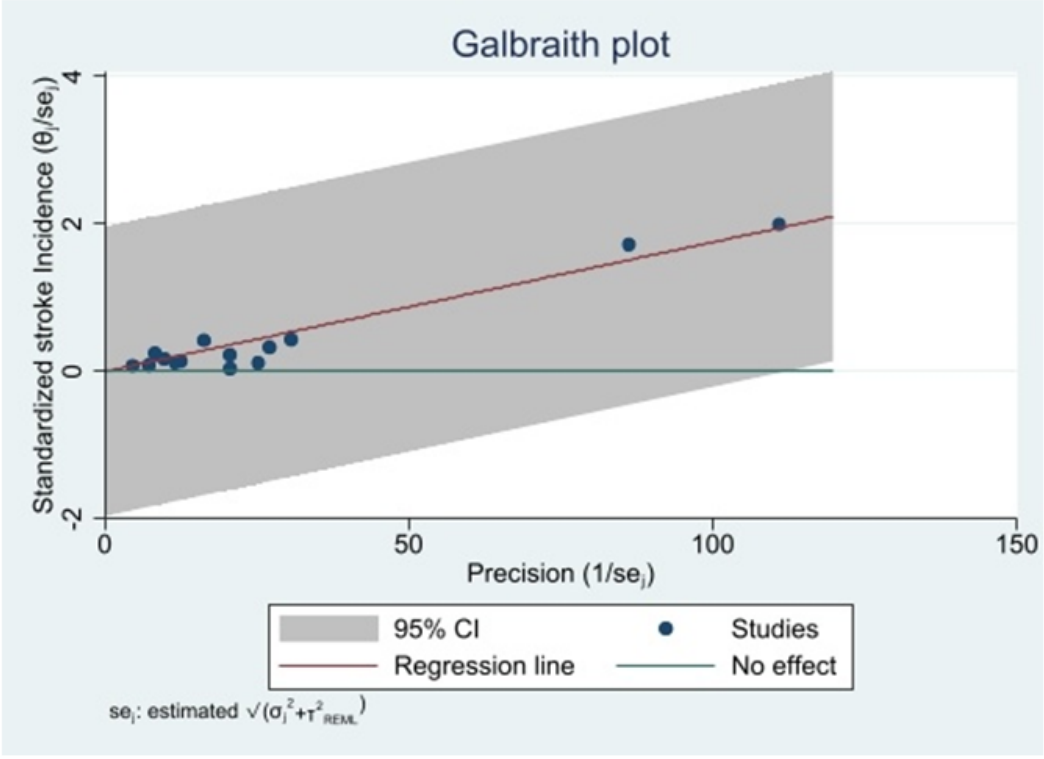

Figure 5: Galbraith plot of stroke incidence in COVID-19 patients based on a random-effects model. CI: confidence interval.

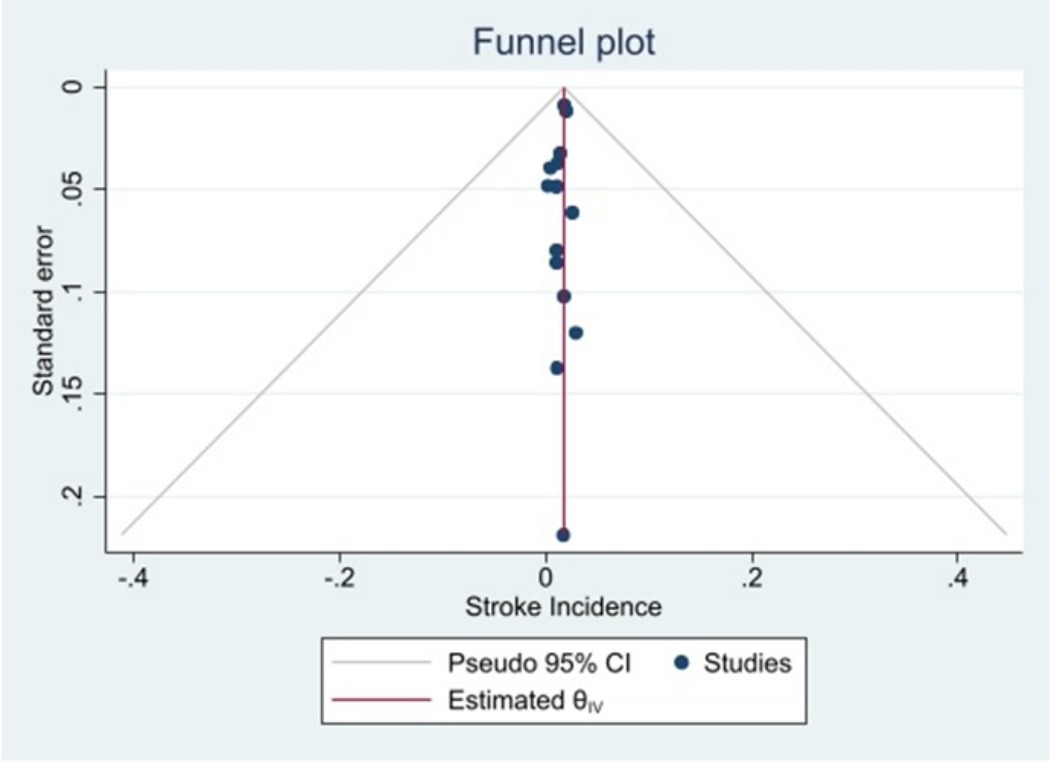

Figure 6: Funnel plot of stroke incidence in COVID-19 patients based on a random-effects model. CI: confidence interval.

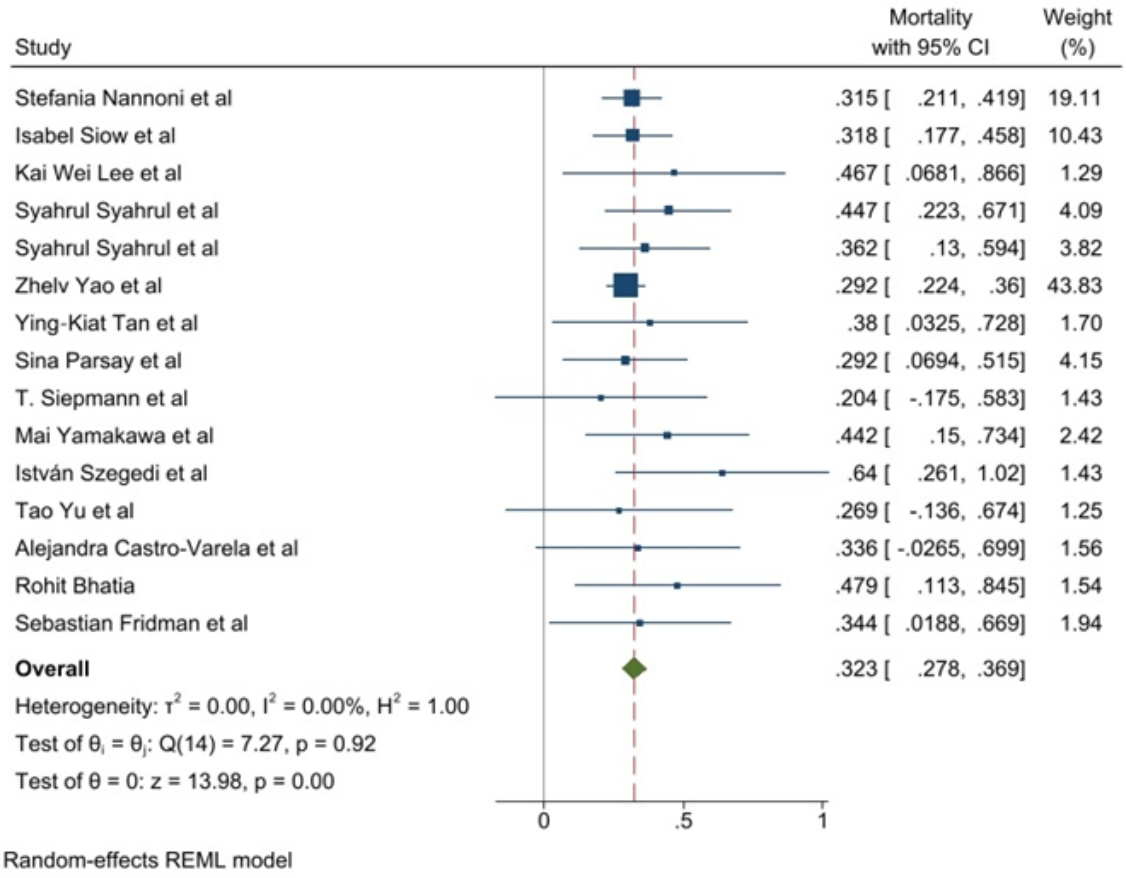

Figure 7: Forest plot of mortality percentage among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

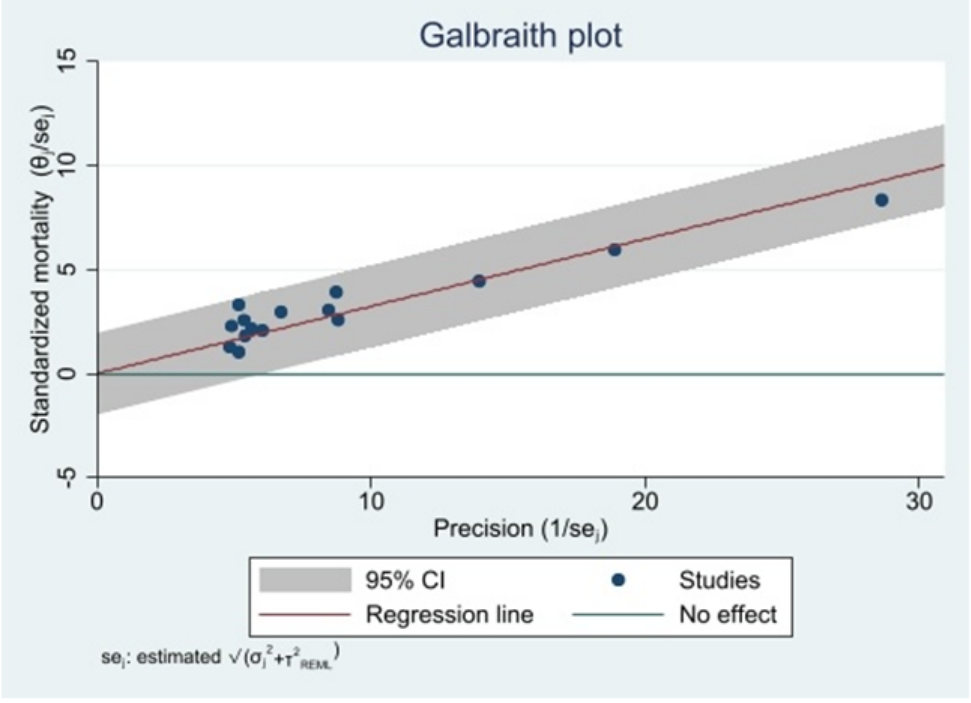

Figure 8: Galbraith plot of mortality percentage among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

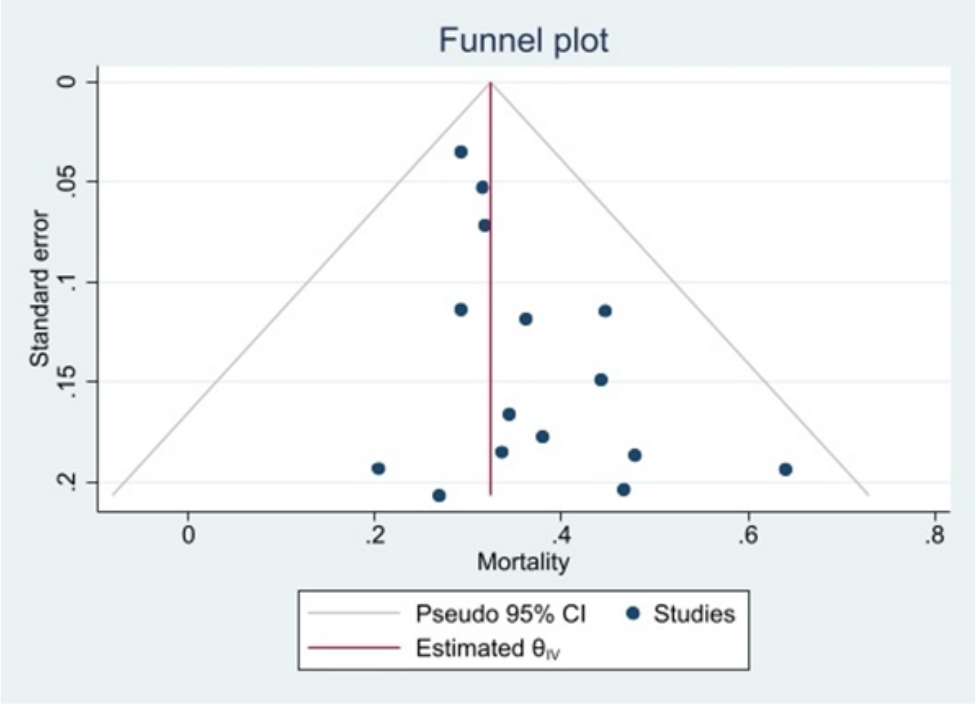

Figure 9: Funnel plot of mortality percentage among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

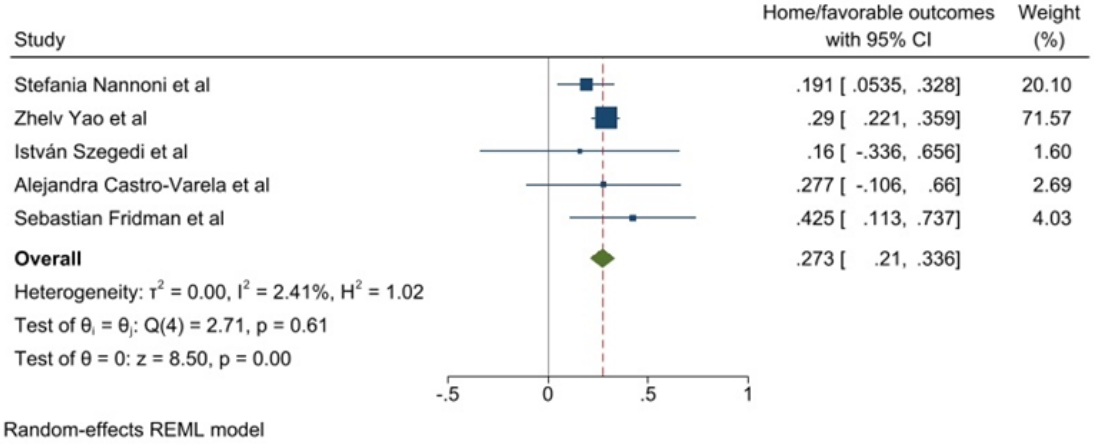

Figure 10: Forest plot of percentage of discharge with very mild complications among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

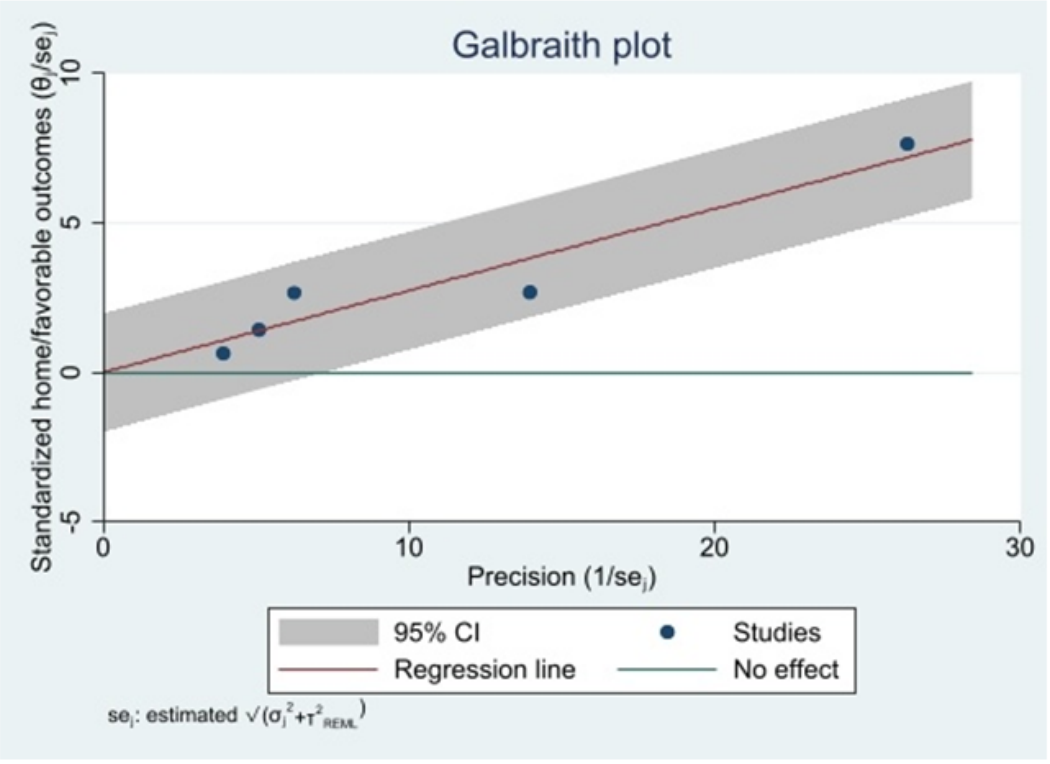

Figure 11: Galbraith plot of percentage of discharge with very mild complications among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

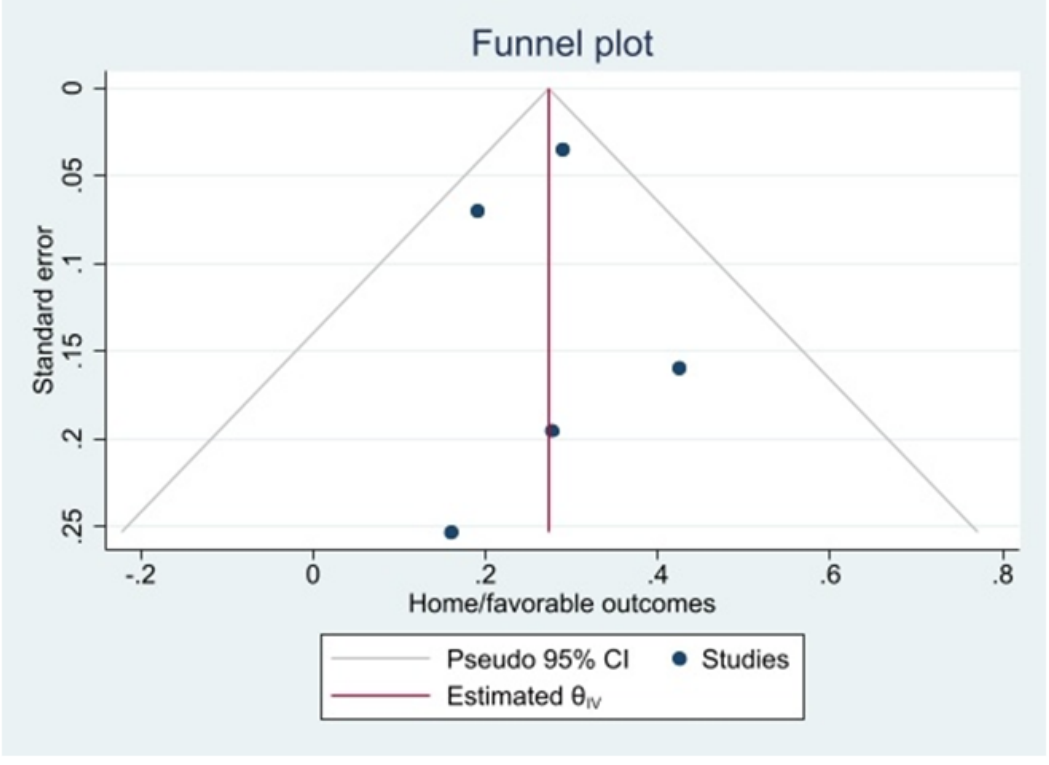

Figure 12: Funnel plot of percentage of discharge with very mild complications among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

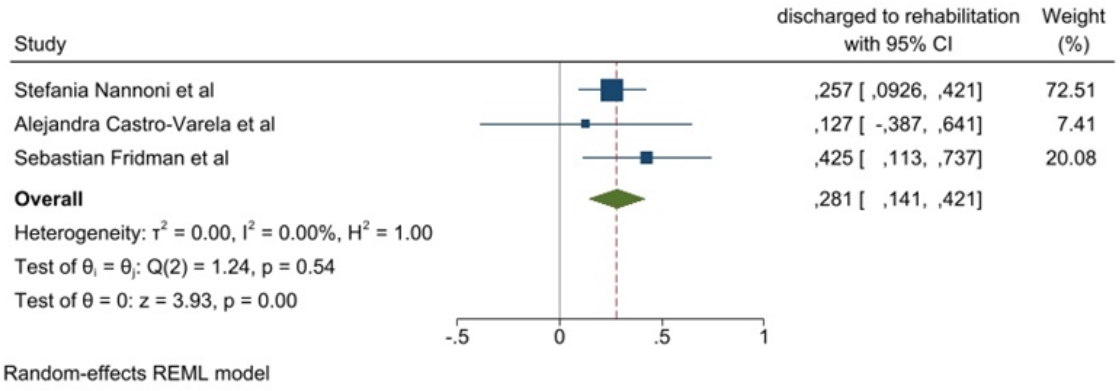

Figure 13: Forest plot of percentage of referral to rehabilitation among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

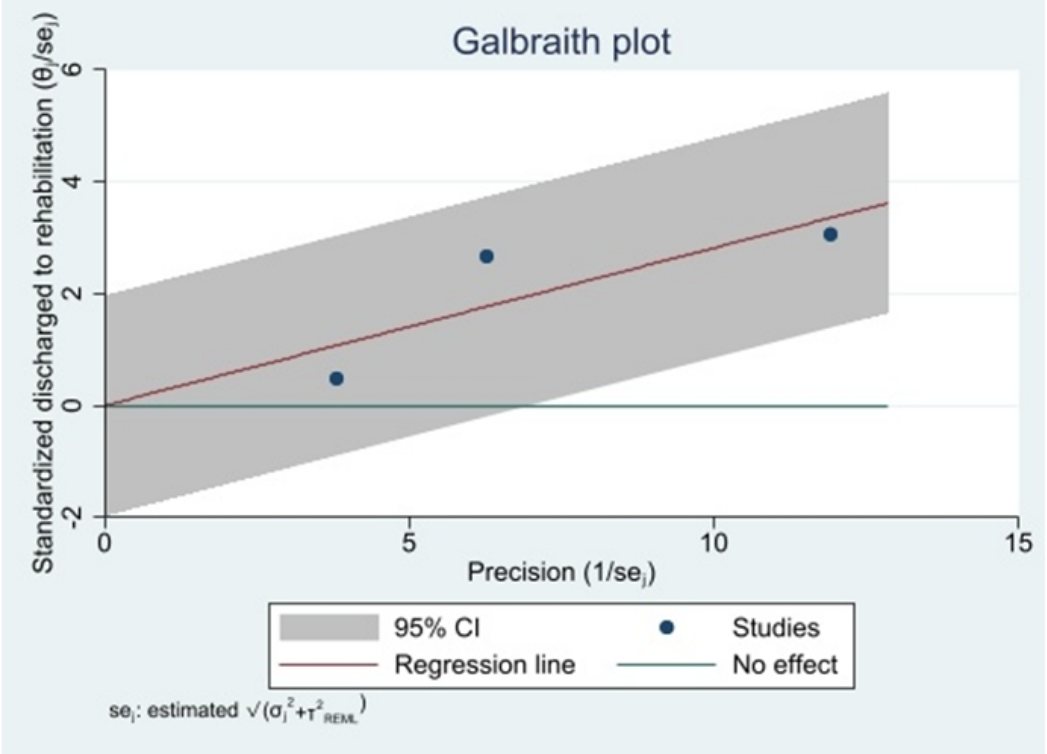

Figure 14: Galbraith plot of percentage of referral to rehabilitation among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

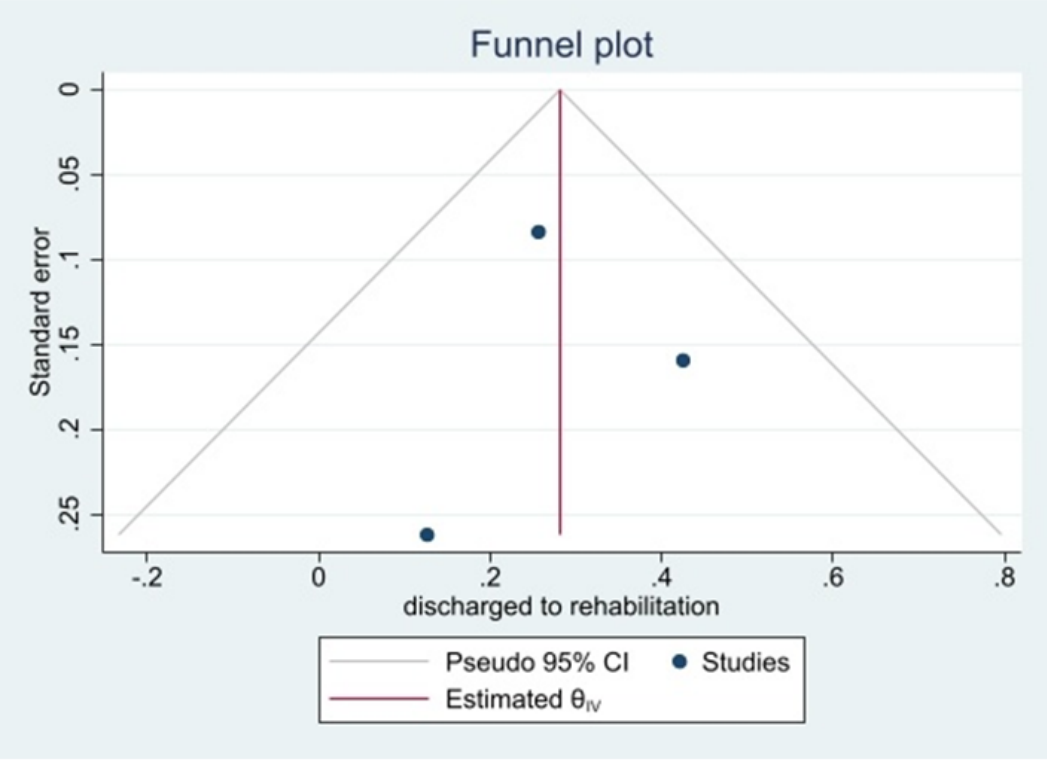

Figure 15: Funnel plot of percentage of referral to rehabilitation among COVID-19 patients with stroke based on a random-effects model. CI: confidence interval.

Table 1: Characteristics of included studies in this umberella review

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Stefania Nannoni et al. 2021 UK	A systematic review and meta-analysis	1906/145	57 case reports, 51 case series, 4 case-control studies, 33 cohort studies	PRISMA	The most common manifestation was AIS (87.4%); ICH (11.6%). TIA (0.1%), CVT (0.5%)	84.1%, of patients manifested COVID-19 symptoms at stroke onset.	There were a total of 108,571 COVID-19 patients. Median age was 65.3 (61.4–67.6) years, and the majority were male (62.4%).	Radiological signs of pneumonia were detected in 86.7% (198/246) of patients and signs of PE in 14.8% (9/61).	Elevated median D-dimer (3720 mg/L) Elevated median fibrinogen (459 mg/L). Antiphospholipid antibodies (available in 87 stroke cases): 17.2% tested positive for IgM/IgG anticardiolipin or anti-b2-glycoprotein I antibodies	-	Out of the 1655 patients with information on mortality, Hospital death: 31.5% (521) Discharged home: 19.1% (379/1315) Discharged to rehabilitation: 25.7% (228/744)	108,571 COVID-19 patients /1106 ischemic or IS Incidence of acute CVD:1.4% (95% CI: 1.0–1.9). IS:(87.4%) Intracerebral hemorrhage: (11.6%). Transient ischemic attack: 0.1% Cerebral venous thrombosis: 0.5%	Acute cerebrovascular diseases are not uncommon in patients with COVID-19, especially in those who are severely infected and have pre-existing vascular risk factors. The pattern of large vessel occlusion and multi-territory infarcts suggest that cerebral thrombosis and/or thromboembolism could be possible causative pathways for the disease.
Isabel Siow et al. 2021 Singapore	A Systematic Review and Meta-Analysis	326/30	16 studies cross-sectional 14 case series	PRISMA	-	Unilateral hemiparesis or hemiplegia: (66.7%) Loss of consciousness or decreased levels of consciousness :(66.0%) Headache: (11.9%)	55,176 patients including 899 with stroke were included. The mean age: 65.5 (Range: 40.4-76.4) years, 70.5% male.	-	AST levels were raised, with an average of 51.9 u/L (Range: 28_116 u/L). ALT levels were mildly raised, with an average of 58.2 u/L (Range: 28-75 u/L). CRP levels were within normal range, with an average of 10.0 u/L (Range: 2.27-20.80 u/L). D-dimer levels were raised, with an average of 3,301.1 ng/mL (Range: 3-25,261 ng/mL). PT was raised, mean:13.1 s (Range:10.0-15.52 s). aPTT: mean 24.2 s (Range: 2.10 s-55.00 s). Nine studies reported on full blood count. Hb mean: 10.3 g/dL (Range: 9.12-12.89 g/dL). Plt levels average 240,704.3 per mm3 (Range:78,000-319,000 per mm3). WBC average of 10,094.8 cells/mm3 (Range:7,193-12,400 cells/mm3)	-	Mortality rate of patients who suffered from stroke as a complication of COVID-19: 31.76% (95% CI: 17.77% to 47.31%) The pooled mortality rate in severely ill patients: 84.8%	The average incidence of stroke as a complication of COVID-19 was 1.74% (95% CI: 1.09% to 2.51%). The average mortality of stroke in COVID-19 patients was 31.76% (95% CI: 17.77% to 47.31%).	Although stroke is an uncommon complication of COVID-19, when present, it often results in significant morbidity and mortality. In COVID-19 patients, stroke was associated with older age, comorbidities, and severe illness

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Kai Wei Lee et al. 2020 Malaysia	A Systematic Review and Meta-Analysis	568/28 articles included for the systematic review and 7 studies for the meta-analysis	8 retrospective cohort studies, 11 case series, and 9 case reports	PRISMA	Majority of strokes seen among COVID-19 patients: arterial stroke (98.5%) venous stroke was seen only in three patients (1.5%). TOAST criteria: large vessels and cryptogenic were the most common type of stroke (28.9%),	-	A total sample: 8,771 participants The mean age of the participants: 62.9± 12.2 years, Males: (64.1%).	More than half of strokes happened in anterior circulation (60.0%), followed by multiple territories (28.0%) and posterior circulation (12.0%). Among the 29 cases of stroke involving the anterior circulation, 28 cases occurred in the MCA region, and only two cases involved the ACA region.	ESR: “31–86” mm/1 h. CRP:“0.101-1,920” mg/L Ferritin:“392-4609.33” mg/L D-dimer:“0.71-28.5” mg/L LDH: “406-860.4” IU/L Fibrinogen:”462.8-6,050” mg/dL, Antiphospholipid: a majority of the studies did not capture information on the presence of antiphospholipid. Procalcitonin: three studies had a blood test result of below 1.0 mg/mL, ranging “0.23-0.8” ng/mL IL-6: “3-10.5” pg/mL Troponin: Three out of the seven studies reported an abnormally elevated troponin concentration Plt: the mean ranged from 112 to 303 ×109, and the levels were all within the normal range in the included studies, except one study which had a slightly elevated level (409 × 109). PT levels range: “11–13.5” s.	-	The average mortality rate for stroke patients with COVID-19 and non-COVID-19 infection was 46.7 and 8.7%, respectively.	The pooled frequency of stroke in COVID-19 patients was 1.1% (95% CI: 0.8, 1.3).	The occurrence of stroke in patients with COVID-19 infection is uncommon, but it may pose as an important prognostic marker and indicator of severity of infection, by causing large vessel occlusion and exhibiting a thromboinflammatory vascular picture.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Yanhua Cui et al. 2022 China	A Systematic Review and Meta-Analysis	785/4	3 retrospective cohort studies; 1 prospective cohort study	PRISMA	-	-	31,634 participants including 171 COVID-19 positive patients with IS were included. The mean age of COVID-19-positive patients with IS:69.45 years (Range: 63–77 years) Male patients: 56%.	-	-	-	-	The risk of IS (combined OR: 2.41; 95% CI: 1.08–5.38) was significantly increased. Four included studies were significantly heterogeneous (I^2= 75.2%, P = 0.007)	This meta-analysis showed a strong correlation between the increased incidence rate of IS and COVID-19, especially among COVID-19 patients in North America. Further study is required to develop effective treatments to decrease the IS risk in COVID-19 patients.
Wenzhang Luo et al. 2022 China	A systematic review and meta-analysis	5107/10	Articles with original data (e.g., cohort, retrospective, case-control studies)	PRISMA and MOOSE	Large vessel disease, small vessel disease, cardioembolic, cryptogenic, and other defined mechanisms. Cryptogenic stroke subtype: 35% (95% CI 12–59%; p < 0.01)	-	The studies involved a total of 26,691 patients. Mean age: "48.1-75.7" years, and 35.1% (52 of 148; 8 studies) of the patients were female.	-	-	-	Morbidity of stroke in COVID-19 patients: ranged from 0 to 5%.	The pooled prevalence of IS in COVID-19 : 2% (95% CI 1–2%; p < 0.01; I^2 = 86%; based on random-effects model.	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% of patients with COVID-19 infection could present with IS.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Ritesh G. Menezes et al. 2023 Saudi Arabia, Pakistan, Ireland	A systematic review and meta-analysis	5877/37	Retrospective observational, case series, prospective observational,	PRISMA	-	-	The total number of patients included in analysis: 294,249. Events: 1963	-	-	-	-	Pooled results show that the incidence of acute CVD events in COVID-19-positive patients is 2.6% (95% CI: 2.0-3.3; P<0.001).	COVID-19 infection is associated with an increased risk of acute CVD and is associated with cardioembolic and cryptogenic etiologies and the risk factors of atrial fibrillation, coronary artery disease, diabetes, and hypertension in COVID-19-positive patients.
Syahrul Syahrul et al. 2021 Indonesia Bangladesh Saudi Arabia India	A systematic review and meta-analysis	1416/18 Only 16 studies were included in the meta-analysis	17 retrospective cohort; 1 prospective cross-sectional	PRISMA	IS (incidence: 71.58%) IS (incidence: 28.42%)	For COVID-19 patients who experienced a stroke, hospital admission with respiratory symptoms were more commonly reported than that with neurological symptoms	58,104 COVID-19 Patients	Diffuse microhemorrhages have been previously observed in COVID-19 patients, via brain imaging, and such microhemorrhages are scattered mostly in the juxtacortical white matter, corpus callosum, and brain stem.	-	-	Mortality rate of COVID-19 patients who experienced a IS: 44.72% (95% CI 36.73%–52.98%) Mortality rate of COVID-19 patients who experienced an IS: 36.23% (95% CI 30.63%–42.24%),	Prevalence of HS: 0.46% (95% CI 0.40%–0.53%; I^2=89.81%) among 67,155 COVID-19 patients Prevalence of IS: 1.11% (95% CI 1.03%–1.22%; I 2=94.07%) among 58,104 COVID-19 patients	Although the occurrence of hemorrhagic and ischemic strokes is low, the mortality rates of both stroke types in patients with COVID-19 is concerning, and therefore, despite several potential pathogeneses that have been proposed, studies aimed at definitively elucidating the mechanisms of hemorrhagic and IS in individuals with COVID-19 are warranted.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Zhelv Yao et al. 2022 China; United Kingdom	A systematic review and meta-analysis	4842/38	32 were cohort; two were case control, four cross-sectional	-	Cryptogenic stroke was the most common type with 41.0%, Cardioembolism: 26.4% large vessel atherosclerosis: 13.9% small vessel stroke: 7.6%,	nic	76,894 individuals	Patients with COVID-19 showed a higher proportion of large vessel occlusion (LVO) (OR: 1.68, 95% CI: 1.10 – 2.57; I^2: 75%; 8 studies) and multi-territory infarcts (OR: 2.64, 95% CI: 1.62 – 4.29; I^2: 0%; 4 studies) than those without COVID-19. Stroke was more likely to occur in the anterior circulation (OR: 2.29, 95% CI: 1.03 – 5.10; I^2: 37%; 7 studies), particularly in the internal carotid artery (OR: 1.85, 95% CI: 1.19 – 2.88; I^2: 0; 7 studies).	Higher levels of CRP and D-dimer Prolonged aPTT and PT. No difference was detected in leukocytes and Plt	-	13.2% of patients had hemorrhagic transformation. 29.2% died during hospitalization. 29.0% had a favorable outcome on discharge.	Cryptogenic stroke was the most common type (41.0%, 95% CI: 33.9 – 48.0%; I^2: 76.1%; 17 studies).	Patients with AIS who had COVID-19 infection tended to have cryptogenic LVO and multi-territory infarcts with high CRP and D-dimer levels. These patients had more severe stroke syndromes, worse functional outcomes, and a higher in-hospital mortality rate, with or without reperfusion treatment.
Ying-Kiat Tan et al. 2020 Singapore	A systematic review and meta-summary of the literature	4965/39	-	PRISMA	-	The majority of patients manifested typical COVID-19 symptoms, namely fever (63.7%, 65/102), acute respiratory symptoms (76.0%, 73/96) and dyspnea (58.6%, 34/58).	A total of 39 studies comprising 135 patients were studied. The mean age was 63.4 ± 13.1 years, and the majority were male patients (62.3%, 81/130).	The majority of AIS neuroimaging patterns observed was large vessel thrombosis, embolism or stenosis (62.1%, 64/103), followed by multiple vascular territory (26.2%, 27/103).	Elevated mean D-dimer (9.2 ± 14.8 mg/L) and fibrinogen (5.8 ± 2.0 g/L). Antiphospholipid antibodies were detected in a significant number of cases.	-	Mortality rate: 38.0%, (Out of the 129 patients with information on mortality, 49 (38.0%) had demised at the time that the respective reports were published).	The pooled incidence of AIS in COVID-19 patients from observational studies was 1.2% (54/4466) with a mean age of 63.4 ± 13.1 years. The mean duration of AIS from COVID-19 symptoms onset was 10 ± 8 days, and the mean NIHSS score was 19 ± 8. A high mortality rate was reported (38.0%, 49/129).	The pooled incidence of AIS in COVID-19 patients is 1.2%, with a high mortality rate. Elevated d-dimer, fibrinogen, and the presence of antiphospholipid antibodies appear to be prominent in COVID-19 patients with concomitant IS, but further mechanistic studies are required to elucidate their role in the pathogenesis of AIS.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Aristeidis H. Katsanos et al. 2020 Canada; Greece; USA; France; Italy; Singapore	A systematic review and meta-analysis	554/18	18 cohort studies	PRISMA	Among patients with SARS-CoV-2, 1.3% hospitalized for cerebrovascular events, 1.1% for ischemic stroke, 0.2% for IS 0.03% Cerebral sinus venous thrombosis	-	67,845 patients	-	-	-	Odds of in-hospital mortality were higher among SARS-CoV-2 stroke patients compared to non-infected contemporary or historical stroke patients (OR = 5.60, 95% CI = 3.19–9.80, I^2 = 45%).	Among patients with SARS-CoV-2, 1.3% hospitalized for cerebrovascular events, 1.1% for ischemic stroke, 0.2% for IS 0.03% Cerebral sinus venous thrombosis	Patients infected by SARS-CoV-2 appear to have increased odds of IS rate, particularly the cryptogenic subtype, when compared to contemporary or historical noninfected controls.
Sina Parsay et al. 2021 Iran	A systematic review and meta-analysis	243/17	-	PRISMA	-	-	25,586 COVID-19 cases 375 cases of acute ischemic CVA The majority of COVID-19 cases were male. Mean age: at least 60 years old (63.4±13.1)	-	-	-	Studies regarding mortality in patients who died from ischemic CVA to all COVID-19 cases revealed a 0.5% mortality rate. The mortality rate of patients with CVA who suffered from COVID-19 infection and ischemic CVA simultaneously was 29.2%.	Included studies reported a pooled average incidence of 1.7% for ischemic CVA, ranging from 1.3% to 2.3%. Mortality of COVID-19 cases was 0.5%, ranging from 0.4% to 0.6%.	Analysis revealed a pooled incidence of 1.7% for ischemic CVA in the setting of COVID-19 infection, with a mortality rate of 29.2% amongst the COVID-19 patients with ischemic CVA.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Shuwen Li et al. 2022 China	A systematic review and meta-analysis based on adjusted effect estimates	4252/4744	Retrospective Cohorts; 2 Prospective Cohorts; 1 Ambispective Cohort	PRISMA	-	–	7267055 patients mean age : 16 studies < 60 years old; 29 studies, ≥ 60 years old proportion of males: 13 studies, <50%; 31 studies, ≥ 50%	-	-	-	-	The stroke was associated with higher COVID-19 mortality (pooled effect = 1.30, 95% confidence interval (CI): 1.16–1.44; I^2 = 89%, P < 0.01; random-effects model)	Stroke was independently associated with a significantly increased risk for mortality in COVID-19 patients.
T. Siepmann et al. 2021 Germany	A multicenter study and meta-analysis	761/2	2 Cohort studies	PRISMA	-	None of the stroke patients from the multicenter COVID-19 cohort had neurological symptoms previously linked to infection with SARS-CoV-2 such as impairment of taste or smell.	165 patients hospitalized for COVID-19 (49.1% male, median age = 67 years [57–79 years]TT, 72.1% severe or critical) Systematic review:576 laboratory-confirmed COVID-19 patients (60.9% male, average ages ranging from 53 to 66 years) Meta-analysis: 741 laboratory-confirmed COVID-19 patients (58.3% male, average age ranging from 52 to 67 years)	-	Lymphocyte count, Thrombocyte count, D-dimer, INR, C-reactive protein, and Interleukin-6 admission were reviewed	-	In-hospital death COVID-19,(n = 165): 32/157 (20.4) + Stroke, (n = 7): 2 (20.4) – Stroke, (n = 158): 30 (20)	Of 165 patients hospitalized for COVID-19 included in the multicenter study, the overall stroke rate was 4.2% Systematic review: Of 576 laboratory-confirmed COVID-19 patients reported in these studies, 15 patients (2.6%) were reported to have a stroke related to COVID-19 hospitalization. Meta-analysis: The overall rate of stroke was 2.9% (95% CI: 1.9–4.5) in the pooled COVID-19 population.	severity of COVID-19 is associated with risk of AS.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Mai Yamakawa et al. 2020 USA; Japan	A Systematic Review and Meta-Analysis	215/26	10 retrospective cohort studies, 6 case series, and 10 case reports	PRISMA	Cryptogenic stroke was the most common etiology with 50.7%	Unilateral weakness:65.7%, Altered mental status:51.4%, Dysarthria:34.3%, As for symptoms of COVID-19, cough was most common (77.6%).	183 patients with COVID-19 and stroke; Mean age was 66.6 ([58.4-74.9], I^2=95.2%); 65.6% were male (61/93 patients).	Middle cerebral arteries: (30.5%, 25/82 patients), Internal carotid arteries: (18.3%, 15/82 patients), Vertebrobasilar arteries (7.3%, 6) 82 patients), Posterior cerebral arteries: (3.7%,3/82 patients)	D-dimer:3.3 mg/mL Mean CRP : 127.8 mg/L Troponin : 0.051 ng/mL	-	The case fatality rate in this population with stroke and COVID-19 was conspicuously high at 44.2%	The frequency of detected stroke in hospitalized COVID-19 patients was 1.1% Stroke type (ischemic vs hemorrhagic): 96.6% IS.	The frequency of detected stroke in hospitalized COVID-19 patients was 1.1% and associated with older age and stroke risk factors. Frequent cryptogenic stroke and elevated D-dimer level support increased risk of thromboembolism in COVID-19 associated with high mortality.
István Szegedi et al. 2020 Hungary	A Narrative and Systematic Review of the Literature	315/25	Case reports /case series	PRISMA	AIS is the most frequent type of stroke occurring in infected patients. 19 patients had HS, Four of them had SAH, Six patients had TIA, 170 patients had AIS. One patient had HS followed by AIS	-	198 cerebrovascular patients; The median age of stroke patients was 60 (interquartile range [IQR]: 50–70). Among the patients whose sex was reported, a slight male predominance was found (87/136, 63.97%)	-	D-dimer levels were elevated or highly elevated in most patients, with a median value of 3250 ng/mL. Fibrinogen levels were slightly elevated at admission, consistent with systemic inflammation (median: 5.3 g/L, IQR: 4.63–7.39 g/L). Prothrombin time was slightly prolonged in most patients. CRP and ferritin levels were elevated in most cases. Severe thrombocytopenia was not observed in any of the reported cases. Plt counts were normal or only mildly decreased.	-	Data were available in only 116/198 cases: 74 patients died (64%), 23 patients had unfavorable outcomes (19%), 19 patients had favorable outcomes (16%). - In the remaining cases, no detailed functional outcome was reported.	AIS is the most frequent type of stroke occurring in infected patients.	well-designed studies are needed to better understand the risk of stroke in COVID-19, to optimize treatment, and to improve stroke care.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Tao Yu et al. 2021 China	A Systematic Review	31	15 single-case reports and 16 case series	-	167 cerebrovascular events including : IS: 119 Cerebral hemorrhage: 33 Subarachnoid hemorrhage: 3 cerebral venous thrombosis: 12	The most prevalent clinical manifestations in the 119 patients with COVID-19- AIS: Cough (n=65, 54.6%); The most common reported symptoms in IS: hemiplegia (n=38), hemiparesis (n=19, 16.0%); -The most common reported hemorrhage symptoms were reduced consciousness (n=8, 24.2%)	167 cerebrovascular events IS Patients (n=119) The mean age : 61.8±14.1 years. 51 male [42.9%] and 30 female [25.2%]; the sex of the remaining 38 patients was unknown. Cerebral Hemorrhage Patients (n=33) Median age (range, years): 58(19–81) Male sex, n(%): 24(72.7) Female sex, n(%):9(27.3)	IS: Of the patients with AIS, 56 had large vessel stenosis and 9 had small vessel occlusion; Location of cerebral hemorrhage, n(%) Frontal lobe: 11(33.3) Parietal lobe: 5(15.2): Temporal lobe: 5(15.2) Brain stem: 4(12.1) Basal ganglia: 4(12.1) Cerebellar hemisphere: 2(6.1)	IS: 67/2% (80/119) patients had high D-dimer levels. 42.0% (50/119,) patients had high CRP. Cerebral Hemorrhage: Increased D-dimer: 48.5% Increased CRP: 24%	-	IS: 26.9% (32/119) patients had a fatal outcome. 17/6% (21/119) did poorly, i.e. were bedridden, hospitalized, critically ill, or remained in the intensive care unit (ICU). Cerebral Hemorrhage: In total, 60.6% (20/33) of patients did poorly or died. Discharged: 21.2%	167 cerebrovascular events including IS, cerebral hemorrhage, subarachnoid hemorrhage, and cerebral venous thrombosis in patients with confirmed COVID-19.	Cerebrovascular disease is a common neurological complication in patients with COVID-19. However, the cases of SARS-CoV-2-associated CVD that were reported lack direct evidence, and CVD appears to occur more frequently and with more severity in patients with COVID-19 than in those without.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Alejandra Castro-Varela et al. 2023 Mexico	A Systematic Review	1981/104	cohort	PRISMA	-	Arm or leg weakness: 57 (43.5) Slurred speech/aphasia: 44 (33.6) Face drooping: 26 (19.8) Visual disturbances: 12 (9.2) Headache: 4 (3.1) Seizure: 3 (2.3)	There were a total of 220 COVID-19 patients. IS: n = 131 Median age was 60 (50-70) years, and the majority were male (57/3%, 126/220).	One artery: 47 (35.9) Middle cerebral artery: 25/47 (53.2) Carotid artery: 11/47 (23.4) Posterior cerebral artery: 4/47 (8.5) Anterior cerebral artery: 3/47 (6.4) Basilar artery: 2/47 (4.3) Vertebral artery: 2/47 (4.3) Two arteries: 12 (9.2) More than two arteries: 10 (7.6)	Hb, g/dL (n = 45) 12.0 (11.0–14.1) WBC,109/L (n = 64) 11.9 (8.5–16.2) Neutrophils, 109/L (n = 35) 7.4 (5.4–11.3) Lymphocytes, 109/L (n = 55) 1.1 (.7–2.0) Glucose, mg/dL (n = 22) 176.0 (125.1–282.2) Plt, 109/L (n = 72) 239.0 (163.5–363.8) PT, seconds (n = 43) 14.1 (12.7–15.5) LDH, U/L (n = 48) 571.5 (396.3–943.8) CRP, mg/dL (n = 122) 11.3 (3.9–22.9) Procalcitonin, ng/mL (n = 18) .6 (.2–1.2) Ferritin, ng/mL (n = 46) 667.9 (356.0–1451.5) Fibrinogen, mg/dL (n = 50) 550.0 (335.2–695.3) Biomarkers D-dimer, ng/mL (n = 143) 4238.0 (1552.5–10380.0) Standard troponin, ng/mL (n = 26) .8 (.2–1.9)	Unvaccinated COVID-19 Patients	Outcomes Death 74 (33.6) Discharge to home 61 (27.7) Rehabilitation 28 (12.7) Disability 11 (5.0) Critical 10 (4.5) Nursing facility 3 (1.4) Still admitted 2 (.9)	This systematic review identified a high proportion of isolated IS (patients with only one event of cerebral arterial thrombosis). The most frequent bleeding complication was intracranial hemorrhage, primarily with isolated stroke. Overall mortality was 33.6% (74/220).	-

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Simone Vidale 2021 Italy	A Systematic Review of Literature	14	-	-	-	-	93 patients; The median age was 65 (IQR: 55–75) years, with prevalence in males (n: 62; 70.5% of patients with available data).	-	-	-	-	Stroke occurred after a median of 6 days from COVID-19 infection diagnosis. Median National of Institute of Health Stroke Scale (NIHSS) score was 19. Cryptogenic (Cry) strokes were more frequent (51.8%), followed by cardioembolic etiology.	IS in COVID-19-infected patients were clinically severe, affecting younger patients mainly with Cry and cardioembolic etiologies.
Ganna Trepet et al. 2021 Ukraine	A Systematic Review	1074/10	-	PRISMA	-	-	-	-	PT(secs): elevated Fibrinogen (mg/dl): raised D-Dimer (ng/ml): raised APTT (secs): raised Ferritin (ug/L): elevated Plt (x103 mm3): normal range WBC (x103 mm3): normal range CRP (mg/dl): elevated	-	-	All markers of hypercoagulability were elevated, but only Prothrombin Time corresponded with C-reactive protein (CRP).	Inflammatory markers were not useful in forecasting the development of acute IS, but CRP levels may be a possible marker to further research. D-dimer is a tried and true lab test that should be part of management guidelines in the ongoing COVID pandemic

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Rohit Bhatia 2020 India	A Systematic Review	2801/30	16 case reports, 8 case series, 5 retrospective observational studies, 1 prospective observational study	PRISMA	TOAST category (n=71) Large artery disease (35.25) Small vessel disease (8.4%) Cardioembolic (14.1%) Other (9.9%) Cryptogenic (32.4%)	-	115 patients with acute or subacute stroke infected with SARS-CoV-2; The mean±SD age of the patients was 62.5±14.5 years. The majority of the patients were male (42 [62%]).	Imaging modality for stroke (n=95) CT (88.4%) Magnetic resonance imaging 11.6% Vascular imaging (n=56) CT angiography (92.9%) Magnetic resonance angiography (7.1%) Abnormal chest X-ray (n=13): 11 (84.6%)	CRP (n=63) (mg/L): 101.1 D-dimer (n=69) (μg/L): 3,442 (1,159–10,000) Ferritin (n=17) (μg/L): 655 (134–1,708) WBC (n=29) (×109/L): 8.7 (6.7–11.7) Lymphocyte (n=25) (×109/L) : 0.9±0.5 Plt (n=27) (×109/L): 183 (141–305) LDH (n=20) (U/L): 546±254 aPTT (n=19) (sec): 35±13 PT (n=10): 14.1 (13.2–15.7) Fibrinogen (n=16) (g/L): 5.5±1.8	-	Outcome mortality (n=90): 35 (47.9%)	Type of stroke (n=115) IS: (87.8) ICH: (5.2%) ICH with SAH: (1.7%) CVT: (2.6%) IS with SAH: (0.9%) SAH: (0.9%) TIA: (0.9%	The association between stroke and COVID-19 is probably multifactorial including an amalgamation of traditional vascular risk factors, proinflammatory, and a prothrombotic state.
Samuel R. Daly et al. 2021 USA	A systematic review	33	-	-	-	-	33 patients, who suffered SAH during COVID-19 infection	The most common type of IPH was unilateral lobar (N = 9). The most common location for the aneurysm was the posterior communicating artery (N = 3).	-	-	The mortality rate for hospitalized COVID-19 with intracranial hemorrhage : between 50% and 84.6%.	The rate of ICH in all hospitalized COVID-19 patients: between 0.1% and 3.3% (for patients > 80 years old, the rate was reported at 6.8%.)	Among all hospitalized COVID-19 patients, the rate of intracranial hemorrhage is between 0.1% and 3.3%, and it likely increases for patients>80 years old. The data reviewed suggest that the development of an intracranial hemorrhage during COVID-19 infection is associated with increased rates of morbidity.

Table 1: Characteristics of included studies in this umberella review (continue)

Authors Year Location	Type of review	Number of included studies	Types of included studies	Checklist	Type of acute CVD	Clinical manifestations	Total no./sex/age	Imaging findings	Lab findings	Vaccination history	Outcome	Results	Conclusion
Sebastian Fridman et al. 2020	Systematic review and newly reported cases	42 studies and 1 additional study that is currently under review	-	-	IS 126 (78.8) Intracerebral hemorrhage 24 (15.0) Subarachnoid hemorrhage 3 (1.9) Cerebral venous thrombosis 7 (4.4)	Severe/critical COVID-19, n (%): 92 (57.5) No COVID-19 symptoms before stroke, n (%): 49 (30.8)	Characteristics of 160 patients with COVID-19 with all types of stroke: 160 cases Median (IQR) age, y 65.0 (54.0, 76.3) Female sex, n (%)a 55 (43.0)	About 126 patients with COVID-19 with IS: Vascular and brain imaging, n (%): Large vessel occlusionc 46 (46.9) Infarct limited to the left side 30 (32.3) Infarct limited to the right side 42 (45.2) Bilateral infarcts 20 (21.5) MCA territory 72 (76.6) ACA territory 8 (8.5) PCA territory 12 (12.8) Vertebrobasilar territory 17 (18.1) Multiple territories 29 (30.9)	Laboratory findings, n (%): Elevated D-dimer 96 (82.1) Positive APLA 12 (54.5) Prolonged PTT 18 (20.2) Thrombocytopenia 12 (11.2) Elevated fibrinogen 35 (85.4) Elevated cardiac troponin 30 (40.5)	-	Outcomes, n (%): Venous thromboembolismd 11 (11.8) Deceased 55 (34.4) Home/rehabilitation 68 (42.5)	1.8% (95% CI 0.9%–3.7%) of patients with COVID-19 experienced a new stroke; Event type, n (%): IS 126 (78.8) ICH 24 (15.0) SAH 3 (1.9) CVT 7 (4.4)	Stroke is relatively frequent among patients with COVID-19 and has devastating consequences across all ages. The interplay of older age, comorbid conditions, and severity of COVID-19 respiratory symptoms is associated with extremely elevated mortality.
Amira Athanasios et al. 2021 USA	A Systematic Review	71/28	16 case reports; 11 case series	PRISMA	-	–	73 patients 42% were female The average age of the study population was 60 years	-	-	-	-	The most common preexisting conditions were hypertension and diabetes mellitus. Of the patients hospitalized with COVID-19 infection and CVA, those with no past medical history were significantly younger than those with one or more underlying medical conditions, with an average age of 47 as compared to 64, respectively.	The data suggest SARS-CoV-2 is a risk factor for developing stroke, particularly in patients with hypertension and diabetes. Furthermore, the younger average age of stroke in patients with SARS-CoV-2, particularly those with zero identifiable preexisting conditions, creates high suspicion that SARS-CoV-2 is an independent risk factor for development of stroke.

CVD: Cerebrovascular disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CI: Confidence interval; AST: Aspartat transaminase; ALT: Alanine transaminase; CRP: C-reactive protein; PT: Prothrombin time; aPTT: Activated partial Thromboplastin time; TOAST: The trial of ORG in Acute Stroke Treatment; AIS: acute ischemic stroke; HS: hemorrhagic stroke; SAH: subarachnoid hemorrhage; TIA: transient ischemic attack; ICH: intracerebral hemorrhage; CVT: Cerebral venous thrombosis; PE: Pulmonary embolism; Hb: Haemoglobin; Plt: Platelet; WBC: White blood cell; MCA: middle cerebral ; ACA: anterior cerebral artery; CRP: C-reactive protein; LDH: Lactate dehydrogenase; PCA: Posterior cerebral artery; SAH: subarachnoid hemorrhage; AS: acute stroke; IS: Ischemic stroke; CVA: Cerebrovascular accident

Table 2: Summary of quality assessment of included systematic reviews using AMSTAR2

Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall assessment
Stefania Nannoni et al.	Y	Y	Py	Y	Y	Y	N	Py	N	Y	Na	Na	N	N	N	Y	Low
Isabel Siow et al.	Py	N	Y	Py	Y	N	N	Y	Y	Y	Y	N	N	N	N	Y	Low
Kai Wei Lee et al.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Moderate
Yanhua Cui et al.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Wenzhang Luo et al.	Py	N	Y	Py	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Moderate
Ritesh G. Menezes et al.	Y	N	Y	Y	Py	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Syahrul Syahrul et al.	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Py	N	Y	Moderate
Zhelv Yao et al.	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Ying Kiat Tan et al.	Py	N	Y	Py	Y	Py	N	Y	Y	Y	Na	Na	N	N	Na	Y	Moderate
Aristeidis H. Katsanos et al.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Sina Parsay et al.	Y	N	Py	Py	Y	Py	N	Y	N	Y	Y	N	N	N	Y	Y	Low
Shuwen Li et al.	N	N	Y	Y	Py	Py	N	Y	N	Y	Y	N	N	Y	Y	Y	Low
T. Siepmann et al.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y	Moderate
Mai Yamakawa et al.	Y	N	Y	Py	Py	Py	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
István Szegedi et al.	Py	N	Py	Py	Py	Py	N	Py	N	Y	Na	Na	N	N	Na	Y	Low
Tao Yu et al.	N	N	Py	N	Py	N	N	Y	N	Y	Na	Na	N	N	N	Y	Critically low
Alejandra Castro-Varela et al.	N	Y	Y	Y	Y	Y	N	Py	N	Y	Na	Na	Y	Y	N	Y	Moderate
Simone Vidale	N	N	Py	Py	N	N	N	Y	N	Y	Na	Na	N	N	Na	Y	Critically low
Ganna Trepet et al.	N	N	Py	Py	Y	Y	N	Y	Y	Y	Na	Na	N	N	Na	Y	Low
Rohit Bhatia	Y	N	Y	Y	N	Py	N	Y	Y	Y	Na	Na	N	N	Na	Y	Low
Samuel R. Daly et al.	N	Y	Y	N	N	N	N	Y	N	Y	Na	Na	N	N	Na	Y	Critically low
Sebastian Fridman et al.	N	N	Y	Py	Py	Py	N	Py	Y	Y	Y	Y	Py	Y	Y	Y	Moderate
Amira Athanasios et al.	N	N	Y	N	Py	Py	N	Y	Py	Y	Py	Py	N	N	N	Y	Critically low

*N: no; Na: not applicable; Py: partially yes; Y: yes. A MeaSurement Tool to Assess systematic Reviews (AMSTAR)-2 overall assessment rating: High-High-quality reviews offer a precise and thorough overview of study results relevant to the research question;Moderate-quality reviews have multiple weaknesses but lack critical flaws, potentially providing an accurate summary of available studies; Low-Low-quality reviews possess critical flaws and may not accurately summarize relevant studies; or Critically low-Critically low-quality reviews have multiple critical flaws and should not be trusted for an accurate and comprehensive summary of available studies.

Q1: Did the research questions and inclusion criteria for the review include the components of PICO?

Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Q3: Did the review authors explain their selection of the study designs for inclusion in the review?

Q4: Did the review authors use a comprehensive literature search strategy?

Q5: Did the review authors perform study selection in duplicate?

Q6: Did the review authors perform data extraction in duplicate?

Q7: Did the review authors provide a list of excluded studies and justify the exclusions?

Q8: Did the review authors describe the included studies in adequate detail?

Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

Q10: Did the review authors report on the sources of funding for the studies included in the review?

Q11: If meta-analysis was performed, did the authors use appropriate methods for statistical combination of results?

Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Q15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Supplementary table 1: Search strategy of the present umbrella review

Embase
('coronavirus disease 2019'/exp/mj OR '2019 novel coronavirus disease':ti,ab OR '2019 novel coronavirus epidemic':ti,ab OR '2019 novel coronavirus infection':ti,ab OR '2019-nCoV disease':ti,ab OR '2019-nCoV infection':ti,ab OR 'COVID':ti,ab OR 'COVID 19':ti,ab OR 'COVID 2019':ti,ab OR 'COVID-10':ti,ab OR 'COVID-19':ti,ab OR 'COVID19':ti,ab OR 'SARS coronavirus 2 infection':ti,ab OR 'SARS-CoV-2 disease':ti,ab OR 'SARS-CoV-2 infection':ti,ab OR 'SARS-CoV2 disease':ti,ab OR 'SARS-CoV2 infection':ti,ab OR 'SARSCoV2 disease':ti,ab OR 'SARSCoV2 infection':ti,ab OR 'Wuhan coronavirus disease':ti,ab OR 'Wuhan coronavirus infection':ti,ab OR 'coronavirus disease 2':ti,ab OR 'coronavirus disease 2010':ti,ab OR 'coronavirus disease 2019':ti,ab OR 'coronavirus disease-19':ti,ab OR 'coronavirus infection 2019':ti,ab OR 'nCoV 2019 disease':ti,ab OR 'nCoV 2019 infection':ti,ab OR 'novel coronavirus 2019 disease':ti,ab OR 'novel coronavirus 2019 infection':ti,ab OR 'novel coronavirus disease 2019':ti,ab OR 'novel coronavirus infection 2019':ti,ab OR 'paucisymptomatic coronavirus disease 2019':ti,ab OR 'severe acute respiratory syndrome 2':ti,ab OR 'severe acute respiratory syndrome CoV-2 infection':ti,ab OR 'severe acute respiratory syndrome coronavirus 2 infection':ti,ab OR 'severe acute respiratory syndrome coronavirus 2019 infection':ti,ab) AND ('cerebrovascular accident'/exp/mj OR 'CVA':ti,ab OR 'accident, cerebrovascular':ti,ab OR 'acute cerebrovascular lesion':ti,ab OR 'acute focal cerebral vasculopathy':ti,ab OR 'acute stroke':ti,ab OR 'apoplectic stroke':ti,ab OR 'apoplexia':ti,ab OR 'apoplexy':ti,ab OR 'blood flow disturbance, brain':ti,ab OR 'brain accident':ti,ab OR 'brain attack':ti,ab OR 'brain blood flow disturbance':ti,ab OR 'brain insult':ti,ab OR 'brain insultus':ti,ab OR 'brain vascular accident':ti,ab OR 'cerebral apoplexia':ti,ab OR 'cerebral insult':ti,ab OR 'cerebral stroke':ti,ab OR 'cerebral vascular accident':ti,ab OR 'cerebral vascular insufficiency':ti,ab OR 'cerebro vascular accident':ti,ab OR 'cerebrovascular accident':ti,ab OR 'cerebrovascular arrest':ti,ab OR 'cerebrovascular failure':ti,ab OR 'cerebrovascular injury':ti,ab OR 'cerebrovascular insufficiency':ti,ab OR 'cerebrovascular insult':ti,ab OR 'cerebrum vascular accident':ti,ab OR 'cryptogenic stroke':ti,ab OR 'insultus cerebralis':ti,ab OR 'ischaemic seizure':ti,ab OR 'ischemic seizure':ti,ab OR 'stroke':ti,ab OR 'thrombotic stroke':ti,ab) AND (('systematic review'/mj OR 'review, systematic':ti OR 'systematic review':ti) OR ('meta analysis'/exp/mj OR 'analysis, meta':ti OR 'meta analysis':ti OR 'meta-analysis':ti OR 'metaanalysis':ti) OR (review/exp/mj OR 'review':ti))
Scopus
(TITLE-ABS-KEY ("coronavirus disease 2019" OR "2019 novel coronavirus disease" OR "2019 novel coronavirus epidemic" OR "2019 novel coronavirus infection" OR "2019-nCoV disease" OR "2019- nCoV infection" OR "COVID" OR "COVID 19" OR "COVID 2019" OR "COVID-10" OR "COVID-19" OR "COVID19" OR "SARS coronavirus 2 infection" OR "SARS-CoV-2 disease" OR "SARS-CoV-2 infection" OR "SARS-CoV2 disease" OR "SARS CoV2 infection" OR "SARSCoV2 disease" OR "SARSCoV2 infection" OR "Wuhan coronavirus disease" OR "Wuhan coronavirus infection" OR "coronavirus disease 2" OR "coronavirus disease 2010" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "coronavirus infection 2019" OR "nCoV 2019 disease" OR "nCoV 2019 infection" OR "novel coronavirus 2019 disease" OR "novel coronavirus 2019 infection" OR "novel coronavirus disease 2019" OR "novel coronavirus infection 2019" OR "paucisymptomatic coronavirus disease 2019" OR "severe acute respiratory syndrome 2" OR "severe acute respiratory syndrome CoV-2 infection" OR "severe acute respiratory syndrome coronavirus 2 infection" OR "severe acute respiratory syndrome coronavirus 2019 infection") AND TITLE-ABS-KEY ("cerebrovascular accident" OR "CVA" OR "accident, cerebrovascular" OR "acute cerebrovascular lesion" OR "acute focal cerebral vasculopathy" OR "acute stroke" OR "apoplectic stroke" OR "apoplexia" OR "apoplexy" OR "blood flow disturbance, brain" OR "brain accident" OR "brain attack" OR "brain blood flow disturbance" OR "brain insult" OR "brain insultus" OR "brain vascular accident" OR "cerebral apoplexia" OR "cerebral insult" OR "cerebral stroke" OR "cerebral vascular accident" OR "cerebral vascular insufficiency" OR "cerebro vascular accident" OR "cerebrovascular accident" OR "cerebrovascular arrest" OR "cerebrovascular failure" OR "cerebrovascular injury" OR "cerebrovascular insufficiency" OR "cerebrovascular insult" OR "cerebrum vascular accident" OR "cryptogenic stroke" OR "insultus cerebralis" OR "ischaemic seizure" OR "ischemic seizure" OR "stroke" OR "thrombotic stroke") AND TITLE ("systematic review" OR "meta analysis"))
Web of sciences
((("cerebrovascular accident" OR CVA OR "accident, cerebrovascular" OR "acute cerebrovascular lesion" OR "acute focal cerebral vasculopathy" OR "acute stroke" OR "apoplectic stroke" OR apoplexia OR apoplexy OR "blood flow disturbance, brain" OR "brain accident" OR "brain attack" OR "brain blood flow disturbance" OR "brain insult" OR "brain insultus" OR "brain vascular accident" OR "cerebral apoplexia" OR "cerebral insult" OR "cerebral stroke" OR "cerebral vascular accident" OR "cerebral vascular insufficiency" OR "cerebro vascular accident" OR "cerebrovascular accident" OR "cerebrovascular arrest" OR "cerebrovascular failure" OR "cerebrovascular injury" OR "cerebrovascular insufficiency" OR "cerebrovascular insult" OR "cerebrum vascular accident" OR "cryptogenic stroke" OR "insultus cerebralis" OR "ischaemic seizure" OR "ischemic seizure" OR stroke OR "thrombotic stroke") OR ("cerebrovascular accident[Other Term]" OR "CVA[Other Term]" OR "accident, cerebrovascular[Other Term]" OR "acute cerebrovascular lesion[Other Term]" OR "acute focal cerebral vasculopathy[Other Term]" OR "acute stroke[Other Term]" OR "apoplectic stroke[Other Term]" OR "apoplexia[Other Term]" OR "apoplexy[Other Term]" OR "blood flow disturbance, brain[Other Term]" OR "brain accident[Other Term]" OR "brain attack[Other Term]" OR "brain blood flow disturbance[Other Term]" OR "brain insult[Other Term]" OR "brain insultus[Other Term]" OR "brain vascular accident[Other Term]" OR "cerebral apoplexia[Other Term]" OR "cerebral insult[Other Term]" OR "cerebral stroke[Other Term]" OR "cerebral vascular accident[Other Term]" OR "cerebral vascular insufficiency[Other Term]" OR "cerebro vascular accident[Other Term]" OR "cerebrovascular accident[Other Term]" OR "cerebrovascular arrest[Other Term]" OR "cerebrovascular failure[Other Term]" OR "cerebrovascular injury[Other Term]" OR "cerebrovascular insufficiency[Other Term]" OR "cerebrovascular insult[Other Term]" OR "cerebrum vascular accident[Other Term]" OR "cryptogenic stroke[Other Term]" OR "insultus cerebralis[Other Term]" OR "ischaemic seizure[Other Term]" OR "ischemic seizure[Other Term]" OR "stroke[Other Term]" OR "thrombotic stroke[Other Term]") AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) AND (("coronavirus disease 2019" OR "2019 novel coronavirus disease" OR "2019 novel coronavirus epidemic" OR "2019 novel coronavirus infection" OR "2019-nCoV disease" OR "2019-

Supplementary table 1: Search strategy of the present umbrella review (continue)

nCoV infection" OR COVID OR "COVID 19" OR "COVID 2019" OR COVID-10 OR COVID-19 OR COVID19 OR "SARS coronavirus 2 infection" OR "SARS-CoV-2 disease" OR "SARS-CoV-2 infection" OR "SARS-CoV2 disease" OR "SARS-CoV2 infection" OR "SARSCoV2 disease" OR "SARSCoV2 infection" OR "Wuhan coronavirus disease" OR "Wuhan coronavirus infection" OR "coronavirus disease 2" OR "coronavirus disease 2010" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "coronavirus infection 2019" OR "nCoV 2019 disease" OR "nCoV 2019 infection" OR "novel coronavirus 2019 disease" OR "novel coronavirus 2019 infection" OR "novel coronavirus disease 2019" OR "novel coronavirus infection 2019" OR "paucisymptomatic coronavirus disease 2019" OR "severe acute respiratory syndrome 2" OR "severe acute respiratory syndrome CoV-2 infection" OR "severe acute respiratory syndrome coronavirus 2 infection" OR "severe acute respiratory syndrome coronavirus 2019 infection") OR ("coronavirus disease 2019[Other Term]" OR "2019 novel coronavirus disease[Other Term]" OR "2019 novel coronavirus epidemic[Other Term]" OR "2019 novel coronavirus infection[Other Term]" OR "2019-nCoV disease[Other Term]" OR "2019-nCoV infection[Other Term]" OR "COVID[Other Term]" OR "COVID 19[Other Term]" OR "COVID 2019[Other Term]" OR "COVID-10[Other Term]" OR "COVID-19[Other Term]" OR "COVID19[Other Term]" OR "SARS coronavirus 2 infection[Other Term]" OR "SARS-CoV-2 disease[Other Term]" OR "SARS-CoV-2 infection[Other Term]" OR "SARS-CoV2 disease[Other Term]" OR "SARS-CoV2 infection[Other Term]" OR "SARSCoV2 disease[Other Term]" OR "SARSCoV2 infection[Other Term]" OR "Wuhan coronavirus disease[Other Term]" OR "Wuhan coronavirus infection[Other Term]" OR "coronavirus disease 2[Other Term]" OR "coronavirus disease 2010[Other Term]" OR "coronavirus disease 2019[Other Term]" OR "coronavirus disease-19[Other Term]" OR "coronavirus infection 2019[Other Term]" OR "nCoV 2019 disease[Other Term]" OR "nCoV 2019 infection[Other Term]" OR "novel coronavirus 2019 disease[Other Term]" OR "novel coronavirus 2019 infection[Other Term]" OR "novel coronavirus disease 2019[Other Term]" OR "novel coronavirus infection 2019[Other Term]" OR "paucisymptomatic coronavirus disease 2019[Other Term]" OR "severe acute respiratory syndrome 2[Other Term]" OR "severe acute respiratory syndrome CoV-2 infection[Other Term]" OR "severe acute respiratory syndrome coronavirus 2 infection[Other Term]" OR "severe acute respiratory syndrome coronavirus 2019 infection[Other Term]") AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) OR ((Stroke) AND (COVID-19 OR SARS-CoV-2)) "Filters: Meta-Analysis, Review, Systematic Review" **Pubmed**
Search: ((("cerebrovascular accident"[Title] OR "CVA"[Title] OR "accident, cerebrovascular"[Title] OR "acute cerebrovascular lesion"[Title] OR "acute focal cerebral vasculopathy"[Title] OR "acute stroke"[Title] OR "apoplectic stroke"[Title] OR "apoplexia"[Title] OR "apoplexy"[Title] OR "blood flow disturbance, brain"[Title] OR "brain accident"[Title] OR "brain attack"[Title] OR "brain blood flow disturbance"[Title] OR "brain insult"[Title] OR "brain insultus"[Title] OR "brain vascular accident"[Title] OR "cerebral apoplexia"[Title] OR "cerebral insult"[Title] OR "cerebral stroke"[Title] OR "cerebral vascular accident"[Title] OR "cerebral vascular insufficiency"[Title] OR "cerebro vascular accident"[Title] OR "cerebrovascular accident"[Title] OR "cerebrovascular arrest"[Title] OR "cerebrovascular failure"[Title] OR "cerebrovascular injury"[Title] OR "cerebrovascular insufficiency"[Title] OR "cerebrovascular insult"[Title] OR "cerebrum vascular accident"[Title] OR "cryptogenic stroke"[Title] OR "insultus cerebralis"[Title] OR "ischaemic seizure"[Title] OR "ischemic seizure"[Title] OR "stroke"[Title] OR "thrombotic stroke"[Title]) OR ("cerebrovascular accident"[Other Term] OR "CVA"[Other Term] OR "accident, cerebrovascular"[Other Term] OR "acute cerebrovascular lesion"[Other Term] OR "acute focal cerebral vasculopathy"[Other Term] OR "acute stroke"[Other Term] OR "apoplectic stroke"[Other Term] OR "apoplexia"[Other Term] OR "apoplexy"[Other Term] OR "blood flow disturbance, brain"[Other Term] OR "brain accident"[Other Term] OR "brain attack"[Other Term] OR "brain blood flow disturbance"[Other Term] OR "brain insult"[Other Term] OR "brain insultus"[Other Term] OR "brain vascular accident"[Other Term] OR "cerebral apoplexia"[Other Term] OR "cerebral insult"[Other Term] OR "cerebral stroke"[Other Term] OR "cerebral vascular accident"[Other Term] OR "cerebral vascular insufficiency"[Other Term] OR "cerebro vascular accident"[Other Term] OR "cerebrovascular accident"[Other Term] OR "cerebrovascular arrest"[Other Term] OR "cerebrovascular failure"[Other Term] OR "cerebrovascular injury"[Other Term] OR "cerebrovascular insufficiency"[Other Term] OR "cerebrovascular insult"[Other Term] OR "cerebrum vascular accident"[Other Term] OR "cryptogenic stroke"[Other Term] OR "insultus cerebralis"[Other Term] OR "ischaemic seizure"[Other Term] OR "ischemic seizure"[Other Term] OR "stroke"[Other Term] OR "thrombotic stroke"[Other Term]) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) AND (("coronavirus disease 2019"[Title] OR "2019 novel coronavirus disease"[Title] OR "2019 novel coronavirus epidemic"[Title] OR "2019 novel coronavirus infection"[Title] OR "2019-nCoV disease"[Title] OR "2019-nCoV infection"[Title] OR "COVID"[Title] OR "COVID 19"[Title] OR "COVID 2019"[Title] OR "COVID-10"[Title] OR "COVID-19"[Title] OR "COVID19"[Title] OR "SARS coronavirus 2 infection"[Title] OR "SARS-CoV-2 disease"[Title] OR "SARS-CoV-2 infection"[Title] OR "SARS-CoV2 disease"[Title] OR "SARS-CoV2 infection"[Title] OR "SARSCoV2 disease"[Title] OR "SARSCoV2 infection"[Title] OR "Wuhan coronavirus disease"[Title] OR "Wuhan coronavirus infection"[Title] OR "coronavirus disease 2"[Title] OR "coronavirus disease 2010"[Title] OR "coronavirus disease 2019"[Title] OR "coronavirus disease-19"[Title] OR "coronavirus infection 2019"[Title] OR "nCoV 2019 disease"[Title] OR "nCoV 2019 infection"[Title] OR "novel coronavirus 2019 disease"[Title] OR "novel coronavirus 2019 infection"[Title] OR "novel coronavirus disease 2019"[Title] OR "novel coronavirus infection 2019"[Title] OR "paucisymptomatic coronavirus disease 2019"[Title] OR "severe acute respiratory syndrome 2"[Title] OR "severe acute respiratory syndrome CoV-2 infection"[Title] OR "severe acute respiratory syndrome coronavirus 2 infection"[Title] OR "severe acute respiratory syndrome coronavirus 2019 infection"[Title]) OR ("coronavirus disease 2019"[Other Term] OR "2019 novel coronavirus disease"[Other Term] OR "2019 novel coronavirus epidemic"[Other Term] OR "2019 novel coronavirus infection"[Other Term] OR "2019-nCoV disease"[Other Term] OR "2019-nCoV infection"[Other Term] OR "COVID"[Other Term] OR "COVID 19"[Other Term] OR "COVID 2019"[Other Term] OR "COVID-10"[Other Term] OR "COVID-19"[Other Term] OR "COVID19"[Other Term] OR "SARS coronavirus 2 infection"[Other Term] OR "SARS-CoV-2 disease"[Other Term] OR "SARS-CoV-2 infection"[Other Term] OR "SARS-CoV2 disease"[Other Term] OR "SARS-CoV2 infection"[Other Term] OR "SARSCoV2 disease"[Other Term] OR "SARSCoV2 infection"[Other Term] OR "Wuhan coronavirus disease"[Other Term] OR "Wuhan coronavirus infection"[Other Term] OR "coronavirus disease 2"[Other Term] OR "coronavirus disease 2010"[Other Term] OR "coronavirus disease 2019"[Other Term] OR "coronavirus disease-19"[Other Term] OR "coronavirus infection 2019"[Other Term] OR "nCoV 2019 disease"[Other Term] OR "nCoV 2019 infection"[Other Term] OR "novel coronavirus 2019 disease"[Other Term] OR "novel coronavirus 2019 infection"[Other Term] OR "novel coronavirus disease 2019"[Other Term] OR "novel coronavirus infection 2019"[Other Term] OR "paucisymptomatic coronavirus disease 2019"[Other Term] OR "severe acute respiratory syndrome 2"[Other Term] OR "severe acute respiratory syndrome CoV-2 infection"[Other Term] OR "severe acute respiratory syndrome coronavirus 2 infection"[Other Term] OR "severe acute respiratory syndrome coronavirus 2019 infection"[Other Term]) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) OR (("Stroke"[Mesh]) AND ("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh])) **Filters:** Meta-Analysis, Review, Systematic Review