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Association between SARS-CoV-2 and stroke: perspectives from a metaumbrella-review

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Abstract

In the face of the global COVID-19 pandemic, the need arose to investigate potential complications associated with SARS-CoV-2, including the risk of stroke.

Objective

This study aimed to verify the association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the risk of stroke on the basis of systematic reviews and meta-analyses to assess the inclusion of the virus as a new risk factor for cerebrovascular diseases.

Methods

A metaumbrella study was conducted, which included 34 systematic reviews, of which 4 were selected for the final analysis on the basis of methodological quality and consistency. The analysis aggregated the results of 70 primary studies, considering different stroke subtypes and outcomes associated with COVID-19. Study heterogeneity was assessed via the I^2 index, and significance bias was verified via Egger's test.

Results

COVID-19 severity was significantly associated with an increased risk of stroke (eOR = 2.48; 95% CI: 1.55–3.95), particularly ischemic stroke (eOR = 1.76; 95% CI: 1.11–2.80) and hemorrhagic stroke (eOR = 3.86; 95% CI: 1.79–8.33). Additionally, patients with cerebrovascular comorbidities had higher mortality (eOR = 2.48; 95% CI: 2.48–19.63), as did those who had previously suffered a stroke (eOR = 6.08; 95% CI: 3.73–9.91).

Conclusion

The association between SARS-CoV-2 and stroke incidence was consistent and significant, suggesting that COVID-19 should be considered a new risk factor for cerebrovascular diseases. However, the high heterogeneity among the studies analyzed reinforces the need for further research to consolidate this relationship.

Keywords SARS-CoV-2, Stroke, Risk factors, Metaumbrella, Systematic review

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Introduction

Stroke is responsible for millions of deaths annually and is a global public health challenge [1–3]. It is a sudden neurological deficit, which can be transient or permanent, caused by a vascular injury that results in ischemia or hemorrhage in areas of the brain [2]. Stroke is a multifactorial disease caused by a combination of modifiable, nonmodifiable, and environmental risk factors [1, 4, 5].

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, triggered a global health crisis [6, 7]. Although it is recognized primarily for causing respiratory infections, recent studies have associated COVID-19 with an increased risk of stroke [8–10].

This association raises concerns about the mechanisms by which SARS-CoV-2 may be linked to neurological damage. Hypotheses include systemic inflammation, direct invasion of the nervous system by the virus, and complications of the immune response [12, 13]. In addition, individuals with preexisting risk factors for stroke, such as hypertension and diabetes mellitus, seem to be more likely to develop more severe cases of COVID-19 and, consequently, a higher risk of stroke [14–19].

This study aimed to verify the association between SARS-CoV-2 and stroke, using systematic reviews as a guiding reference. This investigation aims to contribute to the scientific debate on the possible inclusion of the virus as a risk factor for cerebrovascular diseases.

Methodology

This study is characterized as a Umbrella Review [20], which aims to synthesize evidence from multiple systematic reviews [21, 22]. The methodology used followed the PRIO-harms [23] checklist to ensure the rigor and quality of the analysis. The formulation of the research question considered the following elements: population, phenomenon of interest, result, context, type of overview and general objective [24–26]. On the basis of the hypothesis that SARS-CoV-2 infection is associated with an increased risk of stroke, the following guiding question was formulated: "Does the association between SARS-CoV-2 and stroke presuppose the need to include it as a new risk factor in the list for cerebrovascular disease?". The protocol of this study was registered in the International Prospective Register of Systematic Reviews, under number CRD42022323750.

Search strategy

Studies published in English, Spanish, or Portuguese from March 2020 to March 2023 that address the associations between COVID-19 and ischemic or hemorrhagic stroke or small or large vessels in any age group were selected. The databases consulted were PubMed/MEDLINE, LILACS, Scopus, and Web of Science. The search strategy used a strategic combination of terms and keywords in all three languages. The terms used were 'stroke', 'COVID-19', 'neurological complications', and 'systematic review.

To complement and broaden the search, the following terms were used in different combinations, with Boolean operators used to improve the results: (STROKE* OR CEREBROVASCULAR* OR NEUROLOGICAL*) AND (COVID* OR SARS-CoV-2*) AND (SYSTEMATIC* AND REVIEW*).

Selection criteria

Scientific articles that included systematic reviews, systematic reviews with meta-analyses of case studies, case series, case–control studies and, preferably, randomized, prospective and retrospective cohort studies were selected. Reviews that were not available in full, incomplete manuscripts, studies outside the context of systematic review, and nonoriginal research articles, such as editorial comments, opinion articles, letters, protocols, reports, and book chapters, were excluded. Nonclinical features, such as nonneurological complications, as well as studies that presented a diagnosis of COVID-19 without any reports of stroke as a complication, were also excluded.

Data extraction

The selection of articles was carried out by two independent reviewers (AMLBS and EFA) in two stages. First, the titles and abstracts were independently evaluated, and any disagreements were resolved by consensus. The full texts of the selected articles were subsequently analyzed in the same way, with consensus being used to resolve disagreements.

Agreement between the reviewers was assessed via Cohen's kappa coefficient [27]. In the screening phase of the titles and abstracts, the kappa coefficient was 0.62511, indicating substantial agreement among the reviewers. This result suggests that the selection criteria were well defined and understood, resulting in a consistent initial selection of studies.

The use of Covidence [28] software significantly improved the review process, facilitating the organization and analysis of the data, including the calculation of the kappa index and the generation of the PRISMA flowchart. This online tool allows real-time collaboration between reviewers, simplifying the resolution of disagreements and ensuring the transparency of the process.

Quality assessment

The methodological quality of systematic reviews was assessed via the ROBIS [29] tool, a validated and widely used instrument to assess the risk of bias in systematic reviews in healthcare. The ROBIS tool is especially useful for evaluating reviews that address interventions, diagnosis, prognosis, and etiology and is therefore suitable for the scope of this study.

The evaluation process with the ROBIS tool is divided into three main phases: Phase 1: Assessment of the relevance of the systematic review to the research question. In this step, whether the selected systematic review

directly addresses the research question of the Umbrella Review is verified.

Phase 2: Identification of concerns with the systematic review process. This phase investigates four critical domains that may be sources of bias: study eligibility criteria, which evaluate whether the inclusion and exclusion criteria of the primary studies are adequate and well defined. Identification and selection of studies: Analyze the search and selection process of studies and check whether there is a risk of publication bias. Data collection and study evaluation: Examines the quality of data collection and the assessment of risk of bias in primary studies. Synthesis and findings: Evaluates the presentation and synthesis of the results, considering the heterogeneity between the studies.

Phase 3: Judging the overall risk of bias for the systematic review. On the basis of the analyses of the previous phases, the overall risk of bias of the systematic review was classified as low, high, or unclear.

Data analysis

Initially, for each identified factor evaluated in more than one individual study, we performed a separate random-effects meta-analysis to obtain a pooled estimate of the effect size, which we assumed would follow a normal distribution with variance equal to the sum of the weights of the studies [30] (method of DerSimonian and Laird, 1986). The results of the meta-analyses were the effect sizes with their corresponding 95% confidence intervals (95% CI) and *p* values, as well as the statistics needed to assess the level of evidence. We used the effect size measure used in each original meta-analysis (i.e., RR, OR, or SMD) and calculated the OR equivalents (eORs) for all effect size statistics.

We evaluated the heterogeneity between studies with an I^2 *index of* [31]. I2 values > 50% indicated high heterogeneity [32]. We also assessed whether there was evidence of effects from small studies via Egger's test [33], where statistical significance would indicate potential publication bias [34].

In addition, a rating system for the strength of evidence was used, which has been widely used in previous umbrella reviews [35, 36]. Specifically, we classified the levels of evidence of the significant associations between each factor into convincing evidence (class I), highly suggestive evidence (class II), suggestive evidence (class III), or weak evidence (class IV). Convincing evidence would require a number of studies ≥ 10, a number of cases ≥ 500, $I^2 \leq 50\%$, and no signs of influence of small studies in the meta-analysis (Egger test ≥ 0.10). The suggestive evidence required a number ≥ 10 studies, a number ≥ 400 cases, an Egger test with a *p* value ≥ 0.10, and $I^2 \leq 50\%$. Weak evidence with a case count ≥ 300, Egger's test with a *P* value ≥ 0.10, $I^2 \leq 75\%$, and very weak evidence did not require a specific number of cases and $p < 0.05$.

Finally, the meta-analyses were repeated to estimate heterogeneity with the Hartung–Knapp–Sidik–Johkman method for random effects. This method estimates variance as the weighted mean square error divided by degrees of freedom and assumes a distribution t [37–39]. The main difference between a normal distribution and a distribution t is that in the former, we assume that we can know variance, whereas in the latter, we do not make this assumption, as is indeed the case. This difference can be negligible when the number of studies is large, but it can be relevant when the number of studies is small. All analyses were performed with version 1.0.11 of the metaumbrella package, implemented in the R environment.

Results

Identification and selection of studies

From an initial search of databases and registries, 2,490 studies relevant to the investigation of the association between COVID-19 and stroke were identified. After removing 1,289 duplicate references, 1,201 studies were screened. Among these, 141 were excluded because they did not meet the relevant criteria and focused mainly on management or medications, which was not the focus of this study. This resulted in the detailed evaluation of 1,060 studies for their eligibility.

Of these 1,060 studies, 1,026 were excluded for various reasons, including a focus on nonneurological manifestations of COVID-19, specific nonpertinent populations, medical conditions unrelated to COVID-19, inadequate methodologies, or unrelated interventions.

At the end of this process, 34 studies were considered eligible. Of these, four studies were selected for analysis in the metaumbrella, on the basis of high methodological quality and consistency with the established criteria (Fig. 1).

Characteristics of the included studies

The main characteristics of the 34 studies initially found demonstrated important cohesion in the demographic and geographic profiles of the patients evaluated. The mean age of the patients was 61.2 years, which indicates that the study population consisted predominantly of individuals in an age group at higher risk for stroke. In addition, there was a clear predominance of males, with an average of 59.9% of participants being men. This disparity may be associated with men's greater susceptibility to developing severe forms of COVID-19 and its complications, including stroke.

Although the impact of sex was not directly analyzed in this study, recent reviews indicate important

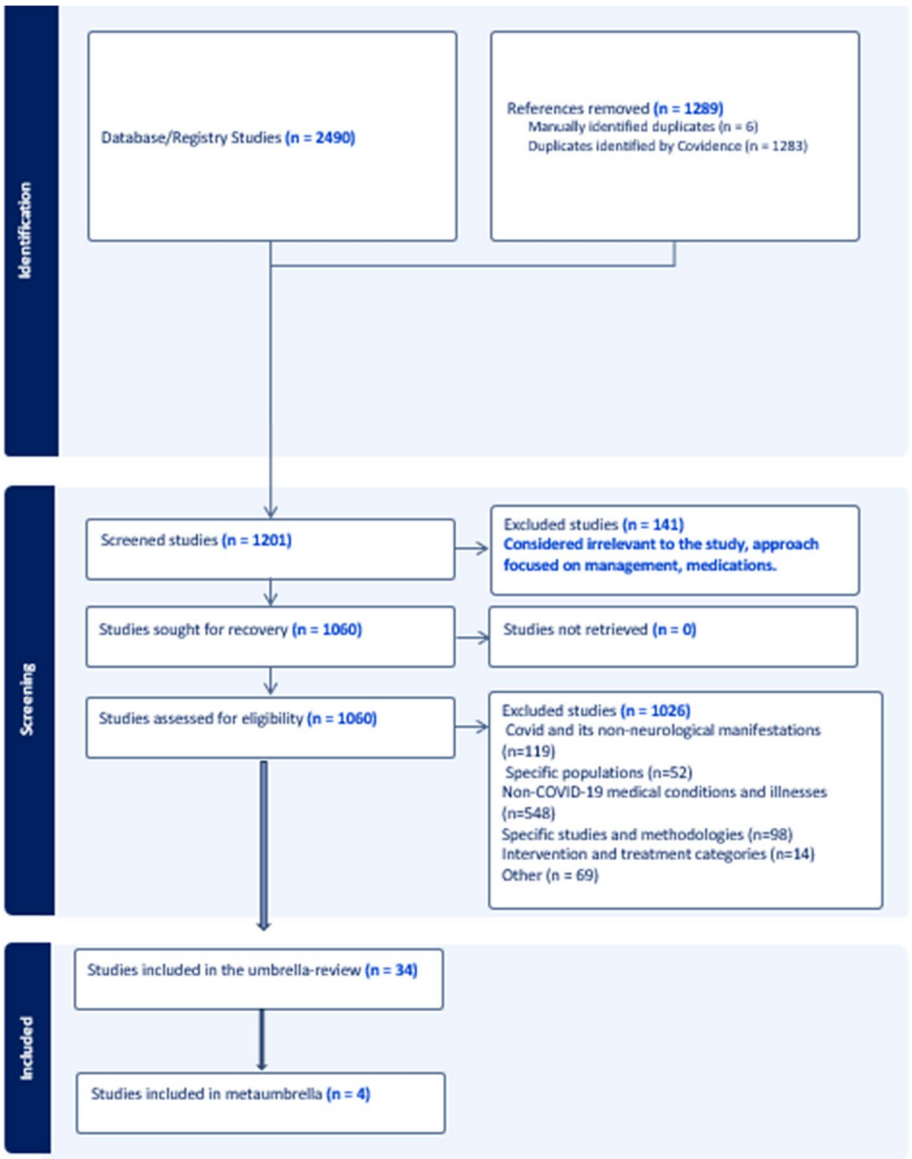

Fig. 1 Prism

sex-related clinical differences in risk factors, stroke subtypes, and outcomes [40].

Geographically, these studies were conducted in a variety of countries, reflecting the global spread of the pandemic. Among the most frequently cited places are the United States, Italy, India, Brazil, and Spain, with particular emphasis on China. This country has emerged as the most frequently represented location, possibly because of the initial and significant impact of the COVID-19 pandemic on its territory, which has led to increased production of data and studies on the neurological complications associated with SARS-CoV-2.

Risk of bias assessment

Figure 2 shows the evaluation of the methodological quality of the 34 studies included in the review using the ROBIS tool. Most studies were at low risk of bias in terms of criteria such as eligibility, identification and selection of studies, and data collection. However, some studies have shown uncertain or high risks, particularly in the selection of studies and the synthesis of results.

Among the four studies selected for the meta-umbrella, the assessment of bias was predominantly favorable, with all being classified as low risk in terms of overall bias.

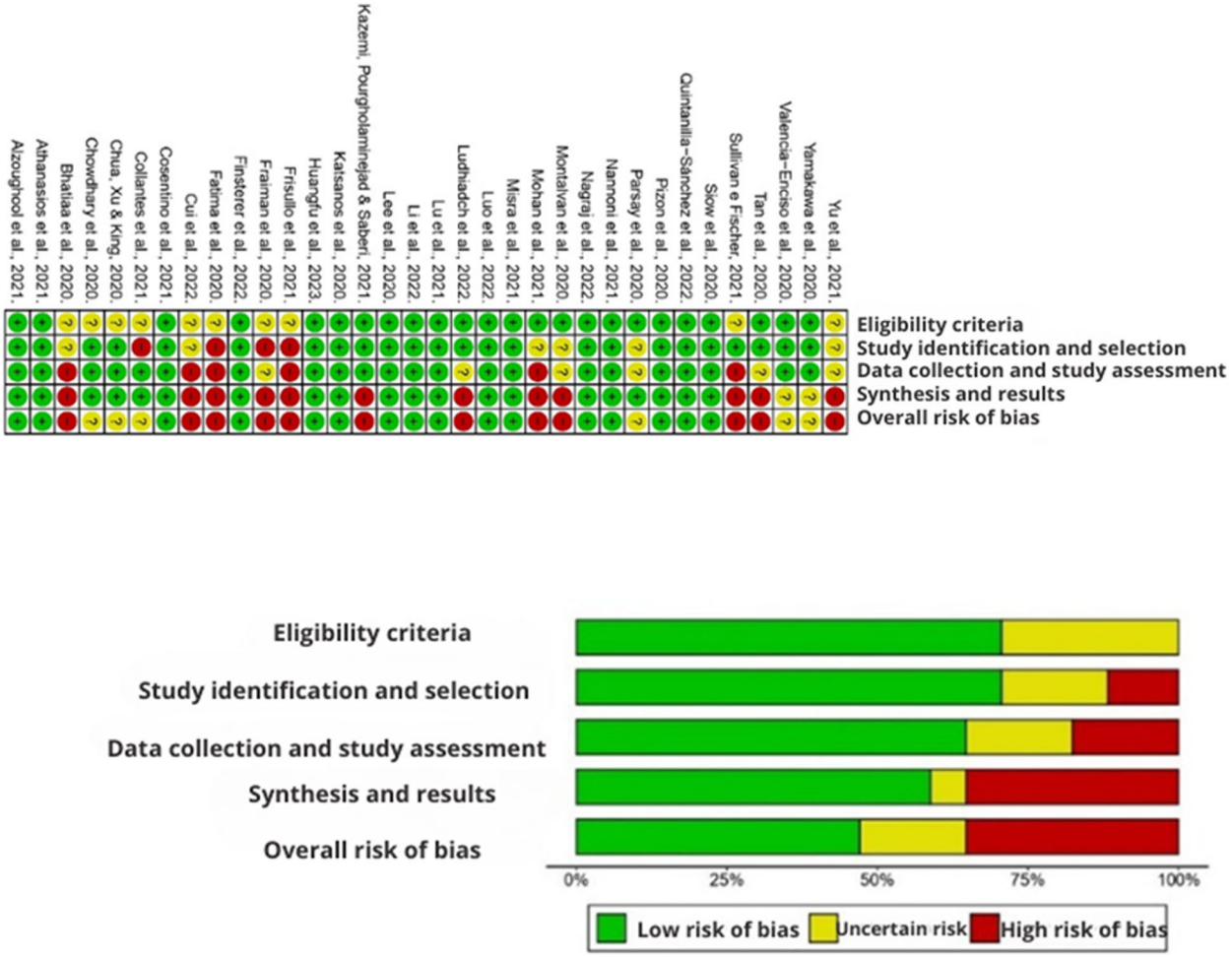

Fig. 2 Quality of the ROBIS studies

Metaumbrella results

The results of the metaumbrella (Fig. 3), which included four systematic reviews with meta-analyses, covered a total of 70 primary studies that evaluated the association between COVID-19 and stroke in five different study subjects. These objects of study were as follows:

1. "COVID-19 severity and stroke risk": The meta-analysis revealed a significant association between COVID-19 severity and increased stroke risk, with an odds ratio (eOR) of 2.48 (95% CI: 1.55–3.95). These findings indicate that patients with severe COVID-

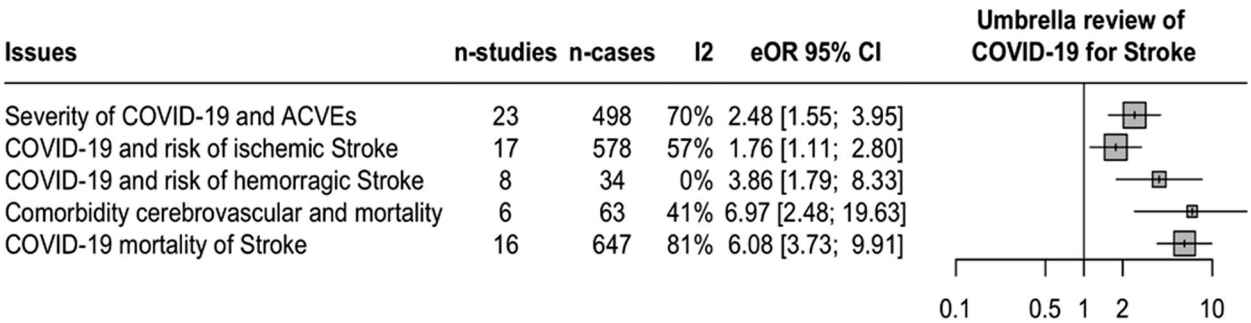

Fig. 3 Meta-Umbrella showing the association between COVID-19 and stroke

19 are significantly more likely to develop stroke than are those with less severe forms of the disease.

2. "COVID-19 and ischemic stroke risk": A significant association was found between COVID-19 and a higher risk of ischemic stroke, with an eOR of 1.76 (95% CI: 1.11–2.80). These findings suggest that COVID-19 may be a risk factor for the development of ischemic stroke.

3. "COVID-19 and hemorrhagic stroke risk": The analysis also revealed an association between COVID-19 and increased risk of hemorrhagic stroke, with an eOR of 3.86 (95% CI: 1.79–8.33). This finding indicates that, in addition to ischemic stroke, COVID-19 may also be related to an increased risk of hemorrhagic stroke.

4. "Cerebrovascular comorbidity and mortality in patients with COVID-19": Patients with cerebrovascular comorbidities who contracted COVID-19 had higher mortality than did those who did not have a stroke, with an eOR of 2.48 (95% CI: 2.48–19.63). This result highlights the adverse impact of preexisting cerebrovascular conditions on the survival of COVID-19 patients.

5. "COVID-19 and stroke mortality": Mortality was significantly greater among COVID-19 patients who already had a history of stroke, with an eOR of 6.08 (95% CI: 3.73–9.91). These data underscore the severity of the impact of COVID-19 on patients who had previously experienced a stroke.

In addition to these results, an overlap of two primary studies (Qureshi [41] and Merkler [42]) was observed (Fig. 4) in three distinct systematic reviews (Cui 2022 [43], Huangfu 2023 [44], and Quintanilla-Sánchez 2022) [45]. The overlap of these studies in the different reviews indicates that they are important and frequently cited references in the literature on the relationship between COVID-19 and stroke. These findings reinforce the strong association between COVID-19 infection and the risk of different types of stroke and highlight the increased mortality associated with stroke in patients with COVID-19.

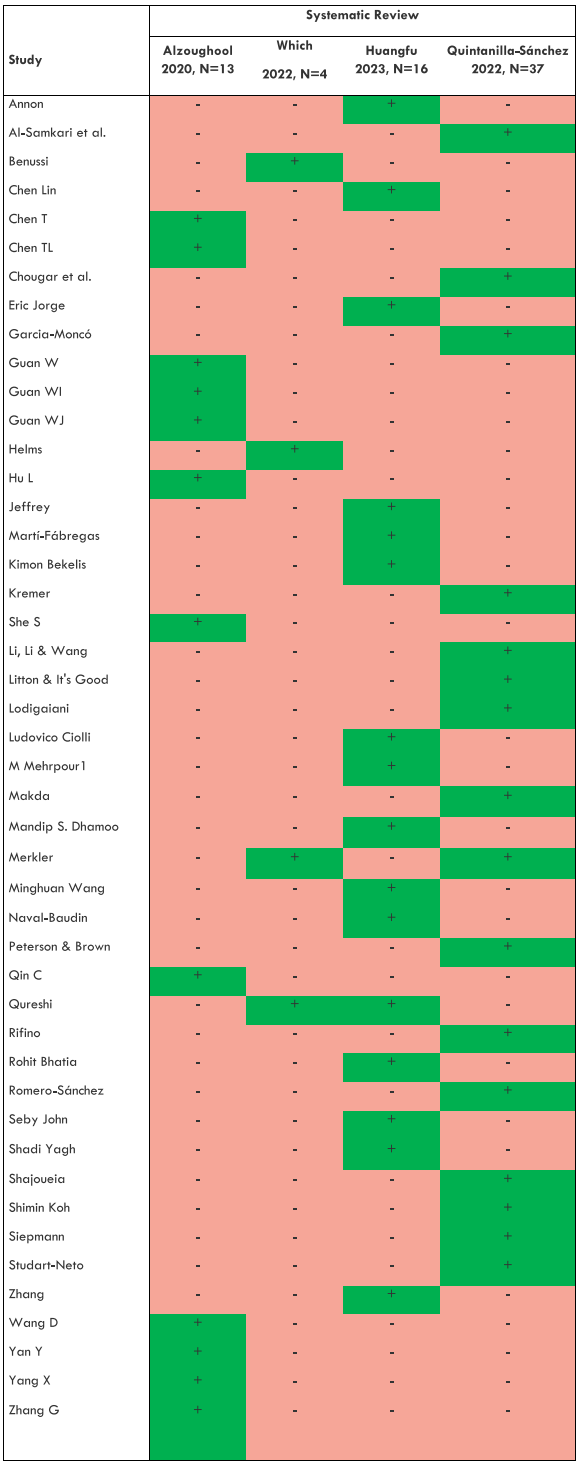

Fig. 4 Matrix of overlapping studies in the systematic review

Analysis of heterogeneity and bias

Table 1 presents the metaumbrella stratified by the classification of the evidence. Two of the study subjects showed low heterogeneity, with I^2 *values* less than 50%. This indicates that the variability between the studies included in these studies was relatively low, suggesting greater consistency in the results. In particular, the "severity of COVID-19 and stroke" and "cerebrovascular comorbidities and mortality" demonstrated this characteristic of low heterogeneity, which strengthens confidence in the interpretation of the observed effects.

None of the study subjects analyzed showed the effect of small studies, as indicated by the nonsignificant values

Table 1 Total participants and *P* values from the Egger and JK tests

Object of study	Number of patients	Number of Cases	Number of Controls	Egger p	ESB p
COVID-19 Severity and stroke	15,279	498	14,781	8.45E-01	5.14E-01
COVID-19 and ischemic stroke risk	36,154	578	35,576	2.84e-01	1.59e-02
COVID-19 and hemorrhagic stroke risk	1303	34	1269	1.81e-01	7.31e-01
Cerebrovascular comorbidities and mortality	2271	63	2208	8.07e-01	9.56e-01
COVID-19 and stroke mortality	4781	647	4134	1.10e-01	0.252e-02

Egger p = Probability value for Egger's test

ESB p = Probability value for Excess Significance Bias

of the Egger test (Egger p). This suggests that the results of the meta-analyses were not significantly influenced by smaller studies, which could skew the conclusions.

However, two study subjects showed excess significance bias (ESB), which was identified by significant *p* values: "COVID-19 and stroke mortality" ($p = 0.0252$) and "COVID-19 and risk of ischemic stroke" ($p = 0.0159$). This bias occurs when there is an excessive number of studies with positive results relative to what would be expected from the normal distribution of true effects, indicating that findings in these domains should be interpreted with caution.

The five study objects evaluated had a statistically significant effect size ($p < 0.05$), which reinforces the validity of the findings. However, on the basis of the criteria previously established for the classification of evidence, three of these study objects were classified as having weak evidence. This reflects limitations such as possible biases or inconsistencies in the results, suggesting the need for further studies to confirm these associations.

Figure 5 complements this information by stratifying the metaumbrella by the classification of evidence, visually highlighting the relative robustness of each object of study. This detailed analysis allows for a more nuanced understanding of the effects of COVID-19 in relation to stroke while identifying areas where the evidence is weaker and where future studies could be more informative.

Discussion

This study provides a comprehensive synthesis of evidence, emphasizing the significant association between SARS-CoV-2 and stroke. The most relevant findings include the increased risk of ischemic and hemorrhagic stroke associated with severe COVID-19, as well as heightened mortality rates in patients with cerebrovascular comorbidities, started from the hypothesis that SARS-CoV-2 infection is associated with an increased risk of stroke and sought to answer the following guiding question: "Does the association between SARS-CoV-2 and stroke presuppose the need to include it as a new risk factor in the list for cerebrovascular disease?" Since then, an understanding of the influence of COVID-19 on stroke risk, a global public health problem that is among the main causes of death and disability, has been proposed [46, 47].

A point to consider is the incidence of stroke in patients with COVID-19, which is significantly greater than that

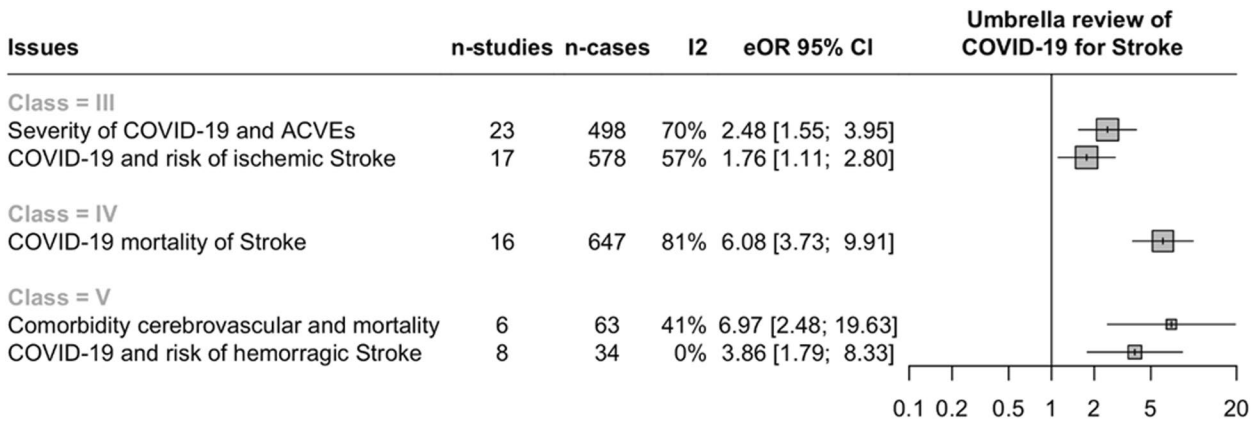

Fig. 5 Umbrella Goal stratified by evidence classification

in patients infected with other coronaviruses, suggesting a specific pathological mechanism associated with SARS-CoV-2 that predisposes them to stroke [48].

The meta-umbrella methodology used in this study offers significant advantages over individual systematic reviews. The comprehensive analysis of multiple meta-analyses, considering the overlap of primary studies, as exemplified by the inclusion of the studies by Qureshi [41] and Merkler [42] in different analyses, ensures greater robustness and reliability of the results. The convergence of evidence from multiple sources, confirming the associations between COVID-19 and different stroke subtypes, as well as associated mortality. The findings suggest a potential association between COVID-19 and stroke, though this relationship requires further investigation to establish causality.

The finding of a link between COVID-19 and increased risk of stroke, especially the ischemic type, corroborates the literature that points to prothrombotic mechanisms induced by the virus [11, 12, 14]. Among these mechanisms, SARS-CoV-2 infection stands out, as it triggers an acute inflammatory response that can result in endothelial dysfunction and a prothrombotic state [43].

COVID-19 is associated with a state of hypercoagulability, increasing the risk of blood clots forming that can obstruct blood vessels in the brain, leading to stroke. SARS-CoV-2 can directly damage endothelial cells, which line blood vessels, making them more prone to the formation of these clots [49, 50]. The high incidence of thrombotic complications in patients with severe COVID-19 reinforces the link between coagulation and viral infection, confirming the relevance of the findings of this study.

It is essential to consider differential diagnoses in acute stroke etiology, particularly hematological disorders, which are commonly underrecognized causes of ischemic stroke. This aligns with findings in previous studies [51].

The identification of SARS-CoV-2 as a risk factor for stroke has crucial implications for the prevention, diagnosis, and treatment of this condition [52]. It is essential to integrate this information into clinical practice, adopting measures such as monitoring patients with COVID-19 for neurological symptoms, especially those at high risk of stroke; considering prophylactic anticoagulation in patients with COVID-19 and a high risk of thromboembolic events; and implementing screening protocols for stroke in patients hospitalized with COVID-19, especially those with additional risk factors for cerebrovascular diseases [53].

Despite including studies with low risk of bias, the possibility of publication bias remains. Additionally, variations in sample sizes and the lack of control for confounding factors such as hypertension and diabetes may have influenced the results. Finally, the predominance of data from specific regions limits the generalizability of the findings.

Future prospective, multicenter studies are essential to investigate the mechanisms underlying the association between COVID-19 and stroke in greater depth, to develop comprehensive clinical guidelines for the management of patients with COVID-19 and stroke risk, and to evaluate the efficacy of preventive interventions, such as anticoagulation, in reducing the incidence of stroke in patients with COVID-19.

Conclusion

The consistent and significant association between SARS-CoV-2 and stroke highlights the potential for COVID-19 to be considered as a risk factor for cerebrovascular diseases. However, due to the high heterogeneity among studies, further research is required to confirm this relationship, past explore preventive strategies, including anticoagulation protocols and targeted therapies for patients with COVID-19 and high stroke risk. Multicenter prospective studies are needed to elucidate the underlying mechanisms and validate these interventions.

Abbreviations

AVC	Stroke (Acidente Vascular Cerebral)
CAPES	Coordination for the Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior)
CI	Confidence Interval (Intervalo de Confiança)
COVID-19	Coronavirus Disease 2019
eOR	Equivalent Odds Ratio (Razão de Chances Equivalente)
I^2	I-squared (Heterogeneity Index—Índice de Heterogeneidade)
JK	Jackknife Test (Teste de Jackknife)
LILACS	Latin American and Caribbean Health Sciences Literature (Literatura Latino-Americana e do Caribe em Ciências da Saúde)
OR	Odds Ratio (Razão de Chances)
PRIO-harms	Lista de Verificação PRIO-harms
PROEX	Academic Excellence Program (Programa de Excelência Acadêmica)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBIS	Risk of Bias in Systematic Reviews
RR	Risk Ratio (Razão de Riscos)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMD	Standardized Mean Difference (Diferença de Média Padronizada)
UNICAMP	University of Campinas (Universidade Estadual de Campinas)
PubMed/MEDLINE	Public/Publisher MEDLINE (Medical Literature Analysis and Retrieval System Online)
Scopus	Abstract and Citation Database curated by Elsevier
Web of Science	Multidisciplinary Citation Index curated by Clarivate Analytics

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Authors' contributions
AMLB Souza contributed to the conception and design, analysis and interpretation of the data, writing of the article, and final approval of the version to be published. EFA collaborated with the conception and design, writing of the article and interpretation of the data. NCJ – analyses statistics, ACR collaborated with the conception and design, writing of the article and interpretation of the data. AC Pereira contributed with a relevant critical review of the intellectual content and final approval of the version to be published. MCM contributed with a relevant critical review of the intellectual content and final approval of the version to be published.

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Data availability
The extraction sheets for this review can be requested via the corresponding author's email at andrezamlb@gmail.com.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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