The Impact of SARS-CoV-2 on Stroke Epidemiology and Care: A Meta-Analysis

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Objective: Emerging data indicate an increased risk of cerebrovascular events with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and highlight the potential impact of coronavirus disease (COVID-19) on the management and outcomes of acute stroke. We conducted a systematic review and meta-analysis to evaluate the aforementioned considerations.

Methods: We performed a meta-analysis of observational cohort studies reporting on the occurrence and/or outcomes of patients with cerebrovascular events in association with their SARS-CoV-2 infection status. We used a random-effects model. Summary estimates were reported as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Results: We identified 18 cohort studies including 67,845 patients. Among patients with SARS-CoV-2, 1.3% (95% CI = 0.9–1.6%, I^2 = 87%) were hospitalized for cerebrovascular events, 1.1% (95% CI = 0.8–1.3%, I^2 = 85%) for ischemic stroke, and 0.2% (95% CI = 0.1–0.3%, I^2 = 64%) for hemorrhagic stroke. Compared to noninfected contemporary or historical controls, patients with SARS-CoV-2 infection had increased odds of ischemic stroke (OR = 3.58, 95% CI = 1.43–8.92, I^2 = 43%) and cryptogenic stroke (OR = 3.98, 95% CI = 1.62–9.77, I^2 = 0%). Diabetes mellitus was found to be more prevalent among SARS-CoV-2 stroke patients compared to noninfected historical controls (OR = 1.39, 95% CI = 1.00–1.94, I^2 = 0%). SARS-CoV-2 infection status was not associated with the likelihood of receiving intravenous thrombolysis (OR = 1.42, 95% CI = 0.65–3.10, I^2 = 0%) or endovascular thrombectomy (OR = 0.78, 95% CI = 0.35–1.74, I^2 = 0%) among hospitalized ischemic stroke patients during the COVID-19 pandemic. Odds of in-hospital mortality were higher among SARS-CoV-2 stroke patients compared to noninfected contemporary or historical stroke patients (OR = 5.60, 95% CI = 3.19–9.80, I^2 = 45%).

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Interpretation: SARS-CoV-2 appears to be associated with an increased risk of ischemic stroke, and potentially cryptogenic stroke in particular. It may also be related to an increased mortality risk.

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In December 2019, a novel coronavirus causing pneumonia and severe acute respiratory syndrome was first reported in Wuhan, China.[1] The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus quickly spread worldwide and a coronavirus disease (COVID-19) pandemic was declared by the World Health Organization on March 11, 2020.[2] Emerging literature suggests a potential increased risk of cerebrovascular events in patients infected with SARS-CoV-2,[3–5]and raises concerns regarding the impact of COVID-19 pandemic and imposed health care and social restrictions on the management and care of stroke patients.[6–8] Observational cohorts and anecdotal reports of declining stroke admission volumes during the COVID-19 pandemic are accumulating,[7,8] with other reports highlighting novel challenges in stroke treatment delivery.[9,10]

We performed a systematic review and meta-analysis to assess the impact of SARS-CoV-2 infection on stroke epidemiology and care across the world. We analyzed observational cohort studies published after the declaration of the COVID-19 pandemic on March 11, 2020, comparing demographics, stroke rates, acute ischemic stroke treatment delivery, and in-hospital mortality between SARS-CoV-2–infected patients and contemporary or historical controls.

Materials and Methods

Study Design

We performed an aggregate data meta-analysis of observational cohort studies (prospective or retrospective) reporting on demographics, cerebrovascular event occurrence, acute ischemic stroke treatment delivery, and/or mortality in association with the SARS-CoV-2 infection status of hospitalized patients. We followed a prespecified study protocol that has been published in the international prospective register of ongoing systematic reviews PROSPERO (CRD42020188467) and reported our findings according to the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) statement.[11]

Search Strategy and Selection Criteria

Observational cohort studies (prospective or retrospective) suitable for inclusion in the present systematic review were identified through an independent search by 3 researchers (A.H.K., L.P., M.R.) of the databases PubMed and Scopus. The following keywords were used in all database searches: "coronavirus", "COVID", "COVID-19", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "stroke", "cerebrovascular disease", "intracranial hemorrhage", "intracerebral hemorrhage", "cerebral venous sinus thrombosis", and "subarachnoid hemorrhage". No language or other restrictions were employed in the literature search. The last literature search was performed on August 7, 2020. The complete search algorithm used in the MEDLINE search is available in Supplementary Table S1. Reference lists of included articles were also screened to identify potential studies missed by the initial literature search. Any disagreements between the 3 researchers performing the literature search were resolved after discussion with the corresponding author (G.Ts.). All case reports, nonconsecutive case series, and surveys were excluded from further consideration.

Observational studies including adult patients (age = 18 years or older) and reporting diagnoses of cerebrovascular events (ischemic stroke, hemorrhagic stroke, cerebral venous sinus thrombosis [CVST], subarachnoid hemorrhage, stroke unclassified) stratified by the results of the SARS-Cov-2 screening test were considered eligible and were included in the present systematic review and meta-analysis.

Quality Control and Bias Assessment

Quality control and bias identification in included studies were performed by 2 independent reviewers who were involved in the literature search (A.H.K., L.P.) with the use of the Newcastle–Ottawa Scale.[12] All emerging conflicts were resolved via consensus and discussion with the corresponding author (G.Ts.).

Outcomes

Our predefined primary outcome measure was ischemic stroke rates among patients testing positive for SARS-CoV-2 compared to ischemic stroke rates among either contemporary patients testing negative for SARS-CoV-2 or historical noninfected cohort groups from the same institution.

We also assessed for differences according to SARS-CoV-2 infection status (patients testing positive for SARS-CoV-2 compared to contemporary or historical noninfected controls) for the following secondary outcomes of interest: (1) all cerebrovascular events rate, (2) intracranial hemorrhage (ICH) rates, (3) cryptogenic ischemic stroke rate among all patients with ischemic stroke, (4) intravenous thrombolysis with tissue plasminogen activator (tPA) treatment among all ischemic stroke patients, (5) endovascular thrombectomy (EVT) treatment among all ischemic stroke patients, and (6) in-hospital all-cause mortality rates for stroke patients (as provided by each included study).

We also evaluated for potential differences in demographics and vascular risk factors between groups of patients stratified by their SARS-CoV-2 infection status. Finally, we estimated the cumulative rates of all cerebrovascular, ischemic stroke, and ICH events for patients testing positive for SARS-CoV-2.

Statistical Analysis

We calculated the rate of cerebrovascular events in SARS-CoV-2 patients by dividing the number of patients with cerebrovascular events by the total number of patients testing positive for SARS-CoV-2. We first transformed proportions using the Freeman–Tukey double arcsine method[13] and then performed an inverse variance random-effects meta-analysis (DerSimonian and Laird)[14] to calculate the pooled estimates. Stroke rates between the SARS-CoV-2 patients and controls were reported with the use of odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Heterogeneity between included studies was assessed with the Cochran Q and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, and values of at least 75% indicated considerable heterogeneity.[15] The significance level for the Q statistic was set at 0.1. Small-study effect (used as a proxy for publication bias) across individual studies was evaluated for all outcomes of interest using funnel plot inspection. For outcomes reported in 10 or more studies, funnel plot asymmetry was also assessed with the Egger linear regression test.[16]

We performed subgroup analyses for cerebrovascular events rates in SARS-CoV-2–infected patients based on their site of admission (hospital ward beds, intensive care unit [ICU], etc). We also stratified studies by the use of contemporary or historical controls, and performed the corresponding subgroup analyses for all comparisons according to SARS-CoV-2 infection status.

All statistical analyses were conducted using the OpenMetaAnalyst[17] and Stata Statistical Software Release 13 for Windows (StataCorp, College Station, TX).

Results

Literature Search and Included Studies

Our search algorithm in the MEDLINE and Scopus databases retrieved 549 and 411 records, respectively (Fig 1). After excluding duplicates, case reports, nonconsecutive case series, and surveys, we retrieved the full text of 48 records that were potentially eligible for inclusion. After reading the full-text articles, we excluded 30 of these records due to their study design (nonconsecutive case series or surveys), or for not providing data on the SARS-CoV-2 infection status and/or the predefined outcomes of interest (Supplementary Table S2). Finally, we identified 18 observational cohort studies including a total of 67,845 patients who qualified our predefined inclusion and exclusion criteria (Supplementary Table S3).[18–35] Nine of the included studies reported imaging confirmation of reported cerebrovascular events.[21–24,26,27,33–35]

Quality Control of Included Studies

The risk of bias in included cohort studies assessed using the Newcastle–Ottawa Scale is presented in Supplementary Table S4. The overall score was 132 of 162 (81%), which is considered to be indicative of moderate quality.

Most studies were deemed to have satisfied the selection and exposure ascertainment criteria. However, cohorts of certain studies were judged not to be truly representative of community patients suffering from COVID-19, as they included only specific patient subpopulations: patients less than 50 years of age,[18] patients with acute respiratory distress syndrome,[22] patients admitted to the ICU,[22,25] patients infected with SARS-CoV-2 who had neurological manifestations and had undergone magnetic resonance imaging investigation,[26] or patients with acute ischemic stroke attributed to a large vessel occlusion.[21] In addition, description of the derivation of the nonexposed cohort was not applicable for 5 studies without controls.[20,23,25,26,32] Comparability was considered satisfactory in most of the included studies, with the exception of the aforementioned 5 studies that included no control groups.[20,23,25,26,32] These studies were included only in the single-group analyses to assess the rate of cerebrovascular events in SARS-CoV-2–infected patients. All studies assessed the outcomes of interest based on medical record linkage.

Overall and Subgroup Analyses

The pooled rates of all cerebrovascular events, and ischemic and hemorrhagic strokes among hospital admissions of patients infected by SARS-CoV-2 were 1.3% (95% CI = 0.9–1.6%, I^2 = 87%, 8 studies), 1.1% (95% CI = 0.8–1.3%, I^2 = 85%, 11 studies), and 0.2% (95% CI = 0.1–0.3%, I^2 = 64%, 7 studies), respectively. The pooled rate of CVST was 0.03%, (95% CI = 0.01–0.05%, I^2 = 0, 2 studies). The corresponding rates of cerebrovascular events, and ischemic and hemorrhagic strokes among ICU admissions were 2.7% (95% CI = 0.7–5.8%, 1 study), 2.0% (95% CI = 0.8–3.8%, 2 studies), and 0.7% (95% CI = 0–2.6%, 1 study), respectively. Among SARS-CoV-2–infected patients admitted to neurological wards, 76.8% (95% CI = 64.9–86.8%, 1 study) were reported to suffer from stroke symptoms, 44.1% (95% CI = 12.6–78.5%, 2 studies) were diagnosed with ischemic stroke, and 5.4% (95% CI = 1.0–12.7%, 1 study) were diagnosed with hemorrhagic stroke (Table).

SARS-CoV-2 infection was associated with increased odds for ischemic stroke (OR = 3.58, 95% CI = 1.43–8.92, I^2 = 43%, 3 studies; Fig 2A) and cryptogenic stroke events (OR = 3.98, 95% CI = 1.62–9.77, I^2 = 0%, 2 studies; see Fig 2B). Although the relevant odds for ischemic stroke between SARS-CoV-2–positive patients and controls were higher for patients admitted to general hospital wards (OR = 8.13, 95% CI = 2.48–26.64) compared

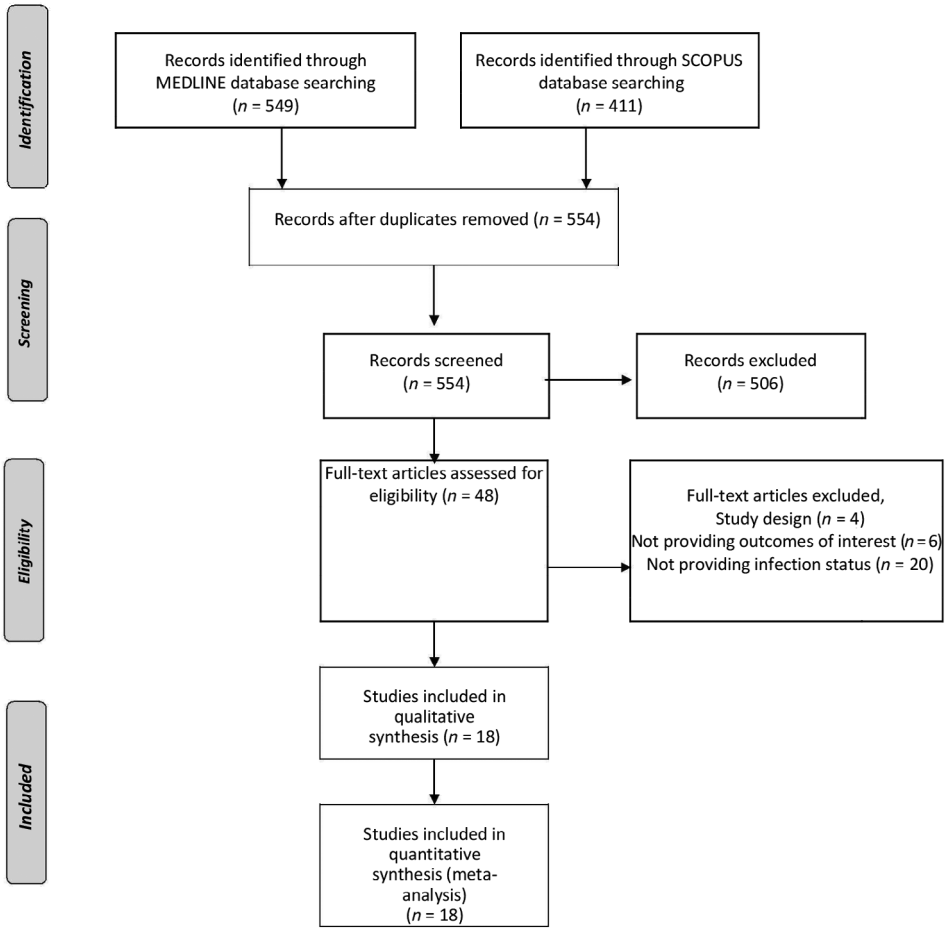

FIGURE 1: Flow chart presenting the selection of eligible studies.

to patients admitted to neurological wards (OR = 2.23, 95% CI = 1.16–4.29), this difference did not reach statistical significance (p for subgroup differences = 0.17).

In the analyses of baseline characteristics (Supplementary Table S5), diabetes mellitus was found to be more prevalent among SARS-CoV-2–infected stroke

TABLE. Overview of Analyses of the Rates of Cerebrovascular Events in Patients Testing Positive for SARS-CoV-2

	Hospital Admissions			ICU Admissions			Neurological Admissions		
Outcome	n	Rate (95% CI)	I^2, p for Cochran Q	n	Rate (95% CI)	I^2, p for Cochran Q	n	Rate (95% CI)	I^2, p for Cochran Q
All strokes	8	1.3% (0.9–1.6%)	87%, <0.001	1	2.7% (0.7–5.8%)	—	1	76.8% (64.9–86.8%)	—
Ischemic stroke	11	1.1% (0.8–1.3%)	85%, <0.001	2	2.0% (0.8–3.8%)	0%, 0.365	2	44.1% (12.6–78.5%)	94%, <0.001
Intracerebral hemorrhage	7	0.2% (0.1–0.3%)	64%, 0.011	1	0.7% (0–2.6%)	—	1	5.4% (1.0–12.7%)	—
Cerebral sinus venous thrombosis	2	0.03% (0.01–0.05%)	0%, 0.478	—		—	—	—	—

n = number of studies; ICU = intensive care unit.

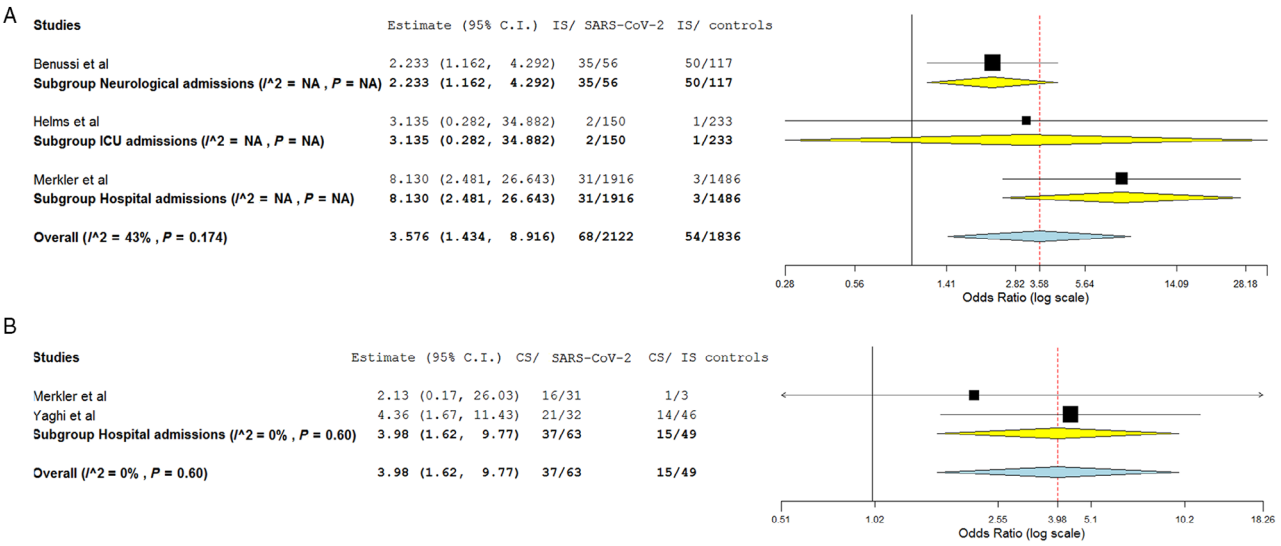

FIGURE 2: Pooled analysis on the probability of (A) ischemic stroke (IS) and (B) cryptogenic ischemic stroke (CS) in patients infected with SARS-CoV-2 compared to contemporary or historical controls. C.I. = confidence interval; ICU = intensive care unit; NA = not applicable. [Color figure can be viewed at www.annalsofneurology.org]

patients compared to noninfected historical stroke patients. Substantial heterogeneity was uncovered in the reported odds of hypertension, smoking, and coronary artery disease prevalence in stroke patients infected with SARS-CoV-2, when compared to either contemporary or historical controls.

Among patients with ischemic stroke, SARS-CoV-2 infection status did not affect the probability of receiving treatment with either intravenous tPA (OR = 0.72, 95% CI = 0.38–1.37, I^2 = 52%, 5 studies; Fig 3A) or EVT (OR = 1.12, 95% CI = 0.28–4.42, I^2 = 67%, 5 studies; see Fig 3B) for acute ischemic stroke treatment. However, significant heterogeneity (p = 0.008) emerged in the probability of SARS-CoV-2 patients receiving tPA treatment when compared to contemporary (OR = 1.42, 95% CI = 0.65–3.10, I^2 = 0%, 3 studies) or to historical controls (OR = 0.41, 95% CI = 0.26–0.66, I^2 = 0%, 2 studies). In addition, SARS-CoV-2 infection status was not related to the odds of receiving EVT when comparing contemporary stroke patients to those without infection with SARS-CoV-2 admitted during the COVID-19 pandemic (OR = 0.78, 95% CI = 0.35–1.74, I^2 = 0%, 3

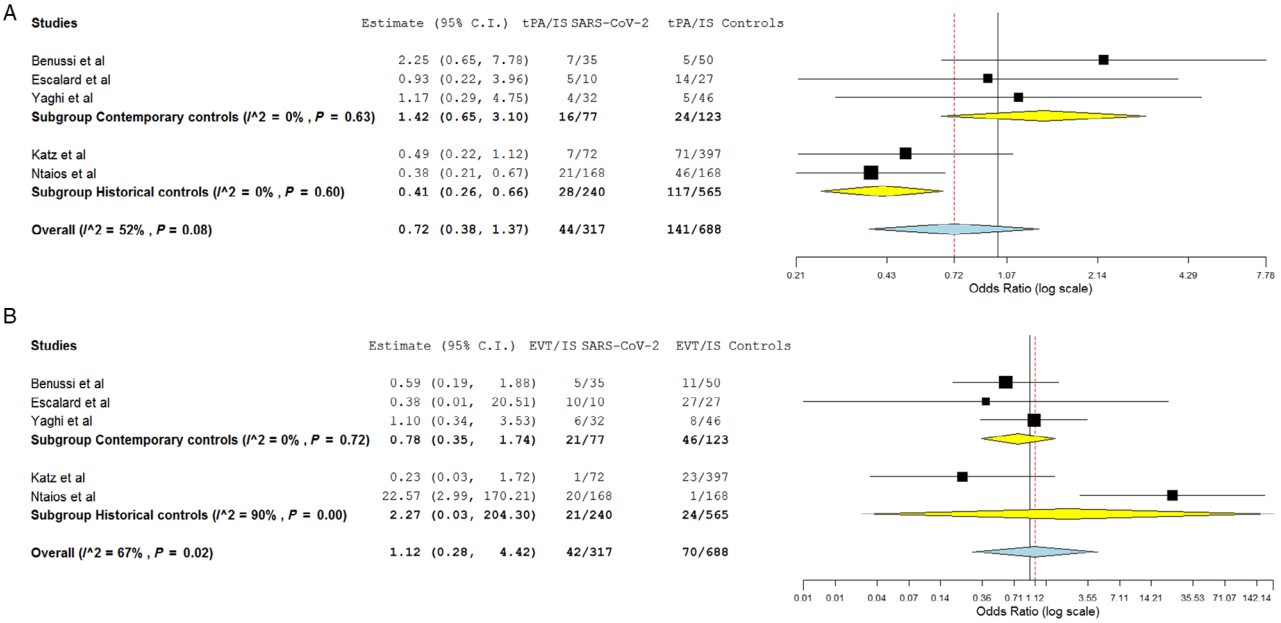

FIGURE 3: Pooled analysis on the probability of treatment delivery with (A) intravenous thrombolysis and (B) endovascular thrombectomy (EVT) for acute ischemic stroke (IS) patients infected with SARS-CoV-2 compared to contemporary or historical noninfected IS patients. C.I. = confidence interval; tPA = tissue plasminogen activator. [Color figure can be viewed at www.annalsofneurology.org]

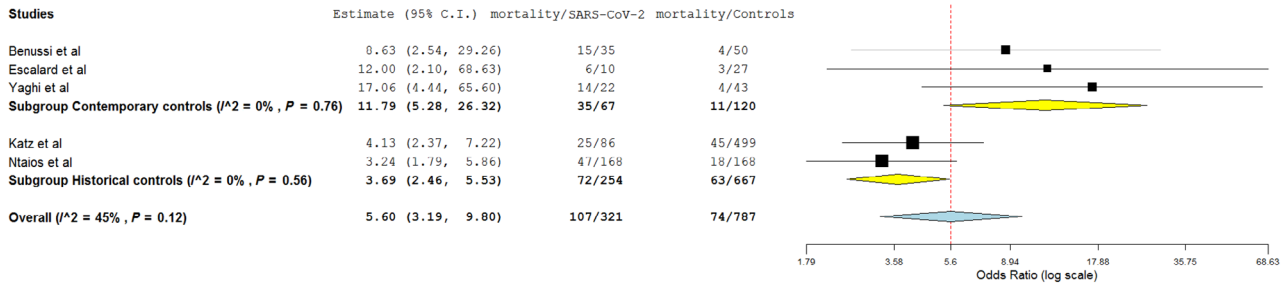

FIGURE 4: Pooled analysis of the probability of in-hospital mortality for patients with cerebrovascular events infected with SARS-CoV-2 compared to contemporary or historical noninfected patients with cerebrovascular events. C.I. = confidence interval. [Color figure can be viewed at www.annalsofneurology.org]

studies). SARS-CoV-2 infection status was also not related to the odds of receiving EVT when comparing to historical stroke patients; however, significant heterogeneity was uncovered between the results presented by the 2 included studies (I^2 = 90%).

Patients suffering from cerebrovascular events were found to have higher odds for in-hospital mortality when infected with SARS-CoV-2 compared to their contemporary noninfected or historical counterparts (OR = 5.60, 95% CI = 3.19–9.80, I^2 = 45%, 5 studies). A significant difference (p = 0.01) in the odds of in-hospital mortality for patients infected by SARS-CoV-2 suffering a cerebrovascular event was documented between studies using contemporary noninfected controls suffering a stroke (OR = 11.79, 95% CI = 5.28–26.32, I^2 = 0, 3 studies) and studies using historical noninfected stroke patients (OR = 3.69, 95% CI = 2.46–5.53, I^2 = 0, 2 studies) as reference groups (Fig 4).

In funnel plots, asymmetry was uncovered in the reported rates of both ischemic (Fig 5A) and hemorrhagic stroke (see Fig 5B) in SARS-CoV-2–infected patients.

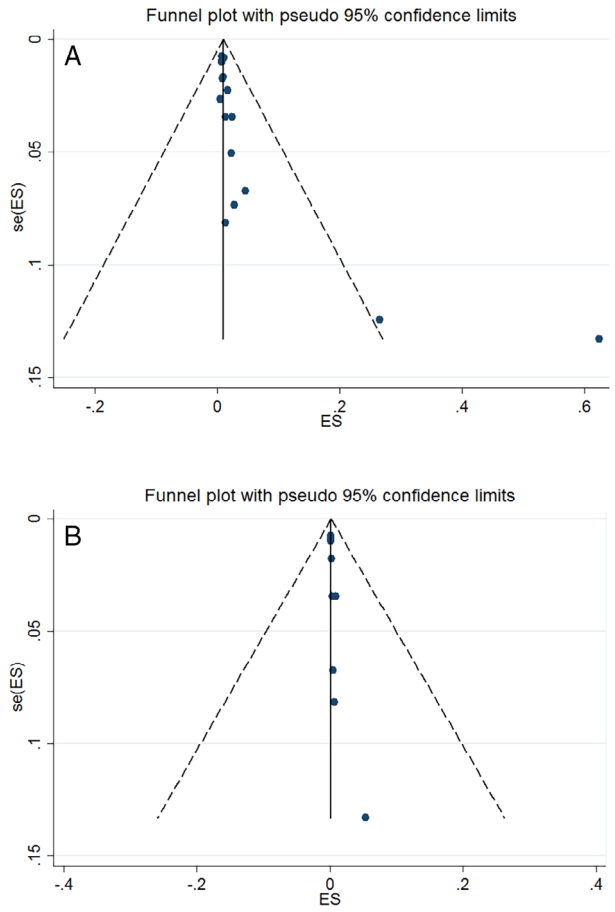

FIGURE 5: Funnel plot on the reported prevalence rates of (A) ischemic stroke and (B) hemorrhagic stroke in patients infected with SARS-CoV-2. ES=effect estimate; se=standard error. [Color figure can be viewed at www.annalsofneurology.org]

Discussion

In the present systematic review and meta-analysis, we report that patients infected by SARS-CoV-2 appear to have increased odds of ischemic stroke rate, particularly the cryptogenic subtype, when compared to contemporary or historical noninfected controls. Diabetes mellitus was found to be more prevalent among SARS-CoV-2–infected stroke patients compared to noninfected stroke patients. SARS-CoV-2 infection status was not related to the likelihood of receiving systemic or endovascular reperfusion treatment among hospitalized acute ischemic stroke patients during the ongoing COVID-19 pandemic. We also found an approximately 5-fold increased mortality risk for patients infected by SARS-CoV-2 suffering from cerebrovascular events compared to noninfected stroke patients, which was more salient in studies using contemporary noninfected cerebrovascular patients as the reference group.

The higher risk of ischemic and cryptogenic stroke, in particular, uncovered in our analyses could be related to blood hyperviscosity and a hypercoagulable state that has been linked to an immune-mediated response following SARS-CoV-2 infection.[36] Hospitalized patients with COVID-19 have been acknowledged to bear an increased risk of both arterial and venous thromboembolic events,

even within the first 24 hours after admission.[28] Dehydration, acute inflammatory response, and protracted immobilization are considered to be factors that potentially augment the risk of thrombosis in patients with COVID-19.[37] The results of inflammatory and coagulation tests according to SARS-CoV-2 infection status have been reported in 2 of the included studies,[19,34] suggesting the presence of significant differences in acute-phase proteins and coagulation profiles between COVID-19 stroke patients and controls. In COVID-19 patients with acute respiratory distress syndrome, the use of mechanical ventilation may result in increased pulmonary artery pressure, which in turn can lead to a reversal of the normal interatrial pressure gradient and increased right-to-left shunt gradient in patients with patent foramen ovale.[38,39] The potential of paradoxical embolism in COVID-19 patients suffering from a cryptogenic stroke as the underlying pathophysiological mechanism is a hypothesis that deserves further investigation.[39]

The presence of the neurological disease has previously been identified as an independent predictor of mortality in hospitalized COVID-19 patients, with the history of previous stroke being associated with a 3-fold increase in the mortality risk and a 2.5-fold increase in the odds of severe illness and poor outcome.[40–42] In our meta-analysis, we report that stroke patients infected with SARS-CoV-2 had an almost 5-times higher probability of in-hospital mortality when compared to their noninfected counterparts.

In the subgroup analyses, we detected a difference in the probability of receiving tPA treatment according to SARS-CoV-2 infection status for studies including contemporary versus historical controls (see Fig 3A). The lower likelihood in tPA treatment administration between contemporary SARS-CoV-2 patients and historical controls found in our meta-analysis could partially be explained by the lack of prompt symptom recognition due to social distancing and/or hesitance regarding prompt hospital presentation due to the fear of SARS-CoV-2 infection, coupled with increased transportation and in-hospital delays as a result of both health care system overload and preventive measures following the COVID-19 pandemic outbreak.[43–46] Furthermore, many patients with COVID-19 are diagnosed with stroke during their hospital admission and may have unique contraindications to thrombolysis when compared to either historic or contemporary controls (eg, empirically anticoagulated, intubated/sedated, critically ill, delays in imaging due to critical illness, delay in symptom recognition during hospitalization). Moreover, it needs to be highlighted that the significance of the aforementioned difference is limited by the small sample size, associated publication bias, and the indirect comparison between different populations. Notably, the finding that SARS-CoV-2–infected stroke patients had similar odds of receiving acute systemic or endovascular reperfusion therapies compared to their noninfected counterparts hospitalized during COVID-19 pandemic is encouraging and may be partly attributed to the implementation of specific protocols that have been recently developed for acute stroke care of patients with cerebrovascular diseases and concomitant SARS-CoV-2 infection.[47–49]

Another intriguing finding is that diabetes mellitus was found to be more prevalent among stroke patients infected with SARS-CoV-2. Diabetes is one of the most serious comorbidities linked to the severity of COVID-19.[50] Patients with diabetes have an increased risk of severe complications,[33,50] and alternative mechanisms that may additionally account for the increased risk of stroke in COVID-19 diabetic patients include excessive uncontrolled inflammation responses, reduced angiotensin-converting enzyme 2 expression, hypercoagulable state associated with dysregulation of glucose metabolism, and acute hyperglycemia.[51,52]

Some limitations need to be acknowledged for the correct interpretation of the current systematic review and meta-analysis. First, we need to highlight that this is an aggregate data meta-analysis and thus reported associations in study populations cannot be adjusted for potential confounders and participant characteristics. Of note, only one of the included studies used a propensity-matched algorithm to match SARS-CoV-2–infected patients with historical controls.[22,30] It should be noted that included study populations vary considerably in their disease severity (general hospital vs ICU admissions), admission diagnosis, baseline characteristics, SARS-CoV-2 screening process, stroke ascertainment, and outcome assessment. As included studies have taken place in both different countries and different regions within the same country, both national and regional health care policy disparities are expected,[53] for which the present meta-analysis cannot accommodate or adjust. For example, the study setting in terms of population density (urban vs suburban vs rural) is a factor that could account for reported stroke prevalence rates in patients with SARS-CoV-2 infection. Higher volume centers are more likely to admit milder stroke cases and become overwhelmed by the increased volume of admissions, which can limit imaging resources to facilitate prompt stroke detection. Although we found a higher prevalence of strokes in patients infected by SARS-CoV-2 assigned as cryptogenic, it is unclear whether this increase could be related to suboptimal stroke workup due to infection status and/or poor medical condition. In one of the included studies, only a third of the cryptogenic stroke cases were found not to meet criteria for any of the other stroke subtypes, with the rest of them being included in the cryptogenic stroke category due to multiple competing

mechanisms (19%) or incomplete workup (50%).[29] Therefore, incomplete etiologic evaluation of stroke patients infected with SARS-CoV-2 may be a significant confounder in the reported rates of cryptogenic stroke, due to pursuit of comfort measures, insufficient follow-up, or rapid progression from stroke to death.[34] Furthermore, this meta-analysis includes both patients presenting primarily to the hospital due to stroke-related symptoms, independent of the presence of infectious symptoms and before testing positive for SARS-CoV-2, and patients who were found to have a stroke event, either symptomatic or asymptomatic, while being hospitalized for infectious symptoms due to SARS-CoV-2. In any case scenario, the temporal association between stroke occurrence and SARS-CoV-2 infection is challenging to postulate from the included studies.[54] For this reason, incidence rates and causality cannot be inferred by either the included studies or the current systematic review and meta-analysis. Finally, it should be noted that there is a possibility of small-study effects in included studies. However, the substantial heterogeneity in reported outcomes between studies, the difference in included patient populations, and the limited number of studies reporting on the majority of the outcomes hinder significantly the interpretation of funnel plots. Therefore, any asymmetry uncovered in the funnel plots of the present meta-analysis should be interpreted as an indicator of underlying heterogeneity between studies, rather than as direct evidence of publication bias presence.[55]

In conclusion, the findings of the present meta-analysis indicate that SARS-CoV-2 might be associated with increased thromboembolic risk, suggested especially by the increased rate of cryptogenic strokes in patients infected with SARS-CoV-2. The concurrence of SARS-CoV-2 infection with stroke seems to increase the risk of mortality. The preliminary observations of the present systematic review and meta-analysis require independent confirmation in prospective observational studies investigating further causality and underlying pathophysiological mechanisms.

Author Contributions

A.H.K., L.P., and G.Ts. contributed to the conception and design of the study, acquisition and analysis of data, and drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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