EBioMedicine 59 (2020) 102939

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Research paper

Risk of stroke in hospitalized SARS-CoV-2 infected patients: A multinational study

Shima Shahjouei[a], Soheil Naderi[a,bb], Jiang Li[b], Ayesha Khan[a], Durgesh Chaudhary[a], Ghasem Farahmand[c,l], Shailesh Male[d], Christoph Griessenauer[a], Mirna Sabra[e], Stefania Mondello[f], Achille Cernigliaro[g], Faezeh Khodadadi[h], Apoorva Dev[h], Nitin Goyal[i], Sakineh Ranji-Burachaloo[c,l], Oluwaseyi Olulana[a], Venkatesh Avula[a], Seyed Amir Ebrahimzadeh[j], Orkhan Alizada[k], Mehmet Murat Hancı[k], Askar Ghorbani[l], Alaleh Vaghefi far[m], Annemarei Ranta[m,n], Martin Punter[m,n], Mahtab Ramezani[o], Nima Ostadrahimi[bb], Georgios Tsivgoulis[i,p], Paraskevi C. Fragkou[q], Peyman Nowrouzi-Sohrabi[r], Emmanouil Karofylakis[q], Sotirios Tsiodras[q], Saeideh Neshin Aghayari Sheikh[s], Alia Saberi[s], Mika Niemelä[t], Behnam Rezai Jahromi[t], Ashkan Mowla[u], Mahsa Mashayekhi[v], Reza Bavarsad Shahripour[i], Seyed Aidin Sajedi[w], Mohammad Ghorbani[x], Arash Kia[y], Nasrin Rahimian[z], Vida Abedi[b,aa], Ramin Zand[a,i,*]

[a] Neurology Department, Neuroscience Institute, Geisinger Health System, Danville, PA, USA
[b] Department of Molecular and Functional Genomics, Geisinger Health System, Danville, PA, USA
[c] Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[d] Neurology Department, Vidant Medical Center, Greenville, NC, USA
[e] Neurosciences Research Center (NRC), Lebanese University/ Medical School, Beirut, Lebanon
[f] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[g] Regional Health Authority of Sicily, Palermo, Italy
[h] PES University, Bengaluru, Karnataka, India
[i] Neurology Department, University of Tennessee Health Science Center, Tennessee, USA
[j] Radiology Department, Yasrebi Hospital, Kashan, Iran
[k] Neurosurgery Department, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey
[l] Neurology Department, Tehran University of Medical Sciences, Tehran, Iran
[m] Department of Neurology, Wellington Hospital, Wellington, New Zealand
[n] Department of Medicine, University of Otago, Wellington, New Zealand
[o] Neurology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[p] Second Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, "Attikon" University Hospital, Athens, Greece
[q] Fourth Department of Internal Medicine, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece
[r] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
[s] Neurology Department, Poursina Hospital, Guilan University of Medical Sciences, Guilan, Iran
[t] Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland
[u] Division of Stroke and Endovascular Neurosurgery, Department of Neurological Surgery, Keck School of Medicine, University of Southern California, California, USA
[v] Internal medicine Department, Tabriz University of medical sciences, Tabriz, Iran
[w] Neuroscience Research Center, Department of Neurology, Golestan University of Medical Sciences, Gorgan, Iran
[x] Divisions of Vascular and Endovascular Neurosurgery and Neurology, Firoozgar Hospital and Rasoul-Akram hospital, Iran University of Medical Sciences, Tehran, Iran

Collaborators - The Multinational COVID-19 Stroke Study Group:

Prof Mohammad Hossein Harirchian, MD,[1] Nazanin Ahmadzadeh, MD,[2] Thomas Yasuda, MD,[3] Fabricio Cardoso, MD,[3] Asadollah Mirghasemi, MD,[4] Alireza Janbakhsh, MD,[5] Mohammad Hossein Zamanian, MD, [5] Zeinab Mohseni Afshar, MD,[5] Ali H. Kassem, MD,[6] Haidar H. Hoummani, MD,[6] Arefeh Babazadeh, MD,[7] Soheil Ebrahimpour, MD, [7] Sima Mohseni, MD, MPH,[7] Firas Kobeissy, PhD[8,9] Navneet Singh Dang, MD,[10] B. V. Ganesh, MBBS,[11] Radha Krishna Ramesh, MD,[12] Sedighe Basirjafari, MD,[13] Janardhanan Saravanan, Pharm Ph. D,[14] Faissal Qak, MD,[15] Prof Afshin Borhani-Haghighi.[16]

[1]Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran;
[2]Istanbul Bilim University, Istanbul, Turkey;
[3]Neurology Department, Centro Médico de Campinas, São Paulo, Brazil;
[4]Department of Anesthesiology, University of Ottawa, Canada;
[5]Infection Disease Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran;
[6]Lebanese University/Beirut Governmental University Hospital, Beirut, Lebanon;
[7]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
[8]Program of Neurotrauma, Neuroproteomics and Biomarker Research (NNBR), University of Florida, Florida, USA;
[9]Lebanese Ministry of Health, Beirut, Lebanon;
[10]Department of Medicine, Geisinger Health System, Pennsylvania, USA;
[11]ESIC Hospital, Karnataka, India;
[12]C.V. Raman General Hospital, Karnataka, India;
[13]Department of Radiology, Hashemi Rafsanjani Hospital, Khorasan, Iran;
[14]PES University, Bengaluru, Karnataka, India;
[15]Department of Anesthesiology, University of Ottawa, Canada;
[16]Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

* Corresponding author at: Neurology Department, Neuroscience Institute, Geisinger Health System, 100 North Academy Ave. Danville, PA 17822, USA.
E-mail address: rzand@geisinger.edu (R. Zand).

https://doi.org/10.1016/j.ebiom.2020.102939

[y] Icahn school of medicine at Mount Sinai, Department of Population Health Science and Policy, Institute for Healthcare Delivery Science, New York, USA
[z] Neurology Department, Yasrebi Hospital, Kashan, Iran
[aa] Biocomplexity Institute, Virginia Tech, Blacksburg, Virginia, USA
[bb] Neurosurgery Department, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received 15 June 2020
Revised 4 July 2020
Accepted 20 July 2020
Available online 17 August 2020

Keywords:
Cerebrovascular disorders
Stroke
SARS-CoV-2
COVID-19
Venous thrombosis
Intracranial haemorrhage
Neurological complications

ABSTRACT

Background: There is an increased attention to stroke following SARS-CoV-2. The goal of this study was to better depict the short-term risk of stroke and its associated factors among SARS-CoV-2 hospitalized patients.
Methods: This multicentre, multinational observational study includes hospitalized SARS-CoV-2 patients from North and South America (United States, Canada, and Brazil), Europe (Greece, Italy, Finland, and Turkey), Asia (Lebanon, Iran, and India), and Oceania (New Zealand). The outcome was the risk of subsequent stroke. Centres were included by non-probability sampling. The counts and clinical characteristics including laboratory findings and imaging of the patients with and without a subsequent stroke were recorded according to a predefined protocol. Quality, risk of bias, and heterogeneity assessments were conducted according to ROBINS-E and Cochrane Q-test. The risk of subsequent stroke was estimated through meta-analyses with random effect models. Bivariate logistic regression was used to determine the parameters with predictive outcome value. The study was reported according to the STROBE, MOOSE, and EQUATOR guidelines.
Findings: We received data from 26,175 hospitalized SARS-CoV-2 patients from 99 tertiary centres in 65 regions of 11 countries until May 1st, 2020. A total of 17,799 patients were included in meta-analyses. Among them, 156(0.9%) patients had a stroke—123(79%) ischaemic stroke, 27(17%) intracerebral/subarachnoid hemorrhage, and 6(4%) cerebral sinus thrombosis. Subsequent stroke risks calculated with meta-analyses, under low to moderate heterogeneity, were 0.5% among all centres in all countries, and 0.7% among countries with higher health expenditures. The need for mechanical ventilation (OR: 1.9, 95% CI:1.1−3.5, $p = 0.03$) and the presence of ischaemic heart disease (OR: 2.5, 95% CI:1.4−4.7, $p = 0.006$) were predictive of stroke.
Interpretation: The results of this multi-national study on hospitalized patients with SARS-CoV-2 infection indicated an overall stroke risk of 0.5%(pooled risk: 0.9%). The need for mechanical ventilation and the history of ischaemic heart disease are the independent predictors of stroke among SARS-CoV-2 patients.
Funding: None.

1. Introduction

The occurrence of multiple heterogeneous complications associated with Coronavirus disease 2019, SARS-CoV-2 infection, a global pandemic [1,2], has led to several scientific reports and news headlines. Li et al. published one of the first studies describing the risk of stroke among SARS-CoV-2 hospitalized patients [3]. They observed a 5% risk of ischaemic stroke, 0.5% cerebral venous sinus thrombosis, and 0.5% cerebral hemorrhage. However, the study was a single-center report of a limited number of patients (N: 221). Since then, there have been several other case reports and series describing the risk of stroke among SARS-CoV-2 patients [4–6].

Several studies have described different mechanisms in which SARS-CoV-2 can induce neurological disorders and stroke [7,8]. Many of these mechanisms focus on Angiotensin-Converting Enzyme-2 (ACE-2), the binding site for SARS-CoV-2, and the imbalance of its function as a trigger of a cascade of events resulting in vasoconstriction, high blood pressure, or thrombus formation [9,10]. Other studies propose immune-mediated mechanisms and overexpression of cytokines [11], hypercoagulability state, and thromboembolism as potential stroke etiologies [12–14].

However, the increased risk of stroke is not exclusive to SARS-CoV-2 and it has been reported in association with other viral respiratory infections [15–23]. A slight increase in the risk of stroke incidence was reported following influenza infection [18,19], or other β-coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) [20–23], and severe acute respiratory syndrome (SARS) [20–23]. In addition, severe sepsis and critical condition may impose an additional risk for coagulopathy or new-onset of atrial fibrillation, which can increase the risk of stroke [24–27]. Considering the burden of stroke and its association with worse prognosis, compared with non-stroke, among hospitalized patients [28], we designed a multi-national observational study to better depict the short-term risk of stroke and its associated factors among SARS-CoV-2 hospitalized patients.

2. Methods

2.1. Study design

Supplemental Material Document 1 (page 6) includes the details of the study design. The study was conducted and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [29], Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [30], Preferred Reporting Items for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [31], and Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines [32]. This multicentre, multinational observational study was designed by the investigators at the Neuroscience Institute of Geisinger Health System, Pennsylvania, the United States. The study included patients from North America (Canada and the United States), South America (Brazil), Europe (Greece, Italy, Finland, and Turkey), Asia (Lebanon, Iran, and India), and Oceania (New Zealand). Data were recruited up to May 1st, 2020; the beginning date of the study period was defined as the earliest date that each participating center admitted SARS-CoV-2 patients. Centres were included by non-probability sampling; the core investigators invited their collaborators from many countries through personal phone calls, email communications, and announcements on social media platforms for professionals. The investigators and collaborators also contacted local societies, hospitals, and other related organizations, sometimes using local languages, in many of the affected countries as early as March 27, 2020.

For this study, stroke was defined as ischaemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral venous

Research in context

Evidence before this study

The authors have searched Medline, Embase, Google Scholar, MedRxiv, and all popular journals in the field of cerebrovascular diseases, in addition to forward and backward citation tracking of the related articles by April 25, 2020, and updated to the submission date, with no restriction on publication type or language. SARS-CoV-2, SARS-CoV, MERS-CoV, COVID-19, coronavirus, neurological manifestations, cerebrovascular diseases, stroke, thrombosis, intracranial hemorrhage, intracerebral hemorrhage, and related Mesh Terms and Emtree vocabulary were used with different Boolean operations. Our study is not limited to a systematic review of previously reported cases; therefore, we did not provide details of the search strategy in this paper. Our team has reported the search results of neurological complications of SARS-CoV-2 in a separate review paper (currently *in Press*). The relevant evidence before this study was reviewed in the introduction and discussion section of the manuscript. Briefly, there are several case reports of cerebrovascular disease among patients with SARS-CoV-2. The results of a single-center, retrospective, observational analysis of consecutive SARS-CoV-2 patients admitted to Union Hospital, Wuhan, China from 16 January 2020 to 29 February 2020 indicates that out of 221 patients, 5% developed acute ischemic stroke, and 0.5% (1 patient) developed intracerebral hemorrhage. However, the study had several limitations. It was a single-center report and no data about the outcome was available.

Added-value of this study

There are increasing concerns regarding the neurological and specifically cerebrovascular complications of SARS-CoV-2. Articles defining the higher risk of strokes among SARS-CoV-2 patients were published in the New York Times, CNN health, the Washington Post, and several other news outlets as early as April 1st. Understanding the risk and characteristics of cerebrovascular events is critically important given their burden and prognosis. Therefore, the goal of this study was to investigate the risk and associated factors of acute cerebrovascular diseases (ischemic stroke, intracranial hemorrhage including subarachnoid hemorrhage, and cerebral venous thrombosis) among patients with SARS-CoV-2 in a large population.

Implications of all the available evidence

The result of the current study suggests that although there is an increased risk of cerebrovascular events in patients infected with SARS-CoV-2, the risk is comparable to other viral infections and critical conditions. The evidence also indicates that dependency on a ventilator and the presence of ischemic heart disease are predictive of cerebrovascular complications. Therefore clinicians and nurses should be monitoring critically ill patients for symptoms of acute stroke. More studies are needed to describe the etiologies of cerebrovascular diseases among this patient cohort and define effective prevention strategies.

thrombosis [33]. Ischaemic or haemorrhagic stroke was defined as the rapid onset of a neurological deficit when there was evidence of an acute ischaemic or haemorrhagic lesion on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) consistent with the symptoms. Cerebral venous or sinus thrombosis was defined as a hyperintense signal in the involved vein or sinus as evidenced by CT scan or MRI corresponding to other imaging findings and patients' symptoms. Patients who did not have neuroimaging confirmation of an acute stroke were not included in this study. We further subclassified the ischaemic stroke lesions based on the pattern of the lesion on diffusion-weighted imaging (DWI) or CT to lacunar [34], embolic/large vessel athero-thromboembolism [35,36], and other phenotypes (borderzone or equivocal lesions). As part of our protocol, we requested that our local investigator review all the images with the local radiologist and reach a consensus if there was a disagreement. TOAST (the Trial of Org 10,172 in Acute Stroke Treatment) [37] was not assessed in this study since many of the patients had not completed their stroke workup (echocardiogram, long-term cardiac monitoring, etc.) at the time of data acquisition.

2.2. Participants

We included consecutive hospitalized SARS-CoV-2 patients and recorded patients who had a subsequent and confirmed stroke—ischaemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral venous thrombosis. The study cohort in all centres was defined as the total population of patients who were hospitalized with a confirmed diagnosis of SARS-CoV-2, with or without a subsequent stroke. We also included patients who initially presented to the hospital with a stroke-related chief complaint and were found to have an imaging-confirmed acute stroke, but also had positive screening results for SARS2-CoV-2. Many tertiary centres especially in hot spots had routine polymerase chain reaction (PCR) or chest CT scan screening for all admitted patients or for patients who had any symptoms of SARS-CoV-2 infection. In addition, we made attempts to capture SARS-CoV-2 patients who had stroke-related readmission by regular follow-ups. Patients with 24 h of hospitalization were eligible for this study, regardless of their length of stay. The post-discharge follow-up protocol for SARS-CoV-2 patients varied in different countries and different centres. However, every center reported uniform and non-selective follow-ups for the study population. In addition, attempts were made to consider all centres providing neurological services in the captured areas to maximize the chance of recording early post-discharge stroke. In case there was a closed-loop referral system between the different tertiary centres for patients with neurological complications, we considered the total number of hospitalized SARS-CoV-2 patients (whether they had a stroke or not) in the whole referral system to estimate the frequency of stroke.

To minimize the heterogeneity between different regions regarding the population screening protocols, only patients who were hospitalized for more than 24 h were included in this study. The preferred diagnostic criteria for SARS-CoV-2 was defined according to the World Health Organization (WHO) interim guidance [38]. Due to the limited availability of PCR testing or concerns about its low predictive value, several centres used a combination of the history of exposure, symptomatology, and chest CT with or without PCR methods for diagnosis confirmation (Supplemental Table 1, page 9). The onset of SARS-CoV-2 was considered as either the symptoms onset or positive test, whichever was first. There were no age or gender exclusion criteria. Given the high diagnostic error associated with a transient ischaemic attack (TIA) [39–41], patients who had transient stroke-like symptoms and no acute lesion on CT or MRI were not included in this study.

Collaborators were asked to provide three sets of data: (1) number and clinical details of patients with a stroke, (2) total number and high-level summary (age and sex proportion, the severity of SARS-CoV-2 infection, mechanical ventilation, prognosis, and vital status) on the study population, and (3) clinical and laboratory findings of the study population (or at least a randomly generated subset). Data were collected by a predefined common core protocol and detailed documents for stroke cases and study population. Each center had the option of sending either patient- or summary-level data per their internal board approval. We only accepted patient-level data for our

stroke patients. The age, sex, comorbidities, and laboratory findings were requested for the stroke patients and study population. For stroke patients, we also obtained additional data including the onset of stroke and SARS-CoV-2, chest CT scan findings, a need for mechanical ventilation, details of neurological investigations, and localization of the event, National Institute of Health Stroke Scale (NIHSS), and acute management and outcomes.

2.3. Outcomes

The primary goal of this study was to estimate the risk of stroke among hospitalized SARS-CoV-2 patients. Data from the centres that were unable to provide information on hospitalized patients were not used for the calculation of risk estimate. We also compared the baseline characteristics, comorbidities, and laboratory findings among stroke cases and a subset of the study population and investigated the parameters with higher predictive value for stroke occurrence.

2.4. Statistical analysis

Descriptive statistics were used to summarize the data. Demographic data, comorbidities, and laboratory findings were reported as medians (interquartile range [IQR]), mean (standard deviations [SD]), and under stratified categories when possible. Categorical variables were reported as absolute frequencies and percentages. The data which were provided on a qualitative scale rather than quantitative value (such as C-reactive protein-CRP) or equivalents of the requested items (such as glomerular filtration rates instead of creatinine) were excluded from the analyses. The comparison between categorical variables was conducted with the Pearson chi-square test, while the differences among continuous variables were assessed by independent *t*-test. Bivariate logistic regression was used to determine the parameters with predictive outcome value. The model's goodness of fit was assessed by Hosmer and Lemeshow test. Odds ratios (OR) and corresponding 95% confidence intervals (95% CIs) were reported. All tests were performed using IBM SPSS Statistics version 26 [42] and $p<0.05$ was considered statistically significant.

We used the Risk of Bias in Exposure Studies (ROBINS-E) tool [43] to assess the quality of the data received from each center. We evaluated the potential bias on time-varying confounding (cases: the time window between the infection and stroke, potential of capturing late-onset strokes; study population: follow-up and reporting consistency); selection of study participants (cases: influence of outcomes on inclusion, local investigators' judgement on possibility of causality/coincidence for selective reporting of cases, automated data extraction and natural language processing or manual chart review; study population: SARS-CoV-2 hospitalization criteria); verification of exposure/diagnosis (defining the confirmed SARS-CoV-2 based on imaging, symptoms, and PCR); missing data (cases: data to confirmed the diagnosis, stroke imaging pattern, and localization; study population: high level summary data on hospitalized patients); measurement of outcomes (awareness of the local investigators of all strokes admitted in the center, consistent definition when referring to stroke); and measurement of reporting results (cases: reporting all strokes irrespective of management outcome, study population: reporting of all hospitalized SARS-CoV-2 patients). We demonstrated the outcomes in Supplemental Table 1 (page 9) for each center included in the meta-analyses. The summary of the outcomes was presented as a percentage of the centres with no information, low, medium, or high risk of bias under each category.

Heterogeneity among study levels was assessed with the Cochran Q test ($\chi 2$ test for heterogeneity). The proportion of total heterogeneity to total variability was quantified by I^2 and its 95% confidence interval (CI). The Q-test with $p<0.1$ or an I^2 statistic greater than 50% was considered statistically significant [44]. We visualized subsequent stroke risk (95% CIs) following SARS-CoV-2 infection by forest plots. To better present the possible risk difference among centres, we conducted meta-analyses under five different levels: 1) Regions (states/districts) in each country, 2) Countries grouped by continent, 3) Data limited to countries with higher health expenditures, 4) Removal of the centres with the highest and lowest risk estimation, 5) Type of data for study population (individual versus summary level). Details on countries' health expenditures according to the WHO report [45], are available in Supplemental Table 2 (page 15). One center in the United States (New York-2) provided the patient-level data by automated data extraction and natural language processing from their electronic health records system. The investigator in that center was not able to perform a manual chart review of the stroke patients to further validate the findings. We did not include the centres that could not provide an accurate total number of strokes (numerator) or study population (denominator) for risk calculations. To minimize the impact of the low denominator [46], we did not include the regions with fewer than 20 hospitalized patients in the meta-analyses. We used random-effects models with double arcsine transformations and DerSimonian-Laird estimator in all meta-analyses. The meta-analyses were performed using the R version 3.5.0 and *metafor* [47] package.

3. Role of the funding source

There was no funding source for this study.

4. Results

We received data from 26,175 hospitalized SARS-CoV-2 patients from 99 tertiary centres in 65 regions in 11 countries (Supplemental Fig. 1, page 19). A total of 8376 patients were excluded from this study (available study population but unverified stroke cases: 6287; partial reports of stroke patients: 2022; study population less than 20 individuals: 50; no data available on study population: 17; Supplemental Table 3, page 17). The study included 17,799 SARS-CoV-2 infected patients—156 patients with stroke. Table 1 presents the comorbidities and laboratory results among the patients with stroke and a subset of non-stroke patients with available detailed data. Among the 156 stroke patients, 123 (79%) presented with acute ischaemic stroke, 27 (17%) with intracerebral/subarachnoid hemorrhage, and 6 (4%) with cerebral venous or sinus thrombosis (Table 2). We observed mean age of 68.6 (13.9) years among patients with ischaemic stroke, 62.5 (15.3) years in patients with intracranial hemorrhage, and 50.3 (12.9) in patients with cerebral venous thrombosis. Overall, 43 (27.6%) of the stroke patients presented to the medical centres with stroke-related symptoms as the chief complaint, without the prior diagnosis of SAR-CoV-2 infection. Patients with an acute ischaemic stroke had a median NIHSS of 9.5 [6.0−19.0] on admission. Among the available 80 (65%) MR imaging for assessment, the ischaemic strokes could be considered as lacunar in 6 (7.5%), embolic/large vessel athero-thromboembolism in 58 (72.5%), or other phenotypes (borderzone or equivocal; 16, 20.0%). Patients with intracerebral/subarachnoid hemorrhage presented with an NIHSS of 13 [8.0−17.0] and intracerebral hemorrhage (ICH) score of 3.0 [2.0−4.0]. Among the latter, 25 (93%) had an intracerebral hemorrhage, and 2 (7%) had a subarachnoid hemorrhage. Among the 6 patients with cerebral venous thrombosis, 2 (33%) patients had episodes of seizures prior to admission. Supplemental Figures 2−4 (page 21) presents the clinical imaging of selected patients.

The details of the risk of bias assessment are available in Supplemental Table 1A, B (page 9). To summarize, 25 out of 99 (25%) centres (19 strokes in 8376 study population) were excluded from meta-analyses. One center in the United States (New York-2) provided stroke data by automated data extraction and natural language processing without chart review validation. Therefore, all the meta-

Table 1
The baseline characteristics, comorbidities, and laboratory findings among patients with and without stroke.

Parameter	Stroke (*N* = 156)	Without Stroke (*N* = 6200)*	*p*-Value
Age; Mean (SD); Years	66 (15)	58 (14)	<0.0001
Age; Median [IQR]; Years	67 [57–78]	63 [55–63]	<0.0001
<40	6 (5.4)	412 (14)	0.003
40–64	42 (37.8)	2205 (74.7)	
65–74	25 (22.5)	192 (6.5)	
≥75	38 (34.2)	144 (4.9)	
Sex; Female; N (%)	47 (42)	2512 (41)	0.76
Mechanical Ventilation; N (%)	31 (37)	428 (14)	<0.0001
Hypertension; N (%)	61 (65)	1912 (42)	<0.0001
Diabetes Mellitus; N (%)	32 (34)	1312 (28)	0.23
Ischaemic Heart Disease; N (%)	28 (30)	560 (12)	<0.0001
Atrial Fibrillation; N (%)	9 (10)	178 (7)	0.25
Carotid Stenosis; N (%)	8 (9)	349 (13)	0.28
Smoking; N (%)	15 (16)	385 (17)	0.59
Prior Stroke or Transient Ischemic Attack; N (%)	14 (15)	189 (7)	0.003
White Blood Cell Count x10^9/L; Mean (SD)	10.3 (8.4)	10.1 (18.5)	0.93
White Blood Cell Count x10^9/L; Median [IQR]	9.0 [6.3–12.2]	6.9 [5.1–9.9]	0.01
<4 × 10^9/L	2 (2.4)	64 (11.6)	0.003
4–10 × 10^9/L	49 (57.6)	348 (63.2)	
10–20 × 10^9/L	30 (35.3)	113 (20.5)	
≥20 × 10^9/L	4 (4.7)	26 (4.7)	
Neutrophil Count x10^9/L; Mean (SD)	9.6 (12.9)	8.3 (15.4)	0.48
Neutrophil Count x10^9/L; Median [IQR]	6.6 [4.5–9.4]	5 [3.4–8.2]	0.08
<4 × 10^9/L	10 (13.3)	142 (33.2)	0.01
4–10 × 10^9/L	49 (65.3)	217 (50.7)	
10–20 × 10^9/L	13 (17.3)	56 (13.1)	
≥20 × 10^9/L	3 (4)	13 (3)	
Lymphocyte Count x10^9/L; Mean (SD)	1.8 (1.6)	1.1 (3.8)	0.14
Lymphocyte x10^9/L; Median [IQR]	1.4 [1.2–2]	0.9 [0.7–1.4]	<0.001
<1 × 10^9/L	13 (15.5)	2360 (85.9)	<0.0001
1–2 × 10^9/L	49 (58.3)	243 (8.8)	
2–3 × 10^9/L	17 (20.2)	92 (3.3)	
3–4 × 10^9/L	3 (3.6)	31 (1.1)	
≥4 × 10^9/L	2 (2.4)	22 (0.8)	
Neutrophil/Lymphocyte Ratio; Mean (SD)	7.39 (9.74)	6.34 (6.22)	0.21
Neutrophil/Lymphocyte Ratio; Median [IQR]	4.44 [3–7.32]	4.34 [2.5–7.6]	0.96
Platelet Count x10^9/L; Mean (SD)	212.7 (105.7)	200.5 (47.8)	0.02
Platelet Count x10^9/L; Median [IQR]	179.5 [145–283]	195 [152–253]	0.73
<350 × 10^9/L	71 (88.8)	2693 (97.9)	<0.0001
350–500 × 10^9/L	9 (11.3)	57 (2.1)	
Alanine Transaminase (ALT) U/L; Mean (SD)	50.8 (86.4)	38.3 (48.2)	0.07
Alanine Transaminase (ALT) U/L; Median [IQR]	31 [21.7–44.5]	29 [18–44]	0.53
Aspartate Transaminase (AST) U/L; Mean (SD)	59.6 (98.7)	44.1 (41.8)	0.24
Aspartate Transaminase (AST) U/L; Median [IQR]	35 [25–53]	35 [25–50]	0.93
Blood Urea Nitrogen (BUN) mg/dl; Mean (SD)	25.8 (21.9)	22.3 (24.7)	0.25
Blood Urea Nitrogen (BUN) mg/dl; Median [IQR]	19 [13–29.6]	15.8 [9.7–24]	0.12
Creatinine mg/dl; Mean (SD)	1.5 (1.3)	1.3 (1.0)	0.21
Creatinine mg/dl; Median [IQR]	1.1 (0.9–1.5)	1.1 (0.9–1.4)	0.94
C-Reactive Protein (CRP) mg/L; Mean (SD)	60.5 (65.7)†	84 (74.9)	<0.001
C-Reactive Protein (CRP) mg/L; Median [IQR]	31 [12–85.5]†	65 [26.4–119.75]	<0.001

* Data regarding 6200 patients were received in details. Other centers provided summary data that could not be used for comparison.
† Data with qualitative scale were excluded from the analyses.

analyses were repeated based on inclusion (Figs. 1–3) or exclusion of this center (Forest Plots 1–4 in Supplemental Figs. 5–8, page 25).

When considering all the available data after quality and risk of bias assessment, the risk of subsequent stroke in the infected patients with SARS-Cov-2 is 156/17,799 (0.9%, non-weighted simple pooled analysis). A meta-analysis of data from 43 regions (Fig. 1) suggests an overall stroke risk of 0.5% [95% CI, 0.3%–0.7%]. When grouping the centres by continent, the risk of subsequent stroke is 1.2% [95% CI, 0.9%–1.6%] in North America, 0.5% [95% CI, 0.1%–1.1%] in Europe, 0.3% [95% CI, 0.0%–0.9%] in Asia, and 0.0% in Oceania (Fig. 2). To control for possible unseen heterogeneity among countries with higher and lower health expenditures in terms of the diagnosis or quality of care, we repeated the analysis by including only 27 regions with higher health expenditures (Fig. 3). The overall stroke risk among these 27 regions is 0.7% [95% CI, 0.2%–1.6%]. The repeated meta-analysis after removing the centres with the highest and lowest calculated risk suggests a comparable stroke risk of 0.6% [95% CI, 0.5%–0.8%] (Supplemental Figure 8, page 29). Grouping the regions based on the received data type resulted in the risk of 0.6% [0.0%–1.7%] for regions that provided the individual level data for all the study population, and 0.5% [0.2%–0.7%] for regions that either presented summary level data or could provide individual level data for only a subset of the study population (Supplemental Figure 9, page 30). All analyses were conducted under low heterogeneity among study levels (I^2<50%). When comparing patients with and without a subsequent stroke, there were significant differences in age, needs for mechanical ventilation, hypertension, ischaemic heart disease, prior stroke or transient ischaemic attack, platelets counts, white blood cells, neutrophils and lymphocytes counts, and C-reactive protein (CRP) between the two groups (all p<0.01; Table 1).

Table 2
Baseline characteristics and clinical details of patients with cerebrovascular events.

Stroke Parameter	Acute Ischaemic Stroke *N* = 123 (79%)	Intracranial Haemorrhage *N* = 27 (17%)	Cerebral Venous Thrombosis *N* = 6 (4%)
Age; Mean (SD); Years	68.6 (13.9)	62.5 (15.3)	50.3 (12.9)
Age; Median [IQR]; Years	71.0 [58.2–78.0]	62.0 [52.5–71.5]	54.0 [39.0–58.0]
Sex; Female; N (%)	56 (46)	8 (30)	4 (67)
Interval Between SARS—CoV-2 Onset to Stroke; Median [IQR]; Days	3 [0–7]	1 [0–5]	4.5 [2–14]
Stroke-Related Symptoms as the Chief Complaint; N (%)	31 (25)	11 (41)	1 (17)
Large Vessel Occlusion; N (%)	27/72 (37.5)	–	–
Intravenous Thrombolysis; N (%)	7/80 (8.8)	–	–
National Institutes of Health Stroke Scale (NIHSS) Score; Median [IQR]	9.5 [6.0–19.0]	13 [8.0–17.0]	–
Intracerebral Haemorrhage (ICH) Score; Median [IQR]	–	3.0 [2.0–4.0]	–
Imaging Pattern; N (%)	Embolic / large vessel athero-thromboembolism: 58/80 (72.5) *	Intracerebral Haemorrhage: 25 (92.6)	–
	Lacunar: 6/80 (7.5) *	Subarachnoid Haemorrhage: 2 (7.4)	–
	Other: 16/80 (20.0)*,†	–	–

* The magnetic resonance imaging (MRI) details of 80 patients were available.
† Borderzone stroke or equivocal lesions.

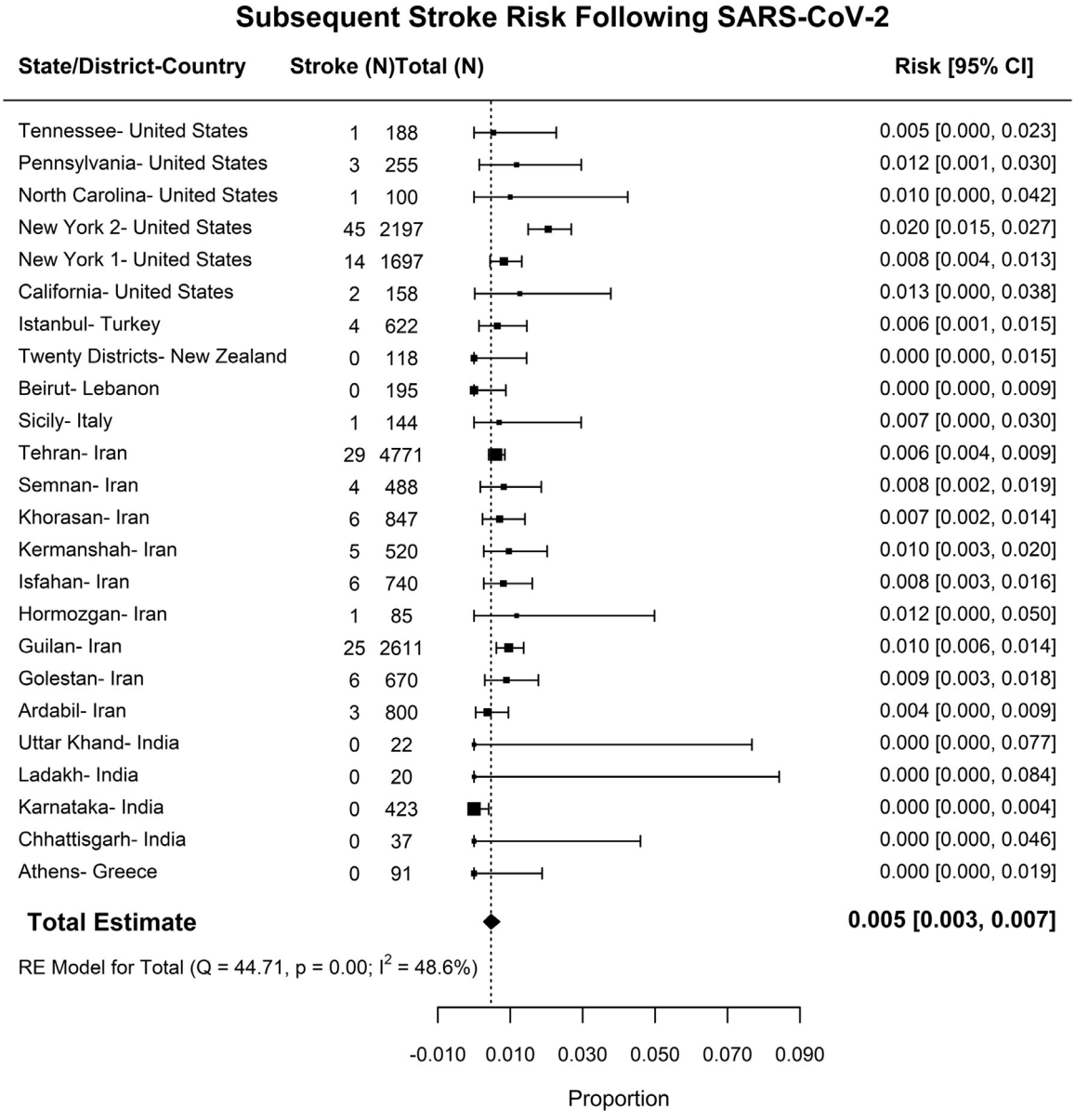

Fig. 1. Forest Plot; risk of subsequent stroke in patients infected with SARS-CoV-2, presented for regions in each country.

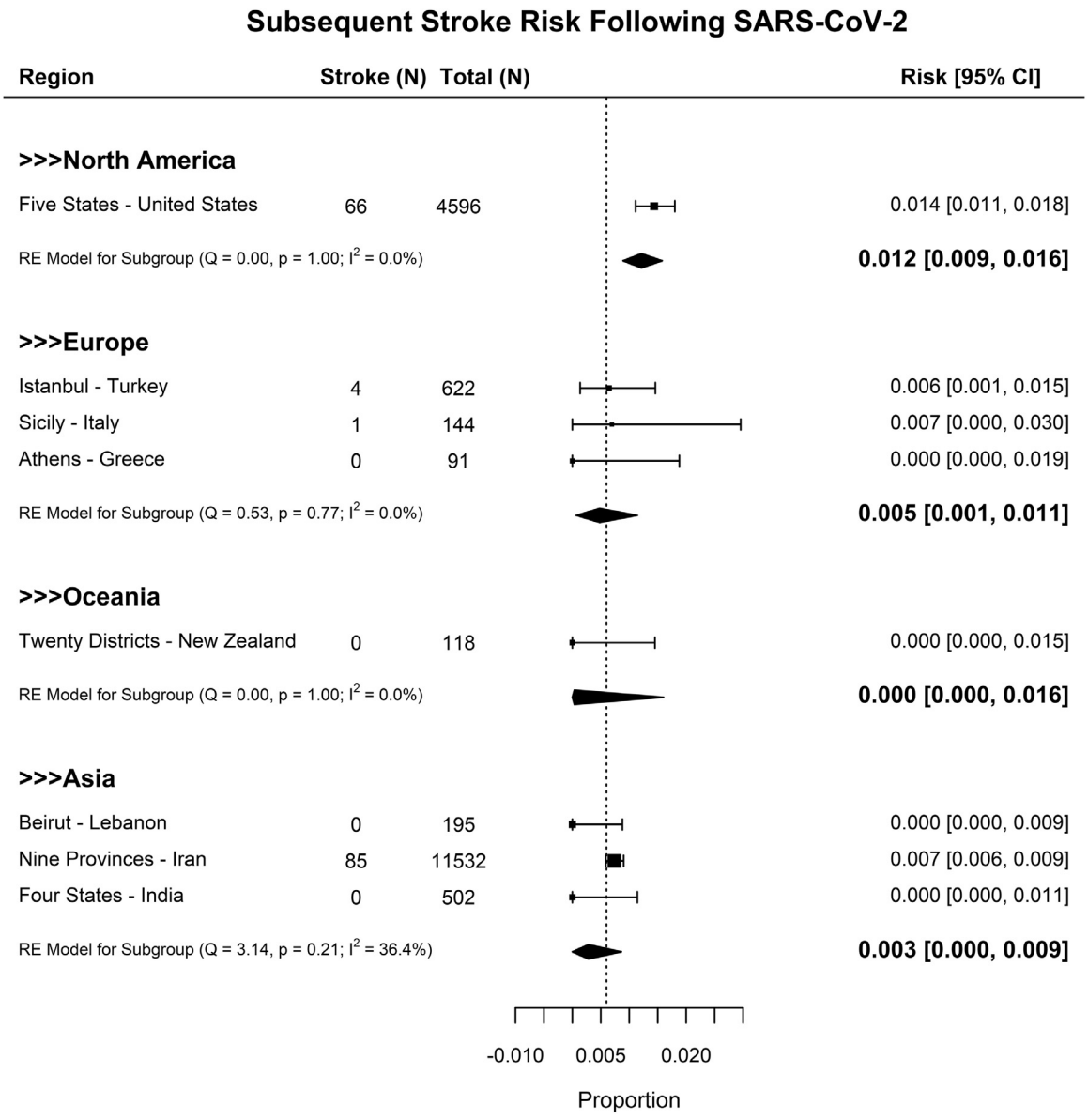

Fig. 2. Forest Plot; risk of subsequent stroke in patients infected with SARS-CoV-2, Presented for countries grouped by continents.

Binary logistic regression (Hosmer and Lemeshow Test *p:* 0.550 and Nagelkerke R Square: 0.152) suggested that mechanical ventilation (OR: 1.9, 95% CI:1.1–3.5, $p = 0.028$), and the presence of ischaemic heart disease (OR: 2.5, 95% CI: 1.4–4.7, $p = 0.006$) are independent predictors of stroke. When we repeated the analysis after excluding the need for ventilation (given the limited number of patients on a ventilator), ischaemic heart disease remained the only independent predictor of stroke.

5. Discussion

The results of this multi-national study on hospitalized patients with SARS-CoV-2 infection indicated an overall stroke risk of 0.5% (pooled risk: 0.9%). This frequency was obtained after a careful quality and heterogeneity assessment of the data. The results of regression models suggest that the need for mechanical ventilation and a history of ischaemic heart disease are the independent predictors of stroke among SARS-CoV-2 hospitalized patients.

Since the onset of the pandemic, a large population across the globe have been diagnosed with SARS-CoV-2 and several had associated neurological symptoms [11,48–50]. Recently, there has been increasing attention on the vascular complications of SARS-CoV-2, and different pathophysiologic mechanisms have been proposed to underpin such events; among them, one can mention vasoconstriction and increased blood pressure through an imbalance of Angiotensin-Converting Enzyme (ACE) and ACE-2 activation, immune-mediated mechanisms and overexpression of the cytokines, vasculitis, and neurological consequences secondary to hypoxemia or hypotension [3,7,8,10,51]. Increased proinflammatory biomarkers [52,53], and COVID-19-associated coagulopathy, characterized by increased fibrinogen/fibrinogen degradation products and D-dimer levels [12–14] were also reported in patients with SARS-CoV-2 infection. Further reports supported higher thrombotic complications such as ischaemic stroke, systemic arterial embolism, and venous thromboembolism in SARS-CoV-2 infected patients [54,55].

To date, several series of strokes in patients with SARS-CoV-2 diagnoses have been reported [3,4,56]. However, to our knowledge, no prior study has determined the rate of these complications at a multinational level. A temporal relationship and increased risk of stroke have been reported in association with different respiratory viral infections [15–23]. A population-based study in the United Kingdom (UK) on 2874 patients demonstrated an increased number

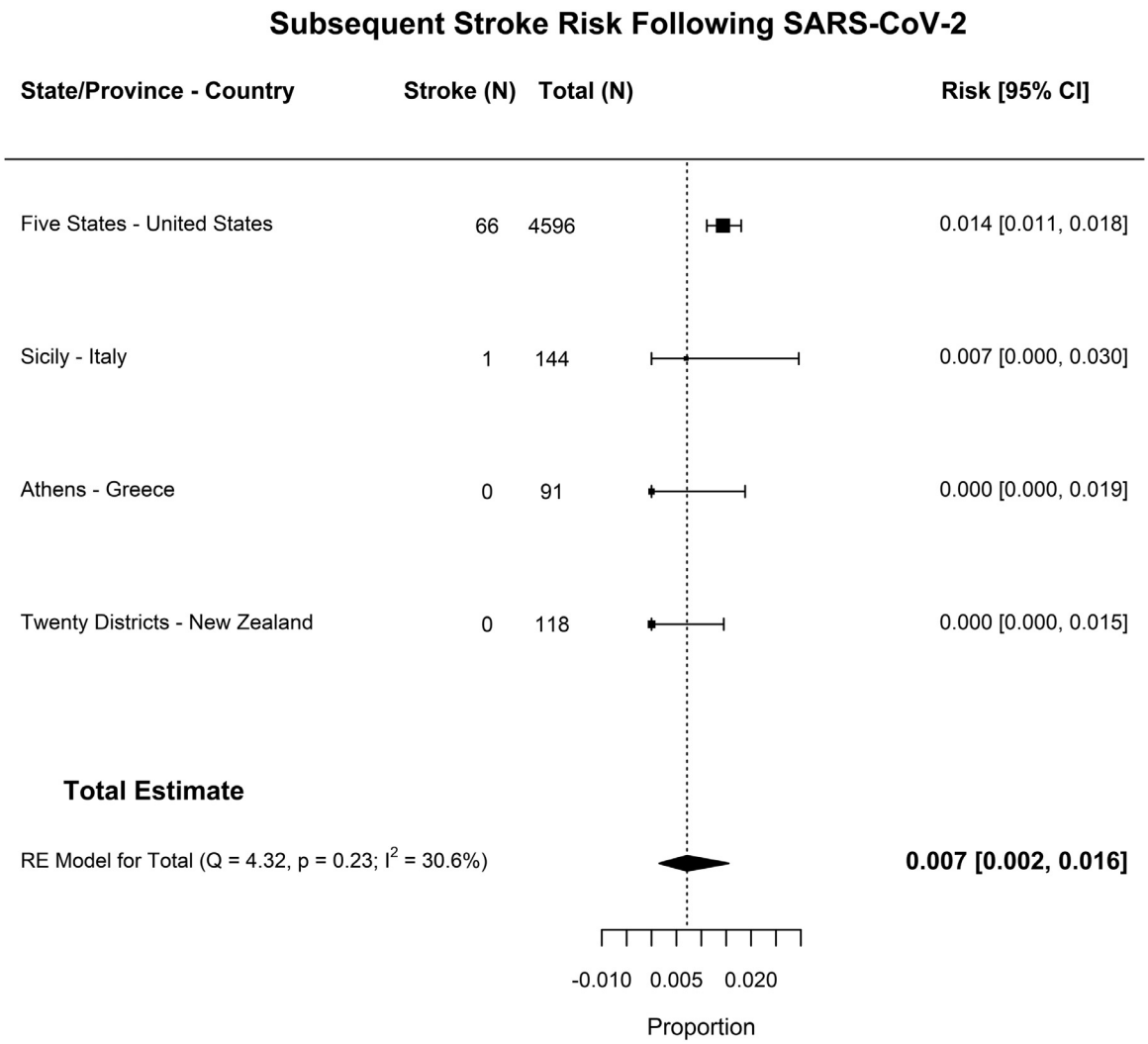

Fig. 3. Forest Plot; risk of subsequent stroke in patients infected with SARS-CoV-2, Data limited to countries with higher health expenditure.

of the first-ever stroke within two (ischaemic stroke) to four weeks (haemorrhagic stroke) after seasonal influenza peak [15]. Another population study from the UK on 22,400 individuals reported an increased risk of vascular events following lower respiratory or urinary tract infections, with an age-adjusted incidence ratio of 3.2 within the first three days, which decreased to 1.33 within three months post-infection [16]. In California, a study of about 37,000 hospitalized ischaemic stroke patients suggested a significant risk of stroke in patients with prior influenza-like illnesses, with odds ratios (OR) of 2.9 in 15 days, decreasing to 1.7 within 365 days post-infection [17]. Based on this study, stroke triggered by influenza-like infections are more likely to occur in patients who are younger than 45 years old (OR: 9.28, in comparison to OR: 2.71 in 45–65 years old, and OR: 2.65 in patients older than 65). A recent meta-analysis showed that influenza vaccination might be associated with a lower risk of ischaemic stroke events [57]. Despite this, the overall risk of subsequent stroke seems to be less than 1%. In another study of over 102,500 patients with a diagnosis of influenza, stroke or TIA incidence rates were reported to be 0.052, 0.035, 0.029 at 1, 3, and 6 months after influenza [19]. Likewise, the United States National Readmissions Database reports on over 46,000 patients hospitalized for influenza indicated that strokes are infrequent (0.3%) causes of 30-day readmission [18].

Strokes were also reported among patients infected with β-coronaviruses such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome coronavirus (MERS-CoV) [20–23]. Five (2%) patients infected with SARS in Singapore developed large artery cerebral ischemia, among them three had no known stroke risk factor [20]. Acute myocardial infarction and disseminated intravascular coagulation (three patients), and generalized hypotension (four patients) preceded the ischaemic stroke event. Bilateral anterior cerebral artery stroke (a diabetic and hypertensive 57-year old man) [21], frontal lobes intracerebral hemorrhage (a diabetic 34-year old woman) [22], and frontal hematoma and subarachnoid hemorrhage extending to ventricles that resulted in subfalcine herniation (a diabetic 42-year old woman, with history of nephrectomy) [23] were reported in association with MERS-CoV infection. To the best of our knowledge, the literature is limited to small case series, and no population-based rate assumption has been provided for these viral infections.

Although an increasing number of reports on neurological symptoms have been published since the onset of the SARS-CoV-2 outbreak, confirmed cases of cerebrovascular events in association with SARS-CoV-2 are limited. Zhang et al. described three Chinese patients who experienced multiple cerebral infarctions [4]. All of these patients were in critical conditions, significant coagulopathy, and antiphospholipid antibodies (positive anticardiolipin IgA, anti–β2-glycoprotein I IgA and IgG). In another case series from China, 13 out of 221 patients (6%) had strokes: large vessel stroke in five, small vessel stroke in three, cardioembolic stroke in three, and two patients were complicated with cerebral venous thrombosis and cerebral hemorrhage [3]. In a series of six patients from the UK, all patients

had large vessel occlusion (three in multiple vascular territories) with elevated D-dimer levels, among whom the stroke was the primary presentation of SARS-CoV-2 in one patient. Five patients had positive lupus anticoagulants, but only one had medium titter antiphospholipid IgM and IgG antibodies. All patients in this series were over 50 years old and had moderate to severe SARS-CoV-2 infection [5]. In a case series from New York City, five patients, younger than 50 years old with a positive test for SARS-CoV-2, developed large-vessel stroke [6]. Three of these patients had prior comorbidities—39 years old with hypertension and dyslipidaemia, 44 years old with diabetes mellitus, and 49 years old with diabetes and prior stroke. The authors stated that based on the routine admission rate of their center over the past year, the rate of young adults with large vessel stroke might be higher. Unfortunately, the authors provided no information regarding the total hospitalized patients with SARS-CoV-2 for further risk calculation.

It is worth mentioning that most of the reported SARS-CoV-2 infected patients with stroke had critical conditions. In this study, the patients with stroke were more likely on a ventilator (36.5% versus 14.0%) and had ischaemic heart disease (29.8% versus 12.1%). Patients who receive invasive mechanical ventilation are more likely to have elevated inflammatory markers, comorbidities, and the need for vasopressor and ionotropic agents [58]. Inflammation, coagulation disorder, and infection in critically ill patients may also favor a stroke [59]. About 0.5% of patients hospitalized with sepsis experience stroke within one year [24]. Sepsis can put patients at higher risks of ischaemic (OR>28) or haemorrhagic strokes (OR>12) through the first two weeks; the risk would remain high even for up to one year [60]. A variety of mechanisms can induce coagulopathy in sepsis [25,26]. In addition, about 6% of patients with severe sepsis experience new-onset of atrial fibrillation, which can put them at a greater risk of in-hospital stroke (2.6%) and in-hospital mortality (56%) [27]. New-onset atrial fibrillation is not limited to sepsis and can occur up to 8% of the ICU admissions, leading to an increased length of stay, mortality, and poor outcomes [61].

The authors communicated with different centres in several countries to increase the representativeness of this study. However, due to the sensitive nature of the SARS-CoV-2 outbreak, the high load of patients, and lack of electronic health records and resources to extract data, or lack of priority, the recruited data were limited to 99 centres from 11 countries. We had to exclude 25% of patients from the analyses due to the unavailability of validated data. The above missingness may have introduced selection-bias and affected the generalizability of the results or weaken the conclusion that can be drawn about the phenotype and mechanisms of stroke in SARS-CoV-2. Nevertheless, we did not observe any significant heterogeneity in our subgroup meta- and sensitivity analyses.

In our study, the overall estimated risk in the meta-analysis of all centres was 0.5%. This risk would be comparable to the reported incidence of stroke following influenza [18,19]. When we conducted the meta-analyses by continent, we observed a subsequent stroke risk of 0.7−1.2% in North America, 0.5% in Europe, and 0.3% in Asia. This difference might be due to many factors including policy variation among different healthcare systems for the hospitalization of SARS-CoV-2 infected patients; some centres had relaxed criteria for admission of positively tested patients, while the others were overwhelmed and adopted strict criteria to hospitalize patients. The other factor might be the confirmation of the SARS-CoV-2 infection. Due to the low sensitivity of PCR [62,63], the testing interval, and also availability and capacity of testing sites, some centres considered chest CT scan in addition to the presence of symptoms indicative of SARS-CoV-2 infection. Nevertheless, in our study, the stroke risk was estimated as 0.7% among countries with higher health expenditures which only used PCR for infection confirmation. This rate was similar to our overall risk estimates; pooled risk estimates of 0.9% and weighted risk of 0.5%. Although our study includes several countries and communities and has high generalization power for the calculated risk, we realize that the risk factors associated with stroke could have been different if the study was done at the community level; secondary to a different profile of vascular risk factors, genetic predisposition, and sociodemographic factors.

We did not have a central adjudication in this study. In addition, we realize that the clinical severity could be assessed through other parameters that could not be collected considering the high number of participating centres, the partial availability of data, and the narrow study time window. Various centres may have had a different treatment protocol based on local experience that could not be fully taken into consideration. Despite these possible limitations, the availability of richer clinical data or care procedures would not suggest results very different from those presented. At the same time, the pooled and meta-analyses for risk calculation did not require detailed clinical data.

We made attempts to capture data from all the regional hospitals for SARS-CoV-2 infection and stroke-related readmissions; however, there is the possibility of not capturing stroke or other cerebrovascular events in the convalescence stage. Despite our attempt to capture the whole referral region, patients' mobility among nearby regions to obtain the best medical services might have introduced bias in the risk estimation. We realize that the SARS-CoV-2 epidemic has affected the care-seeking behaviours of patients with neurological symptoms and has exhausted care deliveries in several health systems. We also recognize that decreased quality of care, long wait-time for conducting neuroimaging, and rapid deterioration of SARS-CoV-2 infected patients or being on a ventilator may have led to some patients with mild stroke-like symptoms not receiving further relevant investigation and diagnosis. To partially alleviate the effect of some of the limitations, we provided different levels of meta-analysis in this study.

The results of this multi-national study on hospitalized patients with SARS-CoV-2 infection indicated an overall stroke risk of 0.5% (pooled risk: 0.9%). This number will be lower if all patients with SARS-CoV-2 diagnosis are considered rather than hospitalized patients. The need for mechanical ventilation and ischaemic heart disease are the independent predictors of stroke among SARS-CoV-2 patients.

Authors' contribution

VA, SS and RZ conceived of the presented idea. SS, JL, VA, and RZ designed the experiments. AyK, SS, VeA, VA and JL performed the analysis. DC, AK, OO, SS, SN, GF, RZ, AG, AsaM, RBS, AJ, MP, FK, AyK, and VeA performed data validation. RZ, SN, NR, SA, GT, StM, AVF, MM, FK, OA, BRJ, MR, AR, GF, SASN, PNS, AB, MiS, ShM, TY, ASaj, NG, ArK, ShM, ZMA, SAE, BRJ, MN, NO, MR, AsaM, MG, AJ, MP, ST, and AshM provided clinical input. AC, EK, ASab, SE, SiM, AD, NA, MH, MiS, AHK, HHH, FC, ASaj, SRB, MHH, NG, ZMA, AR, ASE, MN, MR, ZMA, ND, MG, MHZ, NR, SAE, SASN, FK, OA, AVF, NO, AshM, and MHZ provided data on base population. AC, VA, VeA, EK, ArK, CG, JL, SRB, ABH, AR, AsaM, ND, RBS, MHZ, MP, PF, PNS, HHH, SiM, AD, NO, FC, AGStM, and MH provided statistical and epidemiological insights. RZ, SS, SN, NR, GT, DT, PNS, FK, MiS, GF, PF, ST, ShM, TY, NG, SAE, BRJ, SASN, ASab, NA, OA, AHK, AshM, AyK, OO, and MHZ contributed to the chart review. AVF, GF, SN, SS, MHH, ABH, MN, AG, CG, StM, MR, and SRB contribute to clinical and neurological validation. SS and RZ wrote the initial draft. All authors provided critical feedback and contributed to different sections of the manuscript. All authors reviewed and approved the final version of the manuscript.

Acknowledgements/Funding

This study received no funding support, and the study design, data collection, data analysis, interpretation, writing of the report were not affected by any sponsors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2020.102939.

References

[1] Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020;91:157–60.
[2] Lake MA. What we know so far: COVID-19 current clinical knowledge and research. Clin Med J R Coll Physicians Lond 2020;20:124–7.
[3] Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. SSRN Electron J 2020;19. doi: 10.2139/ssrn.3550025.
[4] Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med 2020;382:e38.
[5] Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry 2020 **0**jnnp-2020-323586.
[6] Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020;382:e60.
[7] Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;30 **S0889-1**30357–3.
[8] Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol 2020: e13473.
[9] Xia H, Sriramula S, Chhabra KH, Lazartigues E. Brain angiotensin-converting enzyme type 2 shedding contributes to the development of neurogenic hypertension. Circ Res 2013;113:1087–96.
[10] Fraga-Silva RA, Da Silva DG, Montecucco F, et al. The angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis: a potential target for treating thrombotic diseases. Thromb Haemost 2012;108:1089–96.
[11] Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology 2020 201187.
[12] Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020 published online April. doi: 10.1182/blood.2020006000.
[13] Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020 published online April. doi: 10.1111/jth.14854.
[14] Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020:1–10. doi: 10.1007/s00134-020-06062-x.
[15] Toschke AM, Heuschmann PU, Wood O, Wolfe CDA. Temporal relationship between influenza infections and subsequent first-ever stroke incidence. Age Ageing 2009;38:100–3.
[16] Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611–8.
[17] Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza-like illness as a trigger for ischaemic stroke. Ann Clin Transl Neurol 2018;5:456–63.
[18] Yandrapalli S, Aronow WS, Frishman WH. Readmissions in adult patients following hospitalization for influenza: a nationwide cohort study. Ann Transl Med 2018;6 318–318.
[19] Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. Cardiology 2009;113:98–107.
[20] Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan 2005;14:113–9.
[21] Arabi YM, Harthi A, Hussein J, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 2015;43:495–501.
[22] Algahtani H, Subahi A, Shirah B. Neurological complications of middle east respiratory syndrome coronavirus: a report of two cases and review of the literature. Case Rep Neurol Med 2016;2016:1–6.
[23] Al-Hameed FM. Spontaneous intracranial hemorrhage in a patient with Middle East respiratory syndrome corona virus. Saudi Med J 2017;38:196–200.
[24] Shao IY, Elkind MSV, Boehme AK. Risk factors for stroke in patients with sepsis and bloodstream infections. Stroke 2019;50:1046–51.
[25] Saracco P, Vitale P, Scolfaro C, Pollio B, Pagliarino M, Timeus F. The coagulopathy in sepsis: significance and implications for treatment. Pediatr Rep 2011;3:119–21.
[26] Simmons J, Pittet JF. The coagulopathy of acute sepsis. Curr Opin Anaesthesiol 2015;28:227–36.
[27] Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA - J Am Med Assoc 2011;306:2248–55.
[28] Cumbler E. In-Hospital Ischaemic Stroke. Neurohospitalist 2015;5:173–81.
[29] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.
[30] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Rev Esp Nutr Humana y Diet 2016;20:148–60.
[31] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283 2008.
[32] Groves T. Enhancing the quality and transparency of health research. Bmj 2008;337:66.
[33] Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American heart association/American stroke association. Stroke 2013;44:2064–89.
[34] Potter GM, Marlborough FJ, Wardlaw JM. Wide variation in definition, detection, and description of lacunar lesions on imaging. Stroke 2011;42:359–66.
[35] Wessels T, Röttger C, Jauss M, Kaps M, Traupe H, Stol E. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. Stroke 2005;36:757–61.
[36] Bang OY, Ovbiagele B, Liebeskind DS, Restrepo L, Yoon SR, Saver JL. Clinical determinants of infarct pattern subtypes in large vessel atherosclerotic stroke. J Neurol 2009;256:591–9.
[37] Love BB, Bendixen BH. Classification of subtype of acute ischaemic stroke definitions for use in a multicenter clinical trial. Stroke 1993;24:35–41.
[38] World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. WHO - Interim Guid 2020;2019:1–7.
[39] Prabhakaran S, Silver AJ, Warrior L, McClenathan B, Lee VH. Misdiagnosis of transient ischaemic attacks in the emergency room. Cerebrovasc Dis 2008;26:630–5.
[40] Sadighi A, Stanciu A, Banciu M, et al. Rate and associated factors of transient ischaemic attack misdiagnosis. eNeurologicalSci 2019;15:100193.
[41] Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. Pract Neurol 2014;14:23–31.
[42] IBM. Downloading IBM SPSS statistics 26. IBM. https://www.ibm.com/analytics/spss-statistics-software (accessed May 11, 2020).
[43] Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280–6.
[44] 9.5.2 Identifying and measuring heterogeneity. https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm (accessed May 30, 2020).
[45] Global Health Expenditure Database. https://apps.who.int/nha/database/Select/Indicators/en (accessed May 30, 2020).
[46] Inthout J, Ioannidis JPA, Borm GF, Goeman JJ. Small studies are more heterogeneous than large ones: a meta-meta-analysis. J Clin Epidemiol 2015;68:860–9.
[47] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
[48] Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;2. doi: 10.1007/s00405-020-05965-1.
[49] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020;92:552–5.
[50] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020:e201127. doi: 10.1001/jamaneurol.2020.1127.
[51] Bennion DM, Rosado CA, Haltigan EA, Regenhardt RW, Sumners C, Waters MF. Serum activity of angiotensin converting enzyme 2 is decreased in patients with acute ischaemic stroke. JRAAS - J Renin-Angiotensin-Aldosterone Syst 2016;17. doi: 10.1177/1470320316661060.
[52] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[53] Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620–9.
[54] Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020. doi: 10.1016/j.thromres.2020.04.013.
[55] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020 jth.14830.
[56] Phan LT, Nguyen T V, Luong QC, et al. Importation and human-to-human transmission of a novel coronavirus in Vietnam. N Engl J Med 2020;382:872–4.
[57] Tsivgoulis G, Katsanos AH, Zand R, et al. The association of adult vaccination with the risk of cerebrovascular ischemia: a systematic review and meta-analysis. J Neurol Sci 2018;386:12–8.
[58] Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020 published online April. doi: 10.1056/nejmc2010419.
[59] Pilato F, Profice P, Dileone M, et al. Stroke in critically ill patients. Minerva Anestesiol. 2009;75:245–50.
[60] Boehme AK, Ranawat P, Luna J, Kamel H, Elkind MSV. Risk of acute stroke after hospitalization for sepsis: a case-crossover study. Stroke 2017;48:574–80.
[61] Moss TJ, Calland JF, Enfield KB, et al. New-onset atrial fibrillation in the critically III. Crit Care Med 2017;45:790–7.
[62] Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA - J Am Med Assoc 2020;323:1239–42.
[63] Long C, Xu H, Shen Q, et al. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol 2020;126:108961.