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Risk of Cerebrovascular Events in Hospitalized Patients with SARS-CoV-2 Infection

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Corresponding Author:	Ramin Zand, M.D., M.P.H. UNITED STATES
First Author:	shima shahjouei
Order of Authors:	shima shahjouei
	Soheil Naderi
	Jiang Li
	Ayesha Khan
	Durgesh Chaudhary
	Ghassem Farahmand
	Shailesh Male
	Christoph Griessenauer
	Mirna Sabra
	Stefania Mondello
	Achille Cernigliaro
	Faezeh Khodadadi
	Apoorva Dev
	Nitin Goyal
	Sakineh Ranji-Burachaloo
	Oluwaseyi Olulana
	Venkatesh Avula
	Seyed Amir Ebrahimzadeh
	Orkhan Alizada
	Mehmet Murat Hancı
	Askar Ghorbani
	Alaleh Vaghefi far
	Annemarei Ranta
	Martin Punter
	Mahtab Ramezani
	Nima Ostadrahimi
	Georgios Tsivgoulis
	Paraskevi C. Fragkou
	Peyman Nowrouzi-Sohravi

	Emmanouil Karofylakis
	Sotirios Tsiodras
	Saeideh Aghayari Sheikh Neshin
	Alia Saberi
	Mika Niemelä
	Behnam Rezai Jahromi
	Ashkan Mowla
	Mahsa Mashayekhi
	Reza Bavarsad Shahripour
	Seyed Aidin Sajedi
	Mohammad Ghorbani
	Arash Kia
	Nasrin Rahimian
	Vida Abedi
	Ramin Zand
Manuscript Region of Origin:	UNITED STATES
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Risk of Cerebrovascular Events in Hospitalized Patients with SARS-CoV-2 Infection

Authors

Shima Shahjouei, MD,[1] Soheil Naderi, MD,[1] Jiang Li, PhD, [2] Ayesha Khan,[1] MD, Durgesh Chaudhary, MD,[1] Ghassem Farahmand, MD, [3, 4] Shailesh Male, MD, [5] Christoph Griessenauer, MD, [1] Mirna Sabra, PhD, [6] Stefania Mondello, MD, [7] Achille Cernigliaro, PhD, [8] Faezeh Khodadadi, Pharm.D, [9] Apoorva Dev, PhD Scholar, [9] Nitin Goyal, MD, [10] Sakineh Ranji-Burachaloo, MD, [3,4] Oluwaseyi Olulana, M.S., [1] Venkatesh Avula, M.S., [1] Seyed Amir Ebrahimzadeh, MD, [11] Orkhan Alizada, MD,[12] Mehmet Murat Hancı, MD, [12] Askar Ghorbani, MD, [13] Alaleh Vaghefi far, MD, [13] Annemarei Ranta, MD, [14,15] Martin Punter, PhD, [14,15] Mahtab Ramezani, MD,[16] Nima Ostadrahimi, [13] MD, Georgios Tsivgoulis, MD, [10, 17] Paraskevi C. Fragkou, MD, [18] Peyman Nowrouzi-Sohravi, PhD,[19] Emmanouil Karofylakis, MD, [18] Sotirios Tsiodras, MD, [18] Saeideh Aghayari Sheikh Neshin, MD,[20] Alia Saberi, MD, [20] Mika Niemelä, MD, [21] Behnam Rezai Jahromi, MD,[21] Ashkan Mowla, MD,[22] Mahsa Mashayekhi, MD,[23] Reza Bavarsad Shahripour, MD, [10] Seyed Aidin Sajedi, MD,[24] Mohammad Ghorbani, MD, [25] Arash Kia, MD,[26] Nasrin Rahimian, MD, [27] Vida Abedi, PhD, [2,28] Ramin Zand, MD[1,10]

Contributors

Mohammad Hossein Harirchian, [4] MD, Nazanin Ahmadzadeh, MD,[29] Thomas Yasuda, MD,[30] Fabricio Cardoso, MD, [30] Asadollah Mirghasemi, MD, [31] Alireza Janbakhsh, MD, [32] Mohammad Hossein Zamanian, MD, [32] Zeinab Mohseni Afshar, MD, [32] Ali H. Kassem, MD, [33] Haidar H. Hoummani, MD, [33] Arefeh Babazadeh, MD, MPH,[34] Soheil Ebrahimpour, MD, PhD, [34] Sima Mohseni, MD, MPH, [34] Firas Kobeissy, PhD [35,36] Navneet Singh Dang, MD,[37] B. V. Ganesh, MBBS, M.S., [38] Radha Krishna Ramesh, MD,[39] Sedighe Basirjafari, MD, [40] Janardhanan Saravanan, Pharm Ph. D, [9] Faissal Qak, MD, [31] Afshin Borhani-Haghighi. [39]

[1]Neurology Department, Neuroscience Institute, Geisinger Health System, Pennsylvania, USA;

[2]Department of Molecular and Functional Genomics, Geisinger Health System, Danville, Pennsylvania, USA;

[3]Neurology Department, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran;

[4]Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran;

[5]Neurology Department, Vidant Medical Center, Greenville, North Carolina, USA;

[6]Neurosciences Research Center (NRC), Lebanese University/ Medical School, Beirut, Lebanon;

[7]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy;

[8]Regional Health Authority of Sicily, Palermo, Italy;

[9]PES University, Bengaluru, Karnataka, India;

[10]Neurology Department, University of Tennessee Health Science Center, Tennessee, USA;

[11]Radiology Department, Yasrebi Hospital, Isfahan, Iran;

[12]Neurosurgery Department, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey;

[13]Neurology Department, Tehran University of Medical Sciences, Tehran, Iran;

[14]Department of Neurology, Wellington Hospital, Wellington, New Zealand;

[15]Department of Medicine, University of Otago, Wellington, New Zealand;

[16]Neurology Department, Shahid Beheshti University of medical sciences, Tehran, Iran;

[17]Second Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, "Attikon" University Hospital, Athens, Greece;

[18]Fourth Department of Internal Medicine, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece;

[19]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran;

[20]Neurology Department, Poursina Hospital, Guilan University of Medical Sciences, Guilan, Iran;

[21]Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland;

[22]Division of Stroke and Endovascular Neurosurgery, Department of Neurosurgical Surgery, Keck School of Medicine, University of Southern California, California, USA;

[23]Internal medicine Department, Tabriz University of medical sciences, Tabriz, Iran;

[24]Neuroscience Research Center, Department of Neurology, Golestan University of Medical Sciences, Gorgan, Iran;

[25]Division of Vascular and Endovascular Neurosurgery, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran;

[26]Icahn school of medicine at Mount Sinai, Department of Population Health Science and Policy, Institute for Healthcare Delivery Science, New York, USA;

[27]Neurology Department, Yasrebi Hospital, Kashan, Iran;

[28]Biocomplexity Institute, Virginia Tech, Blacksburg, Virginia, USA;

[29]Istanbul Bilim University, Istanbul, Turkey;

[30]Neurology Department, Centro Médico de Campinas, São Paulo, Brazil;

[31]Department of Anesthesiology, University of Ottawa, Canada;

[32]Infection Disease Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran;

[33]Lebanese University/Beirut Governmental University Hospital, Beirut, Lebanon;

[34]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

[35]Program of Neurotrauma, Neuroproteomics and Biomarker Research (NNBR), University of Florida, Florida, USA;

[36]Lebanese Ministry of Health, Beirut, Lebanon;

[37]Department of medicine, Geisinger Health System, Pennsylvania, USA;

[38]ESIC Hospital, Karnataka, India;

[39]C.V. Raman General Hospital, Karnataka, India;

[40]Department of Radiology, Hashemi Rafsanjani Hospital, Khorasan, Iran;

[41]Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

Corresponding Author:

Ramin Zand M.D., M.P.H.

Neuroscience Institute, Geisinger,

100 North Academy Ave. Danville, PA, 17822

phone number: 570-214-4101

Fax number: (570) 808-3208

E-mail address: rzand@geisinger.edu; ramin.zand@gmail.com

Laboratory: www.thedecodelab.com

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Abstract:

Background: There has been increasing attention on cerebrovascular events (CVEs) following SARS-CoV-2. The goal of this study was to better depict the short-term risk of CVEs and its associated factors among SARS-CoV-2 hospitalized patients.

Methods: This multicenter, 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 CVEs. The counts and clinical details of the patients with and without a CVE were received 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 CVEs was estimated for individual states/districts, countries, continents, and within industrialized countries 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 26,133 hospitalized SARS-CoV-2 patients from 99 tertiary centers in 65 states/districts. A total of 17,774 patients were included in meta-analyses. Among them, 156 patients had a CVE complication—123(78·8%) ischemic stroke, 27(17·3%) intracerebral/subarachnoid hemorrhage, and 6(3·8%) cerebral sinus thrombosis. The meta-analyses indicated an overall 0·3%-1·2% risk of CVEs. Dependency on a ventilator and the presence of ischemic heart disease were predictive of CVEs.

Interpretation: Although there is an increased risk of CVEs among SARS-CoV-2 patients, the risk is comparable to other viral infections and critical conditions.

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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. Articles defining the higher risk of strokes among SARS-CoV-2 patients were published in the New York Times,(3) CNN health,(4) the Washington Post,(5) and several other news outlets(6–8) as early as April 1st. Li et al. published one of the first studies describing the risk of strokes among SARS-CoV-2 hospitalized patients.(9) They observed a 5% risk of ischemic 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 cerebrovascular events (CVEs) among SARS-CoV-2 patients.(9–11)

Several studies have described different mechanisms in which SARS-CoV-2 can induce neurological disorders and CVEs.(12,13) 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.(14,15) Other studies proposes immune-mediated mechanisms and overexpression of cytokines as the leading cause of CVEs.(16) However, the increased risk of CVEs is not exclusive to SARS-CoV-2 and it has been reported in association with other viral respiratory infections.(17–25)

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.(26–29) Considering the burden of CVEs and its association with worse prognosis among hospitalized patients,(30) we designed a multi-national observational study to better depict the short-term risk of CVEs and its associated factors among SARS-CoV-2 hospitalized patients.

2. Methods

The study was conducted and reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),(31) Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),(32) Preferred Reporting Items for Meta-analysis Of Observational Studies in Epidemiology (MOOSE),(33) and Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines.(34)

2.1. Data Sources:

This multicenter, multinational observational study was designed by the Neuroscience Institute of Geisinger Health System, Pennsylvania, USA. The study included patients from North America (Canada and 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 the center admitted SARS-CoV-2 patients. Centers were included by snowball sampling; the authors posted an announcement on social media platforms for professionals, and contacted their collaborators in different countries. In the US, our collaborators from seven health systems accepted our invitation. Thirteen tertiary centers from five health systems in New York, Pennsylvania, Tennessee, North Carolina, and California provided data by the deadline. In New Zealand, the data on hospitalized patients were provided by the Ministry of Health. Data collection in New Zealand was led by the National Stroke Register Team, which is supported by the National Stroke Network and the New Zealand Ministry of Health. All 20 districts were surveyed for incident cases verified by stroke physicians. In Iran, the invitation was announced by the Iranian Stroke Organization and National Society for Neurologists. Additionally, we communicated with the Departments of Neurology and Neurosurgery in large university hospitals. A total of 24 tertiary university hospitals from 15 provinces provided data. In India, state-level data on hospitalized patients with SARS-CoV-2 diagnosis were collected from Department of Health and Family Welfare (in each state). Detailed data regarding the CVEs were obtained from 26 centers in 19 states in India. Data from all Karnataka districts (Bengaluru, Mysuru, Belagavi,

Kalaburgi, Vijayapura, Chikkaballapur, Bagalkote, Bidar, and Dakshina-Kannada) were obtained from the Government of Karnataka, Department of Health and Family Welfare in Bengaluru. Records of CVEs were rechecked with Stroke Registry in Karnataka and also individual communication with 15 tertiary centers in Bengaluru. In Lebanon, the study was limited to two health systems in Beirut, where over 75% of patients with SARS-CoV-2 diagnosis were hospitalized. In Italy, invitations were sent to centers in Northern and Southern regions; however, only centers in Sicily could provide data in time. In Canada, Brazil, Finland, and Greece data were gathered from individual tertiary centers. Centers in France, China, Iraq, Dubai, Uganda, Kenya, Australia, and Japan also agreed to participate in the study; however, they could not meet our data collection or validation timelines. The study received approval by the Institutional Review Board of Geisinger Health System and other participating institutions when it was required.

2.2. Study Population:

We included consecutive hospitalized SARS-CoV-2 patients and recorded patients who had a subsequent and confirmed CVE—ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral venous thrombosis. The study cohort in all centers was defined as the total population of patients who were hospitalized with a confirmed diagnosis of SARS-CoV-2, with or without a CVE. The post-discharge follow-up protocol for SARS-CoV-2 patients varied in different countries and different centers. However, every center reported uniform and non-selective follow-ups for the study population. We recorded all the CVEs resulted in hospital admission when the test for SARS-CoV-2 was positive on the same day or the next day, or CVE complications during the hospital stay for a SARS-CoV-2 infection. In addition, attempts were made to consider all centers providing neurological services in the captured areas to maximize the chance of recording early post-discharge CVEs. In case there was a closed referral system between the different tertiary centers for patients with neurological complications, we considered the total number of hospitalized patients in the whole referral system to estimate the frequency of CVEs.

2.3. Index Events and Imaging Definition:

For this study, ischemic or hemorrhagic stroke was defined as the rapid onset of a neurological deficit when there was evidence of an acute ischemic or hemorrhagic 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. We further subclassified the ischemic stroke lesions based on the pattern of the lesion on diffusion-weighted imaging (DWI) or CT to lacunar,(35) embolic/ large vessel athero-thromboembolism,(36,37) and other phenotypes (borderzone or equivocal lesions). All the images were evaluated by a local radiologist and a member of our study team. In case of disagreement, a consensus was reached.

2.4. Inclusion and Exclusion Criteria:

To minimize the heterogeneity between different regions regarding the population screening protocols, only patients who were hospitalized for more than 24 hours were included in this study. The preferred diagnosis criteria for SARS-CoV-2 was defined according to the World Health Organization (WHO) interim guidance.(38) Due to the limited availability of polymerase chain reaction (PCR) testing or concerns about its low predictive value, several centers used a combination of the history of exposure, symptomatology, and chest CT with or without PCR methods for diagnosis confirmation (Supplemental Table 1). 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 ischemic 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.

2.5. Outcome Definition:

The primary goal of this study was to estimate the risk of CVEs among hospitalized SARS-CoV-2 patients. Data from centers unable to provide information on the hospitalized patients were not used for the calculation of risk estimate. We also compared the baseline characteristics, comorbidities, and laboratory

findings among CVEs cases and a subset of the study population and investigated the parameters with higher predictive value for CVEs occurrence.

2.6. Study Data:

Collaborators were asked to provide three sets of data: (1) number and clinical details of patients with a CVE, (2) total number and high-level summary (age and sex proportion, the severity of SARS-CoV-2 infection, ventilator dependency, 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 CVE cases and study population. Each center had the option of sending either patient- or summary- level data per internal board approval. Age, sex, comorbidities, and laboratory findings were requested for index cases and study population. For index cases, we obtained additional data regarding the onset of SARS-CoV-2 and the index event, chest CT scan findings, dependency on a ventilator, details of neurological investigations, and localization of the event, National Institute of Health Stroke Scale (NIHSS), and acute management and outcomes.

2.7. Risk of Bias Assessment:

We applied the Risk of Bias in Exposure Studies (ROBINS-E) tool(42) 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 CVE, potential of capturing late-onset CVEs; 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, automatic data pulling 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 subtype and localization; study population: high level summary data on hospitalized patients); measurement of outcomes (awareness of the local investigators of all CVEs admitted in the center, consistent definition when referring to CVE); and

measurement of reporting results (cases: reporting all CVEs irrespective of management outcome, study population: reporting of all hospitalized SARS-CoV-2 patients). We summarized the outcomes in Supplemental Table 1 for each center included in meta-analyses.

2.8. Statistics:

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 in qualitative rather than quantitative values (such as C-reactive protein-CRP test results), or equivalents of the requested items (such as glomerular filtration rates instead of creatinine) were excluded from the analyses. A 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(43) and $p<0{\cdot}05$ was considered statistically significant.

2.9. Investigations of Heterogeneity and Data Pooling:

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). Q-test with $p<0{\cdot}1$ or an I^2 statistic greater than 50% was considered statistically significant. We visualized subsequent stroke risk (95% CIs) following SARS-CoV-2 infection by forest plots. To better present the possible risk difference among centers, we conducted meta-analyses under four different levels: 1) States/districts for each country, 2) Countries sorted by continents, 3) Data limited to industrialized countries, and 4) Removal of the centers with the highest and lowest risk estimation. Because one of the centers in New York provided data based on automatic data pulling rather than full chart review, the forest plots were generated based on including or excluding the patients from this center (New York-2). We did

not include the centers that could not provide accurate total CVEs or study population for risk calculations. To minimize the impact of the low denominator,(44) we did not include the states/districts with <20 hospitalized patients in meta-analyses. We used random-effects models with double arcsine transformations and DerSimonian-Laird estimator in all meta-analyses. Meta-analyses were performed using the R version 3-5-0 metafor(45) package.

3. Results

3.1. Data Sources and Study Population

We received data from 26,133 hospitalized SARS-CoV-2 patients from 99 tertiary centers in 65 states/districts in 11 countries. A total of 8,359 patients were excluded from this study (including 19 cases of CVEs; Supplemental Table 2). The study included 17,774 SARS-CoV-2 infected patients—156 patients with a CVE complication. Detailed clinical and laboratory findings of all cases (with a CVE) and 6,200 patients (without a CVE) were available for further analysis. Several centers only provided summary data for patients without a CVE. Table 1 presents the comorbidities and laboratory findings among the patients with CVEs and a subset of the patients with available detailed data and without CVEs.

3.2. Cerebrovascular Events

Among the 156 patients with CVEs, 123 (78·8%) patients presented with acute ischemic stroke, 27 (17·3%) with intracerebral/subarachnoid hemorrhage, and 6 (3·8%) with cerebral venous or sinus thrombosis (Table 2). Patients with an acute ischemic attack had a median NIHSS of 9·5 [6·0-19·0] on admission. Among the available imaging for assessment 80 (65%), the ischemic strokes could be considered as lacunar 6 (7·5%), embolic/large vessel athero-thromboembolism 58 (72·5%), or other phenotypes (border zone 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 them, 25 (92.6%) had an intracerebral hemorrhage, and 2 (7·4%) had a subarachnoid hemorrhage. Among the patients with cerebral venous thrombosis, 2 (33·3%) patients had episodes of seizures prior to admission.

3.3. Risk of Bias and Quality Assessment of Received Data

The details of the risk of bias assessment are available in Supplemental Table 1. There were concerns regarding time-varying confounding (no information in 15·3%), missing data (high risk in 3·0%, medium risk in 1·5%, and no information in 18·4%), and measurement of outcome (high risk in 16·9%, and 6·1% no information). Overall, 9 (13·8%) centers/states had a high overall risk of bias and were excluded from all meta-analyses. We further excluded the states/districts with less than 20 infected patients with SARS-CoV-2. To summarize, 21 (32·3%) centers/states (19 CVEs in 8,359 study population) were excluded from meta-analyses. One center in the United States (New York-2) provided CVEs data by automatic data pulling and natural language processing without further chart review and validation. All meta-analyses were repeated based on inclusion (Figures 1-3) or exclusion of this center (Forest Plots 1-4 in Supplemental Materials).

3.4. CVE Risk Estimation and Outcome of Meta-Analyses

When considering all available data after quality and risk of bias assessment, the risk of subsequent CVEs in infected patients with SARS-Cov-2 is 156/17,774 (0·87%). Meta-analysis of data from 43 states/districts (Figure 1) suggests an overall CVEs risk of 0·5% [95% CI, 0·3%-0·7%]. When arranging the centers according to the continents, the risk of subsequent CVEs 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 (Figure 2). To control for possible unseen heterogeneity among industrialized countries and other centers in terms of the diagnosis or quality of care, we limited the analysis to 27 states/districts in industrialized countries (Figure 3). The overall CVEs risk among the 27 states/districts is 0·7% [95% CI, 0·2%-1·6%]. The repeated meta-analysis after removing the centers with the highest and lowest calculated risk suggests a comparable CVE risk of 0·6% [95% CI, 0·5%-0·8%] (Supplemental Figure 4). All analyses were conducted under low heterogeneity among study levels (I^2<50%).

3.5. Factors Associated with the Occurrence of CVEs

When comparing patients with and without CVEs, there were significant differences in age, dependency on the ventilator, hypertension, ischemic heart disease, prior stroke or transient ischemic attack, platelets counts, stratified white blood cells, neutrophils and lymphocytes counts, and C-reactive protein between the two groups (all $p<0.01$) Table 1. Binary logistic regression suggested that dependency on a ventilator (OR: 1·92, 95% CI:1·1-3·5, $p= 0·028$), and the presence of ischemic heart disease (OR: 2·54, 95% CI: 1·4-4·7, $p=0.006$) are independent predictors of the CVEs.

4. Discussion:

The results of the current multi-national study on patients hospitalized for SARS-CoV-2 infection indicate an overall 0·3%-1·2% risk of cerebrovascular events. This frequency was obtained after a careful quality and heterogeneity assessment of the data. The results of regression models suggest dependency on ventilation and prior ischemic heart disease as the independent predictors of CVEs in 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 many had associated neurological symptoms.(16,46–48) Recently, there has been increasing attention on the vascular complications of SARS-CoV-2, and several pathophysiological 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 ACE2 activation, immune-mediated mechanisms and overexpression of the cytokines, vasculitis, coagulopathy, and neurological consequences secondary to hypoxemia or hypotension. (9,12,13,15,49) To date, series of CVEs in patients with SARS-CoV-2 diagnosis have been reported.(9–11) However, to our knowledge, no prior study has determined the rate of these complications in a methodologically approved approach at a multinational level.

4.1. Risk of CVEs and other infections

A temporal relationship and increased risk of CVEs have been reported in association with different respiratory viral infections.(17–25) A population-based study with stroke register setup from the United Kingdom (UK) on 2,874 patients demonstrated an increased number of the first-ever stroke within 2 (ischemic stroke) to 4 weeks (hemorrhagic stroke) after seasonal influenza peak.(17) 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 3.19 within the first 3 days, which decreased to 1.33 within 3 months post-infection.(18) In California, a study of about 37,000 hospitalized ischemic stroke patients suggested a significant risk of stroke in patients with prior influenza-like illnesses, with odds ratios (OR) of 2·88 in 15 days, decreasing to 1·66 within 365 days post-infection.(19) Based on this study, stroke triggered by influenza-like infections are more likely to occur in patients who are younger than 45 years (OR: 9·28, in comparison with OR: 2·71 in 45-65 years, 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 ischemic stroke events.(50) Despite this, the overall risk of subsequent CVEs seems to be less than 1%. In another study of over 102,500 patients with a diagnosis of influenza, stroke, or TIA incidence rate was reported to be 0·052, 0·035, 0.029 at 1, 3, and 6 months after influenza.(21) Likewise, US National Readmissions Database report on over 46,000 patients hospitalized for influenza indicated that CVEs are infrequent (0·3%) cause of 30-day readmission.(20)

CVEs were also reported in patients infected with β-coronaviruses such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome coronavirus (MERS-CoV).(51) Five (2·4%) patients infected with SARS in Singapore developed large artery cerebral ischemia, among them three had no known stroke risk factor.(22) Acute myocardial infarction and disseminated intravascular coagulation (3 patients), and generalized hypotension (4 patients) preceded the ischemic stroke in these patients. Bilateral anterior cerebral artery stroke (diabetic and hypertensive 57-year old male),(23) frontal lobes intracerebral hemorrhage (diabetic 34-year old female),(24) and frontal hematoma and subarachnoid hemorrhage extending to ventricles that resulted in subfalcine herniation (diabetic 42-year old female, with

history of nephrectomy)(25) were reported in association with MERS-CoV infection. To our knowledge, the literature is limited to small case series and no population-based rate assumption has been provided for these viral infections.

4.2. Reports of CVEs and SARS-CoV-2 infection

Although an increasing number of reports on neurological symptoms are being 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.(10) All of these patients had critical disease severity and 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 CVEs: ischemic stroke in large vessels in 5, small vessels in 3, and with cardioembolic origin in 3, and 2 patients were complicated with cerebral venous thrombosis and cerebral hemorrhage.(9) In a series of six cases from the UK, all patients had large vessel occlusion (3 in multiple 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 titer IgM and IgG antiphospholipid. All patients in this series were over 50 years and had moderate to critical SARS-CoV-2 disease severity.(52) In a case series from New York City, 5 patients, younger than 50 years with a positive test for SARS-CoV-2, developed large-vessel stroke.(11) Three of these patients had prior comorbidities—39 years old with hypertension and dyslipidemia, 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 in their center to enable us to estimate the rate of CVEs.

4.3. Other conditions associated with higher CVE risk

It is worth mentioning that most of the reported SARS-CoV-2 infected patients with CVEs had critical conditions. About 0.5% of patients hospitalized with sepsis experience stroke within one year.(26) Sepsis can put the patient at advanced risks of ischemic (OR>28) or hemorrhagic strokes (OR>12) through the first two weeks, and the risk would remain high even up to one year.(53) A variety of mechanisms can induce coagulopathy in sepsis.(27,28) In addition, about 6% of the 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%).(29) 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 worse outcomes.(54)

Although there might be a slightly increased risk of CVEs in patients infected with SARS-COV-2, the result of our multinational study suggested that the risk is comparable to other viral infections. This number will be lower if all patients with SARS-CoV-2 diagnosis are considered rather than hospitalized patients.

4.4. Study limitations

We communicated with different centers in several countries to increase the representativeness of this study. However, due to the sensitivity of SARS-CoV-2 issues, 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 centers from 11 countries. In addition, policies for the hospitalization of SARS-CoV-2 infected patients vary considerably among centers; some had relaxed criteria for admission of positively tested patients, while others were overwhelmed and adopted strict criteria to hospitalize patients. The other limitation was the confirmation of the SARS-CoV-2 infection. Due to the low sensitivity of PCR,(55,56) the testing interval, and also availability and capacity of testing sites, some centers considered chest CT scan in addition to the presence of symptoms indicative of SARS-CoV-2 infection. We also realized that the clinical severity could be assessed through other parameters that could not be collected considering the high number of participating centers and the partial availability of data. Various centers 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.

In addition, neurological services were available mostly in tertiary centers. Despite our attempt to capture the whole referral region, patients' mobility among nearby regions to obtain the best medical service makes it impossible to have an accurate risk estimation. We realize that the SARS-CoV-2 epidemic has affected the care-seeking behaviors 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 ventilator dependent 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.

4.5. Conclusion

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.

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.

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Figure 1

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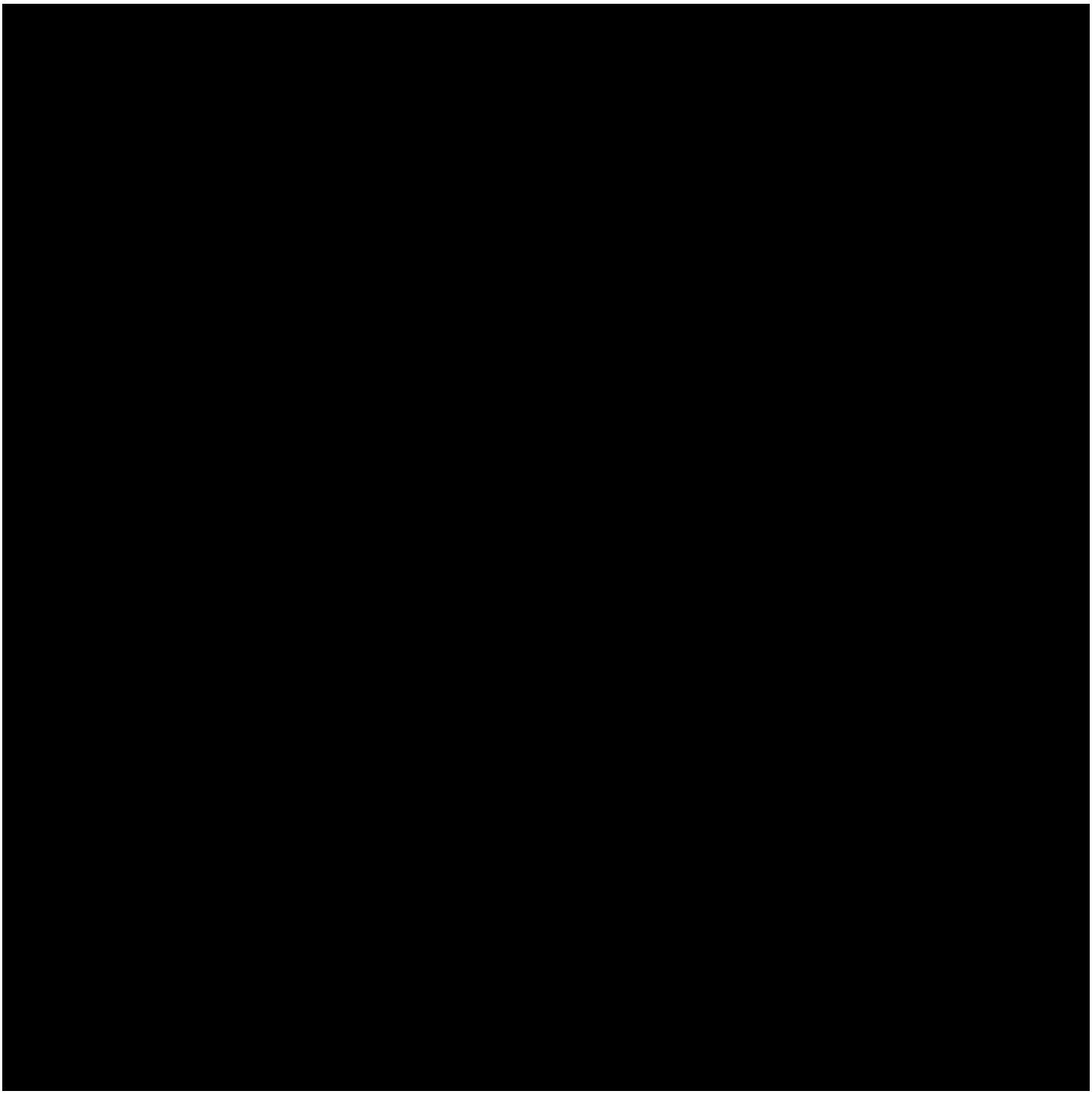

Figure 2

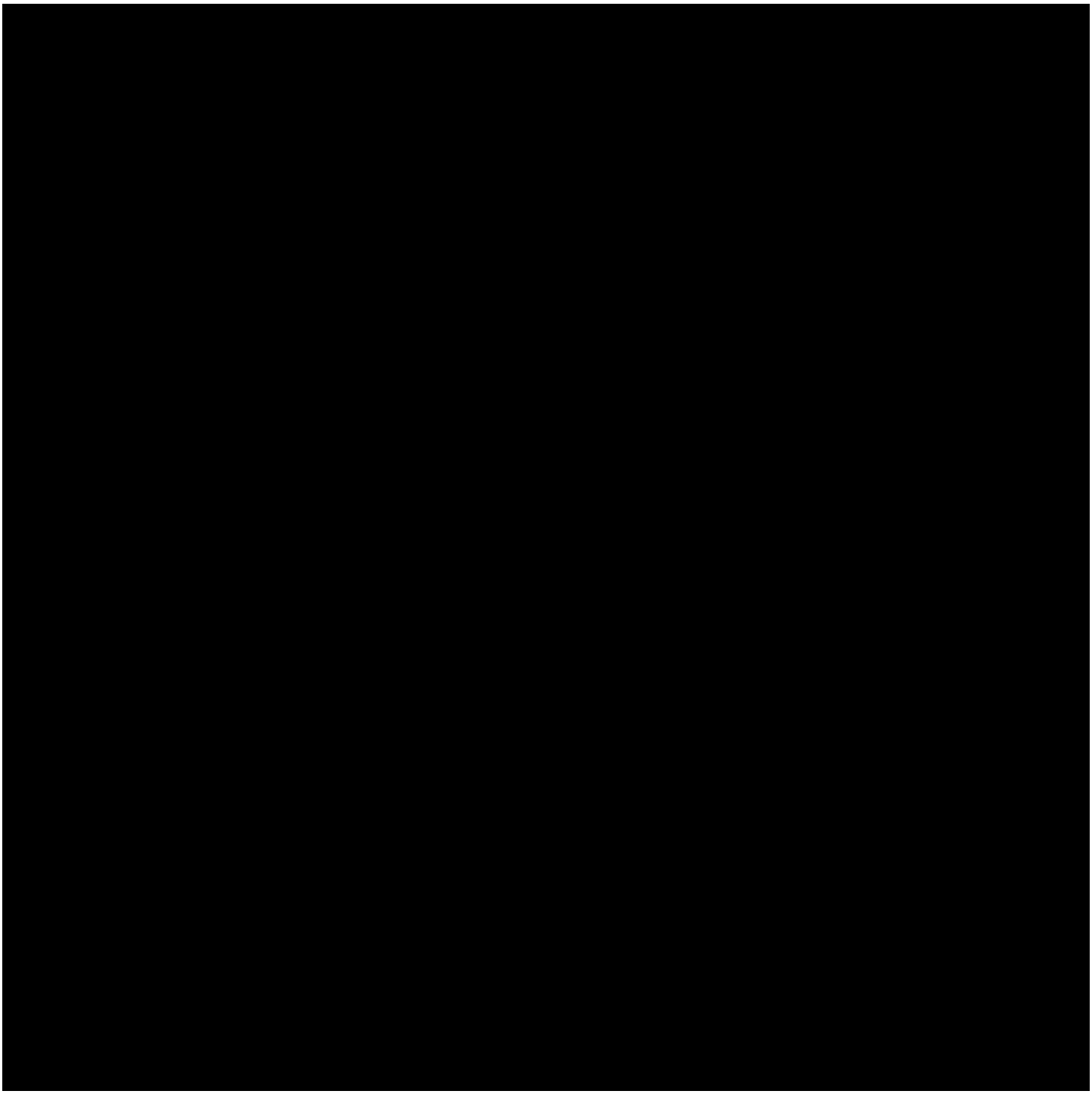

Figure 3

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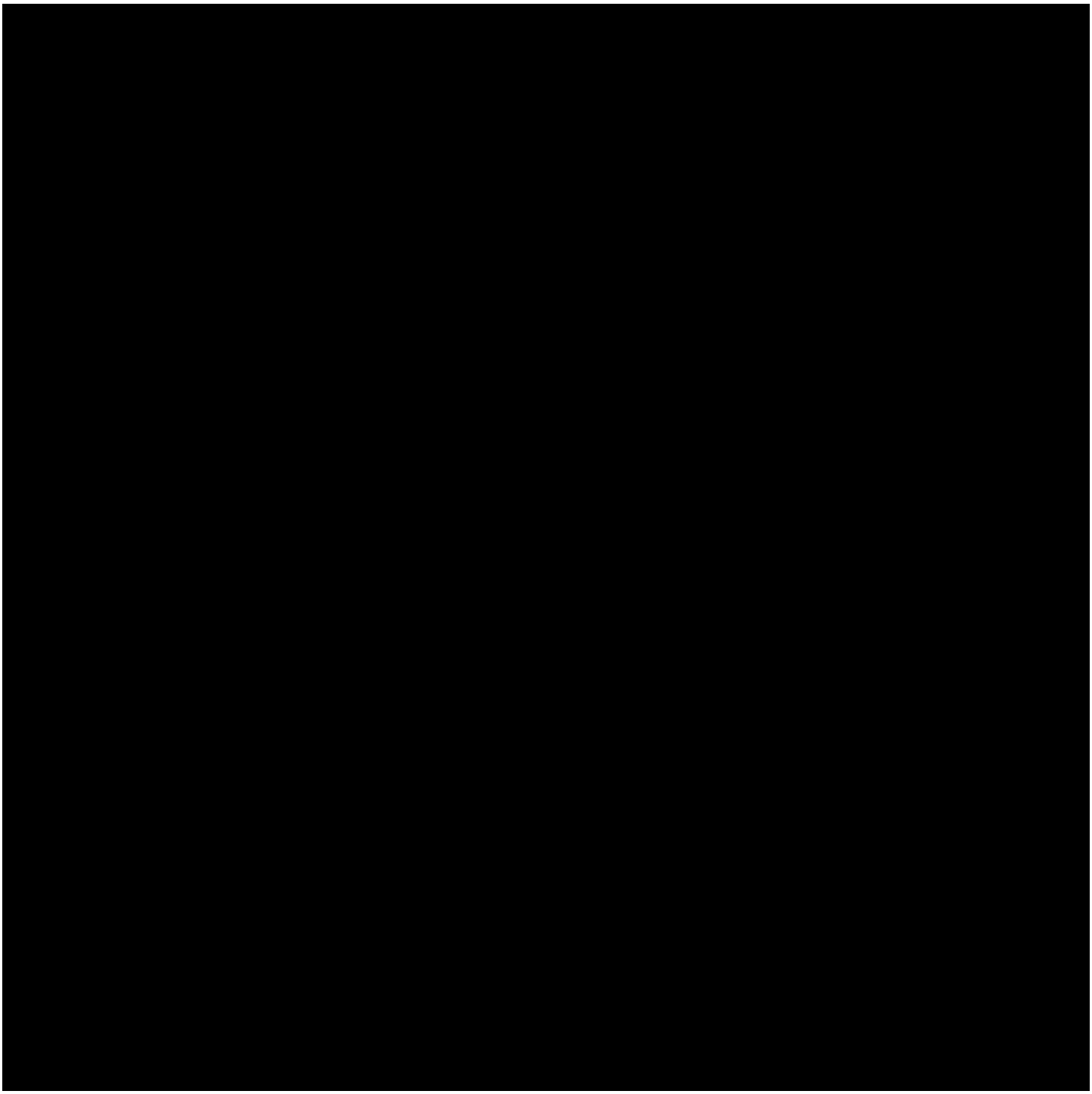


Table 1

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

Parameter	Cerebrovascular Events (N = 156)	No Cerebrovascular Events (N = 6,200)	*p*-Value
Age; Mean (SD); Years	66 (15)	58 (14)	<0·001
Age; Median [IQR]; Years	67 [57-78]	63 [55-63]	-
<40	6 (5·4)	412 (14)	0·003
40-64	42 (37·8)	2,205 (74·7)	
65-74	25 (22·5)	192 (6·5)	
≥75	38 (34·2)	144 (4·9)	
Sex; Female; N (%)	47 (42)	2,512 (40·5)	0·757
Ventilation Dependent; N (%)	31 (36·5)	428 (14)	<0·001
Hypertension; N (%)	61 (64·9)	1,912 (42·1)	<0·001
Diabetes Mellitus; N (%)	32 (34)	1,312 (28·4)	0·228
Ischemic Heart Disease; N (%)	28 (29·8)	560 (12·1)	<0·001
Atrial Fibrillation; N (%)	9 (9·7)	178 (6·6)	0·252
Carotid Stenosis; N (%)	8 (9·1)	349 (13)	0·278
Smoking; N (%)	15 (16·3)	385 (16·8)	0·595
Prior Stroke or Transient Ischemic Attack; N (%)	14 (14·7)	189 (6·7)	0·003
White Blood Cell Count x10^9/L; Mean (SD)	10·3 (8·4)	10·1 (18·5)	0·929
White Blood Cell Count x10^9/L; Median [IQR]	9·0 [6·3-12·2]	6.9 [5·1-9·9]	-
<4 x10^9/L	2 (2·4)	64 (11·6)	0·003
4-10 x10^9/L	49 (57·6)	348 (63·2)	
10-20 x10^9/L	30 (35·3)	113 (20·5)	
≥20 x10^9/L	4 (4·7)	26 (4·7)	
Neutrophil Count x10^9/L; Mean (SD)	9·6 (12·9)	8.3 (15·4)	0·478
Neutrophil Count x10^9/L; Median [IQR]	6·6 [4·5-9·4]	5 [3·4-8·2]	-
<4 x10^9/L	10 (13·3)	142 (33·2)	0·008
4-10 x10^9/L	49 (65·3)	217 (50·7)	
10-20 x10^9/L	13 (17·3)	56 (13·1)	
≥20 x10^9/L	3 (4)	13 (3)	
Lymphocyte Count x10^9/L; Mean (SD)	1·8 (1·6)	1·1 (3·8)	0·143
Lymphocyte x10^9/L; Median [IQR]	1·4 [1·2-2]	0·9 [0·7-1·4]	-
<1 x10^9/L	13 (15·5)	2360 (85·9)	<0·001
1-2 x10^9/L	49 (58·3)	243 (8·8)	
2-3 x10^9/L	17 (20·2)	92 (3·3)	
3-4 x10^9/L	3 (3·6)	31 (1·1)	
≥4 x10^9/L	2 (2·4)	22 (0·8)	
Neutrophil/Lymphocyte Ratio; Mean (SD)	7·39 (9·74)	6·34 (6·22)	0·218
Neutrophil/Lymphocyte Ratio; Median [IQR]	4·44 [3-7·32]	4·34 [2·5-7·6]	-
Platelet Count x10^9/L; Mean (SD)	212·7 (105·7)	200·5 (47·8)	0·026
Platelet Count x10^9/L; Median [IQR]	179·5 [145-283]	195 [152-253]	-

	<350 x10^9/L	71 (88·8)	2,693 (97·9)	0·000
	350-500 x10^9/L	9 (11·3)	57 (2·1)	
Alanine Transaminase (ALT) U/L; Mean (SD)		50·8 (86·4)	38·3 (48·2)	0·073
Alanine Transaminase (ALT) U/L; Median [IQR]		31 [21·7-44·5]	29 [18-44]	-
Aspartate Transaminase (AST) U/L; Mean (SD)		59·6 (98·7)	44·1 (41·8)	0·241
Aspartate Transaminase (AST) U/L; Median [IQR]		35 [25-53]	35 [25-50]	-
Blood Urea Nitrogen (BUN) mg/dl; Mean (SD)		25·8 (21·9)	22·3 (24·7)	0·248
Blood Urea Nitrogen (BUN) mg/dl; Median [IQR]		19 [13-29·6]	15·8 [9·7-24]	-
Creatinine mg/dl; Mean (SD)		1.5 (1·3)	1.3 (1·0)	0·205
Creatinine mg/dl; Median [IQR]		1·1 (0·9-1·5)	1·1 (0·9-1·4)	-
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]	-

* Many centers provided qualitative rather than quantitative data; high missing values.

Table 2

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

Cerebrovascular Event Parameter	Acute Ischemic Stroke N=123 (78·8%)	Intracranial Hemorrhage N=27 (17·3%)	Cerebral Venous Thrombosis N=6 (3·8%)
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 (45·5)	8 (29·6)	4 (66·7)
Interval Between Onset to Index Event; Median [IQR]; Days	3 [0-7]	1 [0-5]	4·5 [2-14]
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 Hemorrhage (ICH) Score; Median [IQR]	-	3.0 [2·0-4·0]	-
Imaging Pattern; N (%)	Embolic / large vessel athero-thromboembolism: 58/80 (72·5) *	Intracerebral Hemorrhage: 25 (92·6)	-
	Lacunar: 6/80 (7·5) *	Subarachnoid Hemorrhage: 2 (7·4)	-
	Other: 16/80 (20·0) *	-	-

* The imaging details of 80 patients were available

Supplemental Materials

Content

Risk of Cerebrovascular Events in Hospitalized Patients with SARS-CoV-2 Infection

Authors

Shima Shahjouei, MD, MPH,[1] Soheil Naderi, MD,[1] Jiang Li, MD, PhD, [2] Ayesha Khan,[1] MD, Durgesh Chaudhary, MD,[1] Ghassem Farahmand, MD, [3, 4] Shailesh Male, MD, [5] Christoph Griessenauer, MD, [1] Mirna Sabra, PhD, [6] Stefania Mondello, MD, MPH, PhD, [7] Achille Cernigliaro, PhD, MPH, [8] Faezeh Khodadadi, Pharm.D, [9] Apoorva Dev, PhD Scholar, [9] Nitin Goyal, MD, [10] Sakineh Ranji-Burachaloo, MD, [3,4] Oluwaseyi Olulana, M.S., [1] Venkatesh Avula, M.S., [1] Seyed Amir Ebrahimzadeh, MD, MPH, [11] Orkhan Alizada, MD,[12] Mehmet Murat Hancı, MD, [12] Askar Ghorbani, MD, [13] Alaleh Vaghefi far, MD, [13] Annemarei Ranta, MD, PhD, FRACP,[14,15] Martin Pnter, MBBS, [14,15] Mahtab Ramezani, MD,[16] Nima Ostadrahimi, [13] MD, Georgios Tsivgoulis, MD, PhD, MSc, [10, 17] Paraskevi C. Fragkou, MD, [18] Peyman Nowrouzi-Sohravi, PhD,[19] Emmanouil Karofylakis, MD, [18] Sotirios Tsiodras, MD, PhD, [18] Saeideh Aghayari Sheikh Neshin, MD,[20] Alia Saberi, MD, [20] Mika Niemelä, MD, PhD,[21] Behnam Rezai Jahromi, MD,[21] Ashkan Mowla, MD,[22] Mahsa Mashayekhi, MD,[23] Reza Bavarsad Shahripour, MD, [10] Aidin Sajedi, MD,[24] Mohammad Ghorbani, MD, [25] Arash Kia, MD,[26] Nasrin Rahimian, MD, MPH, [27] Vida Abedi, PhD, [2,28] Ramin Zand, MD, MPH[1,10]

Collaborators

Mohammad Hossein Harirchian, [4] MD, Nazanin Ahmadzadeh, MD,[29] Thomas Yasuda, MD,[30] Fabricio Cardoso, MD, MPH, [30] Asadollah Mirghasemi, MD, [31] Alireza Janbakhsh, MD, [32] Mohammad Hossein Zamanian, MD, [32] Zeinab Mohseni Afshar, MD, [32] Ali H. Kassem, MD, [33] Haidar H. Hoummani, MD, [33] Arefeh Babazadeh, MD, MPH,[34] Soheil Ebrahimpour, MD, PhD, [34] Sima Mohseni, MD, MPH, [34] Firas Kobeissy, PhD [35,36] Navneet Singh Dang, MD,[37] B. V. Ganesh, MBBS, M.S., [38] Radha Krishna Ramesh, MD,[39] Sedighe Basirjafari, MD, [40] Janardhanan Saravanan, Pharm Ph. D, [9] Faissal Qak, MD, [31] Afshin Borhani-Haghighi. [39]

1 Neurology Department, Neuroscience Institute, Geisinger Health System, Pennsylvania, USA;

2 Department of Molecular and Functional Genomics, Geisinger Health System, Danville, Pennsylvania, USA;

3 Neurology Department, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran;

4 Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran;

5 Neurology Department, Vidant Medical Center, Greenville, North Carolina, USA;

6 Neurosciences Research Center (NRC), Lebanese University/ Medical School, Beirut, Lebanon;

7 Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy;

8 Regional Health Authority of Sicily, Palermo, Italy;

9 PES University, Bengaluru, Karnataka, India;

10 Neurology Department, University of Tennessee Health Science Center, Tennessee, USA;

11 Radiology Department, Yasrebi Hospital, Isfahan, Iran;

12 Neurosurgery Department, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey;

13 Neurology Department, Tehran University of Medical Sciences, Tehran, Iran;

14 Department of Neurology, Wellington Hospital, Wellington, New Zealand;

15 Department of Medicine, University of Otago, Wellington, New Zealand;

16 Neurology Department, Shahid Beheshti University of medical sciences, Tehran, Iran;

17 Second Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, "Attikon" University Hospital, Athens, Greece;

18 Fourth Department of Internal Medicine, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece;

19 Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran;

20 Neurology Department, Poursina Hospital, Guilan University of Medical Sciences, Guilan, Iran;

21 Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland;

22 Division of Stroke and Endovascular Neurosurgery, Department of Neurosurgical Surgery, Keck School of Medicine, University of Southern California, California, USA;

23 Internal medicine Department, Tabriz University of medical sciences, Tabriz, Iran;

24 Neuroscience Research Center, Department of Neurology, Golestan University of Medical Sciences, Golestan, Iran;

25 Division of Vascular and Endovascular Neurosurgery, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran;

26 Icahn school of medicine at Mount Sinai, Department of Population Health Science and Policy, Institute for Healthcare Delivery Science, New York, USA;

27 Neurology Department, Yasrebi Hospital, Kashan, Iran;

28 Biocomplexity Institute, Virginia Tech, Blacksburg, Virginia, USA;

29 Istanbul Bilim University, Istanbul, Turkey;

30 Neurology Department, Centro Médico de Campinas, São Paulo, Brazil;

31 Department of Anesthesiology, University of Ottawa, Canada;

32 Infection Disease Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran;

33 Lebanese University/Beirut Governmental University Hospital, Beirut, Lebanon;

34 Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

35 Program of Neurotrauma, Neuroproteomics and Biomarker Research (NNBR), University of Florida, Florida, USA;

36 Lebanese Ministry of Health, Beirut, Lebanon;

37 Department of medicine, Geisinger Health System, Pennsylvania, USA;

38 ESIC Hospital, Karnataka, India;

39 C.V. Raman General Hospital, Karnataka, India;

40 Department of Radiology, Hashemi Rafsanjani Hospital, Khorasan, Iran;

41 Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding Author:

Ramin Zand M.D., M.P.H.

Neuroscience Institute, Geisinger,

100 North Academy Ave. Danville, PA, 17822

phone number: 570-214-4101

Fax number: (570) 808-3208

E-mail address: rzand@geisinger.edu; ramin.zand@gmail.com

Labratory: https://www.thedecodelab.com/

Supplemental Table 1

Risk of Bias Assessment

Supplemental Table 1. Risk of Bias Assessment of Each State Provided Data for this study.

CVE, Cerebrovascular Events; L, Low; M, Medium; H, High; NI, No Information; PCR, Polymerase-Chain Reaction; Chart, Chart Review Process; Automatic, Automatic Data Pooling; Chest CT, Chest Computed Tomography

Risk of Bias Assessment, Cont…		Athens - Greece	Sicily– Italy	Beirut - Lebanon	Helsinki - Finland	20 Districts- New Zealand	Istanbul - Turkey	California - USA	New York 1 – USA	New York 2 - USA	North Carolina - USA	Pennsylvania- USA	Toronto - Canada
Time-varying Confounding	**Cases: time window between COVID-19 & CVEs**	L	L	L	L	L	L	L	L	NI	L	L	L
	Cases: potential of capturing late onset CVEs	L	L	L	L	L	L	L	L	L	L	L	L
	Study Population: similar interval as used for CVEs	L	L	L	L	L	L	L	L	L	L	L	L
Selection of Study Participants	**Cases: influence of outcome in inclusion**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: local investigators judgement on possibility of coincidence/causality	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: chart review or automatic	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Automatic	Chart	Chart	Chart
	Study Population: COVID-19 hospitalization criteria	Criteria Based	All Patients	All Patients	All Patients	All Patients	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based
Classification of Exposure	**Study Population: defining confirmed COVID-19**	PCR AND/OR Chest CT	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR
Missing Data	**Cases: data to confirm the diagnosis, stroke subtype, and localization**	L	L	L	L	L	L	L	L	H	L	L	L
	Study Population: high level summary data on hospitalized patients	L	L	L	L	L	L	L	L	L	L	L	L
Measurement of Outcome	**Cases: Awareness of the local investigators of all admitted CVEs**	L	L	L	H	L	L	L	L	L	L	L	L
	Cases: consistent definition when referring to CVEs	L	L	L	L	L	L	L	L	L	L	L	L
Measurement of Reporting Results	**Cases: reporting of all CVEs irrespective of management outcome**	L	L	L	L	L	L	L	L	L	L	L	L
	Study Population: reporting all hospitalized COVID-19 patients	L	L	L	L	L	L	L	L	L	L	L	L
OVERALL	**OVERALL ASSESSMENT**	L	L	L	H	L	L	L	L	H	L	L	L
	Including in Meta-Analysis	Y	Y	Y	N	Y	Y	Y	Y	Conditional	Y	Y	N

Risk of Bias Assessment		São Paulo - Brazil	Arunachal Pradesh - India	Assam – India	Chhattisgarh -India	Karnataka - India	Ladakh - India	Meghalaya - India	Mizoram - India	Tamil Nadu - India	Tripura - India	West Bengal- India	Delhi- India
Time-varying Confounding	**Cases: time window between COVID-19 & CVEs**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: potential of capturing late onset CVEs	L	L	L	L	L	L	L	L	L	L	NI	NI
	Study Population: similar interval as used for CVEs	L	L	L	L	L	L	L	L	L	L	NI	NI
Selection of Study Participants	**Cases: influence of outcome in inclusion**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: local investigators judgement on possibility of coincidence/causality	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: chart review or automatic	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart
	Study Population: COVID-19 hospitalization criteria	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients
Classification of Exposure	**Study Population: defining confirmed COVID-19**	PCR AND/OR Chest CT	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR
Missing Data	**Cases: data to confirm the diagnosis, stroke subtype, and localization**	L	L	L	L	L	L	L	L	L	L	NI	NI
	Study Population: high-level summary data on hospitalized patients	M	L	L	L	L	L	L	L	L	L	L	L
Measurement of Outcome	**Cases: Awareness of the local investigators of all admitted CVEs**	H	H	L	L	L	L	L	L	L	L	H	H
	Cases: consistent definition when referring to CVEs	L	L	L	L	L	L	L	L	L	L	L	L
Measurement of Reporting Results	**Cases: reporting of all CVEs irrespective of management outcome**	L	L	L	L	L	L	L	L	L	L	NI	NI
	Study Population: reporting all hospitalized COVID-19 patients	L	L	L	L	L	L	L	L	L	L	L	L
OVERALL	**OVERALL ASSESSMENT**	H	L	L	L	L	L	L	L	L	L	H	H
	Including in Meta-Analysis	N	N	N	Y	Y	Y	Y	N	N	N	N	N

Risk of Bias Assessment, Cont…		Jammu & Kashmir- India	Kerala- India	Odisha- India	Punjab- India	Telangana- India	Tamil Nadu- India	Fars – Iran	Lorestan – Iran	Ahwaz- Iran	Ghazvin- Iran	Kerman- Iran	Semann- Iran
Time-varying Confounding	**Cases: time window between COVID-19 & CVEs**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: the potential of capturing late-onset CVEs	NI	NI	NI	NI	NI	NI	L	L	L	L	L	L
	Study Population: similar interval as used for CVEs	L	L	L	L	L	L	L	L	NI	L	L	L
Selection of Study Participants	**Cases: influence of outcome in inclusion**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: local investigators judgment on the possibility of coincidence/causality	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: chart review or automatic	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart
	Study Population: COVID-19 hospitalization criteria	All Patients	All Patients	All Patients	All Patients	All Patients	All Patients	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based
Classification of Exposure	**Study Population: defining confirmed COVID-19**	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR	PCR
Missing Data	**Cases: data to confirm the diagnosis, stroke subtype, and localization**	NI	NI	NI	NI	NI	NI	L	L	H	L	L	L
	Study Population: high-level summary data on hospitalized patients	L	L	L	L	L	L	L	L	L	L	L	L
Measurement of Outcome	**Cases: Awareness of the local investigators of all admitted CVEs**	H	H	H	H	H	H	L	L	L	L	L	L
	Cases: consistent definition when referring to CVEs	L	L	L	L	L	L	L	L	L	L	L	L
Measurement of Reporting Results	**Cases: reporting of all CVEs irrespective of management outcome**	NI	NI	NI	NI	NI	NI	L	L	L	L	L	L
	Study Population: reporting all hospitalized COVID-19 patients	L	L	L	L	L	L	L	L	L	L	L	L
OVERALL	**OVERALL ASSESSMENT**	H	H	H	H	H	H	NI	NI	NI	NI	NI	L
	Including in Meta-Analysis	N	N	N	N	N	N	N	N	N	N	N	N

Risk of Bias Assessment, Cont…		Ardabil – Iran	Gilan – Iran	Golestan - Iran	Hormozgan - Iran	Isfahan 1– Iran	Isfahan, other centers– Iran	Kermanshah- Iran	Khorasan 1 - Iran	Khorasan, other centers- Iran	Tehran 1 - Iran	Tehran, other centers -Iran	Markazi – Iran
Time-varying Confounding	**Cases: time window between COVID-19 & CVEs**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: potential of capturing late onset CVEs	L	L	L	L	L	L	L	L	L	L	L	L
	Study Population: similar interval as used for CVEs	L	L	L	L	L	L	L	L	L	L	L	L
Selection of Study Participants	**Cases: influence of outcome in inclusion**	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: local investigators judgment on the possibility of coincidence/causality	L	L	L	L	L	L	L	L	L	L	L	L
	Cases: chart review or automatic	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart	Chart
	Study Population: COVID-19 hospitalization criteria	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based	Criteria Based
Classification of Exposure	**Study Population: defining confirmed COVID-19**	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT	PCR AND/OR Chest CT
Missing Data	**Cases: data to confirm the diagnosis, stroke subtype, and localization**	L	L	L	L	L	L	L	L	L	L	L	L
	Study Population: high-level summary data on hospitalized patients	L	L	L	L	NI	L	L	NI	L	NI	L	NI
Measurement of Outcome	**Cases: Awareness of the local investigators of all admitted CVEs**	L	L	L	L	NI	L	L	NI	L	NI	L	NI
	Cases: consistent definition when referring to CVEs	L	L	L	L	L	L	L	L	L	L	L	L
Measurement of Reporting Results	**Cases: reporting of all CVEs irrespective of management outcome**	L	L	L	L	L	L	L	L	L	L	L	L
	Study Population: reporting all hospitalized COVID-19 patients	L	L	L	L	L	L	L	L	L	L	L	L
OVERALL	**OVERALL ASSESSMENT**	L	L	L	L	NI	L	L	NI	L	NI	L	NI
	Including in Meta-Analysis	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N

Supplemental Table 2

Excluded Centers/States

Supplemental Table 2. Excluded centers/states, the number of cerebrovascular events in that center, study population, and the reason for exclusion.

State/ Province	Country	Cerebrovascular Events	Study Population	Exclusion due to
São Paulo	Brazil	1	18	Cases – partially reported / unverified Study Population <20
Ontario	Canada	1	8	Cases – partially reported / unverified Study Population <20
Helsinki	Finland	0	486	Cases – partially reported / unverified
Meghalaya	India	0	11	Study Population <20
Assam	India	0	8	Study Population <20
Tripura	India	0	2	Study Population <20
Arunachal Pradesh	India	0	1	Study Population <20
Mizoram	India	0	1	Study Population <20
West Bengal	India	0	3659	Cases – partially reported / unverified
Delhi	India	0	1451	Cases – partially reported / unverified
Jammu & Kashmir	India	0	70	Cases – partially reported / unverified
Kerala	India	0	462	Cases – partially reported / unverified
Odisha	India	0	52	Cases – partially reported / unverified
Punjab	India	0	31	Cases – partially reported / unverified
Telangana	India	0	562	Cases – partially reported / unverified
Tamil Nadu (Pudukottai,Dharmapuri)	India	0	1	Study Population <20
Markazi	Iran	2	Not Available	Study Population Not Available
Kerman	Iran	1	Not Available	Study Population Not Available
Khorasan	Iran	3	Not Available	Study Population Not Available
Isfahan	Iran	1	Not Available	Study Population Not Available
Ghazvin	Iran	1	Not Available	Study Population Not Available
Tehran	Iran	4	Not Available	Study Population Not Available
Khouzestan	Iran	4	Not Available	Study Population Not Available
Lorestan	Iran	1	Not Available	Study Population Not Available
Fars	Iran	0	1536	Cases – partially reported / unverified

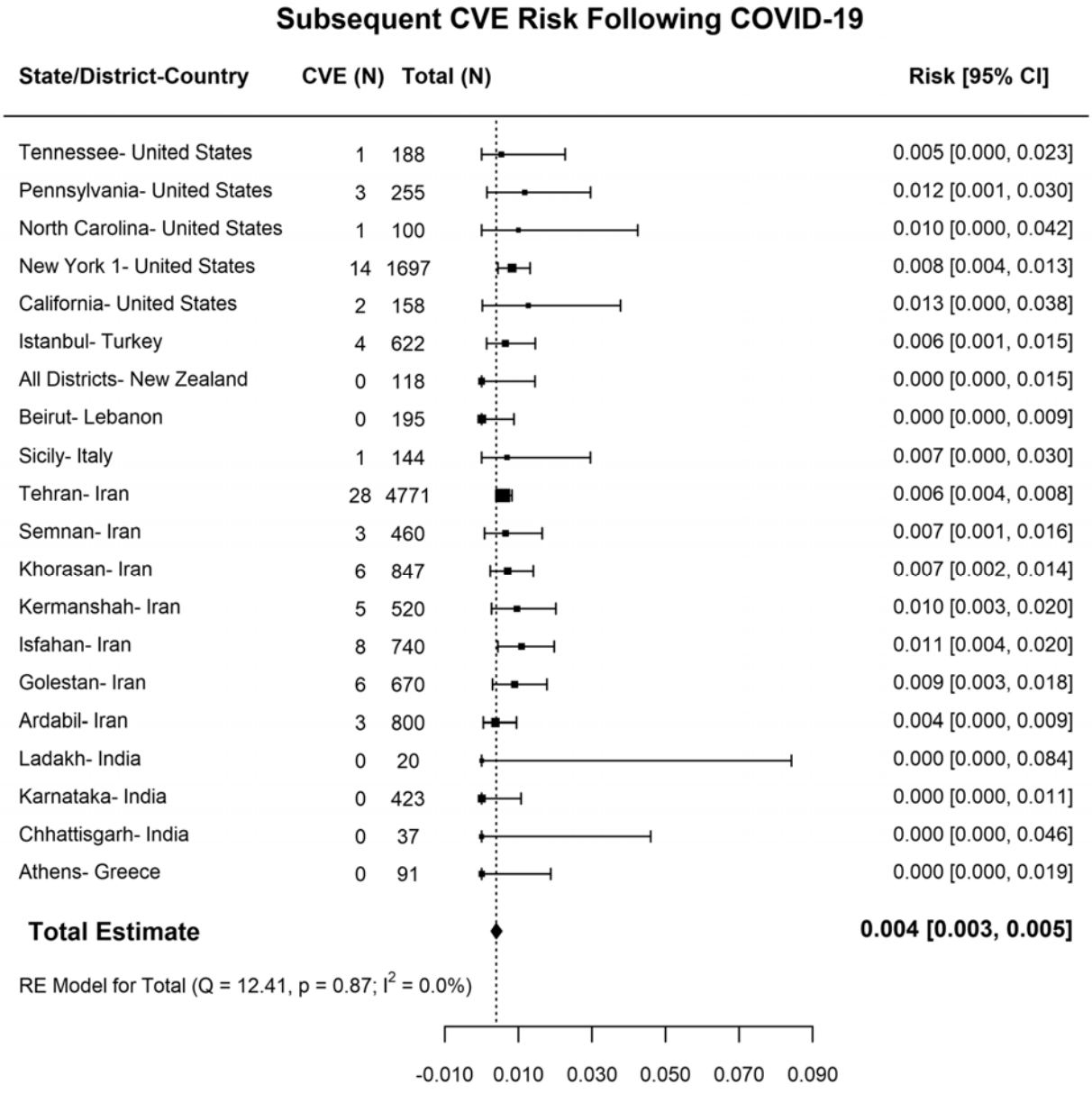
Supplemental Figures 1 - 3

Forest Plots

Supplemental Figure 1

All States/Districts

(Without New York -2)

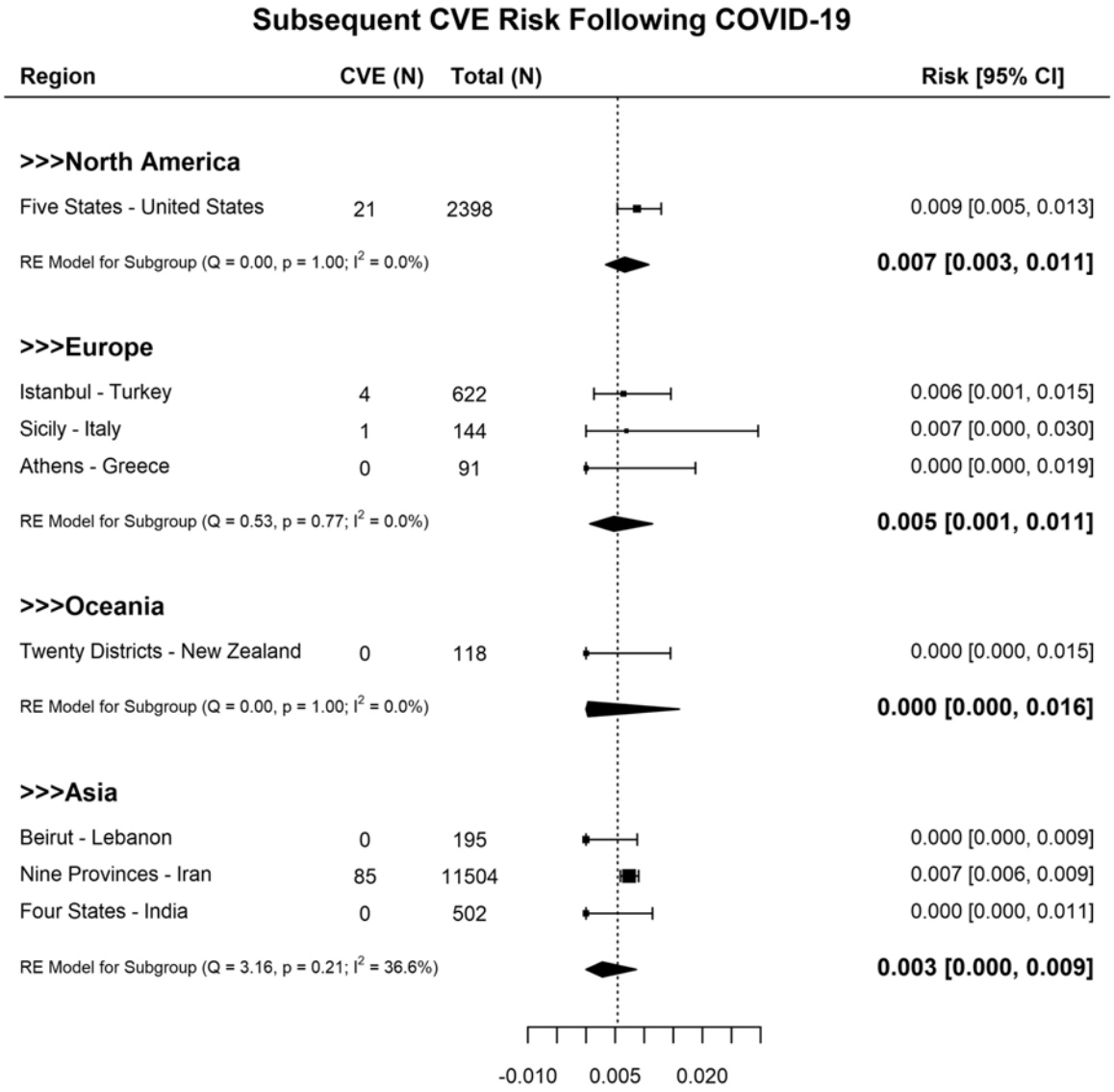


Supplemental Figure 1. Forest Plot; risk of subsequent cerebrovascular events in patients infected with SARS-CoV-2 presented at the state/district level. Due to the possible risk of bias in data received from New York-2 (automatic data gathering), this center was excluded from the meta-analysis.

Supplemental Figure 2

Country-Wise, Sorted by Continents

(Without New York -2)

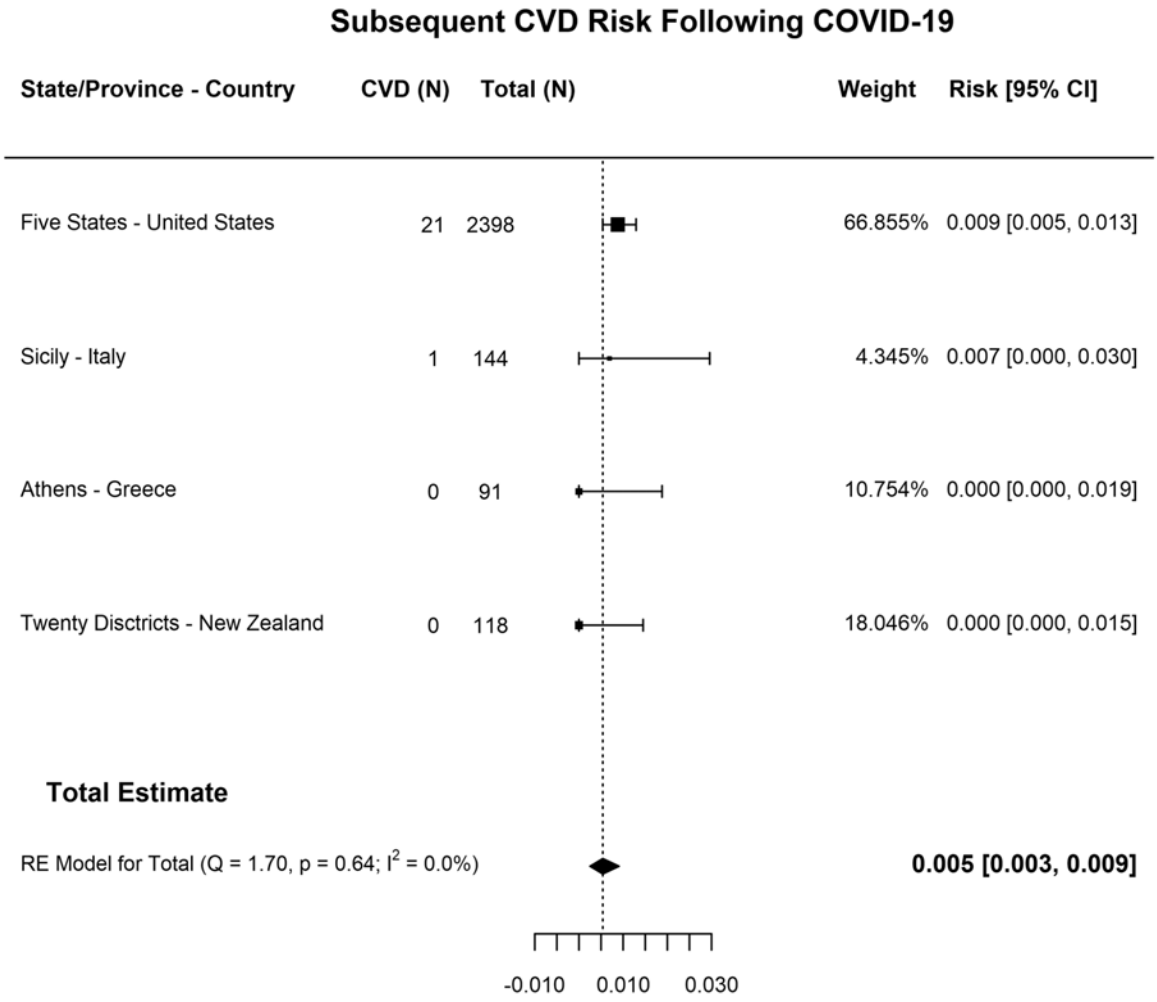


Supplemental Figure 2. Forest Plot; risk of subsequent cerebrovascular events in patients infected with SARS-CoV-2 presented in each country, sorted by continents. Due to possible risk of bias in data received from New York-2 (automatic data gathering), this center was excluded from meta-analysis.

Supplemental Figure 3

Industrialized Countries

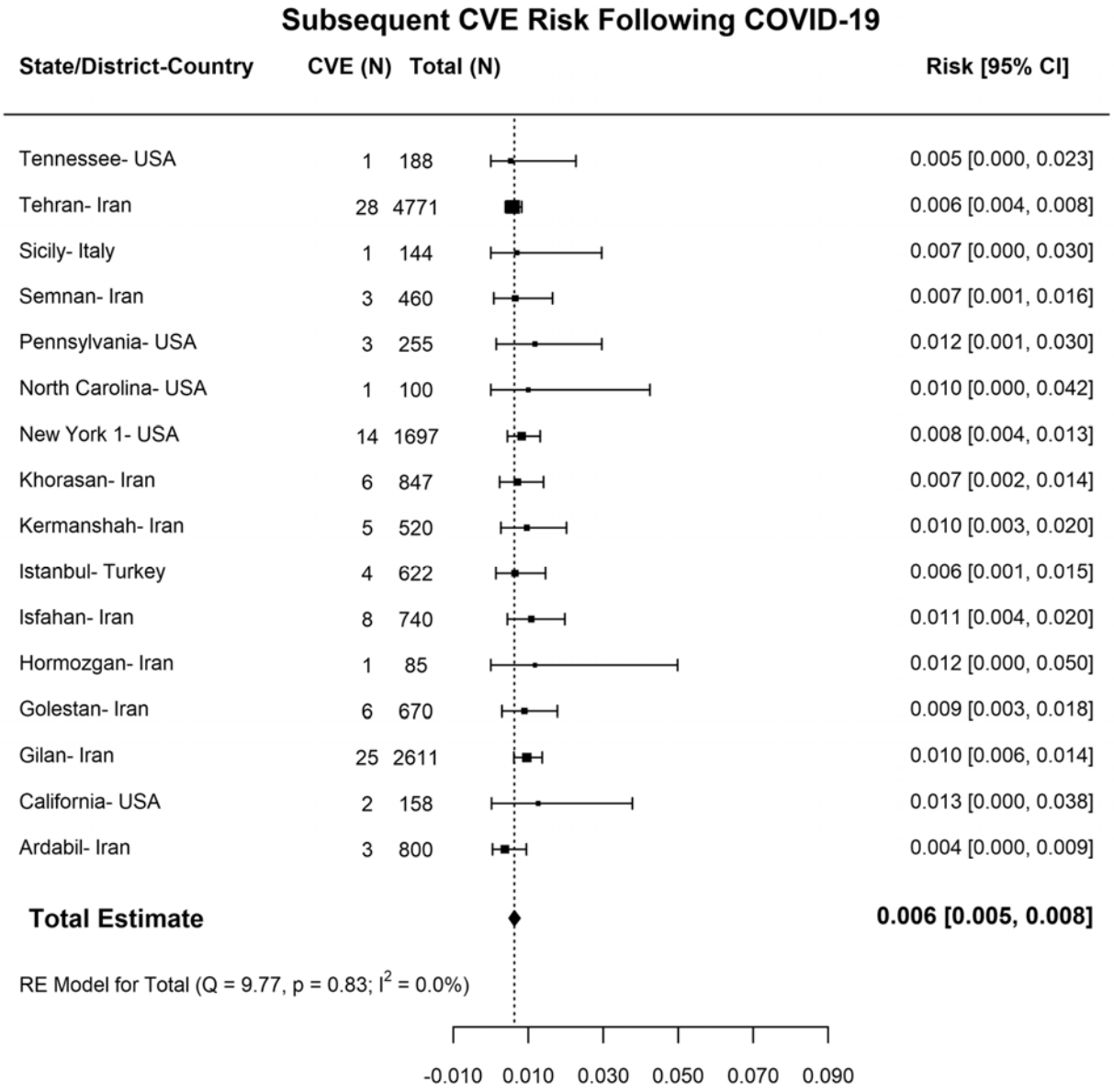
(Without New York -2)



Supplemental Figure 3. Forest Plot; risk of subsequent cerebrovascular events in patients infected with SARS-CoV-2 presented in industrialized countries. Due to the possible risk of bias in data received from New York-2 (automatic data gathering), this center was excluded from the meta-analysis.

Supplemental Figure 4

All States after removal of centers with extrim risks



Supplemental Figure 4. Forest Plot; risk of subsequent cerebrovascular events in patients infected with SARS-CoV-2 presented after removal of centers at the highest and lowest risks.