Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Incidence and Mortality Ratio of Ischemic Cerebrovascular Accidents in COVID-19 Cases: A Systematic Review and Meta-Analysis

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Objectives: Coronavirus disease 2019 (COVID-19) is primarily known as a respiratory illness; however, a wide variety of symptoms and complications of the central nervous system (CNS), such as ischemic cerebrovascular accidents (CVA) have been reported. Hereby, we provide a systematic review and a meta-analysis of the literature, investigating the incidence of ischemic CVA and the mortality due to it in the setting of COVID-19. *Materials and Methods:* Our search databases included Google Scholar, MEDLINE via PubMed, and Scopus. We searched the databases up to July 22, 2020. The primary outcome was the incidence of ischemic CVA in COVID-19 cases, while the secondary outcomes were the ratio of mortality in these cases. Standard meta-analysis methods used to measure the pooled incidence and mortality rates of ischemic CVA in COVID-19 cases. *Results:* After excluding studies with reasons, only 20 articles were eligible to be included in our qualitative synthesis, and 17 studies were evaluated quantitatively in our meta-analysis. Included studies reported a pooled average incidence of 1.7% for ischemic CVA, ranging from 1.3% to 2.3%. Mortality in patients of ischemic CVA to all COVID-19 cases was 0.5%, ranging from 0.4% to 0.6%. The mortality rate of patients with CVA to those who suffered from COVID-19 infection and ischemic CVA simultaneously was 29.2% ranging from 21.6% to 38.2%. Overall, the heterogeneity of the studies was high. *Conclusions:* Our analysis revealed a pooled incidence of 1.7% for ischemic CVA in the setting of COVID-19 infection, with a mortality rate of 29.2% amongst the COVID-19 patients who are suffering ischemic CVA.

Key Words: COVID-19—Ischemic cerebrovascular accidents—Incidence—Mortality

Background

COVID-19 is a disease caused by SARS-CoV-2, a virus that belongs to the Coronaviridae family, which first emerged in December 2019 in China. Shortly after, it was declared as a pandemic, and now it has been known as the disease of the century. Its burden on societies has been hefty and catastrophic, since. This yet poorly understood infectious disease is considered as the crucial concern of the governments and healthcare systems.[1]

Although COVID-19 is primarily known as a respiratory illness, multiple organ involvement has been reported among the majority of COVID-19 patients. The central nervous system (CNS) is one of the extrapulmonary sites of this virus' invasion. CNS involvement signs and symptoms vary from mild manifestations such as headache, anosmia, and dysgeusia to more severe and life-threatening conditions such as stroke, central venous thrombosis (CVT), and acute disseminated encephalomyelitis (ADEM).[2–6]

The mechanism of nervous system involvement is barely understood. It has been postulated that the CNS involvement happens due to direct virus invasion rather than a delayed inflammatory response. However, some studies are

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suggesting the role of antiphospholipid antibodies in this regard.[7−11] The relationship between acute ischemic stroke and COVID-19, especially in patients with the severe form of the disease, has been reported in various studies.[3-12] However, the ischemic cerebrovascular accidents (CVA) in the setting of COVID-19 shows a diverse incidence, according to recent studies. In some reports, the incidence of ischemic stroke among COVID-19 patients was reported in a range from 0.7% to 4.6% with a stroke related mortality rate ranging from 15% to 50%.[8-13,17] While most studies investigating neurologic manifestations of COVID-19 are limited, considering the impacts of COVID-19 on healthcare systems, we aimed to conduct this study to systematically review the so far published literature with a meta-analysis of the reported data.

Methods

Search strategy

Our search databases included Google Scholar, MEDLINE via PubMed, and Scopus. The keywords that were used in this search included "Coronavirus Infections" or "COVID-19" or "SARS-CoV-2", and "Stroke" or "Brain Ischemia" or "Cerebrovascular Diseases" or "CVD" or "Cerebrovascular Accident" or "CVA" or "Cerebrovascular Insult" or "CVI" or "Neurologic Manifestations", or "Central Nervous System Diseases", or "Intracranial Embolism" and "Thrombosis" and their distinct combinations. We searched the databases up to July 22, 2020, and included only studies that were written in English. Furthermore, we investigated the references of the included articles, in case of other relevant studies. Our search was limited to studies incorporating human data. The primary outcome of this study included the incidence of ischemic cerebrovascular diseases (CVD) in patients with COVID-19, and the secondary outcome was to determine the mortality rate in patients that are suffering from ischemic stroke along with COVID-19.

Study selection and data extraction

Two authors went through the articles after the search, thoroughly, and in case of any disagreements, the third author decided where to land. We selected the studies that included patients with proven COVID-19, that had experienced neurological manifestations of ischemia, including a wide range from transient ischemic attack (TIA) to ischemic stroke. However, case reports, case series, and reviews were excluded.

Extracted data included the name of the first author, total number of COVID-19 cases, number of cases with ischemic stroke, age in all patients, and in patients suffering from ischemic CVA. Besides, the sex ratio in CVA cases, risk factors, therapeutic approaches, reported total mortality for COVID-19 cases, along with the number of mortalities in patients with CVA, was recorded.

We prepared our report of the included and excluded studies based on the recommended format of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18,19] The details of the reporting are depicted in Fig. 1.

Statistics

The Comprehensive Meta-Analysis (CMA) software version 2.0, was used to analyze the extracted data. The pooled incidence and mortality rates of ischemic CVA in COVID-19 cases were the measures of interest. Analyzed data are conveyed as mean ± standard deviation (SD). In order to assess heterogeneity among the outcomes, I^2-index was used. In the case of $I^2>50\%$, the random-effect model was used, since it depicts a high heterogeneity.

Results

Study selection

Our search through the mentioned databases rendered 475 studies that included the mentoined keywords of our search (Fig. 1). After adding up the additional records from other sources and then removing the duplicates, we screened 243 abstracts. After excluding studies with reasons, only 20 articles were eligible to be included in our qualitative synthesis. Then, three studies were omitted from our meta-analysis by reason (Table 1); thus, 17 studies were evaluated quantitatively in our meta-analysis.

Demographic and clinical features

Quantitative analysis of the pooled data depicted that generally, 375 cases of acute ischemic CVA cases were reported amongst 25,586 COVID-19 cases. All demographic data are shown in Table 1. These studies were conducted in the USA, Spain, China, Italy, Indonesia, the Netherlands, and Brazil. Generally, CVA-related risk factors and their accumulated ratio in the reported studies were hypertension (72.9%), diabetes mellitus (45.32%), obesity (4.77%), smoking (20.26%), dyslipidemia (54.62%), history of heart failure (12.5%), cerebral vascular accidents (21.93%), coronary artery disease (28.43%), chronic obstructive pulmonary disease (14.28%), and atrial fibrillation (33.75%).

Ultimately, for patients with ischemic CVA, the therapeutic approaches included anticoagulants (e.g., heparin, enoxaparin, nadroparin), antiplatelets (e.g., aspirin, clopidogrel) and in some cases fibrinolytics (e.g., tPA) and/or mechanical thrombectomy.

Furthermore, most studies reported the mean of age for developing ischemic CVA to be above 60 years old, except for one study (13), which merely had investigated patients below 50 years of age.

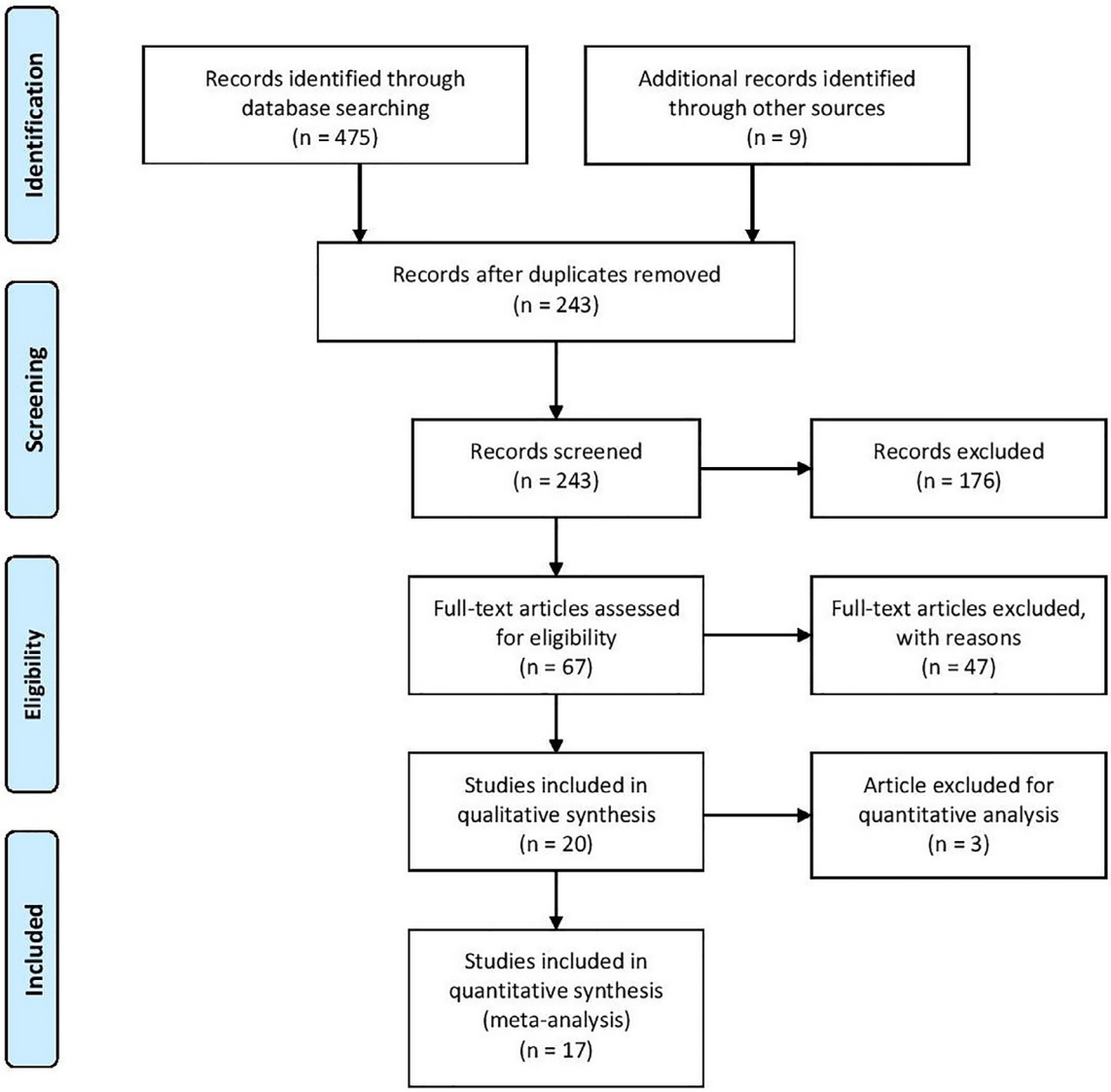

Figure 1. *PRISMA flow chart of the selection of studies for inclusion in the meta-analysis.*

Incidence of ischemic CVA

Since between-study heterogeneity was dramatically high (I^2=86.963), we used the random effect model for pooled incidence estimation. Seventeen studies that were included in the meta-analysis reported a pooled average incidence of 1.7% for ischemic CVA, ranging from 1.3% to 2.3% (Fig. 2).

Mortality in COVID-19 patients with ischemic CVA

Ischemic CVA deaths to the total number of COVID-19 patients

Investigating studies regarding the mortality in patients who died from ischemic CVA to all COVID-19 cases revealed a 0.5% mortality rate, ranging from 0.4% to 0.6% (I^2=73.857) (Fig. 3).

Ischemic CVA deaths to the total number of ischemic CVA – COVID-19 patients

The mortality rate of patients with CVA to those who suffered from COVID-19 infection and ischemic CVA simultaneously was 29.2% ranging from 21.6% to 38.2% (I^2=52.186) (Fig. 4).

General notes on incidence and mortality rates among included studies

Based on our quantitative analysis, an average incidence of 1.7% for ischemic CVA was reported, with the range of 1.3% to 2.3%. Recorded minimum and maximum incidence for ischemic CVA were 0.7% and 4.6%.

Analysing mortality rates in patients deceased with ischemic CVA to all COVID-19 cases depicted a 0.5% mortality rate, ranging from 0.4% to 0.6%. Recorded

Table 1. *Demographic and clinical characteristics of the included studies.*

References	Study location	COVID-19 Cases (n)	Total M:F Ratio	Total Age±SD	Ischemic CVA Cases (n)	Ischemic CVA M:F Ratio	Ischemic CVA Cases Age±SD	Risk Factors (n)	Therapeutic Approach for Ischemic CVA	Total Death	Ischemic CVA Death
Bach et al., 2020[17]	USA	683	-	61.13±15.39	20	14:6	63 ±10.7	HTN:18, DM:13, OBS:10, SMO:5, CVA:2	tPA, MT	178	10
Merkler et al., 2020[25]	USA	2132	1173:959	62 [IQR=48-75]	31	18:13	69 [IQR=66-78]	HTN:30, DM:23, DLP:17, AF:17, CKD:8, CAD:16, COPD:4	tPA, MT	-	9
Yaghi et al., 2020[13]	USA	3556	-	-	32	23:9	62.5 [IQR=52-69]	HTN:18, DM:11, DLP:18, HF:2, CAD:5, AF:6, CVA:1	tPA, MT, Anticoagulant, Antiplatelet	-	14
Hernandez et al., 2020[26]	Spain	1683	-	-	17	13:4	68.2±13	HTN:10, DM:6, DLP:7, SMO:2, CAD:4, AF:4, COPD:2	tPA, MT	-	5
Yao et al., 2020[22]	China	2474	1235:1239	61.0±15.7	25	16:9	74.2±10.6	HTN:745, DM:355, CAD:202	-	179	4
Li et al., 2020[16]	China	219	89:130	53.3±15.9	10	5:5	75.7±10.8	HTN:55, DM:31, CVA:17, Malignancy:14	Antiplatelet, Enoxaparin	-	5
Xiong et al., 2020[9]	China	917	505:412	48.7±17.1	10	-	67.6±15.4	-	-	30	3
Mao et al., 2020[8]	China	214	87:127	52.7±15.5	5	-	-	HTN:51, DM:30, CVD:15, Malignancy:13, CKD:6	-	-	0
Lodigiani et al., 2020[27]	Italy	388	264:124	66 [IQR=55-85]	9	6:3	-	HTN:183, DM:88, DLP:76, CKD:61, SMO: 45, Malignancy:27, COPD:35, CAD:54, CVA:20	tPA, MT, ASA, Heparin, Nadroparin, Clopidogrel	92	2
Munir et al., 2020[28]	Indonesia	114	-	34.5	2	2:0	72 and 87	HTN:2, CVA:2, DM:1, IHD:1	-	-	0
Klock et al., 2020[†41, 42]	Netherlands	184	139:45	64±12	5	-	-	-	-	-	-
Mufti et al., 2020[23]	Multicenter (data from 4 countries)	6698	-	-	88	-	51 [IQR=27-87]	-	MT	-	11
Bilaloglu et al., 2020[43]	USA	3334	2014:1320	64 [IQR=51-57]	54	-	-	-	-	817	20
Luigetti et al., 2020[44]	Italy	213	137:76	70.2±13.9	2	-	-	-	-	40	-
Rothestein et al., 2020[29]	USA	844	405:439	59±18	20	12:8	64±12	HTN:19, DM: 12, DLP:16, SMO:2, CAD:3, OBS:10, CVA:7	MT, Antiplatelet, Anticoagulant	-	5
Studart-neto et al., 2020[45]	Brazil	1208	55:34	57.4±15.9	11	-	-	-	-	-	-
Mah et al., 2020[15]	Italy	725	69:39	68.8±14.8	34	-	-	HTN:55, DM:30, CAD:25, CVA:15, Malignancy:13	-	-	-
Annie et al., 2020[*],[14]	USA	9358	3705:5653	36.7±8.5	64	25:39	39.3±9.0	HTN:39, DM:21, HF:10, SMO:22, OBE:30, CVA:18, CKD:10, COPD:10	-	68	10
Varatharaj et al., 2020[**46]	UK	125	73:44	71 [IQR=58-79]	57	-	73.5 [IQR=64-83]	-	-	44	-
Kemer et al., 2020[***,30]	France	64	43:21	66	17	11:6	75	HTN:12, DM:5, DLP:7, SMO:2, CVA:4	-	7	2

(HTN: Hypertension; DM: Diabetes Mellitus; DLP: Dyslipidemia; HF: Heart Failure; AF: Atrial Fibrillation; CVA: Cerebral Vascular Accidents; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease, OBS: Obesity, SMO: current smoker, tPA: tissue plasminogen activator, MT: Mechanical thrombectomy, ASA: Aspirin, SD: Standard deviation, IQR: Interquartile range).

[†]The 2nd study by Klock et al.[41] was a follow-up, so we counted them as a single study in our qualitative research.Three last studies excluded from the meta-analysis by a reason.

[*]Only patients younger than 50 were included.

[**]125 patients with broad clinical syndromes (cerebrovascular event and altered mental status) associated with COVID-19 included in the study.

[***]Only cases with confirmed COVID-19 and neurologic manifestations with abnormal brain MRI were included.

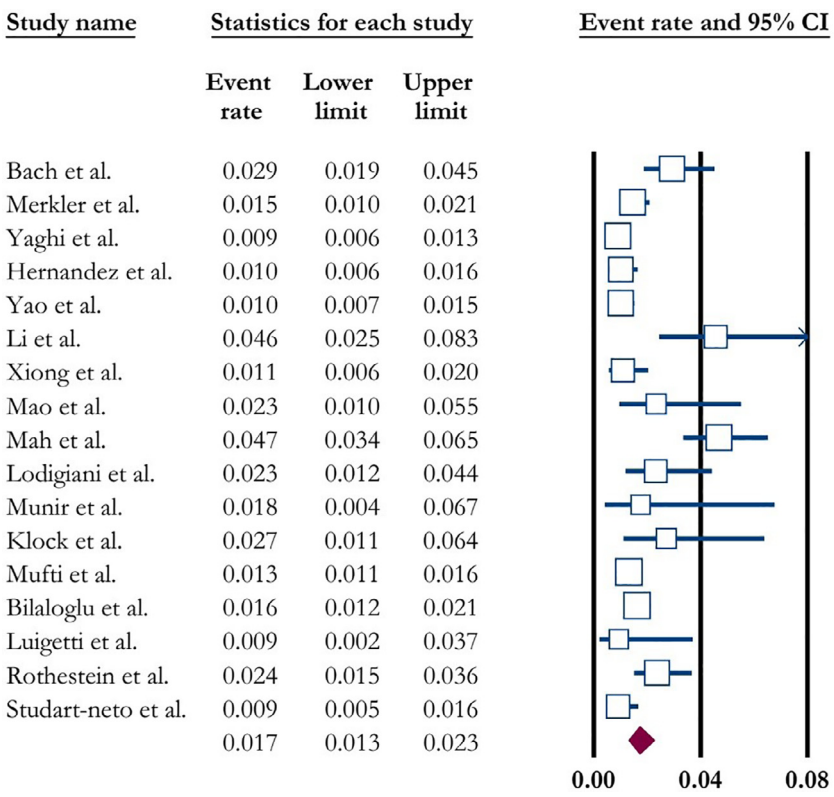

Figure 2. *Forest plot of the incidence estimates for the ischemic CVA in COVID-19 patients. The violet diamond shows the overall pooled incidence. Squares indicate the incidence in each study. Horizontal lines represent 95% confidence interval.*

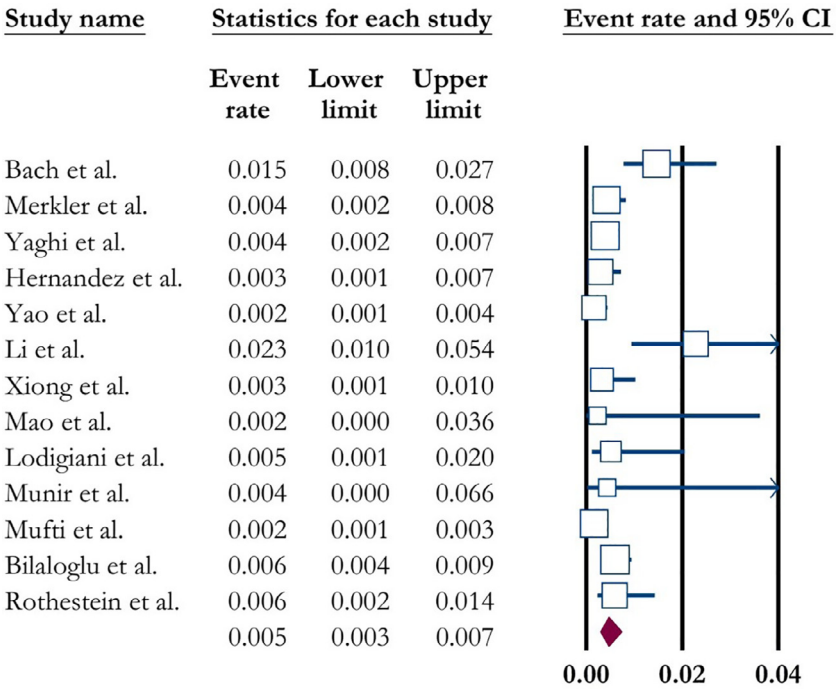

Figure 3. *Forest plot of the mortality rate of the ischemic CVA deaths to the total number of COVID-19 patients. The violet diamond shows the overall pooled incidence. Squares indicate the incidence in each study. Horizontal lines represent 95% confidence interval.*

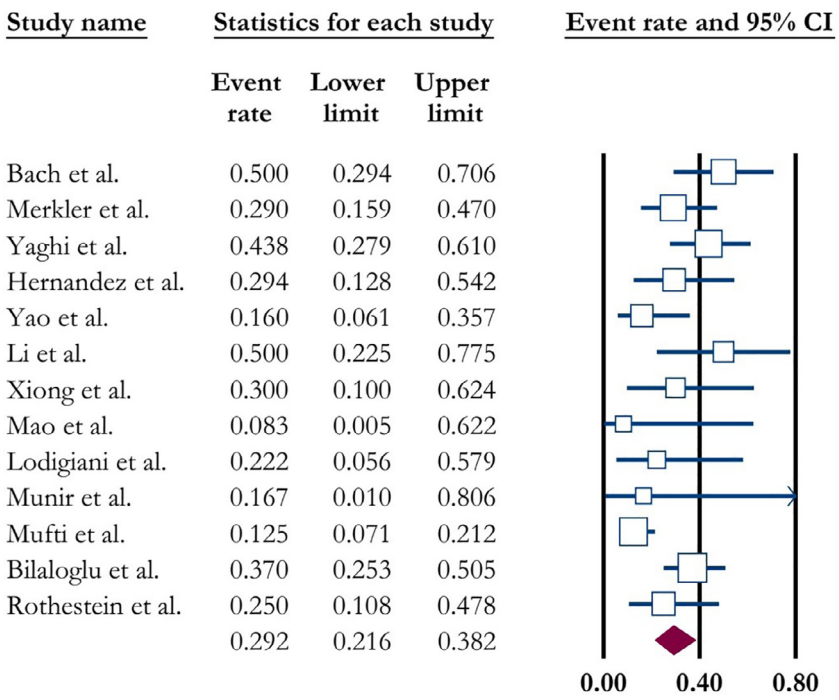

Figure 4. *Forest plot of the mortality rate of the ischemic CVA deaths to the total number of ischemic CVA – COVID-19 patients. The violet diamond shows the overall pooled incidence. Squares indicate the incidence in each study. Horizontal lines represent 95% confidence interval.*

minimum and maximum mortality rate indicated a minimum of 0.2% and a maximum of 2.3% across the included studies.

Risk of bias across studies

Seventeen individual comparisons were included in our quantitative analysis. There was no significant heterogeneity among the records based on the findings of the funnel plot. Egger's regression test showed significant asymmetry of the funnel plot (Fig. 5).

Discussion

In this systematic review and meta-analysis, we aimed to provide a general overview of the ischemic CVA incidence in patients suffering from the novel COVID-19 and to evaluate the possibility of increased risk of ischemic CVA in these patients. Also, we surfed the databases to report the mortality and recorded risk factors in cases of simultaneous COVID-19 infection and ischemic CVA. The quantitative outcomes of our study revealed an average incidence of 1.7% for ischemic CVA, ranging from 1.3% to 2.3%. Evaluation of the included studies revealed a minimum and maximum incidence of 0.7% [14-20] and 4.6%. Based on a report by World Stroke Organization (WSO), the incidence rate in 2016 in the general population was estimated to be 0.02%. Therefore our findings might depict that infection with COVID-19 might be a player in increasing the incidence of acute ischemic stroke.[21]

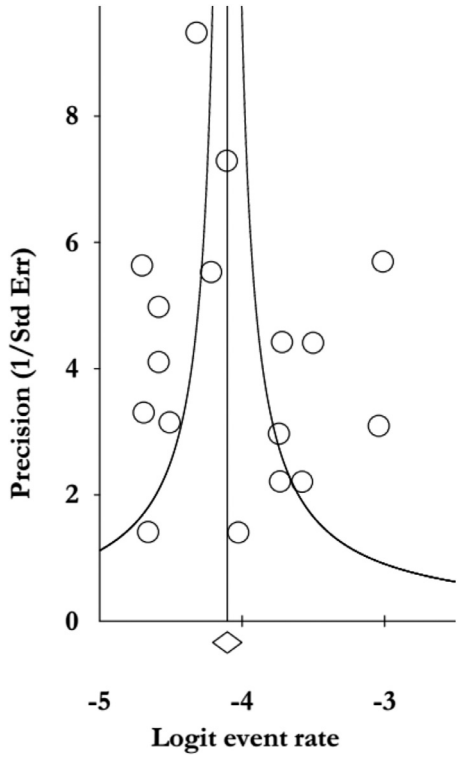

Figure 5. *Funnel plot of the included studies (95% confidence interval).*

The mortality rate analysis in patients who died from ischemic CVA to all COVID-19 cases revealed a 0.5% mortality rate, ranging from 0.4% to 0.6%. The range for this

across different studies concluded a minimum mortality rate of 0.2% in three studies[8,22,23] and a maximum of 2.3%.[20] While, the analysis of mortality rate for patients with stroke to those who suffered from both COVID-19 infection and ischemic CVA, was 29.2%, ranging from 21.6% to 38.2%. Across different studies, this range was minimally 12.5% [23] and maximally 50%.[17]

Regarding the incidence of acute ischemic stroke, a similar meta-analysis,[24] reviewing five studies, reported a similar incidence. They reported an incidence of 1.2%, ranging from 0.9% to 2.7%, for acute ischemic stroke in patients suffering from COVID-19 infection. Besides, their analysis showed that 38% of cases that had died with COVID-19 were due to acute ischemic stroke. A similar high mortality rate among the patients dying of COVID-19 infection was calculated in our study.

Based on our systematic review, most of the studies depicted that the majority of COVID-19 cases were males. This ratio was also higher in males who were had acute ischemic CVA.[13,17,22,25-30] Regarding the mean age of the patients suffering from acute ischemic CVA, with a COVID-19 infection, almost all of the included reports showed a mean age of at least 60 years old. Only two studies reported a lower mean of age,[14,23] and one of them had only included patients below 50 years of age.[14] Another meta-analysis of stroke patients with COVID-19 infection also reported a similar above-60-years-old mean (63.4±13.1) for acute ischemic stroke patients.[24]

Most studies reported a handful of comorbidities in most patients, with hypertension, being the most frequent one, followed by diabetes mellitus and dyslipidemia. Other cardiovascular diseases were also recorded, such as ischemic heart disease and heart failure. Altogether, these risk factors might interfere with establishing a direct impact of COVID-19 infection on increasing the risk of ischemic CVA. Since all the mentioned risk factors are already known for increasing the risk of acute ischemic stroke, and therefore, more studies are required to address the possibility of such a theory.

A couple of theories have been suggested so far regarding the mechanism of central nervous system involvement among COVID-19 patients, yet none of them have been confirmed. The mainstay of these theories is considered as either direct viral invasion or inflammatory damage secondary to SARS-CoV-2 infection. Since SARS-CoV-2 enters into target cells via angiotensin-converting enzyme 2 (ACE2), and the ACE2 is expressed by many human cells, including neurons and glial cells. It has been suggested that the virus can directly invade into CNS tissue and cause the neurological manifestation of the disease.[31-33] On the other hand, an increased D-dimer level among the COVID-19 patients detected by some studies indicates the activation of the coagulation cascade in these patients, which could be responsible for further thrombotic vascular events in COVID-19 patients.[5,34,35] Immune response-related mechanisms, including autoantibodies and cytokine-mediated (particularly IL-1 and IL-6) damages have also been suggested by some researchers. Nevertheless, autoimmune-related mechanisms are anticipated to be observed within weeks following the disease.[7,10,36-38] Moreover, the destruction of the lung's parenchyma by viral invasion leads to a gas exchange barrier defect, which then results in generalized chronic hypoxia. This hypoxia in CNS may trigger a vicious cycle and cause further damage to the neuronal tissue.[2,11] Fig. 6 schematically demonstrates these mechanisms.

The incidence of acute ischemic stroke in the setting of COVID-19 might be underestimated for a couple of reasons. First, because of the shutdowns and isolations, based on local policies, many patients might decide not to refer to hospitals, except for in cases of severe symptoms. Therefore, some mild strokes might be missing.[39] Moreover, since severe cases of COVID-19 are bed-ridden, unconscious, and mostly under mechanical ventilation, they might not be diagnosed as well, although an acute CVA might be ongoing. These might give rise to an underestimation of the actual incidence of acute ischemic CVA in COVID-19 patients. On the other hand, the reports are mostly limited to certain countries and regions of the world. This could be due to either restricted testing capabilities, as well as the lack of interest to report the local data. Therefore, this might be another confounding factor, that might lead to either an underestimation or an overestimation of acute ischemic stroke cases, in patients with concurrent COVID-19 infection.

Furthermore, comparing the actual incidence and symptoms of acute ischemic CVA in COVID-19 patients with patients who are not infected with COVID-19, but suffer from acute ischemic stroke is necessary for a realistic estimation of the effects of the infection on acute ischemic stroke. This signifies the importance of a matched cohort study in the future, comparing the severity of symptoms, mortality, and incidence in COVID-19 positive and negative populations with acute ischemic CVA. However, in previous studies, there have been some comparative analyses, between COVID-19 positive patients with acute ischemic stroke and historical COVID-19 negative controls with acute ischemic stroke, and the results have depicted that COVID-19 patients have more severe forms of stroke[13] and face elevated in-hospital mortality, along with a higher incident of delirium and disabilities.[40] Based on the results of this meta-analysis, a high percentage (29.2%) of mortalities in COVID-19 positive patients with ischemic CVA is reported, which is congruent with the findings of the above-mentioned studies, suggesting a possible severe outcome of patients suffering from both the infection and acute ischemic CVA.

Obviously, like many other studies, our systematic review and meta-analysis have limitations. First, since most of the demographic data were missing, we could not perform precise quantitative analysis of the

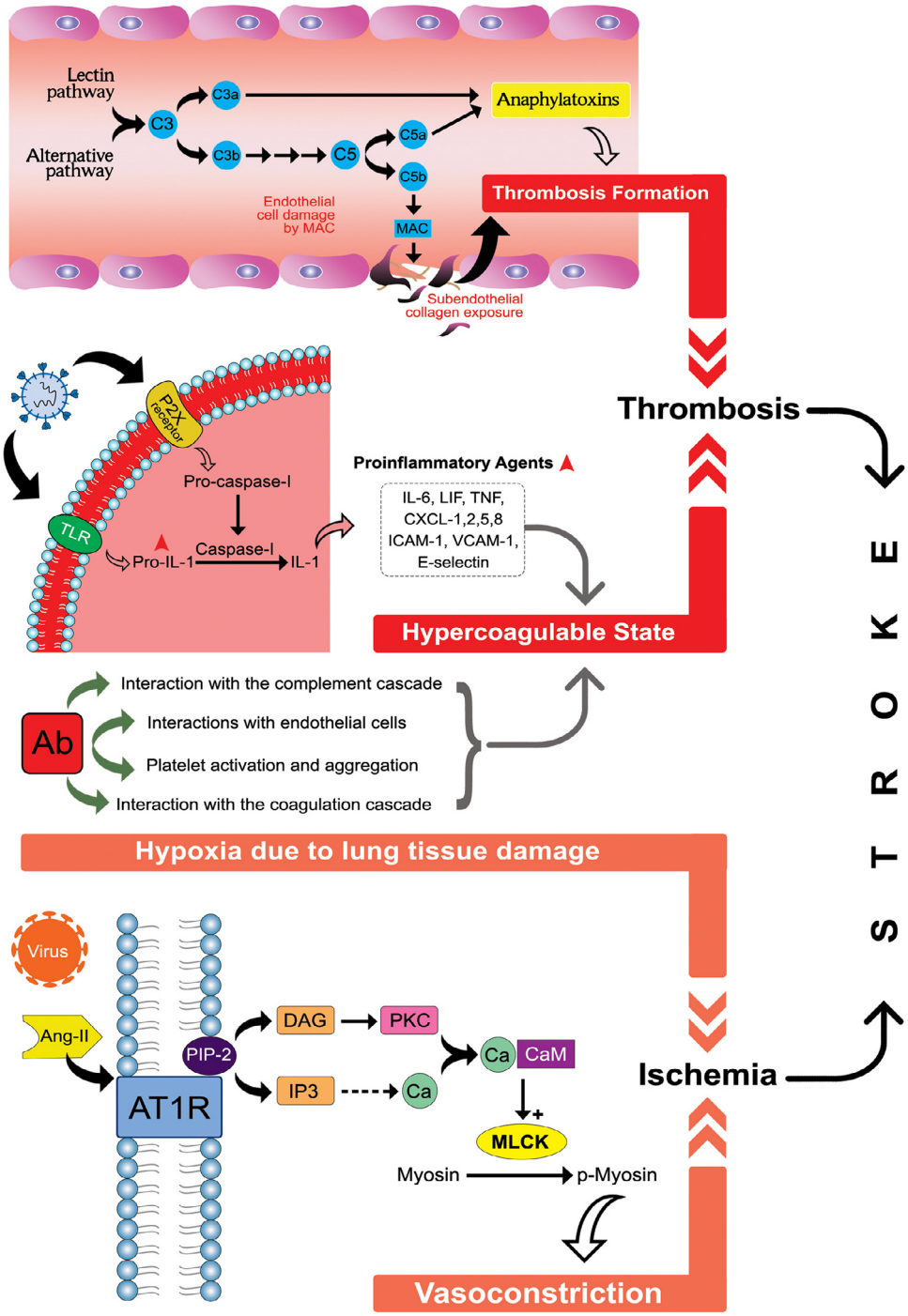

Fig. 6. *Schematic view of mechanisms responsible for ischemic stroke related to SARS-CoV-2 infection. Ab, Antibody; Ang-II, Angiotensin II; AT1R, Angiotensin II receptor type-1; C, Complement protein; Ca, Calcium; CaM, Calmodulin; CXCL, C-X-C Motif Chemokine ligand; DAG, diacylglycerol; ICAM, Induced endothelial cell adhesion molecule; IL, Interleukin; IP3, Inositol 3-phosphate; LIF, Leukocytosis-inducing factor; MAC, Membrane Attack Complex; MLCK, Myosin Light-Chain Kinase; P2X receptor, P2X purinoreceptor; PIP2, Phosphatidylinositol 4,5-bisphosphate; PKC, Protein kinase C; p-Myosin, phospho-Myosin; TLR, Toll-Like Receptor; TNF, Tumor Necrosis Factor; VCAM, Vascular cell adhesion molecule.*

data; therefore, the correlations of the sex, age, and risk factors could not be established with the disease incidence and mortality. Besides, the high heterogeneity of the analysis limited our capability to analyze the data by the most conservative fixed-effects method.

Conclusion

Our analysis revealed a pooled incidence of 1.7% for ischemic CVA in the setting of COVID-19 infection, with a high mortality rate (29.2%) amongst the patients who are suffering acute ischemic stroke and COVID-19 infection at

the same time. However, the results of this meta-analysis are inconclusive regarding the causative effect of COVID-19 infection on the incidence and severity of CVA.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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