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Clinical Characteristics of Stroke with COVID-19: A Systematic Review and Meta-Analysis

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Background: The coronavirus disease 2019 (COVID-19) potentially increases the risk of thromboembolism and stroke. Numerous case reports and retrospective cohort studies have been published with mixed characteristics of COVID-19 patients with stroke regarding age, comorbidities, treatment, and outcome. We aimed to depict the frequency and clinical characteristics of COVID-19 patients with stroke. *Methods:* PubMed and EMBASE were searched on June 10, 2020, to investigate COVID-19 and stroke through retrospective cross-sectional studies, case series/reports according to PRISMA guidelines. Study-specific estimates were combined using one-group meta-analysis in a random-effects model. *Results:* 10 retrospective cohort studies and 16 case series/reports were identified including 183 patients with COVID-19 and stroke. The frequency of detected stroke in hospitalized COVID-19 patients was 1.1% ([95% confidential interval (CI)]: [0.6-1.6], I^2 = 62.9%). Mean age was 66.6 ([58.4-74.9], I^2 = 95.1%), 65.6% was male (61/93 patients). Mean days from symptom onset of COVID-19 to stroke was 8.0 ([4.1-11.9], $p < 0.001$, I^2 = 93.1%). D-dimer was 3.3 μg/mL ([1.7-4.9], I^2 = 86.3%), and cryptogenic stroke was most common as etiology at 50.7% ([31.0-70.4] I^2 = 64.1%, 39/71patients). Case fatality rate was 44.2% ([27.9-60.5], I^2 = 66.7%, 40/100 patients). *Conclusions:* This systematic review assessed the frequency and clinical characteristics of stroke in COVID-19 patients. The frequency of detected stroke in hospitalized COVID-19 patients was 1.1% and associated with older age and stroke risk factors. Frequent cryptogenic stroke and elevated d-dimer level support increased risk of thrombo-embolism in COVID-19 associated with high mortality. Further study is needed to elucidate the pathophysiology and prognosis of stroke in COVID-19 to achieve most effective care for this population.

Keywords: COVID-19—stroke—SARS-CoV2—Meta-analysis—Systematic review

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that caused ongoing worldwide pandemic.[1] Clinical features of COVID-19 range from asymptomatic to fever, cough, shortness of breath, and even death.[2] Associated neurological manifestation included mild disease such as dizziness, headache, impaired sense of smell and taste, and polyneuropathy, as well as impaired consciousness, stroke, seizure, and encephalitis.[3–11] Increasing evidence suggests that coagulopathy due to COVID-19 leads to systemic arterial and venous thromboembolism including but not limited to acute ischemic stroke.[12–15] Initial case reports with stroke and COVID-19 were alarming consisted of young patients without comorbidities,[16] however, there were also reports of older patients with stroke risk factors and worse outcome.[17] There were mixed laboratory data and case fatality rate in case series making it difficult to apprehend the overall characteristics of stroke with COVID-19. Herein, this systematic review and meta-analysis were conducted to illustrate the reported frequency of stroke in hospitalized COVID-19 patients, as well as the demographic and the clinical characterization of all reported patients with COVID-19 and stroke.

Methods

Protocol and registration

A review protocol does not exist for this analysis.

Eligibility criteria

Included studies met the following criteria: the study design was an observational study or a case series or report, the study population was patients with COVID-19 patients and stroke. Articles that do not contain original data of the patients (e.g. guideline, editorial, review, and letter) were excluded from the secondary review.

Information sources and search

All observational studies, case series, and case reports which included patients with COVID-19 and stroke (ischemic or hemorrhagic) were identified using a 2-level strategy. First, databases including PubMed and EMBASE were searched through June 10th, 2020. Search terms included ((SARS-CoV2) OR (COVID-19)) AND ((stroke) OR (cerebrovascular accident) OR (cerebral infarction)). We did not apply language limitations.

Study selection and data collection process

Relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates. Two independent authors (M.Y. and T.K.) reviewed the search results separately to select the studies based on present inclusion and exclusion criteria. Disagreements were resolved by consensus.

Data items

Outcomes included age, sex, comorbidities, symptoms, days from COVID-19 symptom onset to stroke, laboratory data such as d-dimer, C-reactive protein (CRP), and cardiac troponin, etiology, treatment, and case fatality rate. Among symptoms of stroke, any change in mental status such as lethargy, confusion, and coma were summated as altered mental status; this included patients who presented with new change in mental status, and those who continued to be comatose after weaning off of sedation for mechanical ventilation. Fall or syncope was not included in this category. Corresponding authors were contacted individually if there were any values suspicious for a misspelling.

Risk of bias in individual studies

Risk of bias in individual studies was reviewed using assessment of risk of bias in prevalence studies.[18]

Summary measures and synthesis of results

To attempt to calculate frequency of stroke in hospitalized COVID-19 patients, retrospective cohort studies focused on hospitalized COVID-19 patients were utilized. For other estimates (age, days from symptom onset of COVID-19 to stroke diagnosis, d-dimer, CRP, troponin, and case fatality rate), retrospective cohort studies which targeted other population and case series as well as case reports were added to the studies above and combined using one-group meta-analysis in a random-effects model using DerSimonian-Laird method for continuous value and Wald method for discrete value with OpenMetaAnalyst version 12.11.14 (available from http://www.cebm.brown.edu/openmeta/). The frequency of common comorbidities (hypertension, dyslipidemia, diabetes mellitus, acute coronary syndrome /coronary artery disease), atrial fibrillation, stroke/transient ischemic attack, and malignancy), etiology of stroke if specified in the articles, and treatment (tissue plasminogen activator (tPA), mechanical thrombectomy, and anticoagulation were calculated by summation of events divided by the number of total patients from all studies whose information is available for each value. Any anticoagulation therapy except prophylaxis for deep venous thrombosis preceding the stroke diagnosis was included in the calculation, and whether it was intended for treatment of stroke, therapeutic anticoagulation for other thromboembolic complication, or part of treatment protocol for acute respiratory distress syndrome in COVID-19, was delineated in the result section when available. The ProMeta 3 software was used to perform funnel plots (https://idostatistics.

com/prometa3/) for age. We did our systematic review and meta-analysis according to PRISMA guidelines.

Results

Study selection and study characteristics

The database search identified 215 articles that were reviewed based on the title and abstract. Of those, 186 articles were excluded based on article type (clinical guidelines, consensus documents, reviews, systematic reviews, and conference proceedings), conference abstracts, irrelevant topics, and articles without stroke with COVID-19. Twenty-nine articles met the inclusion criteria and were assessed for the systematic review (Fig. e-1). Nine articles were excluded for reasons including duplicate reports and article type. Six articles were added after the second search on June 10, 2020. There were 10 retrospective cohort studies, 6 case series, and 10 case reports with patients of interest.[3,12,13,16,17,19–39]

Risk of bias in individual studies

Summary of risk of bias for prevalence studies for each retrospective cohort study was shown in Table e-1.

Results of individual studies and synthesis of results

Extracted data as above is shown in Tables 1 and 2 for the retrospective cohort studies, and in Table e-2 for the case series and case reports.

Among the 10 retrospective cohort studies, 5 studies defined their population as hospitalized COVID-19 patients, 1 from China,[3] 1 from Italy,[12] 2 from Spain,[19,21] and 1 from USA,[22] with total of 6,368 individuals. The reported frequency of stroke in hospitalized COVID-19 patients was 1.1% ([95% confidential interval]: [0.6-1.6], I^2=62.9%, 66/6,368 patients)[3,12,19,21,22] (Fig. 1A). The other 5 retrospective cohort studies set their population differently and thus were excluded from the calculation of the frequency of stroke in hospitalized COVID-19 patients.[13,20,37–39]

All 10 retrospective cohort studies and 16 case series and case reports were included for further analysis regarding age, symptoms of stroke, symptoms of COVID-19, days from COVID-19 onset to stroke diagnosis, d-dimer, CRP, troponin, the frequency of cryptogenic stroke as etiology if it is specified in the article, location of affected major intracranial arteries if specified, and mortality using one-group meta-analysis in a random-effects model (Fig. 1B-D, Fig. e-2). Mean age was 66.6 ([58.4-74.9], I^2=95.2%). There was slight male preponderance at 65.6% (61/93 patients). The frequency of comorbidities and stroke risk factors were hypertension 69.4% (75/108 patients), dyslipidemia 44.4% (48/108 patients), diabetes 43.5% (47/108 patients), acute coronary syndrome/coronary artery disease 26.9% (29/108 patients), atrial fibrillation 23.1% (25/108 patients), prior stroke/transient ischemic attack 10.4% (8/77 patients), and malignancy 14.8% (8/54 patients). Of note, prior anticoagulation status for patients with atrial fibrillation was not available in majority of included studies, and thus was not included in this analysis.

Of those who stroke type (ischemic vs hemorrhagic) were described, 96.6% (113/117 patients) had ischemic stroke. The three most common presenting symptoms of stroke gathered mainly from case series and case reports were unilateral weakness (65.7%, 23/35 patients), altered mental status (51.4%, 18/35 patients), and dysarthria (34.3%, 12/35 patients). As for symptoms of COVID-19, cough was most common (77.6%, 59/76 patients), followed by fever (63.2%, 48/76 patients) and dyspnea or hypoxia (62.1%, 41/66 patients). Mean days from symptom onset of COVID-19 to stroke was 8.0 ([4.1-11.9], I^2=93.1%) (Fig. 1B). Mean d-dimer was 3.3 μg/mL ([1.7-4.9], I^2=86.3%) (Fig. 1C) and elevated, mean CRP was 127.8 mg/L ([100.9-154.6], I^2 = 0%) also elevated, however, mean troponin was 0.051 ng/mL ([0.002-0.099], I^2 = 91.5%) and was not significantly high. In regards to the etiology of stroke specified by the authors, 50.7% was cryptogenic ([31.0-70.4] I^2=64.1%, 39/71patients). Affected major intracranial arteries were middle cerebral arteries (30.5%, 25/82 patients), internal carotid arteries (18.3%, 15/82 patients), vertebrobasilar arteries (7.3%, 6/82 patients), posterior cerebral arteries (3.7%, 3/82 patients). Of those patients whose detail of stroke localization was available, 29.2% had multifocal stroke (14/48 patients). As for acute treatment, 21.8% (24/110 patients) received tPA, 28.3% (34/120 patients) underwent mechanical thrombectomy. Anticoagulation was documented in 61.3% (46/75 patients); of those, 1 patient was getting therapeutic anticoagulation for pulmonary embolism before diagnosis of stroke,[23] and another patient was started on therapeutic anticoagulation as part of treatment for acute respiratory distress syndrome from COVID-19, however the timing of anticoagulation in relation to the stroke occurrence was unavailable.[25] Other patients were started on anticoagulation therapy for stroke treatment. Case fatality rate was 44.2% (40/100 patients) ([27.9-60.5], I^2=66.7%) (Fig. 1D). Funnel plot for age is shown in Supplemental Figure e-3 (Egger's test: p=0.97).

Discussion

This systematic review of 26 studies identified 183 COVID-19 patients with stroke. The salient findings of the study can be summarized as the followings; (1) the frequency of stroke in hospitalized COVID-19 patients was 1.1%, with mean days from COVID-19 symptom onset to stroke at 8 days, most commonly cryptogenic; (2) even with early case series with younger patients without a pre-existing medical condition, the mean age was 66.6, with slight male preponderance (65.6%); (3) stroke risk factors such as hypertension, dyslipidemia, and prior

Table 1. *Results of Systematic Review with Cohort Studies of COVID-19 Positive Patients - Basic Characteristics.*

Study	Country	Population	Number of Hospitals	Cohort size	Stroke, % (N)	Age	Male, % (N)	Comorbidities, % (N)						
								HTN	DLP	DM	ACS/ CAD	AF	Stroke/ TIA	Malignancy
Mao et al.	China	Hospitalized patients with COVID-19 infection between 1/16-2/19, 2020	3	214	2.8% (6)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lodigiani et al.	Italy	Hospitalized patients with COVID-19 infection between 2/13-4/10, 2020	1	338	2.7% (9)	68.4±5.9	66.7% (6)	NA	NA	NA	NA	NA	NA	11.1% (1)
Yaghi et al.	USA	Hospitalized patients with COVID-19 infection between 3/15-4/19, 2020	3	3556	0.9% (32)	63±25	NA	56.3% (18)	59.4% (19)	34.4% (11)	15.6% (5)	18.8% (6)	3.1% (1)	NA
Cantador et al.	Spain	Hospitalized patients with COVID-19 infection between 2/1-4/21, 2020	1	1419	0.56% (8)	76.4±7.1	87.5% (7)	100% (8)	87.5% (7)	50% (4)	37.5% (3)	25% (2)	25% (2)	62.5% (5)
Romero Sanchez et al.	Spain	Hospitalized patients with COVID-19 infection in March 2020	2	841	1.3% (11)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Merkler et al.	USA	Patients with emergency department visits or hospitalizations with COVID-19 infection between 3/4-5/2, 2020	2	2132	1.5% (31)	69±16.2	58.1% (18)	96.8% (30)	54.8% (17)	74.2% (23)	51.6% (16)	54.8% (17)	NA	NA
Klok et al.	Netherland	ICU patients with COVID-19	1	184	2.7% (5)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Radmanesh et al.	USA	COVID 19 positive patients who underwent MRI or CT in 3/1-3/31 at NYU	1	242	5.4% (13)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Escalard et al.	France	Patients who had stroke with LVO from 3/1 to 4/15	1	37	27% (10)*	59.5 [54, 71]	80% (8)	NA	NA	NA	NA	NA	NA	NA
Kihira et al.	USA	Patients who had confirmed stroke in 3/16-4/5	6	48	37.5% (18)*	NA	NA	NA	NA	NA	NA	NA	NA	NA

Value is shown as median [Q1, Q3] or mean±SD unless specified otherwise. Abbreviations: ACS/CAD − acute coronary syndrome/coronary artery disease; AF − atrial fibrillation; DM − Diabetes; HTN − hypertension; DLP − dyslipidemia; LVO: large vessel occlusion; NA − non-applicable; TIA − transient ischemic attack. * - who were COVID-19 positive.

Table 2. *Results of Systematic Review with Cohort Studies of COVID-19 Positive Patients – Characteristics of Stroke, Treatment, and Mortality.*

Study	Ischemic, % (N)	Days from COVID-19 symptom onset	Laboratory data			Etiology			Treatment			Mortality, % (N)
			D-dimer (μg/mL)	CRP (mg/L)	Cardiac troponin (ng/mL)	Cryptogenic	Cardioembolic	Atherothrombic	tPA	Mechanical thrombectomy	AC	
Mao et al.	83.3% (5)	9 [range 1-18]*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lodigiani et al.	100% (9)	NA	3.6 [0.4, 6.3]	NA	NA	NA	NA	NA	22.2% (2)	22.2% (2)	88.9% (8)	NA
Yaghi et al.	100% (32)	10 [5, 16.5]	3.913 [2.549-10.000]	101.1 [38.8, 214.3]	0.7 [0.3125, 1.36][*3]	65.6% (21)	21.9% (7)	6.3% (2)	12.5% (4)	21.9% (7)	78.1% (25)	37.5% (12)
Cantador et al.	100% (8)	6.3±5.4	2.589 [0.735, 8.156]	100.5 [27, 206]	NA	25% (2)	25% (2)	37.5% (8)	12.5% (1)	NA	Prophylactic 37.5% (3), therapeutic 12.5% (2)	25% (2)
Romero Sanchez et al.	NA	10[*2]	9.929±28.286	NA	NA	NA	NA	NA	NA	NA	NA	NA
Merkler et al.	NA	16 [5, 28]	1.93 [0.559, 5.285]	NA	0.03 [0.03, 0.09]	51.6% (16)	41.9% (13)	NA	9.7% (3)	6.5% (2)	NA	29% (9)
Klok et al.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Radmanesh et al.	100% (13)	NA	NA	NA	NA	NA	NA	NA	NA	23.1% (3)	NA	NA
Escalard et al.	100% (10)	6 [range 2-18]*	NA	NA	NA	NA	NA	NA	50% (5)	100% (10)	NA	60% (6)
Kihira et al.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Days from COVID-19 symptom onset, D-dimer, C-reactive protein (CRP), cardiac troponin – shown as median [Q1, Q3] or mean±SD unless specified otherwise. *1 – specified as "range" in the original article. *2 - mean. *3 - Only 15 patients out of 32 patients had available value in the article. AC – anticoagulation; NA – non-applicable; tPA – tissue plasminogen activator.

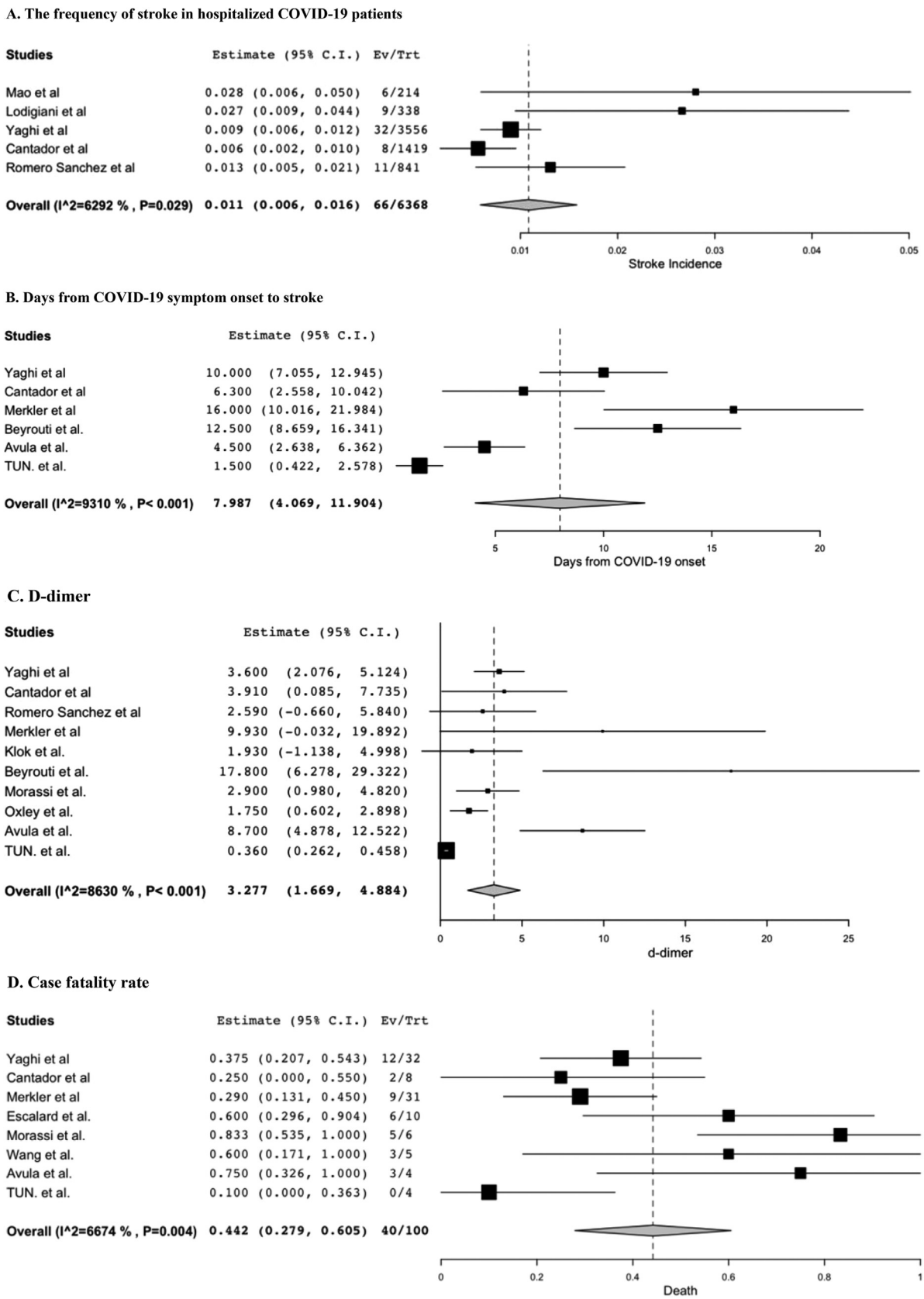

Figure 1. *Forest plots for characteristics of stroke patients with COVID-19 (random-effects model); (A): The frequency of stroke in hospitalized COVID-19 patients; (B): Days from COVID-19 symptom onset to stroke; (C): D-dimer; (D): Case fatality rate.*

strokes were common as comorbidities; altered mental status was as frequent as 51.4% as presenting symptom of stroke; (4) elevation of d-dimer and CRP were reproduced after synthesis of results; (5) case fatality rate was as high as 44.2% in patients with COVID-19 and stroke.

We revealed the frequency of stroke in hospitalized COVID-19 patients was 1.1%. Stroke incidence in general population is estimated from 0.6 to 0.8%.[40] Infection, particularly systemic upper respiratory illness is an important precipitating risk factor for acute ischemic stroke.[41–43] Notably, Boehme et al. reported that risk of acute stroke increases 9 times in young population aged 18-45 within 15 days from onset of influenza-like illness.[41] Furthermore, patients with emergency department visits and hospitalizations with COVID-19 were reported to be approximately seven times as likely to have an acute ischemic stroke as compared to patients with emergency department visits or hospitalizations with influenza.[20] Previous study revealed that stroke risk increases after a systemic respiratory tract infection at most within 3 days from symptom onset.[43] On the contrary, the days from symptom onset to stroke with COVID-19 in our study was 8 days, longer than other systemic respiratory infection in pre-COVID-19 era,[43] potentially supporting late thromboembolism complications caused by immune-mediated coagulopathy of COVID-19.[44] However, this duration between symptom onset of COVID-19 and stroke was variable as represented by a high heterogeneity, and it is notable that some patients presented with stroke even without COVID-19 symptoms.[16] Most common etiology of stroke was cryptogenic up to 50.7% which is twice as high as that of general population at 25%.[45] 29.2% had multifocal stroke among patients whose detail of stroke was available. Collectively, SARS-CoV-2 is potentially a higher precipitating factor for acute ischemic stroke compared to other classic respiratory infection such as influenza, possibly via immune mediated coagulopathy.[12–15]

Early in the course of the pandemic, several cases of younger patients without comorbidities were reported[16,26,27]; however, our synthesized results re-demonstrated classic demographics of the population who are at risk for stroke even in COVID-19 patients, including older age, male gender, and pre-existing medical condition such as hypertension, dyslipidemia, and diabetes. Altered mental status was seen in 51.4% as presenting symptom of stroke, which is more frequent than stroke in general (15–23% in one study).[46] Decreased level of consciousness is reported to be a risk factor for missed diagnosis of stroke in emergency room.[47] Along with delayed presentation and concurrent fever, this could potentially explain the relatively low rates of tPA administration; however, further investigation is needed to depict the safety and effectivity of tPA in patients with stroke and COVID-19.

D-dimer and CRP were elevated on average at 3.3 μg/mL and 127.8 mg/L respectively in our study. Previous report pointed out d-dimer greater than 1 μg/mL is a risk factor for severe COVID-19 and mortality.[48,49] Other report demonstrated d-dimer >2.5 μg/mL and CRP >200 mg/L were related to critical illness of COVID-19, which may be associated with higher risk of hyper-inflammatory states and hypercoagulability and resultant pulmonary emboli and microscopic emboli.[50] As a marker for acute inflammation and coagulopathy, elevated d-dimer was an adverse prognostic factor in H1N1 influenza in 2009[51,52] and also in acute ischemic stroke.[53] Since elevated d-dimer could be used as a risk assessment biomarker of recurrent stroke in general[54,55] and previous observational study showed that anticoagulation might be associated with improved outcomes among patients hospitalized with COVID-19[56], patients with stroke and COVID-19 might benefit from anticoagulation therapy, especially with cryptogenic stroke.[56] However, patients who are intubated under sedation with poor neurological exam warrant extra caution before initiating anticoagulation, since those patients could be at higher risk of ischemic stroke that could have hemorrhagic conversion undetected.[57] Neuroimaging should be considered in this population prior to anticoagulation to avoid iatrogenic hemorrhagic conversion of undiagnosed ischemic stroke.

Lastly, the case fatality rate in this population with stroke and COVID-19 was conspicuously high at 44.2%. It is higher than mortality from stroke in general population that differs significantly by age; according to a report of Medicare beneficiaries over the time period 1995 to 2002, the 30-day mortality rate was: 9% in patients 65 to 74 years of age, 13.1% in those 74 to 84 years of age, and 23% in those older than 85 years of age.[40] Mortality in hospitalized COVID-19 patients reported in the early course of pandemic ranged from 4 to 28%.[48,58–61] This discrepancy in mortality of COVID-19 patients with and without stroke could be secondary to withdrawal of medical care when the neurological prognosis is grave[17,28,33]; another possibility is that stroke is part of multi-organ failure and systemic coagulopathy whose mortality is higher than COVID-19 patients in general. Notably, prior stroke has been described as a risk factor for severe disease in COVID-19 patients even without concurrent acute stroke, which could potentially support vulnerability of patients with cerebrovascular disease to COVID-19 from undetermined cause.[62] The cause of death in this population remains unclear with our study due to limited details about the cause of death from large cohort studies. Further study is needed to elucidate pathophysiology and risk factors for stroke as well as outcome and best treatment measures in hope to lower mortality in COVID-19 patients with stroke.

This study has several limitations. First, this systematic review covered a brief period, and therefore the sample size may still be limited. Second, only limited value was available ubiquitously in the reviewed studies. Third, there was a substantial heterogeneity in patient population given high I^2 and different inclusion criteria of the studies used in

this analysis, such as hospitalization, requirement of intensive care, and large vessel occlusion that warranted mechanical thrombectomy. In addition, the case reports and case series that were included in this review could potentially have publication bias that more severe cases in a younger population without risk factors with large stroke burden tend to be published as this type of articles, compared to those who had stroke risk factors as comorbidities and suffered small lacunar strokes and COVID-19. Furthermore, reported incidence of acute stroke could be lower than actual, since subtle signs of small stroke could have been missed by the providers especially when patients with COVID-19 were sedated and intubated.

Conclusions

This systematic review assessed the clinical characteristics of stroke in patients with COVID-19. The frequency of stroke in hospitalized COVID-19 patients was 1.1% and associated with older age and stroke risk factors. Frequent cryptogenic stroke and elevated d-dimer level support increased risk of thromboembolism in COVID-19 associated with high mortality. Further studies such as prospective collaborative international registries are helpful to decipher the pathophysiology and prognosis of stroke in COVID-19 to achieve the most effective care for this population to decrease mortality.

Declaration of Competing Interest

There is no conflict of interest of this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.105288.

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