COVID-19

Impact of COVID-19 on neurological manifestations: an overview of stroke presentation in pandemic

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Abstract

Corona virus disease 2019 (COVID-19) pandemic has become a globally challenging issue after its emergence in December 2019 from Wuhan, China. Despite its common presentation as respiratory distress, patients with COVID-19 have also shown neurological manifestation especially stroke. Therefore, the authors sought to determine the etiology, underlying risk factors, and outcomes among patients with COVID-19 presenting with stroke. We conducted a systematic review of the electronic database (PubMed, Google Scholar, Scopus, Medline, EMBASE, and Cochrane library) using different MeSH terms from November 2019 to June 2020. A total of 39 patients with stroke from 6 studies were included. The mean age of our included patients was 61.4 ± 14.2 years. Majority of the patients ($n = 36$, 92.3%) with COVID-19 had ischemic stroke, 5.1% ($n = 2$) had hemorrhagic stroke, and 2.6% ($n = 1$) had cerebral venous thrombosis at the time of initial clinical presentation. Almost all of the patients presented had underlying risk factors predisposing to stroke which included diabetes mellitus, hyperlipidemia, hypertension, and previous history of cerebrovascular disease. 51.2% ($n = 20$) of the included patients infected with COVID-19 with stroke died, while remaining patients were either discharged home or transferred to a rehabilitation unit. Exploring the neurological manifestation in terms of stroke among patients with COVID-19 is a step towards better understanding of the virus, preventing further spread, and treating the patients affected by this pandemic.

Keywords COVID-19 · Corona virus · Pandemic · Stroke · Neurological disorders

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Corona virus disease 2019
ACE	Angiotensin-converting enzyme
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has emerged as an unprecedented global crisis. In the tremendous flow of viral pneumonia and life-threatening respiratory complications, the influence of corona virus disease 2019 (COVID-19) on neurological diseases

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remains unclear. Brain is the potential target to COVID-19, just as the lungs, due to expression of angiotensin-converting enzyme (ACE 2) receptors on the glial cells and neurons of the central nervous system [1, 2]. There have been reports on stroke surge, especially among young and middle-age group patients, suffering from COVID-19 [3]. Among patients with COVID-19, serum D-Dimer level is generally increased, which could be the source of embolic vascular event [4]. Study by Klok et al. [5] suggested that the excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation predispose to an increased risk of thrombovascular event reaching up as high as 31% among ICU patients with COVID-19. Many of the patients presenting with stroke might already have underlying cerebrovascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, smoking, or previous history of stroke [6]. The occurrence of cerebrovascular events in critically ill patients with underlying medical co-morbidities is therefore potentially related to the direct effect of the infection itself or inappropriate host response.

Therefore, we carried out a systematic review of all available literature on patients infected with novel COVID-19 presenting with stroke to determine the overall impact of this pandemic and outcomes among patients having neurological manifestations.

Methods

Data search strategy

We followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [7] guidelines for literature search. Two reviewers (NF and AS) conducted a detailed systematic review on electronic databases using PubMed, Google Scholar, EMBASE, Medline, Cochrane library, and Scopus for articles published between November 1, 2019, and June 1, 2020. MeSH terms (using the Boolean operators "and" and "or") which included "stroke", "pandemic", "corona virus", and "COVID-19" were searched. All articles irrespective of the language were included in our study.

Inclusion and exclusion criteria

The inclusion criteria included patients presenting with acute stroke who eventually were found to be positive COVID-19. We included all available type of studies on stroke in our review due to scarcity of literature.

Data extraction and outcome measures

The data were extracted by the authors using a structured template form based on the Cochrane Consumers and Communication Group. We further conducted this meta-analysis in accordance with the criteria set by Cochrane Consumers and Communication Group reviews: Meta-analysis [8]. Any disagreement between the two authors was resolved by discussion. The following data were extracted from each article: (i) demographic characteristics, (ii) clinical condition, (iii) stroke risk factors, and (v) outcome measures.

Evidence quality assessment

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) [9] protocol was used to assess the quality of evidence for each study independently by two reviewers. Each study was rated based on study design, limitations, and results into either high, moderate, low or very low.

Statistical analysis

Rev Manager (Rev Man 5.3) was used for comparing data from the included studies. Pooled weighted mean difference was used to analyze the continuous data, while the odds ratio (OR) was used to analyze the dichotomous data.

Risk of bias across studies

We used the Cochrane Collaboration's tool to assess the risk of bias across the included studies. Double blindness was not achieved in any study.

Results

Study selection

A total of 98 articles were retrieved from electronic databases (PubMed, Google Scholar, Scopus, Medline, EMBASE, and Cochrane library) and reviewed according to PRISMA guidelines [10] (Fig. 1). After screening of the abstracts, 72 articles were excluded as the data was not related to stroke. A total of 11 full text articles were assessed for eligibility, of which 5 articles were excluded based upon the inclusion and exclusion criterion. Hence, 6 articles were included in our review [3, 11–15]. All included studies were categorized under moderate GRADE.

Study results

Our review included 39 patients presenting with cerebrovascular disease, out of which 36 patients (92.3%) had ischemic stroke, 2 patients (5.1%) had hemorrhagic stroke, and 1 patient (2.6%) had cerebral venous sinus thrombosis. The mean age of our included patients was 61.4 ± 14.2 years. Almost all of the patients had underlying risk factors predisposing to
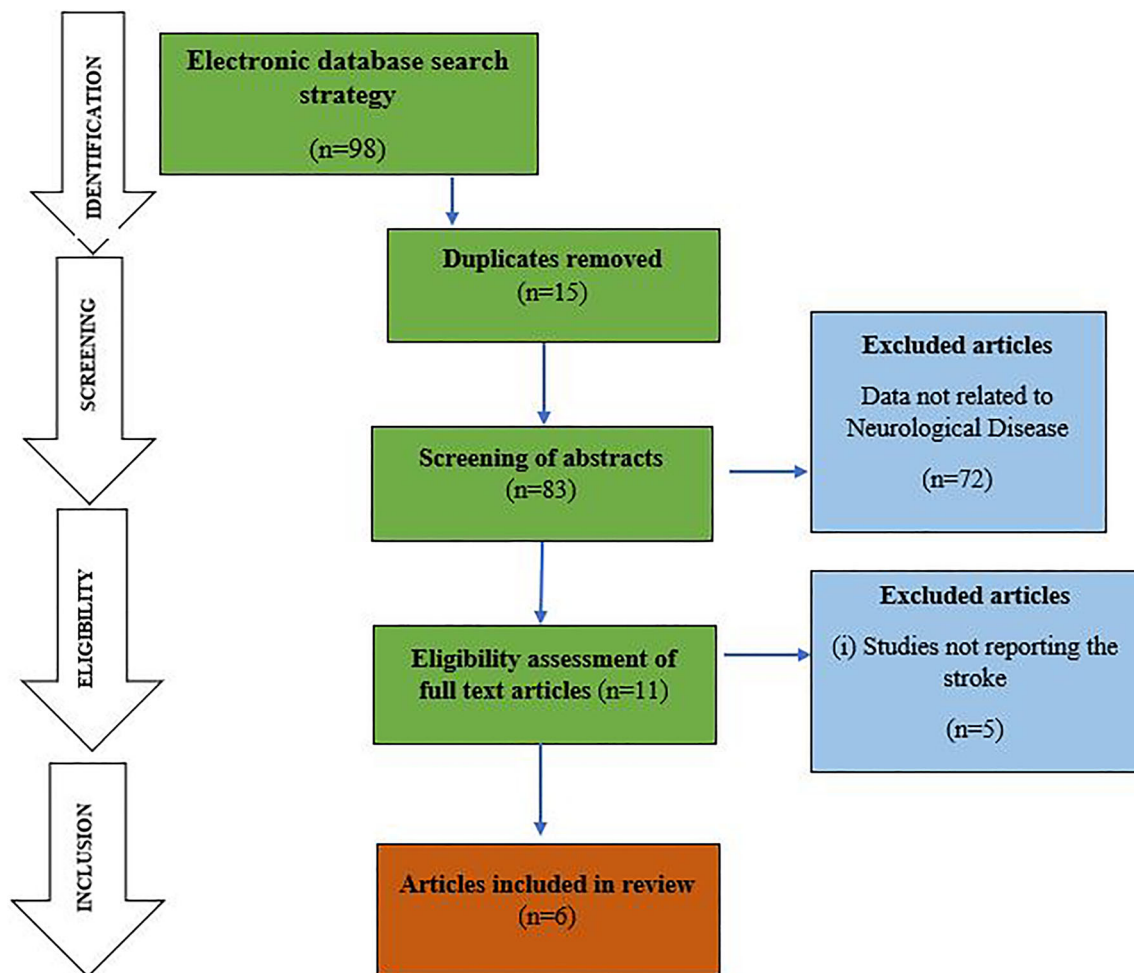
Fig. 1 A database search strategy according to Preferred Reporting Items for Systematic Review and Meta-analysis

stroke which included diabetes mellitus, hyperlipidemia, hypertension, and previous history of cerebrovascular disease. Outcomes included mortality among 51.2% (*n* = 20) of the included patients, while remaining patients survived and were transferred either to rehabilitation unit or home. Baseline and outcome characteristics are shown in Table 1.

Discussion

Our systematic review determined the underlying risk factors leading to stroke among COVID-19 patients, and outcomes among these patients. Our results suggested that the patients with COVID-19 have an apparent association with stroke due to similar risk factors. There is ample evidence that the severity of COVID-19 infection in humans is directly related to the presence of cardiovascular co-morbidities, which include diabetes mellitus, hypertension, and elderly status predisposing to large and small vessel disease [16, 17]. A recently conducted meta-analysis of 8 studies from China, including 46,248

infected patients, showed that the most prevalent co-morbidities were hypertension (17%) and diabetes mellitus (8%), followed by cardiovascular diseases (5%) [18, 19]. In those reported cases without any vascular factors, the SARS-CoV-2-induced hypercoagulability may be the most important mechanism of the cerebrovascular disease [13, 20].

Previously large-vessel stroke was reported to be associated with SARS CoV-1 outbreak in Singapore [21]. Various hypotheses had been suggested to explain the apparent link between viruses and cerebrovascular diseases, which include, but are not limited to, virus-induced inflammation of the vessel wall [22] and induction of prothrombinase gene [23]. Furthermore, Middle East respiratory syndrome corona virus (MERS-CoV) [24] also led to severe neurological manifestation among patients. In the setting of a COVID-19 infection, patients with previous history of vascular risk factors might have an increased risk of stroke due to complications such as shock, hypotension, heart failure, and disseminated intravascular coagulation that can potentially contribute to hypoperfusion, embolic mechanism of stroke, and large vessel

Table 1 Baseline demographic and outcome characteristics of the included studies

Name of the author	Year of study	Disease	Mean age (standard deviation), years	Number of patients	Cerebrovascular disorder	Stroke risk factors	Outcome
Mao Ling et al. 2020 [3]	2020	COVID-19	52.7 (15.5)	214	Ischemic stroke: 5 Cerebral hemorrhage: 1	Severe infection, old age, co-morbidities especially hypertension, lower lymphocyte levels, low platelet counts, higher blood urea nitrogen levels	Patients died from respiratory failure
Oxley T et al. 2020 [11]	2020	COVID-19	40.4 (5.6)	5	Large-vessel ischemic stroke	Patient 1: none Patient 2: none Patient 3: hyperlipidemia, hypertension Patient 4: undiagnosed diabetes Patient 5: mild stroke, diabetes	Patient 1: Dx to rehab Patient 2: Dx home Patient 3: ICU Patient 4: stroke unit Patient 5: Dx to rehab
Li Y et al. 2020 [12]	2020	COVID-19	71.6 (15.7)	221	Ischemic Stroke: 11 Cerebral Hemorrhage: 1 Cerebral venous sinus thrombosis: 1	Hypertension, diabetes, and previous medical history of cerebrovascular disease	Death: 5 Survived: 8
Avula A et al. 2020 [13]	2020	COVID-19	81 (5.43)	4	Ischemic stroke	Patient 1: hypertension, dyslipidemia and carotid stenosis Patient 2: urinary tract Infection, hypertension, hyperlipidemia, diabetes mellitus and neuropathy Patient 3: hypertension Patient 4: hypertension, chronic kidney disease, hyperlipidemia	Death: 3 Survived: 1
Zhao J et al. 2020 [14]	2020	COVID-19	60	1	Ischemic stoke	Hypertension	Survived
Escalard S et al. 2020 [15]	2020	COVID-19	59.5	10	Ischemic stroke	Hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, prestroke anticoagulation	Death: 6 Survived: 4

Dx discharge, *ICU* intensive care unit, *NIHSS* National Institute of Health Stroke Scale, *NA* not available

occlusion [11, 16, 17]. In some recent observational studies of hospitalized patients of COVID-19, shock was observed in 8.7–20% of the patients, acute cardiac injury in 7.2–17% of the patients, and coagulopathy in 19% of the patients [25, 26].

Neurosurgeons and neurologists should keep in mind the potential risks of stroke among these presenting patients. There are recommendations [27–29] set up by the treating physicians for the optimal stroke care during this pandemic crisis. We therefore appreciate the efforts by the neurologists and the vascular neurosurgeons to better understand the underlying risk factors and complications in order to improve the overall outcome of the stroke patients in this pandemic crisis. We carried out a short-systematic review integrating all COVID-19 patients presenting with stroke. This would definitely help in understanding the difference in the age groups and outcomes among these patients presenting at various institutes. However, further studies are needed to understand the presence of specific viral factors causing hypercoagulability, arteritis, endothelial dysfunction, and as a result different types of ischemic and hemorrhagic stroke due to COVID-19.

Compliance with ethical standards

Conflict of interest None

Ethical disclosure Not Applicable

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