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REVIEW

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Ischemic stroke and COVID-19 infection — a review of clinical case reports

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Abstract

Background Despite the availability of vaccines, COVID-19 remains of global concern with seasonal peak in cases across the globe and considering its link to brain pathologies such as stroke. Our aim was to characterize the presence of comorbidities and how the time of COVID-19 infection relative to stroke onset impacts outcomes.

Methods We reviewed 68 cases of COVID-19 in hospitalized patients with acute stroke. We searched for published case reports using PubMed and Google Scholar limited to publications written in English from September 2019 to December 2022. We excluded systematic reviews from our search result and categorized individual cases into four groups: COVID-19-induced stroke (CIS, those who had COVID-19 shortly before stroke onset), stroke then COVID-19 (STC, those who had COVID-infection immediately following stroke onset), COVID-19 and stroke (CAS, those who presented with both stroke and COVID-19 infection). The following information was extracted and analyzed from included search reports: age, NIHSS score, type of stroke, mortality, functional outcomes, and comorbidities listed.

Conclusions Most patients who were reported for admission stroke were of middle age, and only more aged individuals presented with concurrent stroke onset and COVID-19 infection. Hypertension was the most prevalent comorbidity across all four groups, especially among the STC group. The poorest functional outcomes and highest inhospital mortality were observed among the STC group when compared to other groups. The concurrent presentation of stroke and COVID-19 infection had the least impact on functional outcome, but COVID-19 infection during acute stroke hospitalization may worsen clinical outcomes especially among individuals with hypertension.

Keywords Stroke, COVID-19, Comorbidities of stroke, Hypertension

Background

The association of stroke incidence with acute SARS-CoV-2 virus (i.e., COVID-19) infection has been reported since the early days of the pandemic. In Wuhan, China, an early retrospective case study with data collected between January and February 2020 showed that severe infection with COVID-19 led to a higher prevalence of stroke when compared to milder infections of COVID-19 [1]. Similarly, a recent report showed 52% increased risk of stroke among COVID-19 survivors [2]. One systematic review which aimed at shedding mechanistic insight showed a consensus that acute inflammation during infection may be the pathogenic cause for stroke among individuals who were diagnosed with COVID-19 [3]. Also, activation of the fibrinolytic system, interfering with hemostasis, after COVID-19 infection could occur and may lead to stroke. The virus has an affinity towards ACE2 receptors which interferes with the renin-angiotensin system and increases the likelihood of stroke in COVID-19 patients [4]. While there are potential mechanisms pointing to the incidence of stroke among individuals infected with COVID-19 survivors, underlying causative mechanism(s) remain unaddressed.

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Although today the world is less terrified of COVID-19 compared to the early months of its emergence, the regional and seasonal case uptakes across the world are unwavering. In addition, since the global population at risk of stroke is on the rise due to the increasing aging population, the stroke impact of COVID-19 warrants some research consideration and increased understanding. Importantly, it is unclear whether and how poststroke infection with COVID-19 impacts clinical outcomes.

The present review evaluated 68 individual cases of stroke and COVID-19 infections in patients. To determine a research direction, our objective of this study was to explore an association between the risk factors of stroke, clinically relevant outcomes, and the sequence of stroke/COVID-19 incidence by characterizing age distribution, mortality, functional outcome, and the presence of comorbidities/risk factors for stroke among individuals who were hospitalized.

Methods

PubMed and Google Scholar were used to search for case reports with the following search terms: Search terms were as follows: COVID-19 and stroke; comorbidities, stroke, and COVID-19; COVID-19 mechanisms; and stroke mechanisms for a period of 2 months. Systematic reviews were excluded from included results. Once the reports were collated, the following variables were extrapolated from the reports: patients' age, the number of individual patients who were hospitalized for COVID-19 symptoms but developed symptoms of stroke during hospital stay more than 24 h later — termed COVID-induced stroke (CIS) cohorts, the number individuals who presented to the hospital with stroke symptoms but developed COVID-19 infection more than 24 h later, during hospitalization — termed stroke and then COVID (STC) cohorts, the number of patients who presented with concurrent (no more than 24 h apart) COVID-19 infection and stroke symptoms — termed COVID and stroke (CAS) cohorts, the National Institute of Health Stroke Scale (NIHSS) score, type of stroke, mortality, functional outcomes, and listed comorbidities/stroke risk factors reported for each individual (such as hypertension, diabetes, atrial fibrillation, smoking, renal failure and cancer) was accounted for, where possible.

Data and statistical analysis

Patients were classified into three main cohorts based on their stroke-COVID-19 occurrence, i.e., CIS, STC, and CAS as well as based on their age, i.e., young ($\leq$49 years old), middle aged (50–69 years old), and aged ($\geq$70 years old).

Results

Patient distribution by cohort classification, age, and sex

A total number of 68 cases (46 males and 22 females) were included for data evaluation. The overall observation of all patient data revealed that CIS cohorts had the largest case number with 55 patients (40 males and 15 females), STC cohorts with 7 patients (1 male and 6 females), and CAS cohorts with 6 patients (5 males and 1 female, Fig. 1).

Patient data were grouped into three age categories: young (below 50 years), middle aged (50$\leq$70 years), and old (>70 years). Across all three age groups, nearly half (47%) of the patient data were reports on middle-aged patients (32/68). Old patients made up 32% (22/68) of the total population, while 21% (14/68) of the total population were young patients. For some cases, only a range of age (rather than an exact age) could be extrapolated from the original reports. Although CIS had the highest number of patients ($n=55$) compared to the other two cohorts, the majority of reported cases were of middle-aged individuals (49.09% (27/55), old patients represented 29.09% (16/55), and 21.82% (12/55) were young patients. For the CIS distribution, 72.7% (40/55) and 27.3% (15/55) were male and female patients respectively. Young adults had 9 males and 3 females, middle-aged patients had 20 males and 7 females, while old patients were 11 males and 5 females. STC and CAS cohorts had comparable sample sizes (i.e., $n=7$ and $n=6$, respectively). Also, the distribution of all age groups is almost similar. STC cohorts had 14.29% (1/7) of young patients, 42.86% (3/7) of middle-aged patients, and 42.86% (3/7) of old patients, while CAS had 16.7% (1/6) of young patients, 33.3% (3/6) of middle-aged patients, and 50% (3/7) of old patients (Fig. 2). There was only one male (middle aged) among the STC cohorts of seven patients. CAS cohorts had five males (one young adult, two middle aged, and two old) and one (old) female patient (Fig. 2).

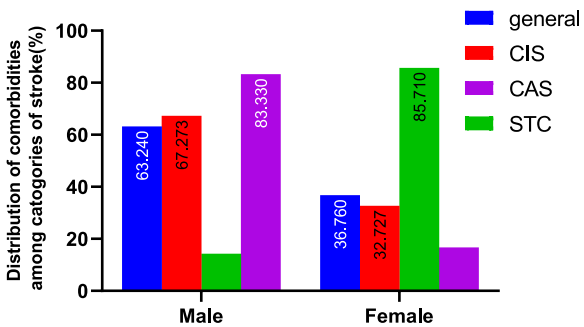

Fig. 1 Distribution of stroke type by gender. Female patients had higher proportion of the patients who got stroke and then COVID, whereas male patients had a higher proportion of patient who got COVID and stroke within 24 h

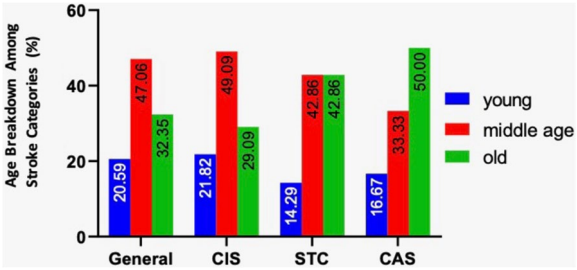

Fig. 2 Age breakdown among stroke categories. Most of the patients were in the middle age category. Older patients made up a higher proportion of COVID and stroke within 24 h. Middle-aged patients made up a high proportion of COVID followed by stroke cases

Hypertension and diabetes are the prominent comorbidities among cohorts

The majority of the cases recorded at least one comorbidity at 82.09% (55/67). One patient had no comorbidities listed but was not defined as having zero comorbidities so that patient was excluded from comorbidity assessment.

Hypertension was the most frequently reported comorbidity among the patients at 53.73% (36/67) (Fig. 3). STC cohorts have the highest percentage of hypertension reports per case when compared to a similar distribution among CIS and CAS cohorts at 52.73% and 50%, respectively (Fig. 3). The second most reported comorbidity was diabetes at 32.84% (22/67). CIS cohorts have a higher representation at 36.36% when compared to the similar frequency among STC and CAS cohorts at 16.67% (Fig. 3). Atrial fibrillation represents the third most frequently reported comorbidity at 10.45% (7/67) (Fig. 3). CAS cohorts at 16.67% had more cases of atrial fibrillation than CIS cohorts at 10.91% (Fig. 3). There was no report of atrial fibrillation for STC cohorts. Chronic kidney disease and cancer were the other comorbidities reported at 5.97% (4/67) and 2.99% (2/67), respectively. While there were no reports of kidney failure nor cancer for STC and CAS cohorts, only CIS cohorts had a 7.27% and 3.64% of kidney failure and cancer cases, respectively (Fig. 3).

Although smoking is not a comorbidity of stroke, it predicts cardiovascular disease and stroke, particularly due to its association with increased platelet activation and aggregation and circulating fibrinogen. Smoking was reported for some patients at 5.97% (4/67) with STC and CAS cohorts having comparable distribution at 16.67%, while smoking was recorded for 3.64% of CIS cohorts.

COVID exacerbates stroke outcomes but does not impact mortality rates

Across all three cohorts, 41 of the 68 cases had records of functional outcome measured by NIHSS score. NIHSS score was higher among STC cohorts 22 ± 9.70 when compared to CIS cohorts (17.03 ± 8.81) and CAS cohorts

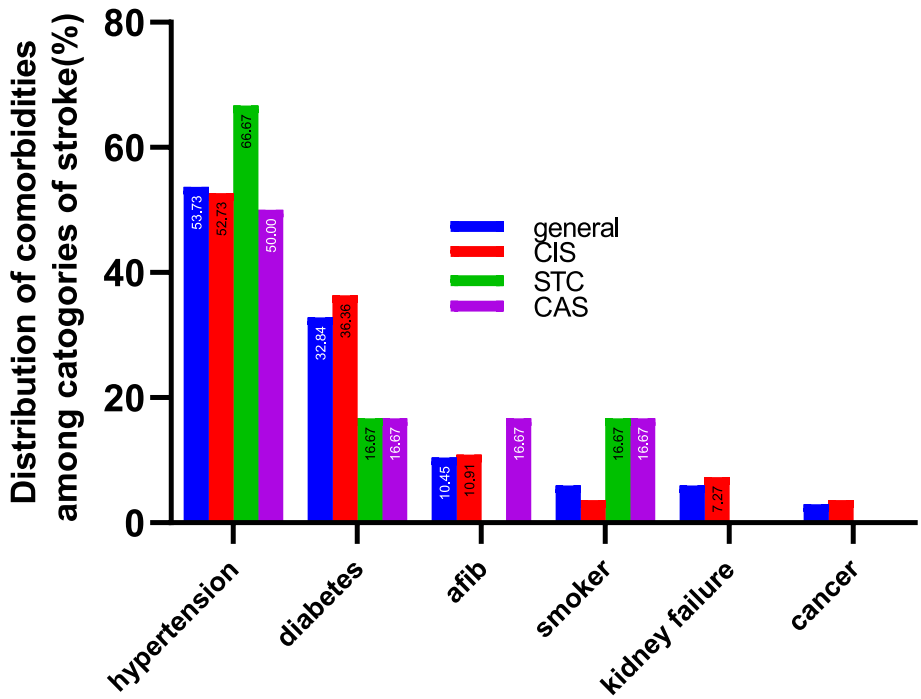

Fig. 3 Distribution of comorbidities among categories of stroke. The largest proportion of patients had hypertension among all categories. This was followed by diabetes and then atrial fibrillation or afib

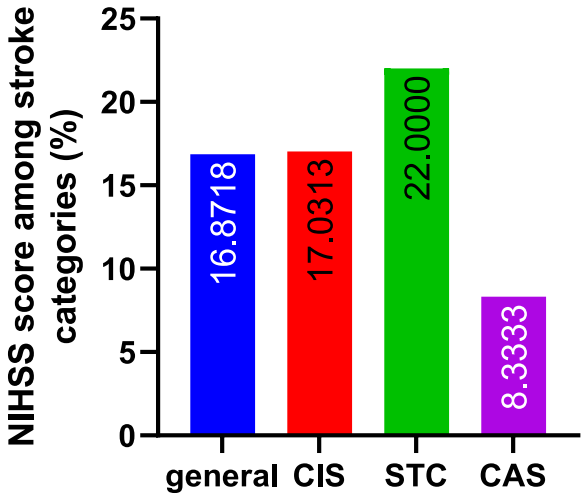

Fig. 4 NIHSS score among categories. Patients with stroke followed by COVID had the highest NIHSS scores on average

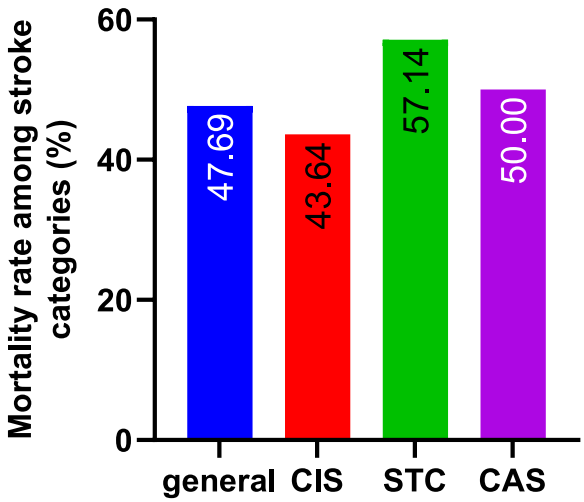

Fig. 5 Mortality rate among categories of stroke. Stroke followed by COVID had the highest rate of mortality among the categories

(8.33 ± 5.51) (Fig. 4). However, while STC cohorts experienced the highest frequency of mortality at 57.14%, 50% mortality was recorded for CAS cohorts, and 43.64% mortality was recorded for CIS cohorts (Fig. 5).

Discussion

With the largest category by a large margin being CIS, it shows that the typical presentation of COVID-19 and stroke in this case series is a patient being hospitalized for COVID-19 and then developing stroke symptoms later. However, with the other two categories still having seven and six patients respectively in the case series, those etiologies for stroke and COVID-19 cannot wholly be disregarded. According to this distribution, the age groups in this series skew more towards patients above 50 which is also a common risk factor for COVID-19-induced stroke. One meta-analysis of over 27,676 patients found that the average age of among the 103 COVID patients with ischemic stroke was 68.8 compared to 54.4 for those with COVID and no stroke [5]. Another analysis of 21,073 patients from the American Heart Association COVID-19 Cardiovascular Disease Registry showed that among the 140 patients with COVID, 67% were male and 33% female which is similar to the gender distribution among the 68 cases [6]. The mortality rate for 68 patients was 47.69% (31/68). In the other studies, this value was 19.4% among the Cerner Real-World Data and 37.5% for the AHA data [5, 6]. There is a greater mortality among the cases than the data from the two meta-analyses which may indicate that this dataset consists of more severe episodes of strokes and COVID-19. This is further supported by the average NIHSS score being 16.87 for our dataset and median of 11 for AHA data [6].

A general data sheet per category of stroke-COVID-19 occurrence was created that had the data of all 68 patients with data listed above. Then we created data sheets for the individual categories CIS, STC, and CAS. Finally, we created charts that compared all the categories together and looked at distribution of comorbidities among categories of stroke, gender breakdown among categories of stroke, and age breakdown among categories of stroke.

The comorbidity data for all 68 cases was first analyzed and recorded under the general category. In the Cerner data, hypertension was 84.5%, diabetes was 56.3%, and atrial fibrillation was 28.2%.

Prevalence of stroke in the United States

In the "AHA Report on Heart Disease and Stroke Statistics," the annual estimate for prevalence of stroke was more than 795,000 people in the United States with 610,000 being first or new strokes [7]. A total of 87% of strokes were ischemic strokes, and this led to a total for stroke-related costs amounting to US $53 billion between 2017 and 2018 [7]. Risk of first stroke is twice as common in African Americans than for Caucasians [7]. Risk of stroke increases with age; however, 38% people hospitalized with stroke were less than 65 years old [7]. The 2017 NIS data showed a mortality rate of stroke at 3.1% [8].

World economic and social burden of stroke

In terms of global data, in 2017, there were 24.1 million stroke cases. This led 15.7 million additional disability-adjusted life years (DALYs) and 700,00 more stroke-related deaths compared to 2016 data [9, 10].

Current issues with COVID

The most recent WHO report at the time of writing of this article showed that global cases remained stable between September 12 and 18, 2022. A total of 3.2 million new cases were reported, and 9800 deaths were reported [11]. As of September 18, there have been 609 million confirmed cases and 6.5 million deaths globally [11]. There were decreases or stable numbers in the amount of COVID cases across all six WHO regions [11]. The most prevalent variant is a descendent of the Omicron variant BA.5 with 76.6% global prevalence and next is BA.4.X with 7.5% prevalence. There are six Omicron variants that are being monitored due to various mutations that are affecting the spike protein, receptor-binding domain [11]. The current data on the vaccines continues to show continued reduction in vaccine effectiveness against the Omicron variant against severe disease, symptomatic disease, and infection compared to initial COVID strains [11].

Inflammatory cascade of COVID

There is evidence that suggests COVID induces a hypercoagulable state in the body, which can be seen with elevated D-dimer, fibrinogen, factor VIII, von Willebrand factor, decreased antithrombin, and TEG results [12]. There are other factors that may contribute to the hypercoagulable state in severe COVID hospitalizations (immobilization, mechanical ventilation, central venous access devices, and nutritional deficiencies) [12]. However, this discussion will focus more on the connection between COVID-induced inflammation and thrombosis. In the COVID-induced pro-inflammatory state, there have been high levels of C-reactive protein, lactate dehydrogenase, ferritin, IL-6, and D-dimer levels reported [13]. Current research believes that COVID-19 enters the alveolar epithelium through the ACE2 receptors and initiates the pro-inflammatory response [14]. There are many parts of the pro-inflammatory response that there is ongoing literature with regard to COVID.

First, there is evidence of localized intravascular coagulopathy in the pulmonary vasculature due to the severe alveolar inflammation which progresses to a more systemic form later [14, 15]. This is also correlated with many COVID-19 patients meeting the threshold for disseminated intravascular coagulopathy [14, 16].

Next, there is evidence of excessive cytokine release in younger patients with severe illness and no preexisting conditions. In these patients, cytokines could cause thrombosis by activation neutrophils, monocytes, and endothelium [14].

Endotheliitis is another proposed mechanism for the pro-thrombotic state in COVID. Endothelial activation has been seen in COVID patients and can be caused by cytokines, complement, or direct infection of endothelial cells by SARS-CoV-2 [17]. The evidence of endothelitiis in COVID patients is supported by elevated levels VWF and FVIII [14, 18].

Some studies of ICU patients with COVID-19 have shown increased populations of CD14 + and CD16 + monocytes that produce IL-6 and TNF-alpha in the blood [19, 20]. Specifically, monocytes could induce a pro-thrombotic state through upregulating the expression of tissue factor (TF) which could induce a coagulation cascade via PAR signaling [19, 21].

Neutrophil extracellular traps (NETs) are extracellular fibers made up of DNA from neutrophils that bind to pathogens. In one study, patients and especially hospitalized and ventilated patients were found to have elevated cell-free DNA, myeloperoxidase-DNA, and citrullinated histones which suggests elevated NETs in these patients [22]. This is relevant to a pro-thrombotic state due to recent literature linking NETs to pulmonary disease and thrombo-inflammation, and NETs might be an underlying cause of the cytokine storm associated with COVID-19 infection [19, 23].

In COVID-19 patients, research has shown complement hyper-activation and association with increased C5a and severe disease [24]. Complement over-activation may be a causative agent of cytokine storm as well. Biopsy findings in patients have shown hyaline thrombi in the lungs and the skin with a complement deposit [19, 25].

Finally, the effects of COVID-19 on the renin angiotensin system (RAS) are significant as well. COVID-19 uses its S-glycoprotein to bind to ACEII receptors in the lung alveolar epithelial cells. This receptor is the homologue of ACE which is key component of RAS. ACE cleaves angiotensin I to generate angiotensin II (ANG II) which then binds to angiotensin type 1 receptor (AT1R). The overall effect is vasoconstriction and increased blood pressure. ACEII, however, inactivates angiotensin II and vice versa which leads to the overall effect of vasodilation. After COVID-19 binds to ACE2, it leads to the internalization of that receptor. This takes away its key role in regulating angiotensin II levels and leads to overactivation of the angiotensin type 1 receptor causing hypertension and lung injury [19, 26]. The angiotensin type 1 receptor has also been implicated in cytokine storm because it stimulates IL-6 release. ANGII and its activation of AT1R are implicated in hypercoagulability by being inducers of tissue factor and plasminogen activator. This may also explain why people with comorbidities fare worse with COVID-19 infections due to the fact that they already have lower baseline ACEII levels which is worsened by infection [19, 27].

Stroke and COVID

The body's inflammatory response to COVID-19 has many avenues with which it promotes a hypercoagulable state. It is interesting to further explore how that hypercoagulable state leads to stroke etiologies.

One molecule of interest that has also been seen as a therapeutic target is the nod-like receptor family pyrin domain-containing 3 inflammasome (NLRP3) which is overactivated in COVID-19. This receptor interacts with the viral viroporin protein 3a and leads to an inflammatory cascade that releases the cytokines interleukin-1β (IL-1β), interleukin-18 (IL-18), pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) [19]. In stroke, the NLRP3 inflammasome activates the immune system as well and contributes to promoting further plaque instability by increasing macrophages, neutrophils, lymphocytes, and vascular smooth muscle cells [28]. Activation of NLRP3 is greater because the NLRP3 is basally activated in patients who are immunocompromised and have diabetes and obesity [29]. This inflammasome could be implicated in the contribution of such risk factors for higher rates of stroke in COVID-19 patients. Some pharmacological therapies that may have benefits in patients that target NLRP3 include statins and colchicine [30, 31].

Proteolytic enzymes such as matrix metalloproteinases and cathepsin cysteine proteases are secreted by macrophages in response to inflammation, and they cause damage to the extracellular matrix which could lead to thromboembolism [32]. Another interesting biomarker that provides evidence for the connection between stroke and COVID-19 is the presence of increased expression lectin-like oxidized lipoprotein 1 receptor (LOX-1) in COVID-19 patients. The expression of this receptor is correlated with increased reactive oxygen species and has been shown in models to increase the risk of stroke and restenosis [33]. NETs which were mentioned in the introduction as a part of the pathogenesis of stroke also could play a role in COVID-19-induced stroke. Autopsy studies of patients with COVID-19 have shown the presence of NET-containing microthrombi [34]. The balance between coagulation and fibrinolysis is disrupted in COVID-19 promoting a pro-thrombotic state. Increased D-dimer levels and fibrinogen along with heparin resistance and the failure of other thrombolytic treatments have been observed in COVID-19 patients suggesting that the virus promotes fibrinolytic shutdown [35–38]. Biomarkers of anticoagulation like protein C, protein S, and antithrombin were also found to be lower in COVID-19 [39].

COVID, stroke, and comorbidities

The interplay between stroke and COVID-19 is exemplified by the coexistence of comorbidities. Diabetes mellitus patients have been shown to be at increased risk for stroke and COVID-19 complication. The mechanism behind the increased risk for COVID-19 comorbidities includes increased ACE-2 expression, increased furin, impaired T-cell function, and increased IL-6 [40–44]. ACE-2 and IL-6 are both mechanisms that have been mentioned above in increasing the hypercoagulable state in the COVID-19 patients as well. Hypertension is also a common comorbidity of COVID-19 and stroke patients. The impact of hypertension on increased ACE-2 expression might contribute to increasing the risk of stroke in patients with hypertension who are diagnosed with COVID-19 as well.

Conclusion

The main point that we can gleam from the data is that among our cases, the narrative that fits most patients for COVID-19 and stroke is that they come to the hospital for COVID and then subsequently develop a stroke. The mechanisms by which COVID induces stroke is not completely understood, but current research is looking into COVID-induced cytokine storms, thrombosis, extrinsic and intrinsic coagulation pathway activation, platelet activation, endothelialitis, and neutrophil extracellular traps (NETs) [45]. Also, among our cases, hypertension was prevalent in more patients than diabetes among all categories. This finding has been corroborated across other case and systemic reviews [5, 46]. Some interesting findings that we could not make conclusions on were the stark gender differences between the STC and CAS categories due to the small number of patients in each category. It would be a future area of study to find larger data sets of these categories to see if the gender differences are holding up with STC being mostly females and CAS being mostly males. If the gender difference holds up in a larger data set, this could be due to gender differences in seeking care [47], or maybe there might be an underlying physiological mechanism involved.

Abbreviations

COVID/COVID-19	Coronavirus disease
CIS	COVID-induced stroke
STC	Stroke then COVID
CAS	COVID and stroke
NIHSS	National Institute of Health Stroke Scale
Afib	Atrial fibrillation
AHA	American Heart Association
WHO	World Health Organization
NIS	National Inpatient Sample
ICU	Intensive care unit
NETs	Neutrophil extracellular traps
TEG	Thromboelastography
TF	Tissue factor
VWF	Von Willebrand factor
FVIII	Factor VIII
RAS	Renin angiotensin system
ACE	Angiotensin-converting enzyme
ANGII	Angiotensin II

NLRP3	Nod-like receptor family pyrin domain-containing 3 inflammasome
IL-1β	Interleukin-1β
IL-18	Interleukin-18
IL-6	Interleukin-6
PAMPs	Pathogen-associated molecular patterns
DAMPs	Damage-associated molecular patterns
LOX-1	Lectin-like oxidized lipoprotein 1 receptor

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Authors' contributions
MM designed the study, collected the data, and participated in the analysis of the data. MM also wrote the initial draft of the manuscript. MP and JP assisted in further interpretation of the data and provided edits for subsequent revisions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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