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Letter to the Editor

# Impact of COVID-19 on Future Ischemic Stroke Incidence

A B S T R A C T

With the ever-expanding population of patients infected with SARS-CoV-2, we are learning more about the immediate and long-term clinical manifestations of coronavirus disease 2019 (COVID-19). Ischemic stroke (IS) is now one of the well-documented additional clinical manifestations of COVID-19. Most COVID-19 related IS cases have been categorized as cryptogenic or embolic stroke of undetermined source (ESUS), which are most often suspected to have an undiagnosed cardioembolic source. COVID-19 is known to also cause cardiac dysfunction, heart failure, and atrial arrhythmias (AA), but the long-term impact of this cardiac dysfunction on stroke incidence is unknown. With millions afflicted with COVID-19 and the ever-rising infection rate, it is important to consider the potential long-term impact of COVID-19 on future IS incidence. Accomplishing these goals will require novel strategies that allow for diagnosis, data capture, and prediction of future IS risk using tools that are adaptable to the evolving clinical challenges in patient care delivery and research.

## 1. Introduction

Several reports have now confirmed that the severe acute respiratory syndrome coronavirus −2 (SARS-CoV-2) infection, coronavirus disease 2019 (COVID-19) is associated with thrombotic events, including ischemic stroke (IS) [1–7]. A possible association between COVID-19 and stroke was first noted early in the pandemic in a retrospective case study published from China [4]. Since this initial publication, several larger retrospective cohorts have reported stroke incidences ranging from 0.9% to 3.3% [3,5–8]. In fact, in comparison to influenza A-B, the odds of developing a stroke have been reported to be seven fold higher with COVID-19 [3]. Patients with COVID-19 that have stroke tend to be more severely affected and have a higher mortality rate than case matched control IS patients [9]. IS tends to occur in those with more medical comorbidities [10], but can also occur in patients without preconditions and/or under the age of 55 [11–13]. Thus, even healthy people are at risk. COVID-19 is thought to lead to increased thrombotic events such as IS secondary to hypercoagulability caused by systemic inflammation, viral-induced endothelial damage, and cardiac dysfunction [8,14–17]. Multiple studies report that most COVID-19 related IS events are cryptogenic or an embolic stroke of undetermined significance (ESUS), which is a stroke subtype thought to be caused mostly by an undiagnosed cardioembolic source [14,18]. Cardiac disease is one of the most frequent complications occurring in COVID-19 patients [19,20], and the damage can be long-standing even after recovery from COVID-19 [21]. Given the increasing prevalence of COVID-19, its predilection for causing cardiac damage, and its known propensity for cryptogenic/ESUS IS, it is important to consider the future impact of COVID-19 on future stroke incidence.

## 2. COVID-19 related stroke and association with COVID-19 related cardiac damage

As mentioned previously, a higher proportion of COVID-19 related IS events have been classified as cryptogenic or ESUS [14,18]. Cryptogenic or ESUS strokes are thought to occur in the setting of thromboembolic predisposition and involve an unknown embolic source. In the landmark trial NAVIGATE-ESUS, 73% of ESUS were eventually attributed to a cardiac source, with 37% associated with atrial cardiopathy and 36% associated with underlying ventricular disease [18]. COVID-19 patients may suffer several cardiac complications including ventricular and atrial arrhythmias (AA), myocardial injury, acute coronary syndrome, and cardiomyopathy [19,20]. These can also result in embolic sources for thrombi and lead to ESUS [ 3,4]. Based on these findings, COVID-19 patients may represent a perfect set-up for ESUS due to the increased risk of AA, cardiomyopathy development, and COVID-19 associated coagulopathy.

Recent evidence suggests that COVID-19 cardiac complications are due to an orchestrated inflammatory response leading to cardiac dysfunction [19] and sympathetic surge [22]. The massive systemic inflammatory response or “cytokine storm” seen in sepsis caused by COVID-19 could also be a significant contributor [19,20]. Cardiac complications associated with COVID-19 were reported in Chinese cohorts in early 2020 and were found to be most notable in the subset of patients who were most critically ill [19,20,23] and had pre-existing risk factors for cardiac disease such as hypertension and obesity [19,20]. A global survey of medical providers reported that 21% of medical providers found atrial fibrillation within their patient population hospitalized with COVID-19, and 5.4% reported atrial flutter [24]. AA has also been reported to be a frequent reason for electrophysiology consultation in a hospital heavily impacted by COVID-19 [25]. Cardiac arrhythmias were detected in up to 17% of patients with incidence increasing to greater than 40% among critically ill patients [19,20]. Analysis of electrocardiograms (ECG) of COVID-19 ICU (n = 69) and non-ICU patients (n = 46) by Colon et al. revealed that around nalyzed the electrocardiograms (ECGs) of COVID-19 ICU patients (17% of their cohort developed an AA [5]. Furthermore, patients who developed an AA, such as atrial fibrillation and atrial flutter, often had a history of hypertension and/or obesity and were the most critically ill, requiring mechanical ventilation and vasopressor support [26]. These findings were further corroborated by a study in Pennsylvania, which reported that patients that developed atrial fibrillation while hospitalized had a higher

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mortality rate, were more likely to be in an intensive care setting, and more likely to have heart failure [27]. These studies suggest that the development of an AA is associated with greater morbidity and mortality within the COVID-19 population. The etiology of COVID-19 related AA is currently unclear and requires further research.

## 3. Limitations of current IS incidence data

Even with current data, there are still several knowledge gaps. Most reported studies have included data from hospitalized patients early during the pandemic. During this time, secondary to stay at home orders and possibly patients wanting to avoid healthcare facilities, stroke volumes decreased significantly [28]. Thus, a sub-group of patients with asymptomatic or mild COVID-19 symptoms and/or mild or transient neurologic deficits may not have been captured in current data sets. It is also important to consider that most hospitalized IS patients are now routinely screened for COVID-19 even if they do not have typical COVID-19 symptoms. As a result, patients who would otherwise be considered asymptomatic from COVID-19 are also being diagnosed with IS. More research is needed to determine if the presence of the SARS-CoV2 infection is always directly or indirectly the cause of the stroke even in asymptomatic COVID-19 cases or if there is a proportion of patients for which the COVID-19 infection is incidentally found through the public health screening. Also, we are still learning about the long-term implications of COVID-19 related cardiac disease, inflammation, and hypercoagulability. Without these questions being addressed, it is more difficult to formulate a comprehensive stroke prevention strategy for COVID-19 patients. Thus, we will not be able to determine which COVID-19 patients are at increased risk of having an IS, nor will we be able to effectively target the mechanism behind the IS (i.e. hypercoagulability, inflammation, cardioembolic/ESUS, or traditional stroke risk factors such as hyperlipidemia, hypertension, diabetes, and atherosclerosis).

This information is needed to provide evidence-based guidance on the most effective forms of stroke prevention in this higher risk population. Several randomized trials further investigating the role of anticoagulation in COVID-19 for prevention of thrombotic events are currently pending (NCT04345848, NCT04362085, NCT04406389). With millions of patients contracting COVID-19 and the estimated risk of IS and persistent cardiac dysfunction in COVID-19 patients, there could be a significant number of new IS cases related to COVID-19, particularly those with pre-existing conditions [1,26].

## 4. Strategizing for the future

Assessment of the long-term risk of IS and cardiac disease that increases risk of ESUS and cryptogenic IS will provide vital information for future risk stratification of COVID-19 patients. Patients who develop severe cardiac complications such as myocardial injury, acute coronary syndrome, or cardiomyopathy may experience further compromise of cardiac function and later development of an AA as natural progression of these cardiac complications [19]. These findings suggest that COVID-19 survivors, both those with and without acute onset of cardiac complications, may be at higher risk of developing an AA in the future. This could further increase their risk for ESUS and cryptogenic IS. Addressing this need could be accomplished with COVID-19 database registries, long-term observational studies of COVID-19 survivors, and studies comparing cardiac and stroke outcomes in COVID-19 patients. At this time in the developing COVID-19 pandemic, long-term follow-up on large cohorts of COVID-19 patients has not yet been reported. However, we do know that patients have been reported to have persistent symptoms even after SARS-CoV2 RNA is undetectable after recovery [21,29].

In addition to capturing data on traditional stroke risk factors and assessment for coagulopathies, COVID-19 registries and observational studies should include clinical outcome variables that can be used to detect patients at highest risk of having an ESUS/cryptogenic IS secondary to COVID-19 as well as provide methods for tracking long-term outcomes. Previously established clinical markers associated with left atrial abnormalities, such as the P-wave terminal force in lead V1 (PTFV1), may be of use in COVID-19 patients, as they serve as indicators of long-term IS risk independent of clinically diagnosed atrial fibrillation [30]. Prospective studies may be designed to assess the risk of AA in COVID-19 patients via outpatient continuous cardiac monitoring in the form of loop recorders or event monitors. Development of reliable methods to monitor these patients in the immediate setting and long-term will be instrumental in the understanding of how COVID-19 may increase the risk of ESUS/cryptogenic IS. This will require novel approaches for data collection and patient participation to compensate for the decreases in healthcare utilization during the pandemic [28]. For example, stay at home orders in Denmark not only reduced diagnosis of new onset atrial fibrillation, but were also associated with increased stroke incidence and mortality related to atrial fibrillation[31]. This demonstrates that adaptions for patient monitoring and systems of care are essential. Other forms of healthcare access such as telemedicine have proven to be successful as demonstrated by the TeleCheck-AF program [32]. In addition, the COVID-19 Symptom study is another example of using remote technology to capture outcomes data in large population of COVID-19 patients (https://covid.joinzoe.com/us/data).

## 5. Conclusion

The COVID-19 pandemic has ushered in a new era of healthcare. It is important to prepare for continued evolution of acute management practices and the discovery of potential long-term disease manifestations that can evolve in COVID-19 survivors, including IS.

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