



Prevalence, Risk Factors, and Management of Stroke in Patients with COVID-19 Infection: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

In the current pandemic, it is imperative to comprehend and advance a search forward to explore the pathogenesis of stroke in COVID-19 infected patients. In this review, we have discussed the prevalence of stroke in COVID-19 infected patients and different risk factors associated with the stroke in COVID-19. We also presented a comprehensive review on management of Stroke Patients during the COVID-19 pandemic. The COVID-19 positive patients with stroke should be treated in a designated COVID-19 health care center as per the guidelines. Study also showed that older patients with a history of cardiovascular diseases, prothrombotic state, smoking, and infection significantly had a higher likelihood of stroke incidence. The study revealed that effective treatment of COVID-19 and reduction of the inflammatory conditions may seem to be the way forward to minimize the symptomatic stroke associated with COVID-19 infection, and rehabilitation of Stroke patients should be optimal during a pandemic.

Keywords: Coronavirus; COVID-19; stroke; management; risk factors.

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1. INTRODUCTION

The outbreak of the novel coronavirus (nCoV) has led to a pandemic and created a health crisis all over the globe. The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Despite strict containment measures, COVID-19 spread quickly and reached across the world and till this day it accounts for 175,987,176 confirmed cases and 3,811,561 deaths globally as of 14 June 2021 [2]. The receptor-binding domain (RBD) of the surface protein of coronavirus binds to the angiotensin-converting enzyme-2 (ACE2) receptor on the cell surface make easy entry to the host cell and release its single-stranded RNA (ssRNA), after that, the virus translates its own RNA replicase, and construct the RNA replicase-transcriptase complex using an RNA template.

The prevalence of stroke among COVID-19 infected patients increases mortality rate [3]. A prior study reported that the incidence of cryptogenic stroke was double in COVID-19 infected patients as compared to non-COVID-19 infected patients. COVID-19-related stroke represented a unique mechanism linked with a superior likelihood of early death [4]. Also, it was found that in ischemic stroke, COVID-19 infection itself acts as a risk factor. COVID-19 positive patients emerge to have a higher risk of acute stroke as compared with influenza patients [5,6].

1.1 Prevalence of Stroke in COVID-19 Infected Patients

A recent systematic review study on COVID-19 patients revealed that ischemic stroke incidence was ranging from about 1 to 2.8% [7]. Astonishingly, in COVID-19 patients with stroke were found significantly associated with elevated severity of acute respiratory symptoms and mortality [8,9]. Prior study also showed that older patients with a history of stroke, smoking, and low *Body Mass Index* (BMI) or underweight significantly have higher likelihood of stroke incidence [8].

1.2 Risk Factors Associated with Stroke in COVID-19

1.2.1 Cardiovascular diseases in COVID-19 patients

Severe heart injury, cardiac arrest, and arrhythmia had been observed in many COVID-19 patients [10,11]. Underlying mechanisms

might be involved in cardiac arrest are acute inflammatory responses, direct myocardial injury, plaque instability, hypercoagulability, and increased metabolic requirements. These mechanisms may lead to cardiac arrest due to myocardial infarction or irregular heartbeat, or both [10,12]. Several reports indicate that age and comorbidities, such as high blood pressure, heart disease, and diabetes are associated with elevated mortality in Coronavirus infected patients [11,13].

A recent study on stroke patients with COVID-19 infection demonstrated that patients had a history of smoking, alcoholism, hypertension, and elevated blood glucose levels upon hospital admission [14]. A recent meta-analysis study (included 76,993 patients) revealed that the incidence of stroke, hypertension, diabetes and smoking history in COVID-19 patients were 2.11%, 16.37%, 12.43%, and 7.63% respectively [15]. The association between stroke and inflammation is multifaceted. Inflammation may indirectly or directly lead to heart attack or stroke [16,17]. The cytokines secretion that causes tissue damage has been associated with these conditions and neuroprotective agents have been tested to lower the inflammation after stroke [18,19]. Many inflammatory responses had been reported in the stroke patients, with COVID-19 infection. These responses include the higher neutrophil and *white blood cells* (WBCs) counts, elevated C-reactive protein (CRP) levels and poor lymphocyte counts [14]. Moreover, level of cytokine had been observed to be elevated among COVID-19 patients in comparison with controls and also it was observed that the interleukin (2, 6, and 10) levels, granulocyte colony-stimulating factor (GCSF), Interferon gamma-induced protein 10 (IP10), *monocyte chemoattractant protein-1* (MCP1), tumor necrosis factor-alpha (TNF α), and macrophage Inflammatory Protein-1 alpha (MIP1A) levels were found higher among ICU COVID-19 patients [13]. These extreme cytokine activities can lead to severe inflammation and thrombotic imbalance in addition to vascular inflammation in existing vessel wall plaques [6], however these events need further in-depth studies.

1.2.2 The prothrombotic state and COVID 19

The major concern arises on prothrombotic state (hypercoagulability) during active COVID-19 disease. Data show that D-dimer levels are elevated in these patients. It is unclear whether this is part of sepsis or is related to the

inflammatory process. However, this raises concerns about the different pathways that lead to cardiovascular problems. In a small number of patients with acute respiratory distress syndrome and acute pneumonia, the study reported the benefits of venous thrombolysis via tissue plasminogen activators (TPAs) in a predetermined protocol. A recent report of antiphospholipid antibody positive in COVID-19 patients demonstrated that this possible mechanism might contribute to the frequency of stroke in COVID-19 infected patients [20,21].

1.2.3 COVID-19 and the ACE 2 pathway

Coronavirus enters into the host cell with the help of Angiotensin converting enzyme-2 (ACE-2) receptor. ACE-2 is mostly expressed in the epithelial cells of the heart, lungs, kidneys, intestines and blood vessels. ACE-2 is more closely related to angiotensin-II and that the cleavage of angiotensin-II has the opposite effect on angiotensin-II, i.e., protection of the heart, and that causes cardiac stimulation. ACE-2 is also found in the brain and can modulate spontaneous responses [22]. The neural orientation of the virus affects the nerve tissue, which can modulate the vascular responses. A recent study has raised concerns that ACE-inhibitors acting on the ACE-1 pathway may exacerbate the disease by controlling ACE-2 and allowing more viruses to enter the host cell [23-25].

1.3 Stroke and Infection

The contribution of infection in the incidence of stroke has been described in ischemic stroke [22,26]. The relationship between stroke and chronic inflammation between *Helicobacter pylori* and *Chlamydia pneumoniae* has been evaluated using serological studies [27,28]. Many viruses like EBV, HIV, CMV, HCV, and HSV are associated with stroke, particularly in children and adolescents. The vasculitis process can also be caused by the coronaviruses that cause *severe acute respiratory syndrome* (SARS), either by being haematogenous with the wall of the uterus or by the possibility of direct neurological intervention.

1.3.1 Neuroinvasion by coronaviruses

Infectious diseases of previously reported SARS and MERS-CoV have been found to cause neurological complications, including stroke. Autopsy samples established the incidence of

the SARS virus in the brain, indicating neural orientation. Nonetheless, only a few reports are currently available because the frequency of the severe conditions is relatively small compared to the scale of the recent COVID-19 pandemic. Coronaviruses can enter the central nervous system (CNS) in rats through the nasal passages. This is supported by the observation that odor loss is a symptom of the recent pandemic of COVID-19 [29-31]. ACE-2 receptors that transmit the virus to the host cell, are thought to be present in the central nervous system. Postmortem data of COVID-19 patients provided insight into the risk of virus attack. In a recent post - mortem examination of three COVID-19 patients and multicellular insufficiency, the study demonstrated indications of an endothelial inflammatory response [32]. Though the human brain has not been postmortem, the possibility of a process similar to "endotheliitis" and "vasculitis with secondary vascular flow" between stroke patients and COVID-19 cannot be ruled out. This explains the incidence of ischemic stroke and ICH in this population.

1.4 Management of Stroke Patients during Pandemic of COVID-19

The management of stroke during the COVID-19 pandemic can be challenging because caring for COVID-19 patients involve pathways to quickly assess and reduce delay in treatment when the health system may already be overloaded. Suspected and infected patients need treatment in hospitals designated for COVID-19, which can make stroke management more difficult since the hospitals may not be fully prepared for stroke management. Inside hospitals, there should be facilities that include special corridors, advance notice to the stroke management team, accessibility of monitoring, imaging, screening, and availability of proper personal protective equipment for health care workers. Guidelines for the management of patients who have suffered a severe stroke during COVID-19 were recently published. These studies introduced the concept of a "protected stroke code" to reduce the delay and increase safety of stroke management. The principles of stroke management are defined to assist teams in stroke management [4].

For effective management, each hospital must establish isolated screening areas prior to emergency COVID-19. A suspected stroke patient should be screened immediately with a high priority COVID-19 risk and a pre-selected

rapid checklist for active disease (infection screen). The stroke management team must be notified instantly and every patient must complete a self-certification form. "Infection control screen" must include assessment of fever, cough, headache, loss of smell, gastrointestinal symptoms, diarrhea vomiting, chest pain, shortness of breath, and myalgias [33,34]. Management of Stroke Patients during COVID-19 is categorized as follows:

1.4.1 COVID-19 suspect patient

A. Patients suspected of having COVID-19 infection should be monitored at the COVID-19 designated health care centers until test reports are on hand. "Standard stroke unit" care is recommended, and consult with stroke specialist/neurologists if possible. The patient will be transported through the designated corridor with the safety of the health system and health care provider. This safety idea has lately been called the "protected stroke code". As time is of the utmost importance in stroke management, therefore hospitals must arrange stroke faculty/neurology, pandemic management team, and the hospital management to identify suitable areas/corridors for stroke patients, also isolate the imaging and angiography areas, and set up the emergency treatment as soon as possible. In the settings, the patient's swabs for the COVID-19 test should be sent immediately and based on the test results, the patient should be transferred to the internal stroke unit/ neurology unit [35].

If the patient lives in a hospital that is not designated for COVID-19, refer the patient to a hospital designated for COVID-19 on the advice of the Ministry of Health, where stroke patients can be treated locally. Moreover, an additional stroke management team must be arranged so that patients can avail the necessary treatment during this qualifying period. However, in cases where this is not possible in a timely manner or in a hospital remotely designated for COVID-19, in view of the time-narrow nature of stroke management and the presence of patients inside the appropriate time frame for treatment of stroke, the patient may be treated at the main contact hospital (hospital may require acute stroke contact) to control the risk [34].

1.5 Management of Stroke Patients with COVID-19 Negative

Once the stroke management team has been notified about COVID-19 negative status, and

then patients will be transferred to the core emergency room or straight to the computed tomography (CT) examination room according to local hospital protocol. After that standardized acute stroke treatment in a timely manner. They should be prudent in the application of general anesthesia and comply with the emergency support team to develop a protocol that does not significantly delay the processing time that allows for rapid incubation. However, if the patient is later found to have COVID-19, the instructions should be followed immediately.

1.6 Management of Stroke Patients with COVID-19 Positive

In confirmed COVID-19 positive case, the patient must be admitted to the designated COVID-19 health care center or hospital for emergency management of stroke as per the local health care guidelines. Stroke, especially those caused by blockage of large blood vessels, is associated with certain thrombotic conditions, and instability or acute hospital care can exacerbate heart attack complications. The risk of heart attack is higher due to the inflammatory thrombotic condition in asymptomatic or induced COVID-19 infection. Therefore, special attention should be paid to the prevention of thrombosis in this population. In patients undergoing treatment for venous thrombosis, thrombolytic prophylaxis should begin as early as 24 hours after thrombolysis, and repeated CT scans may indicate no signs of bleeding or craniotomy. Patients who do not undergo intravenous thrombolytic therapy, can be admitted for thromboprophylaxis initiation [3,36]. Covid-19 Patients with acute stroke who undergo non-contrast computed tomography (NCCT) should also undertake chest CT to detect patches of peripheral pneumonia indicating COVID-19 infection. All COVID-19 patients without contraindications, and venous thromboembolism (VTE) prophylaxis should be referred to IPC. Patients who are already taking anticoagulants should not receive an overdose of pharmacological prophylaxis for venous thromboembolism. Drug selection may depend on local guidelines or institutional preferences, however, in severe cases variable pharmacokinetics resulting from COVID-19 should be considered. Some centers began routine evaluation of coagulation factors using fibrinogen and D-dimer, and introduced a superior level of thromboprophylaxis regimes and remedial anticoagulation in selected COVID-19 infected patients [34].

It is advisable to assess platelet count in COVID-19 patients prior to venous IV-thrombolysis due to cytopenia, which is more common in patients with COVID-19. Moreover, in stroke patients with COVID-19 infection, routine use D-dimer during the treatment is an effective option [37]. Regular monitoring of blood pressure is required with the goal of maintaining a <110 diastolic and <180 systolic blood pressure (BP). If there is a shortage of nursing staff due to the deportation of non-neurotic COVID-19 patients, continuous blood pressure monitoring with low manual blood pressure testing within the first 24 hours may be relied upon. Monitoring and managing complications should be followed according to the guidelines. The risk of developing low molecular weight heparin (LMWH) and antiplatelets within the initial 24 hours of treatment with IV-alteplase is uncertain and should be avoided if no other medical conditions are present [34,38].

Existing international guidelines recommended intravenous thrombolysis for all the patients who can be treated within 3-4 hours of the onset of symptoms. For mechanical thrombectomy, the recommendation is that the existing clinical guideline for inclusion criteria be followed and that proper precautions be taken for all individuals within the angiography suite [39]. All members of the stroke management team should be fully responsive to safety procedures and adhere to a strict protocol. Moreover, it is advisable to allow the angiosuite in advance and disinfect the angiosuite after each procedure, if possible at the designated area for such patients during this infectious disease. To minimize the utilization of PPE kits and the exposure risk of health workers, only the minimum staff required and the fundamental principles of post-stroke care will be applied in the emergency ward [34].

COVID-19 viruses bind specifically to the angiotensin converting enzyme (ACE) receptor. There is concern about the use of angiotensin II receptor blockers (ARBs) or ACE inhibitors; however, there was no recommendation to stop ARBs or ACE inhibitors as antihypertensive medications during post-stroke management. Other medications that may be considered are diuretics, calcium channel blocker (CCB), and other types of antihypertensive medications [40]. Stroke patients with COVID-19-positive requires immediate neuro-surgical interventions, and all the suitable measures in accordance with the guidelines need to be in place to ensure sufficient safety of the health care system and

the patient. Designated operating theaters (OTs) in the local health care system should be considered and standard protocols for sterilization must be followed after each procedure.

2. REHABILITATION AND FOLLOW-UP ADVICE

Rehabilitation of Stroke patients should be optimal during a pandemic. However, very restricted guidance must be available to stroke teams to provide stroke rehabilitation services. A physiotherapist, psychologists, and speech therapists have a special role in the rehabilitation of stroke patients. However, in the event of the current pandemic, these services may not be optimally delivered and, based on the urgent needs of the patient; special attention should be given to reducing staff exposure. For COVID-19 infected patient rehabilitation activities in hospital wards or in home required further guidelines. Appropriate precautions are recommended to treat these stroke patients. Remote rehabilitation facilities should be used for maximum availability during these times.

It may be wise to carry out an angiogram during the initial assessment in the same crisis situation. If facilities like echocardiography (ECG) and Doppler (carotid) are accessible in the designated COVID-19 area for monitoring, it is also possible to obtain information about the heart conditions. Follow-up risk assessment should be conducted using routine blood tests, ECG, and imaging. Patients should begin taking statin, aspirin, and other specific classes of medications based on risk factors and potential triggers. Anticoagulation is initiated only if there is some exception in patients with cardiac arrest. The patient should be provided with appropriate medication at their home. Patients will be discharged from the hospital once the condition becomes stable and patients with COVID-19 should be given instruction and consistent, optimal counseling. Follow-up visits can be made by means of telemedicine services wherever possible during the time of pandemic [6, 34].

3. CONCLUSION

The COVID-19 positive patients with stroke should be treated in a designated COVID-19 health care center as per the guidelines. Data collected from stroke patients in large, multi-center groups may shed more light on current pandemic events, behaviors, etiology,

biomarkers, and outcomes of stroke patients. Grippingly, knowing how many asymptomatic patients with COVID-19 who have stroke is necessary to ascertain a relationship or causal association between COVID-19 and stroke. In this pandemic, it is imperative to comprehend and advance a search forward to explore the pathogenesis of stroke in COVID-19 infected patients. Therefore, we should be prepared to deal with the complications of the current global health crisis, and it is crucial to effectively understand the nature of stroke and its causes. Effective treatment of COVID-19 and reduction of the inflammatory conditions may seem to be the way forward to minimize the symptomatic stroke associated with COVID-19 infection.

CONTENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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