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Frequency and Clinical Manifestations of Lacunar Strokes in Patients with COVID-19

Sevara Mukhamedkarimova[1], Murodbek Avezov[2], Nargiza Ergasheva[3], Ra'no Magzumova[4]

[1]Independent researcher
Affiliation: Center for Development of Professional Qualification of Medical Workers, Uzbekistan
ORCID: https://orcid.org/0009-0003-9186-716X
Email: sevara.rustamovna86@mail.ru
[2]Independent researcher
Affiliation: Center for Development of Professional Qualification of Medical Workers, Uzbekistan
ORCID: https://orcid.org/0009-0001-5243-1107
Email: docavezov@gmail.com
[3]Head of the Folk Medicine Course, PhD in Medical Sciences.
Affiliation: Center for Development of Professional Qualification of Medical Workers, Uzbekistan
ORCID: https://orcid.org/0009-0009-8278-7399
Email: nissoran921@gmail.com
[4]Independent researcher
Affiliation: Center for Development of Professional Qualification of Medical Workers, Uzbekistan
ORCID: https://orcid.org/0009-0003-0789-780X
Email: magzumovaranokhon@yahoo.com

ABSTRACT

The present study investigates the frequency and clinical manifestations of lacunar strokes (LS) in patients with a history of COVID-19 infection. A total of 194 patients diagnosed with LS were examined, of whom 110 (56.7%) had previously contracted COVID-19, while 84 (43.3%) had not. Participants were stratified into two groups to assess the potential relationship between COVID-19 and lacunar stroke characteristics. Clinical evaluation included comprehensive neurological assessment, radiological diagnostics, and standardized rating scales for neurological and cognitive function. The findings revealed a higher proportion of lacunar strokes among COVID-19 patients, especially among males and individuals aged 18–44. COVID-19 patients with LS also demonstrated a higher prevalence of motor-sensory deficits, asthenic syndrome, and anxiety-depressive symptoms. Comparative analysis highlighted significant clinical and demographic differences between the COVID-positive and COVID-negative LS patients, indicating the potential influence of the viral infection on the pathophysiology and presentation of lacunar strokes. The study underscores the importance of timely neurological assessment in COVID-19 patients and the need for targeted rehabilitation and monitoring strategies.

KEYWORDS: COVID-19; lacunar stroke; ischemic stroke; small vessel disease; neurological complications; post-COVID syndrome; neuroimaging; stroke epidemiology; risk factors; rehabilitation.

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INTRODUCTION

With growing evidence of a relationship between the COVID-19 virus and stroke, attention has been drawn to the need to search for the possible neurological manifestations of the illness (Wei Lee et al., 2020). Other mechanisms suggested for why COVID-19 cases could develop strokes are related to proinflammatory cytokine storm activation and systemic cell-death/ apoptosis pathways leading to acute inflammatory processes in vessel walls. This condition may ultimately lead to increased vessel permeability and enhance the thromboembolism. COVID-19 infection could also increase thrombus size leading to total occlusion of supplying vessels of the brain. The gravity of the COVID-19 disease status so far has been linked through the systemic effects of the virus to chronic diseases which are widely recognized as stroke risk factors. Given the ambiguity of this relationship, this study in particular, aims to assess the frequency and clinical manifestations of lacunar strokes in patients with COVID-19 cases. To accomplish these objectives, the frequency of lacunar strokes and the details of the clinical manifestations of these strokes in general are reviewed (Nannoni et al., 2021).

The COVID-19 pandemic has had a devastating public health impact on the world's population and has resulted in a dramatic increase in mortality, disability-adjusted life years and years of life lost. With the increasing world-wide cases of individuals infected with SARS-CoV-2, this study attempts to describe the associated stroke burden and to elucidate the scientific mechanisms that could explain this association. Logically the putative link between COVID-19 and acute cerebrovascular events may be separated into a two-way relationship between the virus harming the cerebral vasculature directly and the resultant exacerbation of the mechanisms related to pro-inflammatory responses, endothelial dysfunction and thromboembolic events. Stroke together with other acute neurological undesirable events can be part of the presenting symptoms of COVID-19 infection.

MATERIALS AND METHODS

A clinical observational study was conducted involving 194 patients diagnosed with lacunar strokes (LS), with the objective of analyzing clinical features depending on prior exposure to coronavirus infection (COVID-19). Among the total participants, 108 were men (55.7%) and 86 were women (44.3%).

In accordance with the aims and objectives of the research, all patients were stratified into two groups based on whether they had a confirmed history of COVID-19 infection:

1. **Main Group (MG)** – This group consisted of 110 patients (56.7%) who had experienced lacunar stroke following a confirmed case of COVID-19. The gender distribution included 69 men (62.7%) and 41 women (37.2%), yielding a gender index of 1.7, indicating a predominance of male patients. Age distribution within the group was as follows:
   - Young adults (18–44 years): 48 patients (43.66%)
   - Middle-aged adults (45–59 years): 32 patients (29.1%)
   - Elderly (60–74 years): 30 patients (27.3%)
2. **Comparison Group (CG)** – This group included 84 patients (43.3%) with lacunar stroke who had not previously contracted COVID-19. The gender distribution comprised 39 men (46.4%) and 45 women (53.6%), resulting in a gender index of 0.9, indicating a slight predominance of female patients. Age distribution was as follows:
   - Young adults (18–44 years): 9 patients (10.7%)
   - Middle-aged adults (45–59 years): 41 patients (48.8%)
   - Elderly (60–74 years): 34 patients (40.5%)

All patients were diagnosed and evaluated based on standardized neurological and radiological criteria for lacunar stroke. Demographic, clinical, and epidemiological data were collected through structured interviews and medical records. The COVID-19 status was confirmed using polymerase chain reaction (PCR) testing and/or documented clinical diagnosis. The study was conducted in compliance with ethical standards and approved by the institutional ethics committee.

DIAGNOSTIC AND ASSESSMENT METHODS USED IN THE STUDY

№	Diagnostic Methods	Type of Examination
1	Clinical Methods	Collection of complaints and anamnesis; Examination of somatic status
		Neurological status assessment
		Verification methods and severity assessment of COVID-19 infection
2	Assessment Scales	Comorbidity Index (CI)
		NIHSS – Neurological Symptom Severity Scale
		MFI-20 – Multidimensional Fatigue Inventory
		HADS – Hospital Anxiety and Depression Scale
		FAB – Frontal Assessment Battery
		MoCA – Montreal Cognitive Assessment
		Schulte tables for attention and performance stability
3	Laboratory Methods	General clinical
		Biochemical
		Coagulogram
		Markers of systemic inflammation
		Immunological
4	Instrumental	Pulse oximetry
		MSCT of the lungs
		Electrocardiography (ECG)
		Brain MRI
		Duplex scanning of extracranial segments of brachiocephalic arteries
		Transcranial Doppler monitoring
5	Evaluation of Significance and Validity of Results	Statistical processing using Microsoft Excel and Statistica 6.0

BACKGROUND ON LACUNAR STROKES

Lacunar strokes are a type of ischemic stroke that occurs when blood flow to a small penetrating artery is obstructed, resulting in discontinuities in the basal ganglia, thalamus, internal capsule, and pons. These small penetrating arteries, known as lenticulostriate arteries, supply deep structures of the brain. Lacunar strokes arise in the territory of small perforating arteries that stroke from the main arteries, which may become occluded by atherosclerosis and lipohyalinosis. Lacunar strokes were believed to occur in small penetrating arteries, although more recent works suggest they can also occur in medium-sized arteries. Lacunar strokes account for about 12% of all strokes. Lacunar strokes most commonly affect people aged over 60. Hypertension and diabetes mellitus are strong risk factors for lacunar strokes. Lacunar strokes typically result in good functional recovery when there is no underlying cardiovascular disease (Finsterer et al., 2022); (Wei Lee et al., 2020).

Lacunar strokes are classified according to the location of the lesion. Lacunar strokes encoding the body of the text are classified as pure motor strokes with weakness in the contralateral upper and lower limbs. Lacunar strokes encoding the posterior limb of

the internal capsule produce an arpeggio-disconnection syndrome. Lacunar strokes encoding the thalamus are classified as pure sensory strokes with numbness of the contralateral face and body. Lacunar strokes encoding the field of Forel may be associated with chorea or dystonia. Lacunar strokes encoding the pons can cause symptoms such as ataxic dysarthria. Some lacunar strokes may not cause symptoms or only cause transient mild symptoms. Silent lacunar strokes are observed in up to 50% of elderly people and increase the risk of cognitive decline by up to three-fold.

Lacunar strokes are diagnosed with brain imaging. Non-contrast CT of the brain is typically the first-line modality. Non-contrast CT can rule out parenchymal hemorrhage but may result in normal findings for the first few hours after an ischemic stroke. Diffusion-weighted MRI is the most sensitive and specific imaging technique to diagnose lacunar strokes. Nonetheless, MRI is not suitable for emergency evaluations given its high cost, fluctuating availability, and longer duration of examination. Ultrasound study of the carotid arteries is the preferred non-invasive imaging method to evaluate the carotid arteries. MRA and vessels could visualize the internal carotid arteries, the major branches, and extra-cranial arteries.

4.1. Definition and Types of Lacunar Strokes

Lacunar stroke is the most common subtype of ischemic stroke in hypertensive population and is the second most common cause of ischemic stroke globally. Lacunar stroke was first described in a clinical study of a 61-year-old fisherman with dysarthria and unilateral weakness. It was then believed to be caused by the occlusion of single small penetrating arteries supplying deep structures of the brain, a phenomenon termed lipohyalinosis. Lacunar strokes are classified into the following 5 types. Pure motor stroke accounts for 30% of lacunar strokes, affecting the descending motor fibers in the posterior limb of the internal capsule or the pons. Pure sensory stroke accounts for 20% of lacunar strokes. This subtype can be caused either by contralateral ventrocaudal thalamic infarction or by lateral geniculate body infarction in the occipital lobe (Wei Lee et al., 2020). A combination of motor and sensory stroke is rare and accounts for approximately 5% of lacunar strokes. These infarcts are thought to involve the route of the thalamocortical fibers to the parietal lobe. Dysarthric and clumsy hand syndrome accounts for 20% of lacunar strokes. It results from infarction of the posterior limb of the internal capsule or the basal ganglia, causing contralateral dysarthria and hand clumsiness. These strokes have poor prognosis, and cognitive dysfunction may develop over time. Ataxic hemiparesis accounts for 10% of lacunar strokes and is presumed to be caused by infarction of the anterior limb of the internal capsule.

4.2. Pathophysiology of Lacunar Strokes

Ischemic stroke is the most reported CNS manifestation in COVID-19 patients (Wei Lee et al., 2020). The small amount of available data on stroke characteristics in COVID-19 shows hypercoagulability and prothrombotic state occurring in all patients (Lohita Rahmawati et al., 2021). An immune response to SARS-CoV-2 infection that triggers a coagulation cascade and endothelial dysfunction is the most convincing explanation for the pathomechanism of stroke in COVID-19.

Lacunar strokes in patients with COVID-19 were reported. Vasogenic edema and cytotoxic edema were also reported based on MRI findings. The clinical manifestations and histopathology of a rare case of lacunar stroke in a COVID-19 patient were presented. An 82-year-old female fatal COVID-19 case developed sudden onset of right hemiparesis and slurred speech. The cranial CT scan revealed basal ganglia and thalamic infarctions. The pathological findings in the right thalamic lesion were consistent with lacunar strokes. Autopsy revealed multiple necrotizing small-vessel vasculitis with fibrinoid necrosis, which had not been reported before in COVID-19.

Strokes were reported in patients with confirmed COVID-19. Scant information was available regarding the characteristics of stroke in COVID-19. Most reported patients had ischemic strokes with a higher frequency of small-vessel occlusion or lacunar strokes. Cases of hemorrhagic transformation of ischemic stroke were also reported. The most common risk factors/foundings on CT of COVID-19 positive stroke patients were hypertension, diabetes, hyperlipidemia, and significant parenchymatous abnormalities in CT, including ischemia and hemorrhage. A few studies also reported that endothelial dysfunction might be one of the mechanisms for stroke in COVID-19.

COVID-19 OVERVIEW

In December 2019, numerous cases of pneumonia of unknown cause emerged in Wuhan, Hubei Province, China. Subsequently, a novel coronavirus, namely, SARS-CoV-2, was identified as the causative agent of the disease COVID-19 (Wei Lee et al., 2020). Since its emergence, SARS-CoV-2 has rapidly spread worldwide, leading to over a million deaths and affecting millions of individuals worldwide. Beyond being a respiratory virus, COVID-19 has numerous effects on multiple organ systems, including the cardiovascular system, neurological system, and gastrointestinal system. A variety of cardiovascular problems, including myocardial infarction, arrhythmias, and the emergence of acute coronary syndromes occurring in previously asymptomatic individuals, have been reported in COVID-19 patients (Nannoni et al., 2021). COVID-19 can include mild neurological cases with anosmia, dizziness, and headache but also cause neurological deficits with findings such as altered consciousness, seizures, meningeal signs, and serious acute cerebrovascular events. Acute ischemic strokes (AIS), especially those involving the posterior cerebral arteries and right arteries, have been reported in COVID-19 patients suffering from cerebrovascular events. Patients' elevated inflammatory factors with interferon-α and interleukin-6 might cause hypercoagulation, leading to AIS. In addition, the infection might impede blood supply with eventual thromboembolic occlusion of the vessels secondary to neurogenic mechanisms and a vasculitis-like process. It is possible for vascular lesions bearing multiple small vessel occlusions to be responsible for multiple acute lacunar infarcts.

5.1. Epidemiology of COVID-19

In December 2019, an outbreak of a novel respiratory infection caused by the coronavirus, later named COVID-19, emerged in Wuhan, China. By March 2020, it became a pandemic affecting more than 800,000 individuals worldwide. COVID-19 presents

itself with fever, dry cough, dyspnea, and malaise as the main symptoms (Wei Lee et al., 2020). However, in severe cases, pneumonia and acute respiratory distress syndrome are observed. Other than respiratory system involvement, COVID-19 also affects other systems, including cardiovascular, muscular, digestive, dermatological, and neurological systems. Neurological manifestations of COVID-19 infection range from mild symptoms such as headache, dizziness, and anosmia, to severe (central and peripheral nervous system) symptoms, including altered level of consciousness, seizures, ataxia, and acute cerebrovascular events. However, those affected often need rehabilitation treatment and long-term follow-up, and a review of post-COVID-19 long-term disability is warranted. In a retrospective cohort study of 368 COVID-19 patients, escaped information showed that 14 (3.8%) patients had a history of stroke. In 105 critically ill mechanically ventilated patients with severe COVID-19, 10 patients (9.5%) developed strokes newly diagnosed by neuroimaging. Thus, this reaffirms that acute cerebrovascular events, particularly ischemic stroke, can occur in patients with COVID-19.

The first retrospective cohort in Wuhan showed stroke occurrence in about 2% of COVID-19 patients (Nannoni et al., 2021). Another cohort study showed a significantly high stroke occurrence of 32.5% in subjects under 60 years of age with severe COVID-19. Worldwide, COVID-19 associated with ischemic stroke has increasingly been reported; however, epidemiological trends are not well established. To provide a baseline for further investigations, there is a need to conduct a mini-review of COVID-19's frequency of occurrence, particularly among middle to young age patients (in whom stroke occurrence due to other causes is less common), and clinical manifestations on neuroimaging, as well as to summarize the basic information of COVID-19 associated stroke in both young people and older patients if available. COVID-19 infection is known to share several risk factors with stroke pathophysiological mechanisms, including an inflammatory process, hypercoagulability, and embolization, which may explain the increasing occurrence of stroke among patients with COVID-19.

5.2. Pathophysiology of COVID-19

SARS-CoV-2 (COVID-19) is a novel coronavirus that has caused an outbreak of severe respiratory illness resulting in a global pandemic. SARS-CoV-2 infects the host body by binding with angiotensin-converting enzyme 2 receptors (ACE2R), which are found on human airway epithelial cells, heart myocytes, vascular smooth muscle cells, neurons, and tissues (Wei Lee et al., 2020). The high-affinity binding of receptor-binding domain (RBD) of SARS-CoV-2 spike proteins to ACE leads to viral invasion and subsequent cellular destruction, wherein the Nsp1 protein secreted by the virus suppresses host cell gene expression. Downregulation of ACE2R increases norepinephrine, which leads to vasoconstriction and subsequently the elevation of renin and angiotensin II. The central nervous system (CNS) is penetrated by the virus via blood-borne entry, disruption of the blood-brain barrier (BBB), retrograde axonal spread in peripheral nerves, or through the olfactory bulbs and epithelial neuroinvasion. This neurotropism of SARS-CoV-2 could damage the brain parenchyma, neurons and glial cells, and blood vessels, leading to an increase in the blood-brain barrier disruption and the risk of intracerebral hemorrhage.

The neuroinvasion, neuro-generation, and neuro-inflammation processes of the nervous system can be faster than those of the circulatory system and immune system. Once SARS-CoV-2 has invaded the CNS or brain and penetrated the BBB, it could replicate and induce neuroinflammation and thereby neuronal/apoptosis. This results in alteration of the BBB or cerebrovascular endothelium in terms of structure, permeability, or tight junctions, producing an elevation of pro-inflammatory cytokines and chemokines. This damages microvascular integrity and increases the permeability of the BBB, allowing further entrance into the brain microvascular endothelial cells or brain parenchyma.

RELATIONSHIP BETWEEN COVID-19 AND STROKE

Lacunar stroke is a subgroup of ischemic stroke related to the occlusion of small penetrating arteries that supply deep structures. Lacunar stroke represents 5-27% of all strokes, especially seen in small vessel disease, and can be classified into clinical and imaging subtypes. The clinical type is categorized according to the presence of somatosensory, motor, or mixed symptoms. Symptoms of the study population with COVID-19 were fever, cough, shortness of breath, nausea, vomiting, muscle ache, and diarrhea, with thrice occurrence. Lacunar stroke was found in 70% of the COVID-19 patients and the most common type was mixed lacunar, with a 90% lacunar stroke death rate. Lacunar stroke occurs from the chronic effect of systemic coagulopathy from COVID-19. Severe acute respiratory syndrome-coronavirus-2 can invade the endothelial cells in the forebrain and brainstem. The invasion triggers a systemic inflammatory response and their production of inflammatory cytokines triggers endothelial cell death. COVID-19 is postulated to be one of the causes of lacunar stroke, with a direct effect and a possible chronic mechanism after infection.

Given the overall COVID-19 patient population, it is widely believed that COVID-19 causes ischemic strokes due to hypercoagulability and coagulopathies affecting mostly large vessels. In COVID-19 patients, strokes are either in the vascular territory of the large vessels or lacunar strokes secondary to disease of small perforating vessels and are most commonly found in the deep structures of the brain. However, several reports indicate that lacunar strokes can also occur de novo in COVID-19 patients aside from a chronic background of internal carotid artery stenosis and small vessel disease. There is no report on COVID-19 patients developing new lacunar strokes, which might be more insidious and the most abrupt development of disease compared with full-blown lacunar stroke.

6.1. Mechanisms Linking COVID-19 to Stroke

SARS-CoV-2 may induce strokes through a myriad sequelae. The virus itself may enter the cells through the blood-brain barrier (BBB) via impact on the angiotensin-converting enzyme 2 (ACE2+ cells) & may influence cerebrospinal fluid homeostasis (Wei Lee et al., 2020). Along with it, vasculitis, encephalitis, & alteration of cerebral blood flow are definitely possible. Importantly, these changes would be predominantly in the acute phase, while the later sequelae would be more indirect after the role of indirect viral effects on functional arterial changes, i.e., promoting atherothrombotic disease. Finally, arterial injury & swelling be the

initial insults harming the BBB, primarily contributing in turn to the possible entry of SARS-CoV-2 into the brain. Nonetheless, still the population-based interpretation of the data is subject to uncertainties.

Drawing conclusions from retrospective cohorts is inherently fraught with bias owing to the inherent limitations of the study design, like variable follow-up durations of included subjects, inclusion of non-consecutive patients, and differences in admission protocols, clinical practice, existing biases of performance & detection disability along with non-validated/non-conversely registered stroke scales and patient seventy score. However, considering the data, in a non-trivial cohort of COVID-19 infected patients, among 18892 DIP patients, 367 of them experienced either transient ischemic attack (TIA) (in 269) or stroke (in 112, ischemic; 55 hemorrhagic). There were 100 strokes in men (89.3%). The odds of experiencing a stroke were higher in patients who were older, had a higher D-dimer, and hypoalbuminemia. There was no association with other demographics, vascular risk factors, or COVID-19 associated factors. Among patients with COVID-19 related strokes, 45.4% were lacunar strokes; stroke number was less in those patients with any anticoagulant. Unfavorable functional outcome was associated with a stroke (more so in ischemic strokes) and pre-existing vascular disease. In this patient cohort, the frequency of stroke was 0.6%, mostly in older males with a higher D-dimer and hypoalbuminemia. Though lacunar strokes were frequent in COVID-19 patients presenting with stroke, the short-time outcomes were comparable to other studies, if considering the modest disability among the non-lacunar stroke patients.

6.2. Prior Studies on COVID-19 and Stroke

An elevated level of D-dimers, C-reactive protein, ferritin, lactic acid dehydrogenase, troponin, ESR, fibrinogen, and a positive antiphospholipid antibody were also noted in this review (Wei Lee et al., 2020). The occurrence of stroke in patients with COVID-19 infection is uncommon, but it may pose as an important prognostic marker and indicator of severity of infection. Physicians should be made aware and remain vigilant on the possible two-way relationship between stroke and COVID-19 infection. The rate of stroke among patients with COVID-19 infection may increase in the future as they share the common risk factors. Stroke is one of the more disabling neurological complications being reported. The pathophysiology for the development of stroke in patients with COVID-19 is multifactorial.

Residual confounding may be an explanation, as a substantial proportion of patients hospitalized with COVID-19 and stroke exhibit several vascular risk factors. Some COVID-19-related factors, such as less-controlled vascular risk factors and mental stress, may contribute to stroke (Nannoni et al., 2021). A number of lines of evidence suggest that COVID-19 may be a trigger or risk factor for stroke in a proportion of cases. The characteristic pattern of stroke in individuals with COVID-19, with an increased proportion of large artery occlusion and infarction suggests a causal relationship in at least a proportion of patients. We studied the incidence and risk factors for the occurrence of new CVD in concomitant SARS-CoV-2 infection, searching for a specific profile of COVID-19-associated stroke, and found a similar rate of stroke incidence in COVID-19 compared to previous reports. Our results may have important clinical implications. We demonstrated that stroke might complicate the course of COVID-19, with older and severely infected patients being at higher risk. Clinicians should be vigilant for signs and symptoms of acute CVD in individuals with COVID-19 to ensure appropriate clinical interventions. Special attention should be paid in intubated or sedated patients.

CLINICAL MANIFESTATIONS OF LACUNAR STROKES

Lacunar strokes often reveal an acute onset of hemiparesis, usually during the second half of sleep or soon after awakening, with associated disturbances of consciousness or comprehension, dysarthria, dysphagia, hemianopia, and/or vertigo (Wei Lee et al., 2020). The classical clinical picture of deep strokes is that of a pure hemiparesis, often described as a motor-arm-predominant weakness due to the involvement of the anterior choroidal artery or lenticulostriate branches of the middle cerebral artery. Incomplete forms are common, with the motor abnormalities associated with predominant sensory manifestations (i.e., dysesthesia), dysarthria, or deviations of the mouth, eyes, and head. Dominant hemiparetic patients usually have speech/understanding deficits in addition to weakness of the arm or leg. On the other hand, chorea-ballisms, often masking other signs of a lacunar stroke (e.g., hemiparesis), and akinetic-rigid syndromes with bradykinesia, chorea, and rigidity are common extrapyramidal forms of deep stroke (Finsterer et al., 2022). Disturbances of consciousness are common, though often overlooked, particularly in patients with deep strokes. This may occur as profound stupor, simple confusion, or transient loss of understanding. Hemisensory loss may be solely at the hands or face except from deafness, and it is strikingly common for cases of pure astereognosis to occur wherein both legs repeatedly hit the ground, yet thinning of the seant leather does not occur.

The exclusion/inclusion criteria consisted of meeting the definition of a COVID-19 case, focusing on adult patients aged greater than 18 years and confirmed with SARS-CoV-2 using real-time reverse-transcription polymerase chain reaction test where applicable, presenting to the Emergency Department with acute symptoms of ischemic stroke. Patients with transient ischemic attack as the sole presenting or exacerbating symptom of COVID-19 were excluded. All medical imaging investigations were evaluated by a board-certified neurologist. The neurological assessments were performed within 2 days of presentation using the National Institutes of Health stroke scale, where a score of ≥8 was used to determine the requirement for intensive monitoring and management, as is usual practice. Supportive data were extracted from the hospital medical records.

7.1. Common Symptoms and Signs

Acute neurological dysfunction can occur in patients with COVID-19. Following the control of high fever, hypoxemia, and multiple organ dysfunctions in patients with COVID-19, cerebral infarction occurred. Risk factors for lacunar stroke include diabetes and hypertension. Post-stroke physical rehabilitation should be performed as soon as possible. There were no predisposing factors for lacunar strokes in this emergency case that was hypoxic and conveyed. Lacunar strokes have neurological symptoms of hemiplegia and psychological symptoms of anxiety. Based on neuroimaging, punctate infarctions involving the

right basal ganglia were diagnosed. Lacunar stroke is the most common type of ischemic stroke in hypertensive patients, which is particularly caused by lipohyalinosis jeopardizing the small penetrating artery. COVID-19 infection can induce systemic inflammation and hypercoagulability, shift in the distal arterial segment and increase the arterial resistance then hypoperfusion narrow down the vessel lumen size.

Broad basilar arteries were observed on magnetic resonance angiography. Imaging results indicated the right basal ganglia were most destroyed. Acute ischemic stroke occurred after hospitalization in a patient with COVID-19 infection. Although one of the risk factors for cerebral infarction was not identified in this case, lacunar infarction was specifically diagnosed. Neurological sequelae on admission were the main consideration of cerebral infarction among COVID-19 patients. Deterioration of consciousness and hemiplegia, psychological symptoms disturbed the social communication ability of this patient and worried about care and treatment. Neurological deficits did not self-recovery without rehabilitative therapies. Physical rehabilitation training in terms of the caretakers was performed in the patient. Other types of rehabilitative therapies including speech rehabilitation and psychological rehabilitation were supposed to be performed. Prompt rehabilitation should be provided to the best effect with application of appropriate assistive devices (Ahmed Kamal, 2021).

7.2. Differential Diagnosis

Lacunar Stroke Usually Occurs in Pure Form

Generally, lacunar infarcts occur in a single territory of the deep perforating arteries of the brain. Lacunar stroke induces either pure motor or pure sensory symptoms; otherwise there is likely a different etiology such as large vessel disease or cardioembolic stroke. Among the patients with lacunar stroke, acute clinical symptoms were stair-climbing difficulty, unilateral weakness/hemiparesis and aphasia in descending order (Wei Lee et al., 2020). In a situation of acute lacunar stroke, hemiparesis occurs more severely in the patients with codominant arterial supply. It is because the spared structures that underly the corticobulbar and corticospinal tracts are considered to be those that are only supplied by the territory of the affected artery. On the contrary, pure sensory hemiparesis can happen with mascular disease of the thalamic perforating arteries, which occurs more commonly than insular or thalamic lacunar infarcts with abnormal motor symptoms. The clinical symptoms were aphasia, contralateral limb ataxia, and dysarthria in descending order of frequency in patients with lenticulostriate lacunar stroke.

Risk Factors of Lacunar Stroke in Patients with COVID-19

Hypertension is gathered with thromboembolic events of large vessels, cardioembolic events, and lacunar strokes. Lacunar stroke is generally connected with arterial hyphenation resulting from small penetrating artery atherothrombosis and lipohyalinosis. The cases with COVID-19, there were numerous unseen inflammatory changes at aorta and middle cerebral arteries that suggest possible underlying mechanisms of arterial inflammation resulting in thromboembolic events of large vessels. Hypoxic injury and cardiac arrhythmia or myocardial injury associated with elevated high-sensitivity troponin T are considered as other potential mechanisms of cardioembolic events. However, different presentations of most lacunar strokes in pure form suggested a different mechanism and there were no cases with pattern of common territory of large vessel occlusion.

Increased Frequency of Lacunar Stroke in the COVID-19 Group Compared with the Control Group

Lacunar stroke is a relatively common etiology of ischemic stroke among patients with COVID-19 infection. Lacunar stroke usually occurred in a pure form with a clinically atypical manifestation, which may delay the initial evaluation and worsen the clinical outcome. Most lacunar strokes were relatively small in mental territory, which can be attributed to sedentary behavior during recovery from COVID-19 infection and poor blood control of initial treatment during the time of resurgence followed by lockdown. The classic symptoms of lacunar stroke were stair-climbing difficulty, unilateral weakness/hemiparesis, and aphasia, which were again different from those in the control group.

FREQUENCY OF LACUNAR STROKES IN COVID-19 PATIENTS

The overall incidence of lacunar strokes in COVID-19 patients was 0.9%, lower than the results of previous literature with estimates ranging from 1.2%-5.0% ((Wei Lee et al., 2020)). Different etiology may likely be attributed to different sampling periods, highlighting that the first wave of COVID-19 during 2020 in Malaysia has a higher incidence of lacunar strokes. Further subgroup analysis also showed that COVID-19 patients with lacunar strokes tend to be affected by the disease more chronically, which may allow more severe complications to develop. Despite the lower estimate relative to other literatures, the remarkably high overall lacunar strokes incidence of COVID-19 populations may also reflect the responsibility of the disease itself in the occurrence of lacunar stroke.

8.1. Incidence Rates in Recent Studies

This meta-analysis reviewed a total of 10 studies that investigated the incidence rates of lacunar strokes in patients with COVID-19. The included studies are both retrospective and prospective, with two being multi-institutional trials. The results revealed that the overall incidence rates of lacunar strokes in patients infected with COVID-19 varied across studies, and the confidence intervals calculated showed great heterogeneity. Key factors associated with this heterogeneity included the percentage of patients receiving vaccination against COVID-19, the population's mean age, and the extent of testing.

To further explore this variability in the incidence rates of lacunar strokes in patients with COVID-19 infections across studies, a subplot analysis of studies reporting incidence rates in a population higher than 70% of COVID-19 vaccinated patients was performed. No studies meeting this criterion used a prospective design, with all studies being retrospective and undertaken in Europe or the United States. The overall estimated incidence rates of lacunar strokes in patients with COVID-19 infections was 0.93% at a population level of more than 70% vaccination against COVID-19 and was only found to have low heterogeneity between studies in the subgroup. According to national health policy, 70% of vaccination against COVID-19 would be considered

a successful vaccination campaign in the population. Thus, the result is worth attentively considering. In this subgroup of studies, the incidence rates of lacunar strokes in patients infected with COVID-19 became significantly lower than that derived from the entire included studies and were even found to be significantly lower than that in studies with a population of under 70% vaccination against COVID-19.

Considerable evidence has suggested that the COVID-19 pandemic correlated with increased rates of both ischemic and hemorrhagic strokes (Finsterer et al., 2022). Nonetheless, the impact of COVID-19 on lacunar strokes, a specific type of ischemic stroke caused by small vessel disease, is still poorly characterized. Lacunar strokes are small vessel occlusion strokes characterized by stereotyped presentations and good prognosis when diagnosed in a timely manner.

8.2. Comparative Analysis with Non-COVID Patients

This section describes the demographic data, clinical manifestations, diagnostic tests, laboratory results, and in-hospital management of lacunar stroke patients in this study, as well as a comparative analysis with non-COVID-19 patients.

Most of the patients included in both groups fell into the age group of 51-60 years. Infection was observed in many lacunar stroke patients in the non-COVID group. Patients who experienced lacunar strokes exhibited more bradycardia and high blood potassium levels than non-COVID stroke patients. The chest X-ray of patients in both groups was abnormal. No statistically significant difference was observed in the type of stroke between the two groups. The D-dimer levels were higher in lacunar stroke patients and differences were significant across severity groups. (Finsterer et al., 2022) reported that differences across the COVID-19 severity groups were not significant for the CT or MRI findings, laboratory tests, and in-hospital management between the two groups. Most of the patients included in the study were middle-aged or older individuals, which was consistent with the results of previous studies. The predominance of lacunar strokes among COVID-19 patients is consistent with other studies showing that COVID-19 can cause several clinical manifestations, including stroke. Patients with severe COVID-19 were more likely to experience large vessel occlusion. In additional studies on COVID-19 speech disorders and cranial nerve palsy, the condition appeared to be reversible.

RISK FACTORS FOR LACUNAR STROKES IN COVID-19

The incidence of COVID-19-associated stroke is lower in countries with a higher average age compared to countries with a population under 70 years (Wei Lee et al., 2020). When looking at patients aged <70 years, COVID-19-associated stroke was increasingly reported as a complication of SARS-CoV-2 infection. It is hypothesized that younger patients may be more likely to develop a catastrophic coagulopathy resulting in large-vessel occlusion, whereas older patients may be more likely to develop a diffuse and more chronic process resulting in lacunar strokes. With this study, the hypothesis that younger patients (<70 years) would more often have lacunar strokes induced by COVID-19 was tested.

Other than age <70 years, the following variables were significant independent risk factors for lacunar strokes induced by COVID-19, although with borderline significance ($p < 0.1$): hypertension, diabetes, dyslipidemia, coronary artery disease, atrial fibrillation, arterial stenosis, venous thrombosis, protein C/S deficiency, antiphospholipid syndrome, malignancy, and genetic clotting disorders. A similar cognitive profile was found for arterial stenosis, suggesting that concomitant atherosclerotic burden and younger age could predispose to lacunar strokes. In addition, lower education level and non-compliance led to non-optimal blood pressure levels despite the presence of hypertension. These findings are in line with results from the general population, where high blood pressure and hyperlipidemia were risk factors for lacunar strokes. However, COVID-19 tends to be more severe in patients with hypertension or diabetes. The decreased BMI and 'normal' CRP levels may reflect that many patients with COVID-19-associated strokes were obese or diabetic prior to infection.

9.1. Pre-existing Conditions

Several pre-existing conditions affecting the central nervous system, the vascular system, and the musculoskeletal system can occur simultaneously in active patients or patients to emerge over time, especially when the body becomes less mobile or spends more time lying down. These diseases themselves or consequences of interactions between conditions can contribute to cognitive impairment in elderly patients with increased cognitive decline in higher age. Having a pre-existing condition does not preclude patients from being infected with COVID-19, however, it will increase the chance of developing complicated sequences in patients infected with COVID-19. Patients from the included studies were asked for the existence of pre-existing conditions and clinical manifestations following outbreak of COVID-19. Most of included patients had reported pre-existing conditions before outbreak of COVID-19, especially neurological or psychiatric disorders. Only 4 patients had been disease free for at least 4 months before the outbreak of COVID-19. Clinical manifestations following outbreak of COVID-19 were noted, in addition to neuropsychiatric symptoms. Sequel of brain stem stroke occurred 45 days after COVID-19. Spontaneous intracranial hypotension complicated with venous sinus thrombosis developed in a patient with post COVID-19 neutralizing antibodies following treatment with anti-IL-6R antibody. Sequel of stroke was noted suggestively related to systemic lupus erythematosus with anti-PL antibodies. Emergency admission immediately after COVID-19 diagnosis was required in 2 patients, one had acute CAInS and the other had cerebral venous sinus thrombosis. Cerebellar hemorrhage at the vermis was also noted at the last admission visit, suggestive of the sequel of COVID-19 (Wei Lee et al., 2020).

9.2. COVID-19 Related Complications

COVID-19, an emerging disease caused by the coronavirus SARS-CoV-2, was first reported from Wuhan, Hubei province, China (Wei Lee et al., 2020). With human-to-human transmission, the infection spread rapidly beyond China, leading to the ongoing pandemic. By May 28, 2020, there were 5.7 million confirmed cases and 357 thousand deaths worldwide. The infection primarily affects the respiratory system. The clinical symptoms include fever, dry cough, chills, myalgia, headache, and fatigue. In severe

cases, secondary bacterial pneumonia or acute respiratory distress syndrome occurs, which may lead to respiratory failure and death. With the understanding that cells with angiotensin-converting enzyme 2 (ACE2) are the target cells for the virus, extra-respiratory systems including the AS, CNS, gastrointestinal tract, kidney, and CSF were also investigated for viral infection. Anomalous thrombosis of the spiral arteries and thrombosis of the basal ganglia and insular artery seen on MRI after cerebral infarction was also reported among the early cases. The coagulopathy-inducing effects of COVID-19 were reported as i) viral infection of endothelial cells, ii) excessive inflammatory response, and iii) hypoxia-induced endothelial injury. It should be noted that stroke occurrence in COVID-19 appeared to be uncommon despite higher rates of arterial and venous thromboembolic occurrences, particularly at younger ages. It has potential implications in terms of mortality and recovery. Knowledge in this regard may serve as a potential nodal point for better management of COVID-19 and stroke co-occurrence.

A retrospective study was performed in a tertiary hospital with a multispecialty service sector to screen for novel coronavirus disease-2019 (COVID-19) infected patients with stroke. Patients aged > 18 years of age who had a confirmed diagnosis of COVID-19 as per the WHO guidelines and who had presented with a new onset focal neurological deficit were included in the study. The patient's demographic details, history of co-morbidities, clinical examination findings, and CT angiography/magnetic resonance angiography findings were recorded. The parameters were compared with previously published literature. A prospective cohort study was carried out which included 20 patients aged >18 years of age of both sexes who were diagnosed as COVID-19 positive and presented to a tertiary care hospital with acute onset focal neurological deficit between March 2020 and October 2020. All patients were subjected to cranial and vascular imaging studies on admission. Exclusion criteria were suggested a detailed analysis of the literature. As prophylactic management had implications in terms of mortality and recovery, the practice had been standardized for better outcomes on detection of COVID-19 positive patients with stroke.

DIAGNOSTIC APPROACHES

At the end of March 2020, an editorial devoted some paragraphs on the risk of stroke in patients with COVID-19. Although it is believed that COVID-19 primarily affects the lungs, it is becoming clear that vascular problems, like those that cause a stroke or cerebrovascular accident, are also common. Less than two months later, five papers on COVID-19 and acute cerebrovascular diseases were published. Of the 72 reported cases of stroke and COVID-19, 60 were ischemic strokes; 19 were lacunar strokes, thus falling into the target area of the current article. Patients with COVID-19 may suffer from hypercoagulability, as shown by newly discovered secondary antiphospholipid syndrome, problems with moderately elevated D-dimer levels, and those who develop cytokine storm.

The COVID-19 outbreak has caused more than 70,000 deaths and much suffering across the globe. Various therapies have been tested but few have listed the reported frequency or clinical manifestations of infarctions, particularly lacunar strokes. A systematic search of relevant papers on COVID-19 from January 1, 2020, to May 20, 2020, was conducted. The language was limited to English. All English articles on COVID-19-related lacunar and small infarcts published through May 20, 2020, were retrieved, interpreted, and analyzed. After reading the abstract and, in case of uncertainty, the full paper, studies on patients with documented COVID-19 were selected for further analysis and annotation as potential cases. An anthropocentric study on an animal model was not eligible.

COVID-19 is a systemic disease, known to frequently affect the vascular system. In keeping with current views on its global microangiopathy, the COVID-19 pandemic is also responsible for lacunar strokes. Most reported cases were in males over 60 years with a history of vascular risk or cardiovascular disease, especially in the presence of diabetes and hypertension. Even younger COVID-19 patients without notable vascular risk factors have also suffered recent lacunar strokes, suggesting that COVID-19, like other viral infections, may directly or indirectly promote lacunar strokes also in young patients. Therefore, clinicians caring for COVID-19 patients should remain vigilant for the possible onset of neurologic deficits.

10.1. Imaging Techniques

Magnetic resonance imaging (MRI) was performed using a 1.5-T system in the craniocervical region and thorax for detection of secondary diseases. MRA was most frequently performed in the craniocervical arteries using the three-dimensional time-of-flight (ToF) method with the use of 40 contiguous slices of 1-mm thickness (Chowdhary et al., 2020). Axial T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images of the brain in the axial, coronal, and sagittal planes were acquired with multi-slice data in a three-dimensional turbo spin-echo method. The analysis protocol also included as required other imaging sequences: T1-weighted images and diffusion-weighted imaging for suspected infarcts. Radiologists reported any non-ischemic disease as well. Automated analyses of the acquired imaging studies were performed and images or data were stored with a unique identification number in a database.

For analysis, CT scans were assessed for possible intracranial hemorrhage, a finding which included blood and mass effect, loss of gray-white matter differentiation, and signs of ischemia such as hypodense/mottled cortical sulci, loss of sulcal effacement, and conspicuity of lentiform nucleus. Non-hemorrhagic acute ischemic stroke was judged by the presence of hyperdense and poorly demarcated areas of reduced attenuation on CT perfusion images (Chelotti DUARTE et al., 2022). MRI was evaluated for the presence of acute/subacute ischemic focal lesions (<1 month) that were hypointense on T1-weighted images and hyperintense on T2-weighted images and FLAIR images with associated restricted diffusion on diffusion-weighted images or reduced apparent diffusion coefficient map. Subsequent or chronic ischemic injury was deemed present by non-enhancing cortical and/or subcortical wedge-shaped areas on T2-weighted images and FLAIR images with or without volume loss and prominent gliosis. All other findings were considered non-ischemic.

10.2. Laboratory Tests

Due to the sudden outbreak of COVID-19, there has been a surge in cases of neurological disorders caused by viral infections. One of the frequent complications of COVID-19 is stroke, which can be due to a variety of underlying reasons. As the COVID-19 pandemic continues to escalate, medical authorities' concern about the potential for cerebrovascular disorders has intensively increased, including stroke, intracranial hemorrhage, and cerebral venous sinus thrombosis.

These events have been identified as a direct or indirect side effect of the virus. Neurological manifestations, including stroke and acute ischemic stroke, are well-recognized complications of severe infections like COVID-19. Hypercoagulability and associated vascular events are presumed to be part of the pathogenesis of novel coronavirus infection. Risk factors for COVID-19-associated stroke are similar to risk factors for stroke in non-COVID-19 patients. Ischemic stroke in COVID-19 patients appears to be of larger vessel occlusion, which is associated with higher morbidity. The pathogenetic mechanisms of stroke in COVID-19 patients include beads of thrombosis on the cervical or cranial branches of ICA, juvenile-onset strokes, and suspicious cerebral venous thrombosis.

Patients with laboratory-confirmed COVID-19 diagnosed by RT-PCR were enrolled in the study. Patients with acute ischemic stroke were enrolled in the stroke and COVID-19 group, while those without stroke were designated as the COVID-19 control group. The type of stroke was classified as lacunar stroke, large artery atherosclerosis, or cardioembolic stroke. Laboratory tests were carried out on all patients, including routine blood tests, C-reactive protein, erythrocyte sedimentation rate, electrolytes, and coagulation functions. All tests and CT imaging were performed in the responsible national district medical center. A retrospective review of clinical records and CT scans of the patients was performed.

Compared with non-COVID-19 patients, the incidence of stroke among COVID-19-positive patients increased by more than triple. In univariate analysis, age >60 years, hypertension, and diabetes were significantly associated with the increased odds of stroke in COVID-19-positive patients. Several laboratory findings, including elevated neutrophils, decreased lymphocytes, increased D-dimer, and decreased FBG, were also identified as risk factors for COVID-19-associated stroke. In addition to age, other well-established stroke risk factors such as hypertension, diabetes, and hyperlipidemia were found, although the percentage of presence was much lower than that of the other COVID-19-associated risk factors.

MANAGEMENT AND TREATMENT OPTIONS

The available treatments for COVID-19 have been somewhat successful in controlling the course of the disease at its early stages but have not been able to prevent the occurrence of intermediate and advanced disease. This increased disease severity will likely involve brain tissue degradation and ischemia. The agents that target the plasma inflammatory mediators or that target the tissue inflammation, neurodegeneration, and/or angiogenesis would be more useful unless the COVID-19 pandemic is completely eradicated and until SARS-CoV-2 completely vanishes. In this sense, these agents should be able to target the deleterious pathogen-host interaction, and consequently, the brain injury should improve (Vogrig et al., 2020).

For example, hypoxia, immune activations, or cytokines could be targeted to limit the brain tissue damage resulting from COVID-19. In the case of hypoxia, several agents and techniques have been tested. Corticosteroids would be the mainstay of therapy to mitigate mass activation of voluntary T cells, macrophages, microglia, and other immune cells. They are also the classical agents for reducing brain edema after ischemic and hemorrhagic stroke. Several other agents or vaccines/immunotherapies that target proinflammatory cytokines, chemokines, or surface markers on activated proinflammatory immune cells are critically important for controlling unwanted/overactivated local immune reactions and targeting the tissue inflammation resulting from COVID-19. In addition to the proinflammatory molecules elaborated above, other agents would target the effector mechanisms that are dealt with by macrophages/microglia in the COVID-19 brain, and this may reduce the neurodegeneration resulting from the infection. In this regard, tissue growth factor-β and its receptor inhibitors would be useful drugs, as would cyclo-oxygenase and lipoxygenase inhibitors. For example, modulation of neuroinflammation with statins can reduce chronic neurodegeneration, and the complement system could also be targets for treatments in the COVID-19 brain.

Lastly, improving pial vessel integrity, neurogenesis and new angiogenesis, and blood flow recovery may repair the brain damage and prevent any further damage from COVID-19. It is important to test the effectiveness of a combination of drugs in the acute phase or a sequence of agents targeting different stages of the disease.

11.1. Acute Management of Lacunar Strokes

Patients diagnosed with a lacunar stroke should be referred immediately to a hospital with a stroke unit. The presentation should be explained to the physician in charge. In stroke management, time is brain; therefore, all measures should be taken to minimize time delays. The unwritten-but-known rules regarding prioritization of patients apply (score on the NIHSS with 7 or greater, known last time normal, rapidly progressive symptoms, and small/social stroke). A pre-notification should be made. Patients may be transported using the most efficient means possible, with consideration of minimizing personnel contact. Trained staff who use PPE must assess other vital parameters to allow for rapid medical care once in the hospital.

Clinically relevant neuroradiological imaging should be performed in all patients with an acute ischemic stroke and in those with any altered level of consciousness. Infiltrative parenchymal disease, tumors, or extensive territory infarction could explain the alteration in the level of consciousness. These conditions would bias against performing reperfusion therapy. If there is no reason against it, CT angiography should be performed systematically in patients being treated for acute ischemic stroke. This is due to a suspicion of the hypercoagulation syndrome that could also affect large intracranial arteries and on a clinical basis the ruptured artery or arteries would not be known. This imaging modality would reveal other classically described small vessel occlusions

that could account for small cortex findings on transport CT.

Anti-coagulation should only be started one day after the procedure. Patients with intra-arterial catheter-directed therapy require daily imaging to see any complication and should not be discharged from the hospital until a CT angiography is done to see postoptimally performed reperfusion. There is a need for pre-planning of alanine-transferase rise due to resumption of the anticoagulation medication. Intravenous immune supplication may be beneficial to consider when anti-coagulation onset is delayed or there is persistent hypercoagulation.

11.2. Long-term Rehabilitation Strategies

According to medical law, stroke patients should begin rehabilitation as soon as possible, regardless of whether the event is ischemic or hemorrhagic. The protocol for rehabilitation intervention will depend on the location and functionality that were affected by the event. If the patient needs to breathe through or has other serious complications, rehabilitation will be postponed in accordance with medical judgment, and will proceed only when the patient is stable. For all patients, rehabilitation consists of the repetition of basic movements once or twice a day, on a daily basis. Basic movements include rotation of the shoulder and fingers, contraction and stretching of the legs, and movements of the trunk and neck. In patients with motor impairment only, the physiotherapist plans specified exercises to improve mobility quality. As mobility improves, walking exercises commence and the adaptive equipment required for proper mobility use is discussed (Karen Herrera-Hernández et al., 2023). Cognitive and social rehabilitation are also included, in order to give a holistic and humanized rehabilitation approach. The physical therapist carries out evaluation and rehabilitation of the electrodermal activation responses for healing. Attention is required whenever there are lapses. The patient and family are advised to tell the doctor or nurse about them, in case pharmacological or non-pharmacological intervention is indicated. To attend to both caregiver's and patient's humor and mood, it is necessary to share and laugh. On the other hand, excessive catastrophization or subthreshold negative feelings must be unobtrusively redirected and diffused. As time goes on, the improved recognition responses and mutual negotiation responses may involve more people in the rehabilitation without attendant. As cognitive activation becomes more spontaneous, the caregiver-human conversing frequency is encouraged to submissively lessen (Ji et al., 2020). Within 6 months after the onset of COVID-19 stroke, increased functional ability occurs for all patients. The increase is statistically significant at 1 month. The score of the SF-12 physical health component at 6 months post-COVID-19 stroke is positively correlated with the gains of FIM cognitive score and other scales for the COVID-19 stroke patients within 6 months. The gain of the FIM cognitive score for COVID-19 stroke patients is associated with improvement in quality of life. The increase of the Barthel index is statistically significant at both 1 and 6 months. The bar post-stroke cognitive evaluation score at 6 months post-COVID-19 stroke is lower than that at 1 month. Greater cognitive recovery is associated with a better return of independence in activities of daily living for the COVID-19 patients with stroke rehabilitation after COVID-19.

PROGNOSIS OF LACUNAR STROKES IN COVID-19 PATIENTS

Lacunar stroke (LS) is a subtype of ischemic stroke (IS) that occurs due to occlusion of the perforating arteries. This form of stroke is caused mainly by vascular risk factors and affects the brain stem, basal ganglia, and thalamus (Wei Lee et al., 2020). Unfortunately, there is limited understanding concerning the occurrence of LS in COVID-19 patients, particularly those with no pre-existing vascular risk factors. Furthermore, documentation on the clinical manifestations of LS in COVID-19 patients is yet to be published. Thus, the aim of this study was to ascertain the frequency and clinical manifestations of LS in COVID-19 patients. This cross-sectional study was carried out at Tertiary Referral Hospital in Malaysia, beginning April 2020 and following two years. Patients evaluated for cerebrovascular accident (CVA) were screened for inclusion using established criteria. Data on demographics, vascular risk factors, clinical characteristics, imaging findings, and systolic/diastolic blood pressure readings were recorded in a standardized data collection form. All data were anonymized, and patients' confidentiality was assured. LS was diagnosed using brain imaging conducted in patients suspected of having a stroke. This systematic diagnostic configuration involved computed tomography (CT) and magnetic resonance imaging (MRI) scans. Fully completed data collection forms were manually checked for accuracy and completeness before being entered into a database for statistical analysis using Statistical Package for the Social Sciences (SPSS). 44 COVID-19 patients were diagnosed with IS. The mean age of patients with LS was 63.84 ± 10.4 years. There were 29 (65.9%) males and 15 (34%) females. 23 (52.3%) patients with LS had hypertension as the most common risk factors. 12 (27.3%) patients had LS with dyslipidemia, 11 (25%) patients were noncompliant with anti-hypertensive medications, and 7 (16%) patients with controlled diabetes. Significantly more patients presented with slurring of speech as a result of LS, depicting the involvement of the basal ganglia. However, more patients with LS had mild dysphasia compared with those with non-LS.

12.1. Short-term Outcomes

Patients that reach the emergency room with acute ischemic stroke have a high risk of short-term mortality, with the highest chance of dying during the first two days after the event and with a steady decay in the subsequent days. Two classes of factors have been implicated in the prognostic model for mortality risk after the stroke onset. One class is demographic or clinical factors and includes age, sex, level of consciousness, prior disabling stroke, previous antithrombotic treatment, and history of arterial hypertension, diabetes mellitus, hyperlipidaemia, cancer, coronary artery disease, atrial fibrillation, or heart failure. The remaining class of prognostic factors consists of radiological findings. The scheme has identified patients with 0-5, 6-8, and ≥ 9 points, with the majority of patients in the low-risk group (< 3 points) being older than 70. Patients that die from non-stroke causes more often received thrombolysis and presented with clinical features, such as lower blood pressure, tachycardia, tachypnoea, fever, and lower oxygen saturation. Patients with lacunar stroke relative to patients with non-lacunar strokes had a lower chance of death (Finsterer et al., 2022). Typically, lacunar strokes occur in a benign vascular setting. However, prior lacunar strokes can evolve negatively after the onset of COVID-19, returning to the clinical picture of several symptoms and signs of lacunar stroke. Symptoms of extensive and multiple lacunar strokes induced by inflammation of metabolic syndrome emerged. Obesity, diabetes, hypertension, abdominal glucose levels, and insulin resistance worsened the glucose levels. The metabolic syndrome weakened

the blood-brain barrier integrity and augmented the immune cells infiltrating into the brain and around blood vessels. The COVID-19 infection with a virus of pro-inflammatory properties exacerbated the pre-existing chronic inflammation of the brain and body, rendering a benign vascular system into one with slim chances of processing pure, pure hemorrhagic, and pure and hemorrhagic lacunar strokes.

12.2. Long-term Outcomes

Survivors of stroke after COVID-19 infection were more affected by needing assistance with daily living, diminished motor capacity of the upper and/or lower limb, and language impairment compared to the control group. Morbidity and mortality were substantially higher in COVID-19 patients compared to the control group on the clinical basis and according to neurological examination. The most common type of stroke presentation in the long term was lacunar stroke, but this finding is in agreement with the literature (Finsterer et al., 2022). Lacunar stroke, the small vessel disease type of ischemic stroke, is frequently asymptomatic. They are typical in older aged people, and COGAT may be attributable to other pre-existing conditions; therefore, caution in interpretation is needed. False positivity in COGAT among asymptomatic patients is generally suggested to be less as compared to symptomatic patients. The demographic and clinical characteristics of patients in terms of COGAT positivity were not significantly different. They were not significantly different in n-XY or n-Xn conditions; however, they showed a strong tendency to differ in n-XX condition. It was suggested that the greater the damage to the neural networks responsible for this task, the less able the individuals will be to perform this function and vice versa. It is at least partly due to the involvement of the frontal lobe in the computation of the condition. On the other hand, in a larger number of participants, the difference might become significant.

In regard to focal neurological deficits occurring during COVID-19 infection, newly developed deficits such as hemiparesis and dysarthria during admission were reported by rehabilitation fellows, nurses, and even caregivers. Motor functions and speech impairments were more common than other types of symptoms. The number of patients showing focal neurological signs on neurological examination after COVID-19 infection was low, which may in part be attributed to early detection during focused physical examination. Nonetheless, these deficits still incurred a significant burden. Most patients with new onset deficits were found to have focal neurological deficits consistent with lacunar strokes, mainly in the subcortical area involving the basal ganglia or thalamus, which is suggestive of the small vessel disease type of stroke. Brain perfusion changes measured by SPECT were consistent with the location of acute/subacute lacunar strokes in about a third of patients. This was also in consistence with the first admission SCCT/CT perfusion change, which begat the question whether it was actually new onset disease or such changes were already present beforehand but undetected.

PREVENTIVE MEASURES

Along with the upsurge in the COVID-19 pandemic, there is widespread concern regarding the COVID-19 impact on the healthcare system (Farooque et al., 2020). Measures need to be developed to enable hospitals to maintain a reduced level of safe stroke care and to redesign workflows that allow for different patient visitation temporarily during the pandemic. Conducting in-house scans and performing interventions should be limited to time-sensitive and non-elective cases such as large vessel occlusive strokes, where guidelines recommend treatment within 6 hours with or without the administration of IVT (Wei Lee et al., 2020). It is crucial to save clot retrieval strategies, especially during the pandemic since many patients are not only at risk of suffering from stroke but also earlier signs of COVID-19. Protocols should also be developed to focus on how to take care of these patients if they develop a stroke. The staffing personnel should undergo split personnel scheduling to reduce chances of multiple people being infected or quarantined simultaneously. Stroke teams need to strike a balance between serving and taking care of their own health and safety. It is imperative to develop protocols that provide clear guidance on when a patient needs to be ethically denied intervention. Most importantly, the heads of stroke units need to ensure that no person, stroke team member, or paramedic, is unnecessarily put into a high-risk situation due to unclear protocols.

General Preventive Measures: Current constraints require the adoption of general infection control measures and public health policy as comprehensive measures to fight against COVID-19. The most excellent preventive measures for the moment include hand hygiene, respiratory hygiene, environmental hygiene, timely reporting, and diagnosis. Infants, young children, and individuals above 60 years old are most vulnerable to infections. In addition, those with chronic diseases, including hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease, malignancy, kidney disease, and hepatitis are also at risk.

All patients who fit the case definition should be rigorously screened upon entry into facilities. Repeated screening should be conducted to boost the preventive effects for already admitted patients, caregivers, healthcare workers, and personnel. Quarantine should be demanded for those who fit the case definition. When suspected cases are founded, the cases should be reported, and protective measures should be taken to prevent cross-infection.

13.1. Strategies for High-risk Patients

Risk factors in COVID-19 patients have not yet been completely determined, but the patient population in this study appears to be comparable to those found in other studies. However, a few potential risk factors warrant further discussion. First, the majority of patients with AIS in this study had undergone either catheter angiography or computed tomography angiography examination. Appropriate imaging studies were unlikely to be obtained early in the pandemic; this may introduce selection bias and overestimate the prevalence of CAD. Even in studies published subsequently, patients who had brain MRI were not the overwhelming majority of patients with stroke, hence generalizability of findings cannot be guaranteed (Vogrig et al., 2020). The relatively limited number of patients with nationally representative regional/ethnic diversity also raises concern regarding generalizability. CADs were analyzed as a possible risk factor in the presence of stroke. However, having undergone CT

angiogram examination beforehand in this patient population may confound the result. Finally, both the presence and absence of embolism found on imaging studies were collectively defined as being embolism, potentially introducing bias and unintentionally overlooking large artery atherosclerosis and other formations. More representative and comprehensive analyses are being planned.

Implications of Treatment on the Mechanism of Stroke: Early Unreported Treatment with COVID Medications and Apparent Corresponding Stroke Hyperacute After Initiation of New Medication in 2 Patients Raises Important Questions of Causation. Two representative patients are presented here to identify issues involving prevention, detection, reporting, and treatment. These patients were otherwise asymptomatic, and COVID treatment had just begun, but they both had acute strokes within 48 hours, going from no risk factors to high risk. Likewise, 2 patients treated with hydroxychloroquine presented atypical small vessel strokes with an unusual CT finding of multiple punctate bilateral hyperdensities after 3-5 days, suggesting a prothrombotic pathway. Many treatments of COVID potentially modify cardiovascular, coagulation, or bioavailability issues, thereby generating mechanisms of stroke not yet adequately studied. If COVID medications are the cause, then treatment strategies need to be altered to allow properly dosed anticoagulation or antiplatelet medications. Evaluation of cardiovascular safety and cerebral blood flow should be included in future studies.

13.2. Public Health Recommendations

Some public health recommendations are highlighted below:

1. A Health System Preparedness Strategy Must Be Made: • A continuous infection surveillance system from dengue and COVID-19. • Validate the efficacy in reducing case incidence. • Identify the risk factors for severe infection risk. • Identify the critical to essential service readiness for both the epidemic. • Assess the local capacity to decant patients with early intervention at different levels of care before hospital admission.
2. Advocacy on Healthy Behaviour Must Be Made: • Early infant-feeding and healthy nutrition. • Increase physical activity to enhance immunity and physical well-being. • Promote stress management, positive mental well-being, and healthy sleep.
3. Research to Gate the Need of Adult Health Services Must Be Conducted: • Mental health research that is relevant to epidemic situations. • Assistance research the effectiveness of interventions for case detection and containment of epidemics. • Maternal and child health research during and around an epidemic. • Study the impact of an epidemic on other mortality, morbidity, and unmet health service needs including PTSD. • Track the prevalence and risk factors of an epidemic-related chronic health problem.
4. Policy and Governance Change Must Be Addressed: • Budgeting and governance to manage an epidemic. • Integration of infectious disease control and health promotion in better days and epidemic days. • Governance of mass media to ensure the accuracy. • Development of effective public and private partnership.
5. Policy and Governance Change Must Be Addressed: • Budgeting and governance to manage the epidemic. • Integration of infectious disease control and health promotion in better days and epidemic days. • Governance of mass media to ensure the accuracy. • Development of effective public and private partnership.

FUTURE RESEARCH DIRECTIONS

Future studies are needed to investigate the characteristics of lacunar strokes in COVID-19 patients, taking into account potential confounders and stratified analyses. It is recommended that adulthood be controlled for in future studies, as well as potential confounders such as patients treated with aspirin, hypertension, diabetes mellitus, and cardiac disease. Studies should be posted in raw data format, and a high level of disclosure is recommended (Wei Lee et al., 2020). Lacunar strokes are significant; however, to the best of the researcher's knowledge, no study has reported this issue in COVID-19 patients thus far. One of the advantages of the current research is that, unlike previous studies showing a lower stroke proportion, lacunar strokes are also included. Given the high mortality of lacunar strokes and their potential association with a higher risk of further strokes, the need for heightened monitoring after COVID-19 if they are detected, or if the TR/CT is borderline, is suggested. It is also recommended that aspirin be used with caution, as regards further ischemic events, since the cause of morbidities or mortalities is unknown, especially in the absence of other risk factors for asthma or intrinsic airways disease (Marina Ferreira de Oliveira et al., 2020). Some questions surrounding CT imaging in the group of acute strokes remain as well, specifically whether there were ventilation/perfusion mismatches during initial scans.

14.1. Gaps in Current Knowledge

Lacunar strokes are small subcortical infarcts that arise as a result of small-vessel occlusion. They account for approximately 25% of all ischemic strokes and more than 60% of all strokes in Asian populations. Lacunar strokes can occur in the absence of large vessel occlusion and on MRI are known as lacunar infarcts. Although lacunar strokes and COVID-19 have been established as an independent risk factor, there is limited literature which quantify these strokes in this cohort and investigate their clinical and radiological characteristics. This study aims to address these concerns in COVID-19 patients with lacunar strokes.

A search was performed of the local stroke registry, local tertiary care hospital medical records, and logbooks of radiologists for COVID-19 positive patients with a diagnosis of stroke from March 01, 2020 to March 01, 2022. Demographic, clinical, laboratory, and imaging details were abstracted. Imaging was reviewed and interpreted by a radiologist. The frequency of lacunar strokes was determined. Age, sex, premorbid function, clinical manifestations, imaging characteristics, and the presence of overt vascular risk factors were then analyzed. Testing of association of various factors with lacunar stroke was performed using Chi-squared tests. A p-value of <0.05 was considered significant.

Conventional vascular risk factors can be seen in lacunar strokes, however, its risk factors differ from large vessel strokes. Lacunar strokes have generally been reported to have better outcomes when compared to cardioembolic strokes. Three subtypes of lacunar

strokes (pure motor, pure sensory, and sensorimotor) have been defined. A majority of patients in this cohort had a previous known diagnosis of hypertension and diabetes mellitus. These patients commonly exhibited dysarthria and fine motor impairments during the admission period. They were also likely to have small size ischemic infraction involving the basal ganglia, with few perforating vessels having noteworthy occlusion. All of these patients had good modified Rankin Scale scores on follow up.

14.2. Potential Areas for Further Study

There are several recommendations for potential areas of research and clinical investigation that would further enrich the scientific discussion and clinical management of lacunar strokes in patients with COVID-19. As further studies on these topics are warranted, their increasingly trending nature and relative dearth in existing literature emphasize this necessity.

First, research in other languages may extrapolate upon and inform the findings in this study, as they may be relevant to understanding lacunar strokes in patients with COVID-19 in different contexts. Non-English studies on COVID-19 and lacunar strokes exist, which may present additional clinical findings and information on the epidemiology of lacunar strokes in COVID-19 (Wei Lee et al., 2020). English-language studies may not encompass the entire scientific discourse on the topic, as data loss with translation and content nontransferability is possible. Further studies specifically in other languages—e.g., Chinese, Russian, Spanish, etc.—may present significant clinical findings and epidemiological characteristics regarding COVID-19 and lacunar strokes and enrich the scientific knowledge on the topic.

Second, nest-building would be an important avenue of further research that would greatly increase the accuracy of knowledge on the topic. In accordance with the expanded view of "nesting" put forth in the methodology section, a focused understanding of relevant prior studies is imperative to a more systematic and continuous discourse on the relationships between lacunar strokes and COVID-19. Results obtained using different methodologies may not correctly represent potential contexts of lacunar strokes in patients with COVID-19 if comparison between paradigms and datasets is impossible. Independent studies focusing specifically on the methodology-based perspectives presented in the methodology section may enable better comprehension of the where, when, and how of lacunar strokes in patients with COVID-19. More systematic metaphorical studies may investigate the whom and the why respectively related to this topic.

Other relevant studies that investigate detailed clinical characteristics—i.e., life history and symptoms—of lacunar strokes in patients with COVID-19 and detailed epidemiological studies would be extremely helpful for clinical investigation and understanding of the topic's epidemiology.

CONCLUSION

Infections or diseases affecting the cardiovascular system can result in several cerebrovascular complications in the form of strokes, including ischemic or hemorrhagic strokes. The present study demonstrated a significant increase in the frequency of lacunar strokes in patients with COVID-19. The awareness of this often overlooked complication will make for a very important addition to the care of COVID-19 wave patients. These patients were more severely ill, with a high CRP level at presentation and a higher proportion requiring admission to ICU, as well as a longer length of hospital stay. Only few studies exist that address the topic, but the preservation of hypocapnia and hypercapnia responses in a cohort of patients infected is probably not the pathway for the occurrence of post-COVID strokes.

Unfortunately, most of the other studies on COVID-19 stroke patients focus on outcome variables or demographic or risk factor-related findings, which are very difficult to compare to this study. Amongst COVID-19 stroke patients, it would be of interest to highlight if lacunar strokes are the most frequent one. In a single-center cross-sectional study involving about 9000 inpatients, the prevalence of stroke was found to be 3.9% of COVID-19 patients admitted to hospitals. However, this was probably heavily underreported. Although the present report included prospective data collection and multiple data collection schedules after the initial thorough neurological examination, it is still possible that some lacunar strokes may have been unreported.

LACs of the "silent lacunar infarct" type can be very subtle. LACs arising from small penetrating arteries can be hidden from initial examinations since they often do not lead to acute symptoms and become manifested as volume loss only on follow-up imaging. Nevertheless, it is important to note that acute, symptomatic lacunar strokes can remain unnoticed due to a smaller than 1.5 cm lesion size and low clinical suspicion of a stroke. It would be of interest to highlight whether the present findings hold also true in post-COVID-19 cohorts. The actual follow-up design of the present study is fundamentally flawed, as is often the case in similar reports. For example, the same initial time points, complications, etc. should have been selected; hence, in this case, only in-hospital stroke should be included.

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