

Prevalence of Stroke in Post COVID-19 Patients and their Association with Comorbidities: Literature Review

G. Naga Teja Sri¹, Prasanna Mohan²

¹MPT Final Year Student (Neurological Disorder), Department of Physiotherapy, Garden City University, Bangalore, Karnataka, India

²Associate Professor, Department of Physiotherapy, Garden City University, Bangalore, Karnataka, India

Abstract: Introduction: In early December 2019, several cases of unknown origin pneumonia were described in Wuhan, the capital of Hubei Province in China. In less than a 4month interval, a novel coronavirus, SARS-CoV-2 (COVID-19), was identified as the causative agent, and the infection quickly spread from China to the rest of the world, becoming a pandemic by March 2020. Brain is the potential target to COVID-19, just as the lungs, due to expression of angiotensin-converting enzyme (ACE 2) receptors on the glial cells and neurons of the central nervous system. There have been reports on stroke surge, especially among elderly patients, suffering from COVID-19. Many of the patients presenting with stroke might already have underlying cerebrovascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, smoking, or previous history of stroke. The occurrence of cerebrovascular events in critically ill patients with underlying medical co-morbidities is therefore potentially related to the direct effect of the infection itself or inappropriate host response. Recent research from across the globe indicates that SARS-CoV-2 infection is connected with both ischemic and hemorrhagic strokes. Stroke has emerged as a severe neurological complication of SARS-CoV-2 infection. The need of the study: There are many studies regarding neurological disorders after recovery from COVID-19. This study mainly focuses on COVID-19 related strokes and whether these strokes are causing because of the presence of comorbidities. And their interrelation with each other. It is important to know their relation because of increasing number of COVID related strokes. Objectives: To Review the articles which have studied about COVID-19 related strokes and their association with comorbidities. Sources of data: Relevant studies from onset of COVID-19 i. e. from 2019 – 2022 were obtained from the following data bases: PUBMED, SCIENCE DIRECT, GOOGLE SCHOLAR library using key words COVID-19, corona virus pandemic, Neurological disorders, prevalence of stroke. Conclusion: Cerebrovascular events are relatively common findings in COVID-19 infection, and they could have a multifactorial etiology. COVID-19 Related strokes are more common between the age group 40 – 70. Males are affected more when compared to females. Symptoms like headache, loss of sensation, weakness in extremities, poor cognitive abilities are seen in patients after recovery from COVID-19. Cerebrovascular symptoms began at a median of 10 days (range 0-33) after onset of respiratory illness.

1. Introduction

In December 2019, several cases of unexplained pneumonia were diagnosed in Wuhan, China and then also diagnosed in other regions of (1) world, creating a global pandemic. Corona virus disease 2019 (COVID-19) is caused by a severe acute respiratory syndrome (SARS-Co-V-2). It is transmitted via air droplets during incubation and symptomatic phases, incubation period is about 5 days on average. (2) .

In most patients the disease is characterized by fever, dry cough, dyspnea, and hypoxia, with interstitial pneumonia features on chest x-ray or computerized tomography scan. And it is confirmed with RTPCR or validated antibody test. It is the largest and most severe pandemic since 1918 influenza.

COVID-19 is a multisystem inflammatory disease with neurological involvement. Neurological complications associated with COVID-19 range from mild complications such as headache and anosmia to more severe complications such as encephalitis and stroke. (3) Stroke is a medical condition in which poor blood flow to brain causes cell death. There are two main types of strokes: Ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding. Both cause part of the brain to stop functioning properly.

The incidence of stroke has been observed as a significant neurological complication in individuals infected with SARS-CoV-2. With the surge in COVID-19 cases in India, the occurrence of COVID-related strokes is on the rise.

Brain is the potential target to COVID-19 just as lungs due to expression of (ACE) Angiotensin Converting Enzyme receptors on glial cells and neurons of CNS. Angiotensin converting enzyme 2 (ACE2) is not only enzyme but also a functional receptor on cell surfaces through which SARS-COV-2 enters the host cells. ACE2 is a key regulator of the renin-angiotensin-aldosterone system (RAAS). SARS-COV-2 causes ACE/ACE2 balance disruption and RAAS activation, which leads ultimately to COVID-19 progression, especially in patients with comorbidities, such as hypertension diabetes mellitus, and cardiovascular disease.

Therefore, ACE2 expression may have paradoxical effects aiding SARA-COV-2 pathogenicity. This protein provides entry point for the corona virus to hook into and infect a wide range of human cells. (4)

The SARS-CoV-2 virus enters cells by binding to the angiotensin-converting enzyme 2 (ACE2) through its spike protein (5). Additionally, transmembrane protein serine protease 2 (TMPRSS2) is necessary for viral entry (6). ACE2 is part of the renin-angiotensin system (RAS), which is responsible for regulating blood pressure. Renin, produced in the kidney, converts angiotensinogen, synthesized in the

liver, to angiotensin I. ACE1 then converts angiotensin I to angiotensin II, which binds to angiotensin 1 (AT1) and angiotensin 2 (AT2) receptors. AT1 activation results in vasoconstriction, aldosterone secretion, sodium and water retention, proinflammatory and pro-coagulation effects, and increased blood pressure. Angiotensin II exacerbates heart failure and acute respiratory distress syndrome (ARDS). AT1 blockers are commonly used as antihypertensive drugs and are beneficial for organ protection, including the brain. The virus that caused the 2003 SARS pandemic, SARS-CoV-1, also binds to ACE2 (7) (8).

A comorbidity is any coexisting health condition. The prefix “co” means together and the word “morbidity” is the medical term for a health condition. It can also be described as cooccurring or coexisting conditions. Comorbidities sometimes interact with each other, but they can also exist entirely separately. Some conditions may raise your risk of developing others or may commonly occur together. For example, a heart attack often occurs with stroke or vascular disease. Chronic kidney disease may occur with hypertension and anemia. Comorbidities are often chronic conditions and can include physical or mental health. (9) It’s possible to have many comorbidities at the same time. For example, a person could have depression, arthritis, diabetes, and high blood pressure.

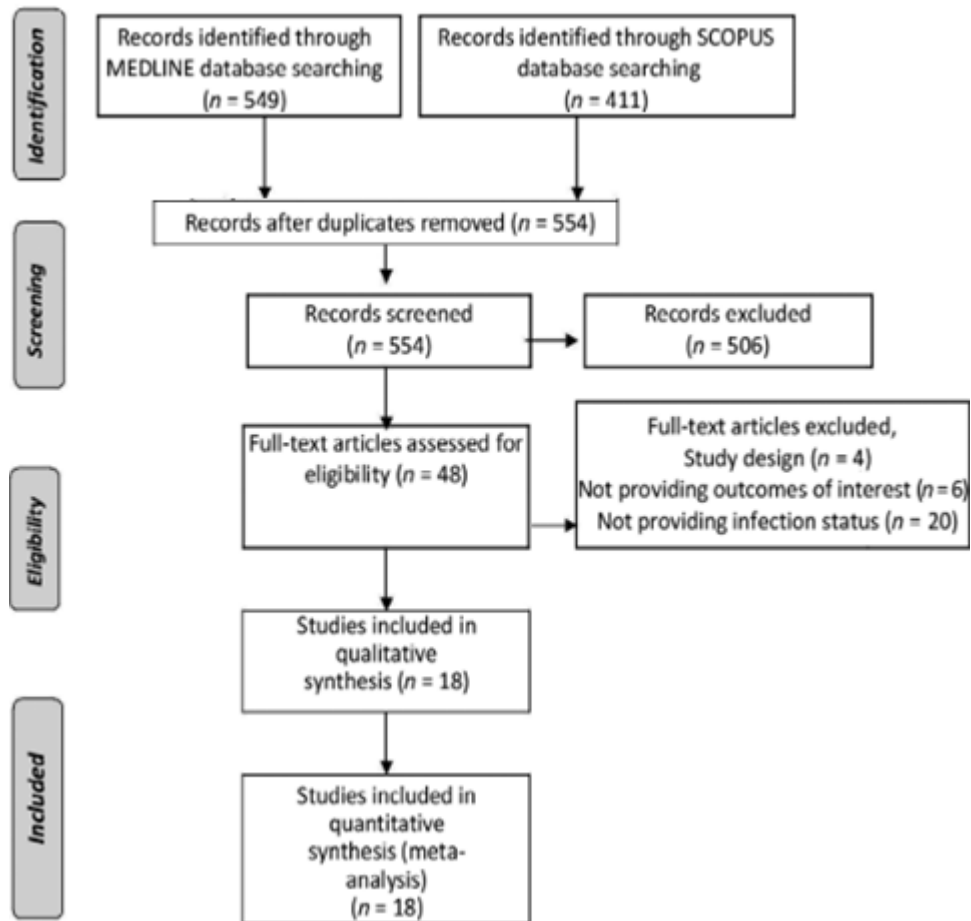
Among patients with COVID-19, serum D-Dimer level is generally increased, which could be the source of embolic vascular event. Studies suggested that excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation predispose to an increased risk of thrombo-vascular event reaching up as high as 31% among ICU patients with COVID-19. Many of the patients presenting with stroke might already have underlying cerebrovascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, smoking, or previous history of stroke. The occurrence of cerebrovascular events in critically ill patients with underlying medical comorbidities is therefore potentially related to the direct effect of the infection itself or inappropriate host response. (10)

Need of the study

- Stroke is one of the leading causes of death and disability in India.
- The estimated adjusted prevalence rate of stroke range, from 84-262/1, 00, 000 in rural and 334-424/1, 00, 000 in urban areas.
- Especially its occurrence in patients who had recovered from COVID-19 is an area which has to be researched further.
- Comorbidity is another aspect of post COVID-19 stroke patients which has a significant role.
- This study helps the society in such a way that people will know the consequences after recovery from COVID and take the necessary precautions after COVID.
- This study is beneficial to those particular people who are at higher risks of developing stroke after recovery from COVID.

2. Methodology

We conducted a comprehensive search for relevant studies from the onset of the COVID-19 pandemic, spanning from 2019 to 2023. We searched the following databases: PubMed, Google Scholar, and ScienceDirect library, using keywords such as COVID-19, coronavirus pandemic, neurological disorders, and prevalence of stroke. A total of 549 records were identified through these searches, and an additional 411 records were identified through Scopus. After removing duplicate and irrelevant records, we were left with 554 articles for screening. Of these, 506 articles were excluded based on our inclusion criteria. The remaining 48 articles underwent full-text review, during which 4 articles were excluded due to study design, and 6 articles were excluded for not providing outcome measures of interest. Additionally, 20 articles were excluded for not providing information on the infectious state. Finally, we included a total of 18 articles in our analysis.



3. Review of Literature

S No.	Author	Year & Journal	Title	Type of Study	Conclusion	Results
1.	Thomas Mathew et al. (10)	2021 – International journal of stroke.	COVID-19 related strokes which are associated with increase in mortality and morbidity rate.	A multicenter comparative study	Amid a state of grave apprehension, developing nations such as India have experienced a notable rise in COVID-19-related fatalities. Individuals diagnosed with COVID-19 commonly suffer from strokes of undetermined origin. COVID-19 has had a more severe impact, resulting in elevated rates of illness and death. Factors such as hypertension, atrial fibrillation, and higher NIH Stroke Scale (NIHSS) scores have been linked to increased mortality.	During the three-month period, there were 62 cases of COVID-19 stroke in 13 centers; There were 60 (97%) ischemic strokes and 2 (3%) hemorrhagic strokes. The average age of patients is 55.66? 13.20 years, with 34 (77.4%) men. Twenty-six percent (16/62) of patients had no conventional risk factors for stroke. Diabetes occurred in 54.8%, hypertension in 61.3%, coronary artery disease in 8%, and atrial fibrillation in 4.8%.
2.	Aristeidis H. Katsanos, MD et al. (1)	2021 – Annals of Neurology.	Impact of SARS-CoV-2 on stroke epidemiology and treatment.	A meta-analysis	SARS-CoV-2 appears to be associated with an increased risk of ischemic stroke, and potentially crypto-genic stroke in particular. It may also be related to an increased mortality risk.	We identified 18 cohort studies including 67, 845 patients. Among patients with SARS-CoV-2, 1.3% (95% CI = 0.9–1.6%, I2 = 87%) were hospitalized for cerebrovascular events, 1.1% (95% CI = 0.8–1.3%, I2 = 85%) for ischemic stroke, and 0.2% (95% CI = 0.1–0.3%, I2 = 64%) for hemorrhagic stroke. Compared to noninfected contemporary or historical controls, patients with SARS-CoV-2 infection had increased odds of ischemic stroke (OR = 3.58, 95% CI = 1.43–8.92, I2 = 43%) and cryptogenic stroke (OR = 3.98, 95%

						CI = 1.62–9.77, I2 = 0%). Diabetes mellitus was found to be more prevalent among SARS-CoV-2 stroke patients.
3.	Isabel Siow et al. (11)	2021-Journal of stroke and cerebrovascular diseases.	Stroke as a neurological complication of COVID-19.	A systematic review and meta-analysis	Although stroke is a rare complication of COVID-19, it is now a common cause of significant morbidity and mortality. In patients with COVID-19, stroke is associated with older age, frailty, and comorbidities.	A total of 5, 599 people had 899 strokes. The average age of stroke patients due to complications of COVID-19 was 65.5 (Range: 40.4?76.4 years). The median incidence of stroke as a complication of COVID-19 was 1.74% (95% CI: 1.09% to 2.51%). The median stroke mortality in patients with COVID-19 was 31.76% (95% CI: 17.77% to 47.31%).
4.	Rizaldy Taslim Pinzon et al. (12)	2021-Hindawi Case Reports in Medicine	Ischemic Stroke following COVID-19 in a Patient without Comorbidities	A case report study	It is important to take into account the possibility of ischemic stroke in COVID-19 patients who do not display symptoms.	A male patient, aged 40, reported symptoms of impatience, inattention, and forgetfulness. The individual had contracted COVID-19 five weeks prior. A non-contrast MSCT scan confirmed the presence of multifocal lacunar cerebral infarction in the left ventricle. Laboratory tests revealed a rise in D-dimer levels, up to 1.22 g/ml.
5.	Zaki, Nazar Alashwa et al. (13)	2020-Diabetes and Metabolic Syndrome: Clinical Research and reviews	Association of high and severe cholesterol and death from hypertension, diabetes, stroke, cancer, kidney disease, and COVID-19.	A systematic review.	Reports of cancer, kidney disease, and stroke with COVID-19 should be interpreted with caution, not only because of the sample size, but also because the patients are older, have a history of smoking, or have other clinical conditions. These factors may be associated with poorer COVID-19 outcomes than the discomfort itself.	A total of 54 articles were considered for the full review. Diabetes, hypertension, and cholesterol levels all have significant correlations with the severity of COVID-19. Other disorders such as cancer, kidney disease, and stroke should also be evaluated to determine a strong association with the virus.
6.	Abhilasha et al. (9)	2020-Annals of the National Academy of Medical Sciences (India)	Association of Comorbidities with Coronavirus Disease 2019	A Review	Despite taking all the necessary steps to contain the spread of COVID-19, the number of cases is still on the rise, majorly due to lack of awareness. The older population and individuals with chronic illness need to take extra precautions, as the mortality rate is higher among them. Although the search for a vaccine or an effective cure is still on, until then, social distancing and hand hygiene remain the best preventive measures against the fight with SARS-CoV-2.	Within 5 months of its existence, COVID-19 has led to a significant impact on national and international policies. Apart from being a medical emergency, it is also affecting the global economy, and without proper measures, it may have severely impacted the socioeconomic statuses of individuals. It has profoundly challenged the healthcare infrastructure, particularly in low-and middle-income nations. Every nation is trying to safeguard its population and the health workers as adequately as possible.
7.	Jay Liuhong Liu et al. (14)	2020 – journal of clinical neuro science	Descriptive analysis of acute ischemic stroke in patients with COVID-19 during the COVID-19 pandemic.	Descriptive Analysis	AIS in COVID-19 is a rare event, and vigilance should be expected, especially in patients with prolonged unexplained encephalopathy, abnormal thrombotic symptoms, and a history of stroke.	35 patients (women [19/35, 54%]; mean Among them were 2512 patients with AIS and COVID-19 (age 63.3 years [SD 13.4, range 30–89 years]). A total of 19 cases of AIS were diagnosed from the first group of 1400 patients with COVID-19 (1.36%), and 16 from the second group of 1112 patients (1.44%).
8.	Wenzhang Luo et al (15)	2021 – Journal of Neurology	The occurrence of ischemic stroke has been linked to COVID-19.	According to asystematic review and meta-analysis.	Ischemic stroke resulting from COVID-19 is characterized by unique clinical features. While traditional risk factors may still be present, their significance could be altered. Moreover, male patients tend to exhibit a greater inflammatory response to COVID-19. Another complication associated with	A total of 280 individuals who had both ischemic stroke and COVID-19 were chosen.

					COVID-19-related strokes is an increase in the occurrence of cryptogenic strokes.	
9.	Cristian Deana et al. (16)	2021-Journal of Brain Hemorrhage	Acute stroke in patients treated in the intensive care unit after infection with COVID-19.	Case Report	There is a direct correlation between the severity of COVID-19 illness and the likelihood of experiencing a stroke. While stroke occurrences are not common among patients in intensive care units (ICUs), cerebral hemorrhage is a severe and deadly complication.	Individuals diagnosed with COVID-19 may necessitate admission to an intensive care unit, primarily due to acute respiratory failure. Nevertheless, neurological symptoms are also frequently observed. Ischemic stroke and cerebral hemorrhage are among these symptoms and can prove fatal. While the mechanism by which SARS-CoV2 causes brain damage is still being debated, the most widely accepted theory involves endothelial activation. This activation raises the risk of thrombus formation, which contributes to the progression of both ischemic and hemorrhagic strokes.

We conducted a comprehensive search for relevant studies from the onset of the COVID-19 pandemic, spanning from 2019 to 2023. We searched the following databases: PubMed, Google Scholar, and ScienceDirect library, using keywords such as COVID-19, coronavirus pandemic, neurological disorders, and prevalence of stroke. A total of 549 records were identified through these searches, and an additional 411 records were identified through Scopus. After removing duplicate and irrelevant records, we were left with 554 articles for screening. Of these, 506 articles were excluded based on our inclusion criteria. The remaining 48 articles underwent full-text review, during which 4 articles were excluded due to study design, and 6 articles were excluded for not providing outcome measures of interest. Additionally, 20 articles were excluded for not providing information on the infectious state. Finally, we included a total of 18 articles in our analysis.

4. Discussion

This review included a total of 9 articles, of which two were systematic reviews and meta-analyses that indicated a strong association between COVID-19 and stroke in patients with comorbidities, severe illness, and advanced age, resulting in a higher risk of mortality and morbidity.

Two of the articles were case report studies that indicated a high likelihood of stroke in severe cases of COVID-19 and suggested that ischemic stroke may occur in patients without comorbidities.

A multicenter comparative study found that strokes related to COVID-19 tend to be more severe and result in higher mortality and morbidity rates compared to strokes in non-COVID-19 patients.

The study with descriptive analysis suggests that acute ischemic stroke (AIS) is an infrequent occurrence in COVID-19, and medical professionals should remain vigilant, particularly in patients with prolonged unexplained encephalopathy, abnormal thrombotic symptoms, and a history of stroke.

The review includes a meta-analysis that suggests SARS-CoV-2 infection is linked to a higher risk of ischemic stroke,

especially cryptogenic stroke. This complication may also increase the risk of mortality.

The systematic review included in this study reports that caution should be exercised when interpreting reports of cancer, kidney disease, and stroke with COVID-19, not only due to the limited sample size, but also because the patients tend to be older, have a history of smoking, or have other underlying clinical conditions. These factors may be associated with worse COVID-19 outcomes than the infection itself.

Older individuals with preexisting cardiovascular comorbidities and severe COVID-19 infection were found to be at higher risk for concomitant stroke. The majority of these patients had been admitted with COVID-19 symptoms and subsequently experienced stroke a few days later. Ischemic stroke was the most common subtype and was often characterized by multiple cerebral infarctions and cryptogenic etiology. Compared to strokes in patients without COVID-19, those with COVID-19 and cerebrovascular disease were younger, had more severe strokes, and were more likely to have large artery occlusion as the cause of their stroke.

COVID-19-related mechanisms, in addition to conventional stroke risk factors, are believed to increase the risk of stroke in infected individuals. Three primary mechanisms that contribute to ischemic strokes in COVID-19 have been identified [8, 9] (see Fig.1): a hypercoagulable state, vasculitis, and cardiomyopathy. Although COVID-19-related systemic and cardiovascular changes could potentially increase the risk of all types of ischemic stroke, the attributable risk is expected to be greater for other and cardiac embolism subtypes (larger arrows). It should be noted that in COVID-19 patients, many large artery occlusions may not be due to atherosclerosis but rather embolization from an intracardiac thrombus or paradoxical emboli from deep vein thrombosis (DVT).

The included review article concludes that despite the precautions taken to prevent the spread of COVID-19, extra care should be given to the older population and people with severe illnesses, as the mortality rate is higher among them.

5. Conclusion

Cerebrovascular events are relatively common findings in COVID-19 infection, and they could have a multifactorial etiology. COVID-19 Related strokes are more common between the age group 40 – 70. Males are affected more when compared to females. Symptoms like headache, loss of sensation, weakness in extremities, poor cognitive abilities are seen in patients after recovery from COVID-19. Cerebrovascular symptoms began at a median of 10 days (range 0-33) after onset of respiratory illness.

References

- [1] Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, et al. The Impact of SARS-CoV-2 on Stroke Epidemiology and Care: A Meta-Analysis. *Ann Neurol*.2021; 89 (2): 380–8.
- [2] Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. *Neurology*.2020; 95 (2): 77–84.
- [3] Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol* [Internet].2020; 19 (9): 767–83.
- [4] Stein LK, Mayman NA, Dhamoon MS, Fifi JT. The emerging association between COVID-19 and acute stroke. *Trends Neurosci* [Internet].2021; 44 (7): 527–37.
- [5] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* [Internet].2020; 395 (10229): 1054–62.
- [6] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*.2020; 181 (2): 271-280. e8.
- [7] Kuhn JH, Li W, Choe H, Farzan M. Angiotensin-converting enzyme 2: A functional receptor for SARS coronavirus. *Cell Mol Life Sci*.2004; 61 (21): 2738–43.
- [8] Eslami N, Aghbash PS, Shamekh A, Entezari-Maleki T, Nahand JS, Sales AJ, et al. SARS-CoV-2: Receptor and Co-receptor Tropism Probability. *Curr Microbiol* [Internet].2022; 79 (5): 1–13.
- [9] Mitra P, Suri S, Goyal T, Misra R, Singh K, Garg MK, et al. Association of Comorbidities with Coronavirus Disease 2019: A Review. *Ann Natl Acad Med Sci*.2020; 56 (02): 102–11.
- [10] Mathew T, John SK, Sarma GRK, Nadig R, Kumar R S, Murgod U, et al. COVID-19-related strokes are associated with increased mortality and morbidity: A multicenter comparative study from Bengaluru, South India. *Int J Stroke*.2021; 16 (4): 429–36.
- [11] Siow I, Lee KS, Zhang JJY, Saffari SE, Ng A, Young B. Stroke as a Neurological Complication of COVID-19: A Systematic Review and Meta-Analysis of Incidence, Outcomes and Predictors: Stroke and COVID-19. *J Stroke Cerebrovasc Dis* [Internet].2021; 30 (3): 105549.
- [12] Pinzon RT, Kumalasari MD, Kristina H. Ischemic Stroke following COVID-19 in a Patient without Comorbidities. *Case Rep Med*.2021; 2021: 2–4.
- [13] Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review. *Diabetes Metab Syndr Clin Res Rev* [Internet].2020; 14 (5): 1133–42.
- [14] Lihong J, Shah K, Marji A, Sareini R, Bhasin A, Rao S. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company ' s public news and information.2020; (January).
- [15] Luo W, Liu X, Bao K, Huang C. Ischemic stroke associated with COVID-19: a systematic review and meta-analysis. *J Neurol* [Internet].2021; (0123456789): 1–10.
- [16] Deana C, Bagatto D. Severe stroke in patients admitted to intensive care unit after COVID-19 infection: Pictorial essay of a case series. *Brain Hemorrhages* [Internet].2021; (xxxx).
- [17] David Spence J, De Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, et al. Mechanisms of Stroke in COVID-19. *Cerebrovasc Dis*.2020; 49 (4): 451–8.
- [18] Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke*.2021; 16 (2): 137–49.
- [19] Hess DC, Eldahshan W, Rutkowski E. COVID-19-Related Stroke.2020; 322–5. (18) (19)
- [20] Ahmed ZM, Khalil MF, Kohail AM, Eldesouky IF, Elkady A, Shuaib A. The prevalence and predictors of post-stroke depression and anxiety during COVID-19 pandemic. *Journal of Stroke and Cerebrovascular Diseases*.