

# A Retrospective Cohort Study on Neurological Manifestations in Hospitalized COVID-19 Patients in a Tertiary-Care Hospital in Dubai, UAE

Kasid A. Nouri. MD<sup>1</sup>, Mallika Mehrotra<sup>2\*</sup>, Jeyaseelan Lakshmanan PhD<sup>2</sup>

<sup>1</sup>From Department of Neurology, Mediclinic Welcare Hospital, Dubai, UAE

<sup>2</sup>From Mohamed Bin Rashid University of Medicine and Health Science, Dubai, UAE

\*Corresponding Author: Mallika Mehrotra, From Mohamed Bin Rashid University of Medicine and Health Science, Dubai, UAE.

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## Abstract

### Introduction

SARS-CoV-2 has caused a worldwide pandemic due to its high transmission rate among humans and causing a threat to global health. Numerous recent research suggests that SARS-CoV-2 has detrimental effects on the brain processes and may even cause significant neurological impairment during this continuing contagion. Some of the main neuro-invasion pathways through which SARS-CoV-2 can cause neurologic events are direct invasion, hematogenic routes, hypoxia, and cytokine storm.

### Objectives

We detailed the potential pathways for SARS-CoV-2 entry into the nervous system, the subtypes of neurological manifestations, the underlying comorbidities, and the critical variables that induced them. The central nervous system (CNS) effects of the SARS-CoV-2 infection are evaluated in their neurological manifestations.

### Methods

In the current work, we collected the data of 500 COVID-19 inpatients from the HIS database from June 2020 to June 2021. From this, 460 inpatients met the inclusion criteria, and amongst them, it was found that 46 COVID-19 patients developed neurological manifestations.

### Results and Conclusion

Through the data collected, we analyzed that the majority of the patients who were afflicted by such neurologic events had a mean age of 63 years  $\pm$  16 years and had associated comorbidities such as diabetes, hypertension, and cardiovascular diseases. The most common neurologic subtype was ischemic stroke, with diabetes being the most prevalent comorbidity.

## Introduction

The World Health Organization (WHO) proclaimed on May 5th, 2023, that SARS-CoV-2 is an ongoing health issue that no longer constitutes a public health emergency. However, since the commencement of the epidemic, the WHO has reported 6.5 million COVID-19 deaths and over 633 million cumulative cases globally.

The hematogenous and neuronal retrograde routes are the two major pathways through which SARS-CoV-2 can enter the central nervous system (CNS). SARS-CoV-2 increases vascular permeability through multiple mechanisms. When the virus enters the cells, it initially binds to the human angiotensin-converting-enzyme receptor 2 (ACE2) on the cell surface. This reduces the expression and activity of ACE2 and indirectly activates the kallikrein-bradykinin pathway (KKS) [28]. KKS plays an essential role in endothelial pathogenesis. In normal human physiology, KKS exterminates pathogens by recruiting neutrophils, and spare bradykinin is degraded by ACE, but when there is a decrease in ACE2 activity, it leads to an excess of bradykinin, which causes an increase of activated neutrophils [6]. Neutrophils

produce reactive oxygen species (ROS), damaging tissue and causing vascular leakage. When SARS-CoV-2 infects the endothelial cells of the blood-brain barrier (BBB), it leads to vascular leakages through the pathogenesis mentioned above and, therefore, permits the virus to enter the blood-CSF barrier. SARS-CoV-2 penetrates the CNS via the “Trojan Horse” mechanism, where the virus infects leukocytes, mainly monocytes, as they express ACE2 receptors, and the infected immune cell can migrate through the paracellular route across the permeable BBB and into the cerebrospinal fluid (CSF) [4]. However, according to (Frontera et al., 2021), there is no evidence of SARS-CoV-2 in the CSF of RT-PCR-positive patients. SARS-CoV-2 can also invade the CNS through a neural retrograde route, where the virus travels through retrograde axonal transport to reach the neuron cell bodies of the central nervous system [15]. Recent research indicates headaches, mental confusion, strokes, and rarely encephalitis may be early signs and symptoms that suggest neurotropism in SARS-CoV-2 [42].

This study aims to establish the frequency of COVID-19 ICU inpatients developing neurological manifestations, which is the outcome of interest, and what underlying exposures, such as associated comorbidities, can predispose the inpatients to build this.

## Methodology

### Research design

A retrospective cohort study was conducted, which included COVID-19 ICU inpatients in Mediclinic Welcare Hospital. Dubai, UAE, between June 1st, 2020, to June 1st, 2021. Mediclinic Welcare was proclaimed a COVID-19 ICU, making it the choice for data collection.

### Participants

The inclusion criteria for this study were inpatients who tested reverse transcriptase PCR (RT-PCR)- positive for SARS-CoV-2 infection, as it was the most sensitive and specific test for detecting COVID-19 and it reduced the risks of a false positive [14]. Furthermore, this study focused on COVID-19 patients admitted into the hostile pressure intensive care unit (ICU), as most of the severe COVID-19 inpatients were welcomed there, allowing us to collect the data on inpatients with a higher chance of developing neurological manifestations. Moreover, we only included COVID-19 inpatients with neurological manifestations who were assessed based on the neurological assessment chart [2] done by a consultant neurologist and had neuroimaging, EEG, or neurophysiological studies done.

The exclusion criteria for this study were inpatients aged  $\geq 18$  years. The majority of COVID-19 inpatients  $\leq 18$  years had a different

disease presentation compared to inpatients  $\geq 18$  years [11].

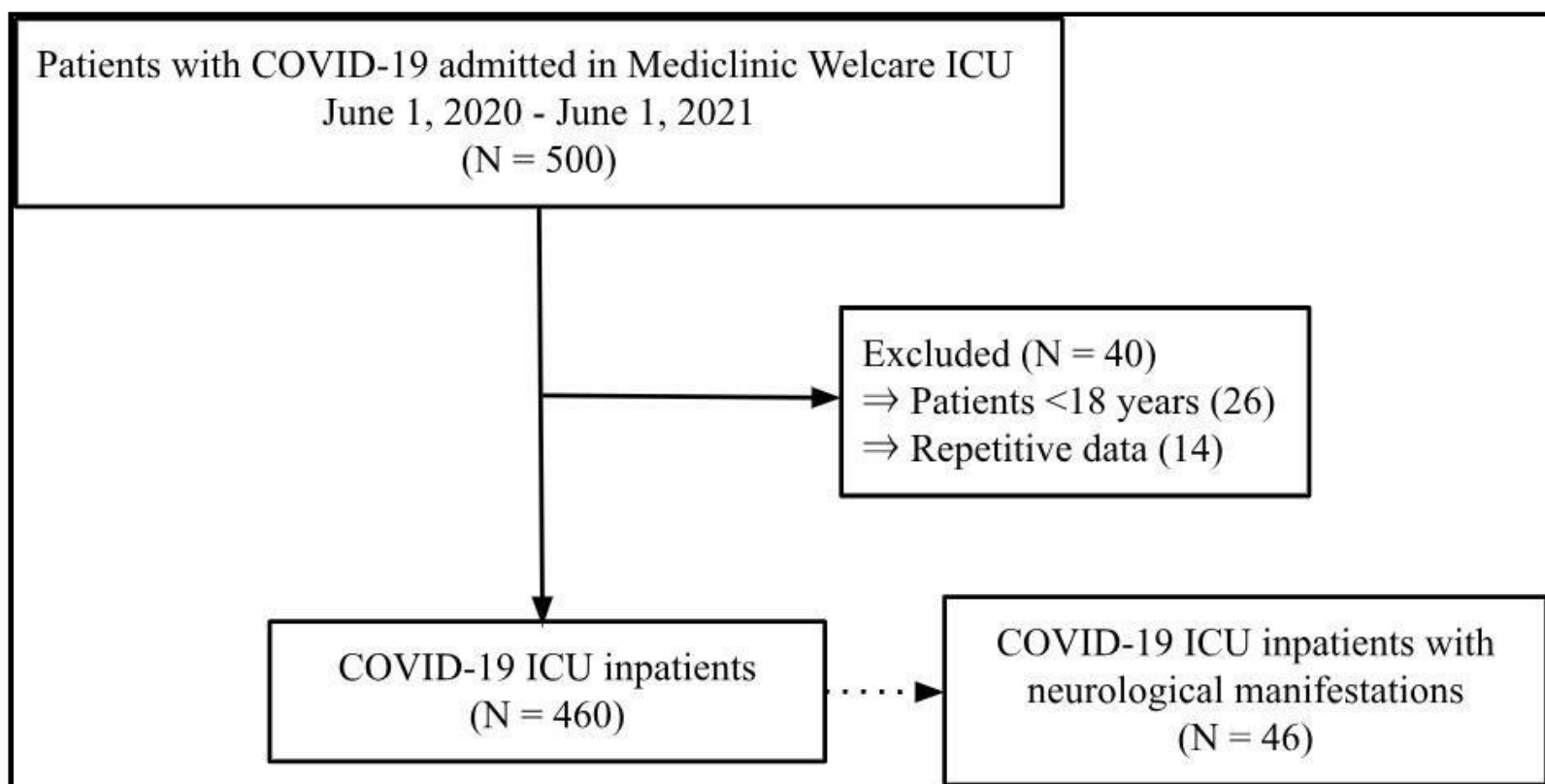
Moreover, inpatients  $\leq 18$  years would have other exposures than the underlying comorbidities this research aims to find. Additionally, repetitive data was also excluded from the data collection. The records of 500 COVID-19 inpatients were collected, and after acknowledging the inclusion and exclusion criteria, we had data of 460 COVID-19 ICU inpatients. Among the 460 inpatients, 46 developed neurological manifestations during their hospitalization.

### Equipment and materials

The equipment used for this research were secure desktop computers found in Mediclinic Welcare Hospital. The data was collected using the HIS database. The database comprises information on the patient's demographics, such as gender, age, and nationality. It also collected data on their past medical records, underlying chronic comorbidities, allergies, and vital status. Furthermore, it contained the data of the patient's vitals, complete blood count (CBC), and chest scans to prove COVID-19 pneumonia. The data found on the database was already recorded, making it scored data. This data was then analyzed on *Statistical Package for The Social Sciences (SPSS)* to find the significance between the development of neurological events and the potential exposures that could have led to the outcome of interest.

## Results

In this retrospective cohort study, of the 460 COVID-19 ICU inpatients (62.0% men), 46 of these inpatients presented with neurological symptoms.



**Figure 1:** Flow chart of study enrolment

The most common subtypes of primary neurologic events seen were Ischemic stroke (60.9%), polyneuropathy (19.6%), seizures (10.9%), and haemorrhagic stroke (6.5%).

**Table 1:** Mean and Standard deviation for continuous data

	Neurological manifestations										P Value
	Yes					No					
	Mean	SD	Median	Percentile		Mean	SD	Median	Percentile		
			25	75				25	75		
Age	63	16	64	56	74	50	14	49	40	59	0.000
Hospital duration	71	67	48	32	91	14	31	7	4	11	0.000
BMI	31	9	28	26	32	30	6	29	26	32	0.443
WBC	12.0	6.1	13.4	6.7	16.1	7.4	4.4	6.2	4.7	8.8	0.000

The mean hospital duration for COVID-19 patients without neurological symptoms was 14 days  $\pm$  31, with a median of 7 days. However, the mean for inpatients who developed neurological events was 71  $\pm$  67, with a median of 48 days. There is a significant difference between the hospital duration for COVID-19 in patients who developed neurological events compared to inpatients who did not, and this can be supported by a  $P < 0.05$  showing the significance. Even though there is a significant difference between the means, the standard deviations are enormous for both groups, indicating a substantial variance in the data, signifying that the data is spread out. Therefore, affecting the reliability of the data collected. Furthermore, there is a significant difference between the mean ages of COVID-19 inpatients who did and did not develop neurological consequences. Patients who did not develop neurological manifestations had a mean age of 50 years  $\pm$  14, whereas patients who did develop neurological manifestations had a mean age of 63 years  $\pm$  16. This shows that, on average, patients with neurological symptoms were older than patients without. This can be supported by the ( $p < 0.05$ ), signifying the link between these two variables.

The BMI of COVID-19 inpatients with neurological manifestations is 31  $\pm$  9 compared to inpatients without any manifestations being 30  $\pm$  6. There isn't a significant difference between the BMIs, and it can also be seen that the medians are very similar, with 28 and 29 BMI, respectively. This is further proven by ( $P > 0.05$ ), showing that the variable is insignificant.

It can also be seen that patients who developed neurological symptoms had a greater mean white blood cell count (WBC) of 12  $\pm$  6.1 as compared to inpatients who did not, with a mean WBC of 7.4  $\pm$  4.4. According to WHO, the range of WBC should be between 4.5 to 11.0  $\times 10^9/L$ , and the mean and median WBC of COVID-19 patients who developed neurological symptoms surpasses that with a WBC of 12 and 13.4, respectively. The ( $p < 0.05$ ) shows a significant correlation between the two variables. A higher WBC count correlates with a more severe infection, thus signifying that patient with neurological manifestations had a more severe COVID-19 illness. Moreover, the standard deviation is slight for both groups; therefore, it is clustered around the mean and thus increases the reliability of the data.

**Table 2:** Status of COVID-19 inpatients with and without neurological manifestations

Status of COVID-19 inpatients						P value
			Status		Total	
			Alive	Dead		
Neurological Manifestations	Yes	Count	32	14	46	0.000
		%	69.6%	30.4%	100.0%	
	No	Count	397	17	414	
		%	95.9%	4.1%	100.0%	
Total		Count	429	31	460	
		%	93.3%	6.7%	100.0%	

The table above shows that the total mortality of COVID-19 ICU inpatients is 6.7% (95% CI: 4.4, 9.0). However, the mortality rate of COVID-19 ICU inpatients who developed neurological events was 30.4%, whereas patients who did not create such events had a mortality of 4.1%. This shows that there was a significant increase in mortality rate when a patient had a neurological manifestation, and this can be further supported by a ( $P < 0.05$ ). Furthermore, in (Frontera et al., 2021), it can be seen that COVID-19 in patients who developed

neurological disorders had a mortality of 35%, which is close to the mortality rate seen in Mediclinic Welcare Hospital.

However, in (Frontera et al., 2021), the mortality rate for COVID-19 inpatients without any neurological disorders is 19%, whereas in Mediclinic Welcare Hospital, it is 4.1%. There is no definitive reason for such a remarkable difference in the mortality rates. However, this difference could be because of the sample size. In (Frontera et al.,



2021), the sample size is 4,491, whereas in this paper, it is 460 inpatients.

According to Table 3, there is no significance between the gender of the patient and whether they will develop neurological consequences. This might be because, in both groups, there is a male predominance, causing asymmetrical distribution and leading to skewed data.

Looking at (Table 3). it can be noted that the most significant comorbidities that could have predisposed COVID-19 inpatients to develop neurological symptoms are diabetes, cardiovascular diseases, and hypertension. Renal disease and hematological conditions. This is proven by (P<0.05).

**Table 3:** Association Between Co-morbidities and Neurological Manifestations

		Neurological Manifestations				P value
		Yes		No		
		N	%	n	%	
Gender	Male	25	8.8%	260	91.2%	0.168
	Female	21	12.0%	154	88.0%	
Diabetes	Yes	34	23.3%	112	76.7%	0.000
	No	12	3.9%	299	96.1%	
Cardiovascular disease	Yes	20	17.9%	92	82.1%	0.002
	No	26	7.5%	319	92.5%	
Hypertension	Yes	32	19.3%	134	80.7%	0.000
	No	14	4.8%	277	95.2%	
Renal disease	Yes	7	30.4%	16	69.6%	0.005
	No	39	9.0%	395	91.0%	
Gastro-hepatic conditions	Yes	4	17.4%	19	82.6%	0.192
	No	42	9.7%	392	90.3%	
Haematological conditions	Yes	6	35.3%	11	64.7%	0.004
	No	40	9.1%	400	90.9%	
Autoimmune conditions	Yes	3	21.4%	11	78.6%	0.158
	No	43	9.7%	400	90.3%	
Past surgery	Yes	5	12.8%	34	87.2%	0.354
	No	41	9.8%	377	90.2%	
Secondary infections	Yes	29	46.8%	33	53.2%	0.000
	No	16	4.0%	380	96.0%	

### Acute stroke

Acute stroke is classified into 2 subcategories, either ischemic or hemorrhagic stroke. As seen in Table 10. the most common neurological event in COVID-19 inpatients was stroke. Around 60.9% of COVID-19 inpatients with neurological events present with ischemic stroke as their primary manifestation (Table 10). and 6.5% current with hemorrhagic stroke Table 11.

The patients were clinically diagnosed with acute stroke using either computed tomography (CT), magnetic resonance imaging (MRI), or angiogram. It also helped determine whether the patient was suffering from an ischemic or hemorrhagic attack. Looking at Table 6. we can see that patients who had a CT scan done have a lower mortality. This is also proven by (P<0.05), making the variable significant and concluding that a CT scan should improve survival rates.

Table 6 shows that an MRI or cerebral angiogram does not significantly affect the mortality rate (P>0.05). According to the article (Vymazal et al., 2012), patients with an acute stroke should be

first evaluated by a CT scan as an MRI is more complicated and time-consuming, which that patient might not at that moment [32]. We are not considering angiogram as that was not the primary modality of diagnosis for patients with acute stroke. There is no significant correlation between the angiogram and the patient's status. While looking into the most efficient modality for diagnostic purposes, it is crucial to note which medication should be given to inpatients with stroke to improve their mortality rate. According to Table 6. the most valuable drugs to improve the mortality of COVID-19 inpatients with neurological manifestations are aspirin and enoxaparin, a low molecular weight heparin (LMWH). One of the main reasons why enoxaparin has a higher survival rate in comparison to heparin is because of its bioavailability, which is around 90% when given subcutaneously [36]. On the other hand, aspirin is a nonsteroidal anti-inflammatory drug which is also antiplatelet. As seen in (Table 6). aspirin also decreases the mortality rate of patients with stroke. Aspirin helps prevent early recurrent ischemic stroke (Coull et al.

2002) [37]. Therefore, it was always administered with enoxaparin or heparin; according to the data, it was only administered without any adjunct, and the patient did not survive, although the sample size is minimal to conclude this statement. However, aspirin does improve

survival rate ( $P < 0.05$ ). Lastly, it can be noted from (Table 7). that there is no significant correlation between the past medical history of stroke and an acute stroke incident in COVID-19 inpatients.

**Table 4:** Frequency of seizures in COVID-19 inpatients

	Seizures	
	Yes	No
Epilepsy relapse	2 4.3%	44 95.7%
Generalized Seizures	11 23.9%	35 76.1%

**Table 5:** Types of seizures according to EEG

Type of seizure		Frequency	Percent	Valid Percent	CumulativePercent
Valid		1	2.2	2.2	2.2
	Generalized epilepsy	2	4.3	4.3	6.5
	Generalized seizures (generalized slowing)	8	17.4	17.4	23.9
	No	34	73.9	73.9	97.8
	PRES syndrome	1	2.2	2.2	100.0
	Total	46	100.0	100.0	

**Table 6:** Management and modality of diagnosis inpatients with stroke and seizure with regards to status

		Alive	Dead	P value
Levetiracetam_seizure	No	1	0	0.000
	Yes	6	2	
EEG_seizure	No	1	1	0.001
	Yes	6	1	
CT Scan_Stroke	No	4	2	0.002
	Yes	16	9	
MRI Scan_stroke	No	7	5	0.076
	Yes	13	6	
Cerebral angiogram_stroke	No	18	11	0.473
	Yes	2	0	
Clexane_Stroke	No	2	5	0.045
	Yes	18	6	
Aspirin_Stroke	No	8	5	0.001
	Yes	12	6	
Heparin_Stroke	No	20	9	0.169
	Yes	0	2	

**Table 7:** Past history of stroke and acute stroke

		Ischemic Stroke		P value
		No	Yes	
Past stroke	No	14	24	0.972
	Yes	3	5	
Haemorrhagic stroke				

Past stroke	No	35	3	0.674
	Yes	7	0	

**Table 8:** Nationality of COVID-19 inpatients

		Neurological Manifestations				P value
		Yes		No		
		Count	Row N %	Count	Row N %	
Nationality	Middle East	18	13.6%	114	86.4%	0.024
	South Asia	27	10.4%	233	89.6%	
	Others	1	1.5%	67	98.5%	

**Table 9:** D-dimer levels of COVID-19 inpatients with neurological manifestations

	StatusR	N	Mean	Std. Deviation	P Values
D Dimer on incident	Alive	30	4107.20	4964.359	0.047
	Dead	13	7372.69	6052.277	

**Table 10:** Primary neurological manifestations

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Encephalopathy	1	2.2	2.2	2.2
	Haemorrhagicstroke	3	6.5	6.5	8.7
	Ischemic stroke	28	60.9	60.9	69.6
	Polyneuropathy	9	19.6	19.6	89.1
	Seizure	5	10.9	10.9	100.0
	Total	46	100.0	100.0	

### Seizures

We are looking at Table 10. we can see that around 10.9% of COVID-19 inpatients with neurological manifestations present with seizures as the main neurological incident. Moreover, 8.7% present with seizures as their second neurological manifestation (**Table 11**).

Seizures were diagnosed clinically using an electroencephalogram (EEG) or neuroimaging. Through this, we were able to subcategorize the seizures into epilepsy or generalized seizures. Looking at (**Table 4**). we can determine the frequency of each subcategory. 11 COVID-19 inpatients developed generalized seizures, of which 2 further developed epilepsy.

Amongst these 2 inpatients, both had a past medical history of epilepsy. One of them developed generalized epilepsy, whereas the other patient developed posterior reversible encephalopathy syndrome (PRES syndrome). Some literature suggests that SARS-CoV-2 can lead patients to have an inflammatory and hypercoagulable state, which could result in them developing PRES syndrome [43].

We are, furthermore, looking at **table 5**. we can see that the most common type of seizure is generalized seizure, where the EEG suggests generalized slowing activity. However, there is no definitive diagnosis for this generalized slowing after these patients presented with a seizure.

For the management of these seizures, the patients were given levetiracetam, which is an antiepileptic drug [35]. According to Table 6. patients have a higher survival rate when administered with levetiracetam, and this is proven by (P<0.05). Furthermore, Table 6. also explores the survival rate of inpatients with seizures who had an EEG done as a diagnostic. Amongst the two inpatients who didn't have an EEG done, one of them passed away, making the mortality rate 50%. Although the numbers are minimal, this is not a conclusive statement. However, the inpatients who did get an EEG had a mortality of 16.7%, and this can be supported by a (P<0.05).

**Table 11:** Secondary neurological manifestations

		Frequency	Percent	Valid Percent	CumulativePercent
Valid	Haemorrhagic stroke	1	2.2	2.2	2.2
	No	36	78.3	78.3	80.4
	Polyneuropathy	5	10.9	10.9	91.3

Seizure	4	8.7	8.7	100.0
Total	46	100.0	100.0	

## Discussion

This study aimed to identify the risk factors predisposing COVID-19 inpatients to develop neurological manifestations. Amongst the 460 COVID-19 ICU inpatients, 46 of them created neurological events. Some risk factors that might influence the potential to establish neurological events are past neurological diseases and chronic non-neurological disorders such as diabetes, hypertension, and cardiovascular risk factors. Other risk factors include demographics such as age, gender, and ethnicity.

One of the significant variables associated with neurological complications was age over 63 years, as indicated by  $p < 0.05$ . Whereas COVID-19 inpatients with a mean age of 50 years  $\pm$  14 did not develop any neurological symptoms. This seems consistent with previous research wherein the study mentions that the risk of developing critical neurologic events is strongly correlated with age above 60. According to previous research, older adults have an increase in age-dependent pro-inflammatory cytokines called inflammation, which increases the expression of CD16 [5].

CD16 is a receptor expressed on Natural Killer cells (NK), and it is found to be the only receptor that can activate a resting NK cell. NK cells are responsible for secreting pro-inflammatory cytokines such as IFN- $\gamma$ , TNF, and GM-CSF. These pro-inflammatory cytokines activate the innate immune cells, including monocytes and neutrophils, which cause oxidative stress and damage the surrounding tissues, resulting in chronic neuroinflammation, therefore inducing neural damage and neurological manifestations seen in older inpatients.

Previous research has suggested that pre-existing chronic medical conditions such as cardiovascular diseases, hypertension, diabetes, and neurological diseases are strongly associated with COVID-19 inpatients developing neurological consequences. The data showed that amongst the 46 COVID-19 patients who developed neurological manifestations, 34 (73.9%) of them had diabetes. Following the study, the expression of ACE2 is upregulated in the blood vessels of COVID-19 patients with diabetes, therefore increasing the ability of SARS-CoV-2 to enter the blood vessels in the brain and leading to the development of cerebrovascular diseases (CVD).

The second most common comorbidity amongst inpatients in this study who developed neurologic events was hypertension. As mentioned previously, SARS-CoV-2 enters the cell through ACE2. ACE2 is part of the renin-angiotensin system (RAS), which helps regulate the salt/water balance and blood pressure. Different parts of the brain have neuronal ACE2 (nACE2), which plays a facilitatory role in the neurotropism of SARS-CoV-2 [18]. When SARS-CoV-2 enters the host cell through nACE2, it causes a downregulation of ACE2 expression. This leads to an elevation in angiotensin II and, thus, an imbalance in RAS, leading to neurogenic hypertension.

Uncontrolled blood pressure in a thickened, narrowed, or damaged blood vessel leads to hemorrhages or other neurological consequences. However, in the study [12], there isn't any correlation between hypertension and the development of neurological consequences as  $p > 0.05$ . According to their research, the second most common comorbidity that causes neurological manifestations is hypertension.

The data showed that the third most prevalent underlying risk factor amongst the 46 inpatients with neurological consequences was cardiovascular diseases, as 20 (43.5%) inpatients had it in their past medical history. However, in previous studies, there isn't any correlation between cardiovascular diseases and the development of neurological manifestations as  $p > 0.05$  [12].

As studied by (Frontera et al., 2021), the most common type of neurologic event caused by SARS-CoV-2 was toxic/metabolic encephalopathy [15]. However, our data suggests that ischemic stroke has the highest frequency. Our results indicate that the majority of the patients who developed neurological manifestations were South Asians **Table 8**. This might be due to the discrepancies like the population amongst the studies. For instance, study [15] took place in China, with a relatively homogenous population [16]. However, the UAE's South Asian population is highly prevalent [3]. South Asian countries such as India and Pakistan have the highest prevalence of people who have diabetes [38]. As seen by our data, diabetes plays a significant role in the development of neurological manifestations. The study (Chen, Rong, et al., 2016) discusses that diabetes is an important risk factor for the development of ischemic stroke with poorer clinical outcomes, therefore supporting the data [39].

This research study has strengths as it has analyzed different risk factors that can cause neurological manifestations. This study has used various databases and published articles to reduce research bias. Moreover, in contrast to prior retrospective studies that focused on COVID-19 patients who developed new neurologic disorders, this study includes COVID-19 inpatients who have primary neurological diseases such as epilepsy and that they developed new neurological manifestations during the period they were RT-PCR SARS-CoV-2-positive. It uses the STROBE guidelines to improve the quality of reporting, and lastly, it has an adequate sample size to minimize data unreliability.

Despite this, the paper has some distinct limitations. The data collected was binary. Therefore, outliers couldn't be removed, and the data is subjective to reporting bias. Secondly, numerous inpatients admitted to the ICU were transferred from Dubai Health Authorities (DHA), and their records were missing, so we can't be sure whether they had a neurologic event before moving into Mediclinic Welcare Hospital. Furthermore, the majority of the patients who developed



neurological manifestations had severe underlying comorbidities; it is unclear whether these neurological events were triggered by SARS-CoV-2 or whether they would have created one either way. To limit this dilemma, we can conduct a standardized test to compare similar in patients who did not have COVID-19 and determine whether they had any neurological consequences. This will help determine the proportion of COVID-19 patients who developed neurological manifestations from SARS-CoV-2 and those who created it due to their associated comorbidities. Lastly, many inpatients needed health insurance, so their records were available or complete. All these factors influence the reliability of the data collected.

This study can further investigate different biomarkers as risk factors. For instance, we can examine whether elevated D-dimer levels can predispose COVID-19 patients to thrombotic strokes. However, even though D-dimer levels were only collected of COVID-19 inpatients with neurological manifestations (**Table 9**), we can firmly conclude

that these patients had significantly elevated D-dimer levels, with alive patients having a mean of 4107.20ng/mL and dead patients having a mean of 7372.69ng/mL. The usual range of D-dimer should be <500ng/mL [40]. There is a significant difference in the D-dimer levels of both groups, proven by  $P < 0.05$ . Therefore, in future research papers, we can look at the implication of increased D-dimer levels in COVID-19 patients with and without neurological manifestations to make a conclusive statement regarding the effects of D-dimer levels in COVID-19 inpatients.

### Disclaimer

The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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