Encephalopathy in Hospitalized Patients with Coronavirus Disease 2019: A Single-center Study

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ABSTRACT

Objective. This study aimed to determine the incidence of encephalopathy among hospitalized patients with COVID-19.

Methods. This was a retrospective observational study conducted in a tertiary hospital in Cebu City, Philippines. This study is a complete enumeration of all records of adult patients admitted for COVID-19 detected through polymerase chain reaction from March 1, 2020 to September 30, 2021. The cases were then classified as to the presence or absence of encephalopathy.

Results. The study determined that 6 in every 1000 admitted COVID-19 patients developed encephalopathy. The clinico-demographic profile of patients with encephalopathy were mostly elderly with a mean age of 67, males (55.7%), and obese stage I (61.1%). Encephalopathy was more likely to develop in patients with type 2 diabetes mellitus (80.1%) and coronary artery disease (40.0%). Most patients who did not have encephalopathy however had a history of CVD. Most patients (66.7%) who developed encephalopathy were dyspneic on presentation. Laboratory examination results showed an increase in fasting blood sugar and elevated levels of LDH, CRP, serum ferritin, procalcitonin, and D-dimer. Majority of patients (66.7%) with encephalopathy were intubated. Taking into consideration the stage of infection and the incidence of encephalopathy, most patients (66.6%) were in the hyperinflammatory stage. The number of hospitalization days and severity of illness did not have any association with developing encephalopathy. Dichotomous categorization of outcomes into deceased and discharged showed that clinical outcomes and the development of encephalopathy were significantly associated, with 66.7% of patients with encephalopathy expiring during their course of hospitalization.

Conclusion. The incidence of encephalopathy among admitted COVID-19 patients was 6 in every 1000 patients. Encephalopathy was more common in elderly males who were obese with type 2 diabetes mellitus and coronary artery disease. The most common presentation of patients who developed encephalopathy was dyspnea. Collated laboratory results showed an increase in fasting blood sugar and elevated levels of LDH, CRP, serum ferritin, procalcitonin, and D-dimer. Majority of patients with encephalopathy were intubated and were in the hyperinflammatory stage of COVID-19 infection. Dichotomous categorization of outcomes into deceased and discharged showed that clinical outcomes and the development of encephalopathy were significantly associated, with most patients with encephalopathy expiring during their course of hospitalization.

Keywords: COVID-19, encephalopathy, brain, SARS-CoV-2, neurological symptoms

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INTRODUCTION

The global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has crippled countries around the world affecting more than 346 million people as of January 2022.[1] The symptomatology of COVID-19 was mainly focused on its pathology on the pulmonary system as manifested by the development of diffuse alveolar damage leading to acute respiratory failure.[2] While COVID-19 generally begins as a respiratory tract infection, the systemic spread of the virus results in damaging effects on multiple organ systems of the human body, including the nervous system.[3]

Neurologic complications are common in hospitalized patients with COVID-19, with more than 80% of patients developing neurologic symptoms during their disease course. Myalgias, headache, encephalopathy and dizziness are the most common neurologic manifestations. Patients with critical illness have a higher frequency of neurologic complications compared to those with milder disease.[4] However, due to COVID-19 being a relatively new disease entity, there is a need for more studies to determine the risk factors involved in the development of encephalopathy in COVID-19 patients, its temporal relationship to the stage and severity of illness, and effects on the short-term outcomes of hospitalized patients.

OBJECTIVES

General Objective

To determine the incidence of encephalopathy among hospitalized patients with COVID-19 in a tertiary hospital in Cebu.

Specific Objectives

1. To describe the baseline characteristics and demographic data of patients with COVID-19 who developed encephalopathy from those without encephalopathy in terms of:
   1.1. Age
   1.2. Gender
   1.3. Comorbidities
   1.4. History of any neurologic disease
   1.5. Vices
   1.6. Medications administered on admission
   1.7. Laboratory markers on admission
   1.8. Admission status
   1.9. Management of the disease
2. To determine the incidence of encephalopathy among patients with COVID-19
3. To determine the temporal association between the following factors with the development of encephalopathy:
   3.1. Stage of infection
   3.2. Day of hospitalization
   3.3. Severity of illness
   3.4. To determine the short-term outcomes of patients with encephalopathy in patients with COVID-19
   3.5 Disposition on discharge

DEFINITION OF TERMS

- **Encephalopathy –** operationally defined as the manifestation of decreased level of sensorium or a Glasgow coma scale (GCS) of less than 14, delirium or agitation that may or may not require the use of restraints.
- **Stage of Infection** – these are the distinct phases of COVID-19 infection:
  - **Early Phase** – the time when viral replication is occurring inside the body and causing flu-like symptoms such as fever, dry cough, diarrhea, and headache.
  - **Pulmonary Phase** – the time when the immune system becomes greatly affected and leads to respiratory symptoms such as cough, shortness of breath and desaturation.
  - **Hyperinflammatory Phase** – the time when there is activation of the immune system causing injury to the other organs resulting in acute respiratory distress syndrome or shock. In this study, intubation would automatically place the patient in this phase.
- **Severity of Illness** refers to mild, moderate, severe, and critical.
  - **Mild Illness** – symptomatic patients presenting with fever, cough, fatigue, anorexia, myalgias and other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, anosmia, and dysgeusia preceding the onset of symptoms with no signs of pneumonia or hypoxia.
  - **Moderate Illness** – patients with clinical signs of non-severe pneumonia such as fever, cough, dyspnea, tachypnea with a respiratory rate of 21-30 cycles per minute and an oxygen saturation of greater than or equal to 92 percent at room air.
  - **Severe Illness** – patients with clinical signs of severe pneumonia such as fever, cough, dyspnea, tachypnea with a respiratory rate of greater than 30 cycles per minute, severe respiratory distress, or oxygen saturation of less than 92 percent at room air.
  - **Critical Illness** – patients who have respiratory failure, sepsis or septic shock, and multiple organ dysfunction.

METHODS

Study Design

This study employed the retrospective medical chart review of all patients admitted in the hospital due to COVID-19 so it can further determine the incidence of encephalopathy among these patients.

Study Setting

The study was conducted in Chong Hua Hospital, a 660-bed capacity tertiary hospital located in Cebu City.

Study Population

This study is a complete enumeration of all records of adult patients, aged 18 years and older admitted in Chong Hua Hospital for COVID-19 pneumonia infection detected through polymerase chain reaction for the period covering March 1, 2020, to September 30, 2021. Otherwise, if patients were transferees from other hospitals before admission to Chong Hua Hospital, and those who developed a decrease in sensorium due to sedation for the purpose of intubation or restraint, then their records were excluded in the chart review.

Data Collection

Records of COVID-19 pneumonia positive patients which qualified according to the inclusion criteria set in this study were reviewed. Permission from the medical records section were sought after the approval of the Chong Hua Hospital - Ethics Committee. Once deemed eligible based on the inclusion and exclusion criteria, the patient's records were included in the study and data were encoded in the Microsoft Excel. Data sources were the medical chart, medical abstract, laboratory tests, and imaging modalities performed.

Data Processing and Analysis

Encoding was manually done, with data validation activated. Coding was done after data cleaning and validation. During analysis, the Microsoft Excel file of the data set was imported to Statistical Package for the Social Sciences for final analysis. Frequency and percentages were used for summarizing categorical variables while mean and standard deviation were used for summarizing normally distributed continuous variables. Independent t-test was used to compare continuous data while Chi-square test was used to determine the association between categorical variables and incidence of encephalopathy.

The conceptual framework for this study is illustrated in Figure 1.

Ethical Considerations

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and National Ethical Guideline for Health and Health-related Research (2017). Prior to the study initiation, the protocol was reviewed and approved by the Research Ethics Committee (REC) of Chong Hua Hospital.

The researcher assured that all records from the participants were treated with strict confidentiality. Patient's names were not reflected in the file for data analysis. Instead, only the numbers which correspond to their names in the source code can be seen. The source code was in possession of the researcher only. Only the researcher and the biostatistician

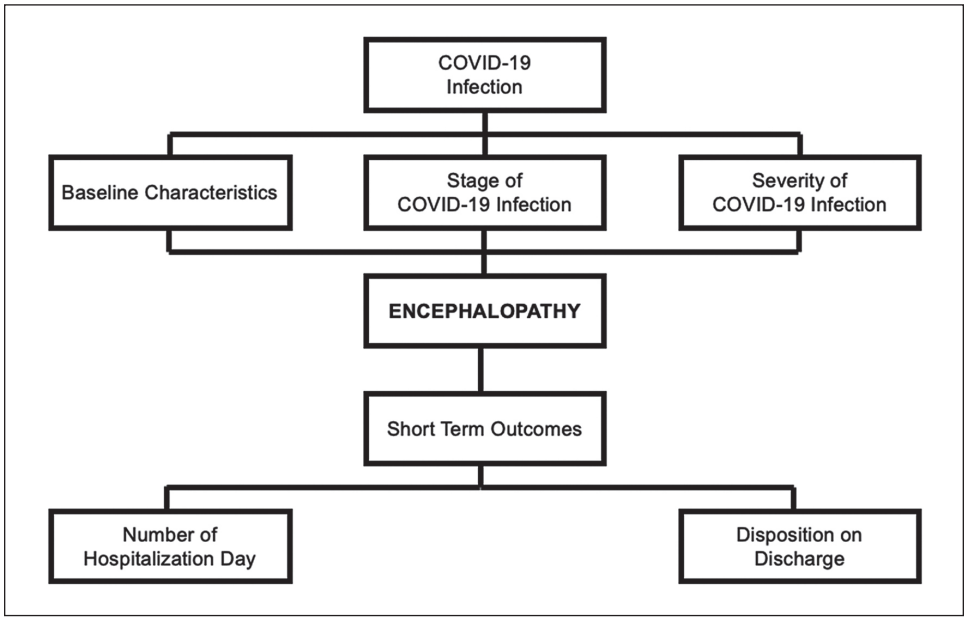

Figure 1. Conceptual Framework.

Table 1. Clinico-demographic Profile of the Patients

Characteristics	With encephalopathy n = 6	Without encephalopathy n = 946	Total n = 952
Age, years	67.0 ± 10.3	56.2 ± 16.2	56.23 ± 16.2
Youngest = 18			
Oldest = 99			
Gender			
Male	4 (66.7)	528 (55.8)	532 (55.9)
Female	2 (33.3)	418 (44.2)	420 (44.1)
Body Mass Index			
Underweight		28 (3.0)	28 (2.9)
Normal	1 (16.7)	189 (20.0)	190 (20.0)
Overweight	1 (16.7)	151 (16.0)	152 (16.0)
Obese 1	4 (66.7)	578 (61.1)	582 (61.1)
Admission Status			
Ward	4 (80.0)	671 (83.1)	675 (70.9)
ICU	1 (20.0)	136 (16.9)	137 (29.1)
Undetermined	(1)	(139)	

have sole access to collected data. Excel sheets for data processing did not contain any information that would give away the identity of patients.

Also, this paper is self-funded. It is not financially or in any aspect supported by a drug company or an individual who might benefit from the results of the study since this study is intended for the compliance of the Adult Neurology Residency Training Program of Chong Hua Hospital.

RESULTS

There were 952 records of COVID-19 patients reviewed in this study and it was found that 6 in every 1,000 admitted had encephalopathy. Those with encephalopathy were older, with mean age of 67 years old while those without has mean age of 56 years old. Most of them were males (55.7%), were considered obese stage 1 (61.1%) according to the Asian standards for body mass index, and were admitted in the COVID wards (70.9%) (Table 1).

Those who developed encephalopathy had type 2 diabetes mellitus (80.0%) and coronary artery disease (40.0%). Those who did not have encephalopathy were mostly hypertensive (80.1%), and have type 2 diabetes mellitus (44.2%). Not one of those with encephalopathy were smokers and alcoholic drinkers. Majority of those who have no encephalopathy had history of cerebrovascular disease (Table 2).

One-third of those with encephalopathy presented with fever, cough, abdominal pains, and had body malaise. Majority (66.7%) were dyspneic while those without encephalopathy had cough (72.8%), fever (68.0%) and were also dyspneic (51.0%) (Table 3).

Average systolic BP of those with encephalopathy is normal (mean = 110, SD = 16.7) while it is slightly elevated (mean = 122, SD = 18.9) for those without. Both groups had normal diastolic BP upon admission. Most of them had normal heart rate but were dyspneic (Table 4).

Looking at Table 5, fasting blood sugar was considered pre-diabetes for those with encephalopathy (mean = 100) while those without showed they were diabetics (mean = 136, SD = 63.89). This is also consistently shown in the hemoglobin A1C, that is above the normal value of 5.7, according to the American Diabetes Association. Those

Table 2. Comorbidities of the Patients (Multiple Response)

Characteristics	With encephalopathy n = 6	Without encephalopathy n = 946
Comorbidities		
Obesity		15 (2.3)
HPN	1 (20.0)	515 (80.1)
Dyslipidemia		16 (2.5)
Peripheral artery disease		4 (0.6)
COPD		12 (1.9)
T1DM		16 (2.5)
T2DM	4 (80.0)	284 (44.2)
Liver disease		12 (1.9)
Chronic kidney disease	1 (20.0)	75 (11.7)
Bronchial asthma		57 (8.9)
Coronary artery disease	2 (40.0)	56 (8.7)
Cardiac arrythmia	1 (20.0)	24 (3.7)
Maintenance HD	1 (20.0)	24 (3.7)
PTB history		6 (0.9)
Malignancy	1 (20.0)	34 (5.3)
HIV		4 (0.6)
Vices		
Smoking		48 (66.7)
Alcohol intake		40 (55.6)
History of neurologic disease		
CNS infection		3 (6.8)
Epilepsy		2 (4.5)
Dementia		1 (2.3)
CVD history		39 (88.6)

Table 3. Presenting Symptoms and Incidence of Encephalopathy (Multiple Response)

Symptoms	With encephalopathy n = 6	Without encephalopathy n = 946
Presenting symptoms		
Fever	2 (33.3)	613 (68.0)
Cough	2 (33.3)	657 (72.8)
Dyspnea	4 (66.7)	460 (51.0)
Fatigue	1 (16.7)	34 (3.8)
Body malaise	2 (33.3)	170 (18.8)
Abdominal pain	2 (33.3)	39 (4.3)

Table 4. Vital Signs upon Admission

Vital Signs	With encephalopathy n = 6	Without encephalopathy n = 946
Blood pressure		
Systolic BP	110.0 ± 16.7	122.3 ± 18.9
Diastolic BP	68.3 ± 7.5	77.5 ± 31.1
Heart rate		
Bradycardia	0 (0.0)	17 (1.8)
Normal	5 (83.3)	509 (54.9)
Tachycardia	1 (16.7)	401 (43.3)
Respiratory rate		
Bradypnea	0 (0.0)	5 (0.5)
Normal	1 (16.7)	404 (43.9)
Dyspnea	5 (83.3)	511 (55.5)

Table 5. Biomarkers upon Admission

Biomarkers	With encephalopathy n = 6	Without encephalopathy n = 946
Fasting blood sugar	100.00 ± 0.0	136.00 ± 63.29
HbA1c	5.95 ± 0.35	6.07 ± 2.02
pH	7.40 ± 0.052	7.44 ± 0.09
Lactate dehydrogenase	442.00 ± 249.68	413.87 ± 294.75
C-reactive protein	1194.75 ± 933.26	790.19 ± 1029.00
Serum Ferritin	1067.08 ± 689.52	1918.93 ± 3611.71
Procalcitonin	0.53 ± 0.37	3.63 ± 19.75
D-dimer	0.93 ± 0.41	2.80 ± 11.19

Table 6. Treatments Received

Management of the Disease	With encephalopathy n = 6	Without encephalopathy n = 946
Convalescent plasma		34 (3.6)
Steroids		445 (47.0)
Inhaled steroids		21 (2.2)
Systemic glucocorticoids		443 (46.8)
Vasopressors	2 (33.3)	135 (14.3)
Non-invasive ventilation		28 (3.0)
Invasive mechanical ventilator	4 (66.7)	168 (17.8)

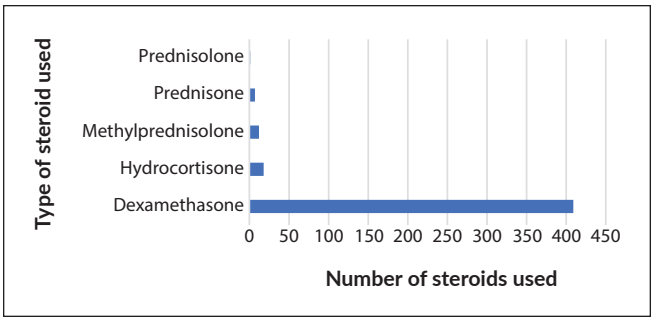

Figure 2. Steroids Used.

without encephalopathy were having alkalosis, (mean = 7.44, SD = 0.09). Both groups have elevated LDH, beyond the normal range of 140 to 280, which is indicative of some type of tissue damage or disease. CRP was severely elevated in both groups, an indication of bacterial infection, however the ones with encephalopathy showed a dangerously elevated CRP level showing severe bacterial infection. Similarly, serum ferritin on both groups were very high showing they have inflammation in their body. Procalcitonin levels for those with encephalopathy showed that there was systemic infection but was alarming on those without encephalopathy because PCT levels showed that systemic infection was likely present (mean = 3.63, SD = 19.75). Lastly, D-dimer showed that there was possible blood clotting on both groups since it was higher than the normal range of 0.50 mg/dL.

Majority of those with encephalopathy were intubated (66.7%), while those without were managed using steroids (47.0%) and systemic glucocorticoids (46.8%) (Table 6). Most of the steroids used was dexamethasone with 409 out of 445 (91.9%), as shown in Figure 2.

Stage of infection, as seen on Table 7 showed that majority of those with encephalopathy were in the hyperinflammatory stage (66.6%) while on those without encephalopathy were on the early (39.5%) and pulmonary stage (42.7%). The proportion of those who were in early to hyperinflammatory stage for both groups were statistically significant, $x^2(2) = 9.6353$, $p = 0.008$. However, days of hospitalization and severity of the illness did not have any association with having encephalopathy.

Table 8 showed the outcomes of patients without encephalopathy with the majority of them discharged alive (78.3%). Those with encephalopathy mostly expired (66.7%), however difference in proportion was not significant. If categorization of outcomes was dichotomous – deceased and discharged only, clinical outcomes and the development of encephalopathy were significantly associated, $x^2(1) = 9.534$, $p = 0.002$.

Table 7. Parameters Associating with the Development of Encephalopathy

Parameters	With encephalopathy n = 6	Without encephalopathy n = 946	Computed stats	p-value
Stage of infection				
Early	1 (16.7)	374 (39.5)	$x^2(2) = 9.6353$	0.008
Pulmonary	1 (16.7)	404 (42.7)		
Hyperinflammatory	4 (66.6)	168 (17.8)		
Days of hospitalization	9.5 ± 3.8	12.3 ± 10.3	$t(950) = -0.677$	0.498
Severity of the illness				
Mild	0 (0.0)	168 (20.4)	$x^2(3) = 9.6353$	0.291
Moderate	2 (33.3)	393 (47.8)		
Severe	3 (50.0)	197 (23.9)		
Critical	1 (16.7)	65 (7.9)		

Table 8. Outcomes of the Patients with Encephalopathy

Outcomes	With encephalopathy n = 6	Without encephalopathy n = 946	Computed stats	*p*-value
Disposition on discharge				
Deceased	4 (66.7)	169 (17.9)	$x^2(5) = 9.574$	0.088
Discharged alive	2 (33.3)	740 (78.3)		
Hospitalized, off MV, w/o superinfection		4 (0.4)		
Hospitalized, off MV, w/ superinfection		23 (2.4)		
Hospitalized, on MV, w/o superinfection		2 (0.2)		
Hospitalized, on MV, w/ superinfection		7 (0.7)		

DISCUSSION

The study showed that 6 in every 1000 admitted COVID-19 patients had encephalopathy. In this study, the clinico-demographic profile of COVID-19 patients who developed encephalopathy were mostly elderly with a mean age of 67, males (55.7%), obese stage 1 (61.1%). COVID-19 encephalopathy was more likely to develop in males and in patients with risk factors such as diabetes, hypertension, and a history of neurologic disorders.[4] In another study, encephalopathy was present in 28% of elderly patients admitted for COVID-19. The study identified older age, vision impairment, and a history of stroke as risk factors for the development of COVID-19 encephalopathy.[5]

Among the comorbidities identified in this study, type 2 diabetes mellitus (80%) and coronary artery disease (40%) were identified as the most common comorbidity among those who developed encephalopathy. As previously stated, diabetes was considered as a risk factor for the development of encephalopathy.[4] Majority of the patients with a history of neurologic disease did not develop encephalopathy, which was in contrast to the findings of the studies mentioned above that identified a history of neurologic disorders such as stroke as risk factors for the development of encephalopathy.[4,5]

Dyspnea was the most common presenting symptom among those patients who developed encephalopathy. In the study by Kennedy et al., fever at 80% was cited as the most common presenting symptom among those patients who developed encephalopathy.[5] A decrease in the GCS, with a score of less than 15 was only seen in very few cases. In the study done by Kennedy et al., they identified delirium as the sixth most common presenting symptom.[5] In another study done by Mao et al., of the 78 patients or 36.4% who presented with neurologic manifestations, 14.8% had an impaired level of consciousness.[6] Yin et al. reported that out of the 106 patients they analyzed, altered sensorium was seen in 17 cases, and was more frequent in severe and critically ill cases in comparison to mild and moderate cases.[7]

Majority of the patients who developed encephalopathy showed increased fasting blood glucose levels with a mean level of 100 mg/dL along with increased HbA1c levels with a mean level of 5.95. This finding is consistent with type 2 diabetes mellitus being a risk factor for the development of encephalopathy.[4] Inflammatory markers such as CRP, LDH, serum ferritin, and procalcitonin levels were all increased in patients with encephalopathy. This was consistent with the findings of a review of encephalopathy in patients with COVID-19 done in 2020 by Garg et al.[8] D-dimer levels were also increased in patients with encephalopathy. Cerebral thromboembolic events were implicated to contribute to the pathogenesis of COVID-19 associated encephalopathy with the hallmark abnormalities in blood coagulation as manifested by increased D-dimer levels.[8,9]

Majority of the patients who developed encephalopathy were intubated (66.7%) and required the use of vasopressors (33.3%). This is reflective of compromise in body organ function leading to multiple organ failure that is characterized by sepsis, shock, and respiratory failure. This is due to an

intense inflammatory response against the virus, triggering a cytokine storm. The hypoxic and metabolic insults subsequently result in diffuse brain dysfunction.[10]

Data on the stages of infection showed that majority of those with encephalopathy were in the hyperinflammatory stage (66.6%). As defined, the hyperinflammatory phase is characterized by activation of the immune system causing injury to other organs. This leads multiple organ failure that would eventually lead to hypoxic and metabolic insults resulting in diffuse brain dysfunction.[10]

With the categorization of outcomes taken dichotomously as deceased and discharged, the development of encephalopathy and clinical outcomes are significantly associated with majority of the patients who developed encephalopathy expired (66.7%). In COVID-19 patients, the presence of neurologic disease including stroke is associated with higher death rates, delirium, and disability. Encephalopathy is a risk factor for poor outcome. In a study done by Liotta et al., hospitalized patients with COVID-19 who developed encephalopathy had longer lengths of stay, worse functional impairment at hospital discharge, and a higher 30-day mortality.[4]

Limitations of the Study

The study was a retrospective observational study, therefore only an inference on the relationship between baseline variables and the development of encephalopathy was made. The study also only involved hospitalized patients therefore, a generalization cannot be made of encephalopathy in the outpatient setting. Another limitation of the study was due to the data collected completely via chart review and electronic records, data not included in the said records could no longer be obtained or reviewed.

The lack of electroencephalograms in the diagnostic work-up of COVID-19 patients who develop encephalopathy was also a limitation. This was due to the hospital protocol that did not allow the performance of this diagnostic modality to prevent the exposure of technicians performing the procedure.

With the study being conducted in a single center, the population size would hinder in making a generalization of the cohort characteristics.

CONCLUSION

Encephalopathy is seen in 28% of patients with COVID-19, especially among older patients with comorbid conditions such as type 2 diabetes mellitus and the presence of neurologic disorders such as stroke. The study aimed to determine the incidence of encephalopathy among hospitalized patients with COVID-19 and determined that 6 in every 1,000 admitted COVID-19 patients had encephalopathy. Patients who developed encephalopathy were males (55.7%), and elderly with a mean age of 67 years. Type 2 diabetes mellitus (80.1%) and coronary artery disease (40.0%) were identified as comorbid conditions among patients who developed encephalopathy. The study however, identified that the majority of patients who did not have encephalopathy had a history of CVD.

Among the presenting symptoms, most patients (66.7%) who developed encephalopathy were dyspneic on presentation. As for the laboratory examination results, an increased fasting blood sugar levels was noted, along with elevated levels of LDH, CRP, serum ferritin, procalcitonin, and D-dimer. Majority of patients (66.7%) with encephalopathy were intubated.

Considering the stage of infection and the incidence of encephalopathy, majority of the patients (66.6%) were in the hyperinflammatory stage. The number of hospitalization days and severity of illness did not have any association with developing encephalopathy. Dichotomous categorization of outcomes into deceased and discharged showed that clinical outcomes and the development of encephalopathy were significantly associated, with 66.7% of patients with encephalopathy expiring during their course of hospitalization.

Recommendations

Given that the COVID-19 pandemic is still ongoing, and with it being a new disease with relatively unknown long-term sequelae, studies on COVID-19 and its many manifestations and complications would benefit the human population as a whole. It has been emphasized that the presence of neurologic manifestations, especially encephalopathy, is associated with a poor prognosis and increased 30-day mortality rate. The study and its methods can be easily reproduced in other centers, increasing the population size. The study can also be done in a prospective study design where those who are at risk for developing encephalopathy are followed-up during their course of hospitalization.

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Statement of Authorship

The author certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The author declared no conflicts of interest.

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