

REVIEW ARTICLE

Association between encephalopathy and clinical outcomes of COVID-19: Findings from the Philippine CORONA Study

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KEYWORDS

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Abstract

Introduction: This study aimed to determine whether encephalopathy is associated with such COVID-19 outcomes as disease severity, mortality, respiratory failure, intensive care unit (ICU) admission, duration of ventilator dependence, and length of ICU and hospital stay.

Methods: We performed a subgroup analysis comparing outcomes in patients with and without encephalopathy, based on data from a nationwide retrospective cohort study among adult patients hospitalized with COVID-19 at 37 hospital sites in the Philippines. The patient outcomes included for analysis were disease severity, mortality, respiratory failure, ICU admission, duration of ventilator dependence, and length of ICU and hospital stay.

Results: Of a total of 10881 COVID-19 admissions, 622 patients had encephalopathy. The adjusted hazard ratios (aHR) for mortality among mild and severe cases were 9.26 and 1.63 times greater ($P < .001$), respectively, in the encephalopathy group compared to the no-encephalopathy group. Encephalopathy was associated with increased risk of severe COVID-19 (adjusted odds ratio [aOR]: 7.95; $P < .001$), respiratory failure (aHR: 5.40; $P < .001$), longer hospital stays (aOR: 1.36; $P < .001$), and admission to the ICU (aOR: 4.26; $P < .001$). We found no sufficient evidence that encephalopathy was associated with length of ICU stay (aOR: 1.11; $P = .522$) or duration of ventilator dependence (aOR: 0.88; $P = .428$).

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PALABRAS CLAVE

COVID-19;
SARS-CoV-2;
Encefalopatía;
Trastorno
neurológico;
Pronóstico

Conclusions: Encephalopathy was associated with COVID-19 severity, mortality, respiratory failure, ICU admission, and longer hospital stays.

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Asociación de encefalopatía con resultados clínicos de COVID-19: hallazgos del Estudio CORONA de Filipinas

Resumen

Introducción: Nuestro estudio tuvo como objetivo determinar si la encefalopatía estaba asociada con los resultados de COVID-19, como la gravedad de la enfermedad, la mortalidad, la insuficiencia respiratoria, el ingreso a la unidad de cuidados intensivos (UCI) y la duración de la dependencia del ventilador, la estancia en la UCI y en el hospital.

Métodos: Realizamos un análisis de subgrupos comparando los resultados de los pacientes con encefalopatía frente a los pacientes sin encefalopatía, basado en datos de un estudio de cohorte retrospectivo a nivel nacional entre pacientes adultos hospitalizados con COVID-19 en 37 hospitales en Filipinas. Los resultados del paciente incluidos para el análisis fueron la gravedad de la enfermedad, la mortalidad, la insuficiencia respiratoria, el ingreso a la UCI y la duración de la dependencia del ventilador, la estancia en la UCI y en el hospital.

Resultados: De las 10.881 admisiones totales por COVID-19, 622 pacientes tenían encefalopatía. Las razones de riesgo ajustadas (aHR) para la mortalidad entre casos leves y graves fueron mayores en 9,26 y en 1,63 ($p < 0,001$), respectivamente, en el grupo de encefalopatía en comparación con el grupo sin encefalopatía. La encefalopatía se asoció con un mayor riesgo de tener COVID-19 grave (razón de posibilidades ajustada [aOR] 7,95, $p < 0,001$), insuficiencia respiratoria (aHR 5,40, $p < 0,001$), estancia hospitalaria más larga (aOR 1,36, $p < 0,001$) e ingreso a la UCI (aOR 4,26, $p < 0,001$). No encontramos suficiente evidencia de que la encefalopatía estuviera asociada con la duración del ingreso a la UCI (aOR 1,11, $p = 0,522$) y la duración de la dependencia del ventilador (aOR 0,88, $p = 0,428$).

Conclusiones: La encefalopatía estuvo asociada con la gravedad de la COVID-19, la mortalidad, la insuficiencia respiratoria, el ingreso a la UCI y una estancia hospitalaria más prolongada.

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Introduction

COVID-19, caused by SARS-CoV-2 infection, primarily affects the respiratory system but is also known to affect the nervous system.¹ The neurological manifestations reported in hospitalized patients with COVID-19 include headache, dizziness, anosmia, ageusia, impaired consciousness, seizures, and stroke.^{2–4} More recently, larger studies on new-onset neurological disorders associated with the disease identified encephalopathy as one of the most common diagnoses, occurring in 20–44% of patients with neurological disorders.^{4–6}

Encephalopathy is a diffuse brain dysfunction characterized by impaired level of consciousness, which can present as delirium, stupor, or coma.⁷ The most common causes of encephalopathy among patients with COVID-19 were sepsis-associated encephalopathy, uremic encephalopathy, and hypoxic ischemic encephalopathy.⁸ The underlying causes of encephalopathy may be attributed to multiple mechanisms, such as neurotropism of the SARS-CoV-2 virus, severe inflammatory response leading to multiple organ dysfunction or acute respiratory distress syndrome, coagulopathy, and hypoxia.^{9,10}

In studies among hospitalized patients in general, altered sensorium and delirium were associated with

longer hospitalization, cognitive impairment, and increased mortality.^{11–13} However, data are still limited on the association between encephalopathy and other outcome measures among patients with COVID-19.

In the Philippines, the recently concluded nationwide, multicenter, retrospective study of neurological manifestations and associated outcomes (the Philippine CORONA Study) identified encephalopathy as the most common new-onset neurological symptom associated with COVID-19.³ The present study aims to further elucidate whether encephalopathy is associated with COVID-19 outcomes including disease severity, mortality, respiratory failure, intensive care unit (ICU) admission, duration of ventilator dependence, and duration of ICU and hospital stays.

Materials and methods

The Philippine CORONA Study design: population and setting

The Philippine CORONA Study was a nationwide, multicenter, comparative, retrospective, cohort study including patients with COVID-19 who were admitted consecutively

to 37 hospital sites across the Philippines between February and December 2020.³ All data were collected from patient medical charts and coded using the Epi Info Software (version 7.2.2.16). Encephalopathy is defined and widely accepted as a disease in which brain function is altered, often with depressed or fluctuating sensorium. Due to the retrospective nature of the study, any physician assessment stating “encephalopathy” on the chart was counted as a case. The study obtained approval from the respective research ethics boards of the participating hospital sites and was registered on ClinicalTrials.gov (NCT04386083). Specific details about the research design, patient enrollment, and data collection procedures were discussed in the published protocol.¹⁴ We included all eligible participants from the main study and classified the patients into 2 cohort groups: those with encephalopathy and those without encephalopathy.

Outcome variables

The main outcomes were disease severity (mild: presence of mild pneumonia or absence of pneumonia; severe: presence of dyspnea, respiratory rate > 30, hypoxia or $\text{SpO}_2 < 93\%$, or 50% lung involvement on imaging within 24–48 h), mortality, respiratory failure (patients with signs or symptoms of respiratory insufficiency: increased work of breathing/respiratory rate of ≥ 22 , a need for supplemental oxygen, or abnormal blood gases), ICU admission, duration of ventilator dependence, duration of ICU stay, and duration of hospital stay, among patients with encephalopathy compared to the no-encephalopathy group.

Statistical analysis

The different variables of interest were summarized according to the independent variable: encephalopathy versus no encephalopathy. Numerical variables are expressed as median and interquartile range (IQR), while the categorical variables are expressed as count and percentage. Comparison of the different clinical characteristics between the 2 groups was conducted using the Mann–Whitney *U* test for numerical variables, to determine differences in median/ranks, and the Chi-square test of homogeneity for categorical variables, to determine differences in proportion.

Associations between the different individual dichotomous outcome variables and the independent variable were determined by binary logistic regression. The logistic regression model was adjusted for the following confounders: age, sex, hypertension, diabetes mellitus, smoking, coronary artery disease, cerebrovascular disease, dementia, epilepsy, and COVID-19 severity. The associations between the independent variable and the time to event for different outcome variables were determined by Cox proportional hazards regression. A stratified analysis of mortality between COVID-19 severity types was also performed. All statistical analyses were conducted using Stata version 17.1.

Results

Study participants

A total of 10 999 patients consecutively admitted due to confirmed COVID-19 from the 37 participating hospital sites were gathered, with 10 881 patients included in the final analysis. The prevalence of encephalopathy among patients with COVID-19 was 5.72% (95% confidence interval [CI], 5.29–6.17). The encephalopathy group comprised 622 patients, whereas the no-encephalopathy group comprised 10 259 patients (Fig. 1). Among patients aged 60 years or older, the prevalence of encephalopathy was higher, at 9.59% (368 of 3834 patients).

Demographic and clinical characteristics

Table 1 shows the comparison of demographic and clinical characteristics in the encephalopathy and no-encephalopathy groups. The median (IQR) age of the entire cohort was 52 years (36–64). The encephalopathy group had a higher proportion of males ($P = .004$) and patients aged 60 years and above ($P < .001$). Presence of hypertension (61.7% vs 31.8%, $P < .001$), diabetes mellitus (41.3% vs 18.9%, $P < .001$), kidney disease (17.2% vs 4.9%, $P < .001$), coronary artery disease (9.5% vs 3.5%, $P < .001$), malignancy (5.6% vs 2.0%, $P < .001$), chronic obstructive pulmonary disease (3.1% vs 1.3%, $P < .001$), and heart failure (3.2% vs 1.0%, $P = .02$) were more frequent in the encephalopathy group compared to the no-encephalopathy group. Smoking was also more common in the encephalopathy group (18.5% vs 8.9%, $P < .001$).

Among patients with previous neurological history, cerebrovascular disease (12.2% vs 2.4%, $P < .001$), dementia (2.4% vs 0.2%, $P < .001$), epilepsy (1.3% vs 0.2%, $P < .001$), movement disorder (0.5% vs 0%, $P = .003$), and central nervous system (CNS) infection (0.3% vs 0%, $P = .029$) were more frequent in the encephalopathy group than in the no-encephalopathy group.

Encephalopathy is significantly associated with the development of new-onset CNS infection (0.64% vs 0.03%, $P < .001$), seizures (11.74% vs 0.51%, $P < .001$), and stroke or cerebrovascular events (11.74% vs 2.38%, $P < .001$) in patients with COVID-19 and encephalopathy, compared to those without encephalopathy.

The presence of cough (55% vs 39.7%, $P < .001$), fever (49.8% vs 35.3%, $P < .001$), dyspnea (49.4% vs 23.4%, $P < .001$), fatigue (10.5% vs 6.3%, $P < .001$), sputum production (10.6% vs 5.6%, $P < .001$), and arthralgia (2.7% vs 1.5%, $P = .02$) was more frequent among patients with encephalopathy than among those without encephalopathy.

COVID-19 outcomes

Table 2 summarizes the comparison of outcomes between the encephalopathy group and the no-encephalopathy group. Overall, mortality, respiratory failure, and number of ICU admissions were higher in the encephalopathy group compared to the no-encephalopathy group ($P < .001$). Table 3 shows the association between encephalopathy and the out-

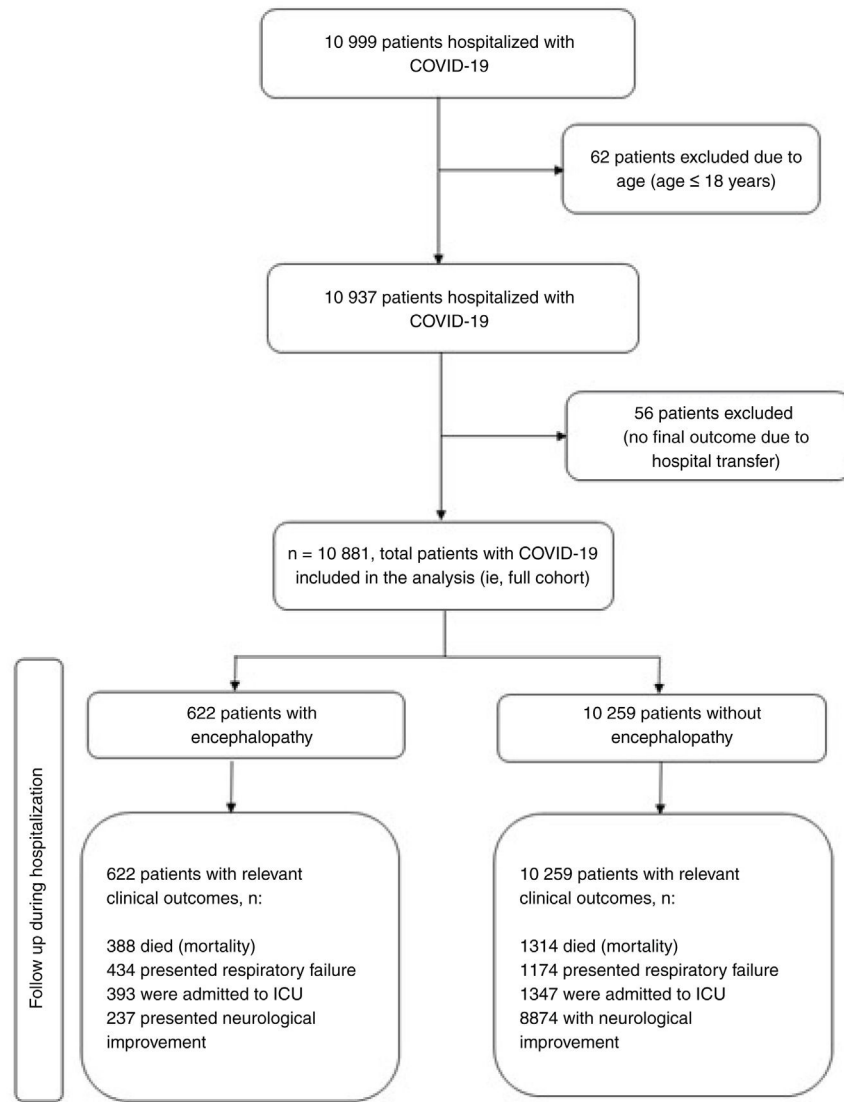


Figure 1 Flow diagram of patients included in the study. ICU: intensive care unit.

comes of interest. [Fig. 2](#) shows the Kaplan–Meier curves for the encephalopathy and no-encephalopathy groups for mortality, respiratory failure, and ICU admission.

COVID-19 severity

Severe/critical COVID-19 was observed in a higher proportion of patients with encephalopathy, compared to the no-encephalopathy group (85.3% vs 34.9%, $P < .001$). After adjusting for confounders, those with encephalopathy were 7.95 times (95% CI, 6.27–10.06) more likely to present severe/critical COVID-19, among patients admitted with COVID-19.

Mortality and associated causes

The mortality rate was higher in the encephalopathy group (62.4%) than in the no-encephalopathy group (12.8%, $P < .001$). The risk of mortality was 1.72 times greater (95% CI, 1.53–1.94) in the encephalopathy group. Acute respiratory distress syndrome and septic shock were the most

common causes of mortality. On stratified analysis, among patients with mild COVID-19, those with encephalopathy presented 9.26 times (95% CI, 5.75–14.92) greater mortality risk than those without encephalopathy. Among patients with severe/critical COVID-19, those with encephalopathy presented a risk of mortality 1.63 times (95% CI, 1.45–1.84) higher than those without encephalopathy. As seen in the Kaplan–Meier curve ([Fig. 2](#)), patients with COVID-19 and presenting encephalopathy had shorter survival times than those without encephalopathy (log-rank test, $P < .001$).

Respiratory failure and duration of ventilator dependence

There was a higher frequency of respiratory failure in the encephalopathy group (69.8% vs 11.4%, $P < .001$), with an adjusted hazard ratio (HR) of 5.4 (95% CI, 4.8–6.07). Patients with COVID-19 and encephalopathy presented a shorter time to respiratory failure than those without encephalopathy (log-rank test, $P < .001$) ([Fig. 2](#)). Meanwhile, encephalopathy was not found to be associated with

Table 1 Comparison of the clinico-demographic profiles of the encephalopathy and no-encephalopathy groups.

	All patients <i>n</i> = 10 881		COVID-19 patients with encephalopathy <i>n</i> = 622		COVID-19 patients without encephalopathy <i>n</i> = 10 259		<i>P</i>
Age group, <i>n</i> (%)							<.001
19–59 years	7047	(64.8)	254	(40.8)	6793	(66.2)	
≥60 years	3834	(35.2)	368	(59.2)	3466	(33.8)	
Sex, <i>n</i> (%)							.004
Female	5099	(46.9)	256	(41.2)	4843	(47.2)	
Male	5780	(53.1)	365	(58.8)	5415	(52.8)	
Comorbidities, <i>n</i> (%)							
Hypertension	3647	(33.5)	384	(61.7)	3263	(31.8)	<.001
Diabetes	2191	(20.1)	257	(41.3)	1934	(18.9)	<.001
Kidney disease	611	(5.6)	107	(17.2)	504	(4.9)	<.001
Bronchial asthma	463	(4.2)	25	(4.0)	438	(4.3)	.764
Coronary artery disease	421	(3.9)	59	(9.5)	362	(3.5)	<.001
Malignancy	244	(2.2)	35	(5.6)	209	(2.0)	<.001
Chronic obstructive pulmonary disease	156	(1.4)	19	(3.1)	137	(1.3)	<.001
Heart failure	127	(1.2)	20	(3.2)	107	(1.0)	<.001
Liver disease	60	(0.6)	8	(1.3)	52	(0.5)	.020
HIV infection	37	(0.3)	4	(0.6)	33	(0.3)	.159
Obesity			4	(0.6)	88	(0.9)	.570
Smoking, <i>n</i> (%)	1026	(9.4)	115	(18.5)	911	(8.9)	<.001
Past neurological history, <i>n</i> (%)							
Cerebrovascular disease	321	(2.95)	76	(12.2)	245	(2.4)	<.001
Dementia	38	(0.35)	15	(2.4)	23	(0.2)	<.001
Epilepsy	27	(0.25)	8	(1.3)	19	(0.2)	<.001
Neuropathy	9	(0.08)	2	(0.3)	7	(0.1)	.090
Movement disorder	6	(0.06)	3	(0.5)	3	(0.0)	.003
Headache syndrome	5	(0.04)	1	(0.2)	4	(0.0)	.255
Neuromuscular junction disorder	5	(0.04)	—	—	5	(0.1)	1.000
CNS infection	5	(0.04)	2	(0.3)	3	(0.0)	.029
PNS infection	3	(0.03)	—	—	1	(0.0)	1.000
Central demyelinating syndrome	2	(0.02)	—	—	2	(0.0)	1.000
Myelopathy	2	(0.02)	1	(0.2)	1	(1.9)	.111
New-onset neurological disease, <i>n</i> (%)							
Anoxic brain injury	51	(0.47)	3	(0.48)	48	(0.47)	.767
CNS infection ^a	7	(0.06)	4	(0.64)	3	(0.03)	<.001
Seizures/status epilepticus	125	(1.15)	74	(11.74)	52	(0.51)	<.001
Stroke/cerebrovascular event ^b	367	(3.37)	123	(19.77)	244	(2.38)	<.001
Movement disorder	3	(0.03)	1	(0.16)	2	(0.02)	.162
Demyelinating disorder ^c	2	(0.02)	—	—	2	(0.02)	>.999
Myelitis	—	—	—	—	—	—	—
PNS disorder ^d	12	(0.11)	2	(0.32)	10	(0.10)	.147
Respiratory and constitutional symptoms, <i>n</i> (%)							
Cough	4411	(40.5)	342	(55.0)	4069	(39.7)	<.001
Fever	3927	(36.1)	310	(49.8)	3617	(35.3)	<.001
Dyspnea	2703	(24.8)	307	(49.4)	2396	(23.4)	<.001
Sore throat	751	(6.9)	25	(4.0)	726	(7.1)	.003
Fatigue	713	(6.6)	65	(10.5)	648	(6.3)	<.001
Sputum production	637	(5.8)	66	(10.6)	571	(5.6)	<.001
Rhinorrhea	607	(5.6)	26	(4.2)	581	(5.7)	.118
Diarrhea	597	(5.5)	43	(6.9)	554	(5.4)	.108
Arthralgia	175	(1.6)	17	(2.7)	158	(1.5)	.022
Hemoptysis	33	(0.3)	—	—	33	(0.3)	.260

Table 1 (Continued)

	All patients <i>n</i> = 10 881		COVID-19 patients with encephalopathy <i>n</i> = 622		COVID-19 patients without encephalopathy <i>n</i> = 10 259		<i>P</i>
<i>COVID-19 severity, n (%)</i>							<.001
Mild	6690	(61.5)	91	(14.7)	6599	(65.1)	
Severe/critical	4061	(37.3)	527	(85.3)	3534	(34.9)	

^a To include encephalitis, meningitis, meningoencephalitis.^b Any acute CVD (inclusive of CVD infarction and CVD hemorrhage).^c To include acute disseminated encephalomyelitis, optic neuritis.^d To include sensory ganglionitis, radiculitis, anterior horn syndrome, peripheral neuritis (GBS, other than GBS), neuromuscular disorder, myositis.

HIV: human immunodeficiency virus; CNS: central nervous system; PNS: peripheral nervous system; CVD: cerebrovascular disease; GBS: Guillain–Barre Syndrome.

Table 2 Comparison of outcomes in patients with COVID-19, with and without encephalopathy.

Outcomes	All patients <i>n</i> = 10 881		COVID-19 patients with encephalopathy <i>n</i> = 622		COVID-19 patients without encephalopathy <i>n</i> = 10 259		<i>P</i>
Mortality and associated causes	1702	(15.6)	388	(62.4)	1314	(12.8)	<.001
Respiratory failure and associated causes	1608	(14.8)	434	(69.8)	1174	(11.4)	<.001
Duration of ventilator dependence							.495
1–5 days	218	(13.6)	63	(14.5)	155	(13.2)	
≥6 days	1390	(86.4)	371	(85.5)	1019	(86.8)	
ICU admission and indications	1740	(16.0)	393	(63.18)	1347	(13.13)	<.001
Duration of ICU stay							.484
1–7 days	272	(15.6)	57	(14.5)	215	(16.0)	
≥8 days	1468	(84.4)	336	(85.5)	1132	(84.0)	
Duration of hospital stay							<.001
1–14 days	6577	(60.4)	292	(47.0)	6285	(61.3)	
≥15 days	4304	(39.6)	330	(53.2)	3974	(38.7)	

ICU: intensive care unit.

Table 3 Association between encephalopathy and the different outcomes of interest.

Outcome	Adjusted OR	95% CI	<i>P</i>
COVID-19 severity (severe/critical)	7.95	6.27–10.06	<.001
Length of hospital stay (15 days or more)	1.36	1.14–1.61	<.001
Length of ventilator dependence (6 days or more)	0.88	0.64–1.21	.428
ICU admission	4.26	3.77–4.80	<.001
Length of ICU admission (8 days or more)	1.11	0.81–1.53	.522
	Adjusted HR	95% CI	<i>P</i> value
Mortality	1.72	1.53–1.94	<.001
Among patients with mild/moderate COVID-19	9.26	5.75–14.92	<.001
Among patients with severe/critical COVID-19	1.63	1.45–1.84	<.001
Respiratory failure	5.40	4.80–6.07	<.001

Adjusted for age, sex, hypertension, diabetes mellitus, smoking, coronary artery disease, cerebrovascular disease, dementia, epilepsy, and COVID-19 severity (as appropriate).

95% CI: 95% confidence interval; HR: hazard ratio; ICU: intensive care unit; OR: odds ratio.

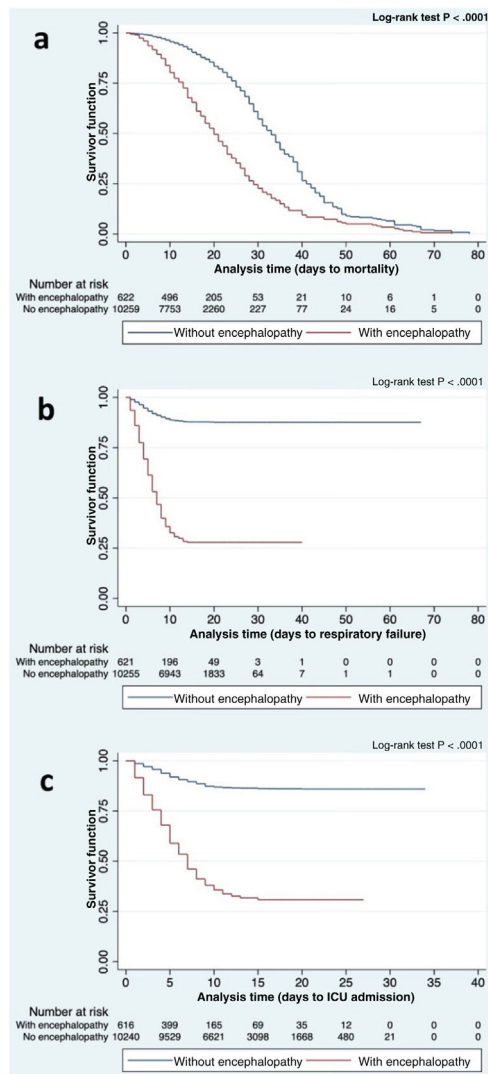


Figure 2 Kaplan–Meier curves for mortality, respiratory failure, and ICU admission. ICU: intensive care unit.

duration of ventilator dependence among patients with respiratory failure ($P = .428$).

ICU admissions and duration of ICU and hospital stays

Patients with encephalopathy presented 4.26 times (95% CI, 3.77–4.80) greater risk of ICU admission. Among patients with encephalopathy, 63.2% were admitted to the ICU, compared to only 13.3% among the no-encephalopathy group ($P < .001$). Based on the Kaplan–Meier curve (Fig. 2), patients with COVID-19 and encephalopathy presented a shorter time to ICU admission compared to those without encephalopathy (log-rank test, $P < .001$). Those with encephalopathy tended to have longer hospital stays compared to the no-encephalopathy group, with 1.36 times (95% CI, 1.14–1.61) higher odds of staying 15 days or more in hospital.

However, there was no difference in the length of ICU stay between the encephalopathy and no-encephalopathy groups ($P = .522$).

Discussion

The results of the Philippine CORONA Study identified encephalopathy as the most common new-onset neurological disorder among patients with COVID-19.³ Overall, our findings suggested that encephalopathy was associated with COVID-19 severity, mortality, respiratory failure, ICU admission, and longer hospital stays; this is consistent with findings of previous studies.^{8,15,16} It is worth mentioning that several studies on delirium and COVID-19 have also established an association with poor clinical outcomes, such as longer duration of mechanical ventilation and mortality.^{16–19}

The 5.7% prevalence of encephalopathy in our cohort is comparable to the rates reported in the recent prospective, multicenter study in New York (6.8%)²⁰ and in the TriNetX COVID-19 Research Network database consisting of 12 601 hospitalized patients (8.7%).²¹ Other studies with smaller sample sizes reported rates of encephalopathy and/or delirium of up to 32–33%.^{15,16} In the ICU setting, a prospective study of 2 ICU cohorts comprising 140 patients from France reported a 79.5% incidence rate of delirium diagnosed with the Confusion Assessment Method-ICU score.¹⁷ These discrepancies in the rate of occurrence of encephalopathy may be due to differences in study design, sample size and demographic characteristics, ICU or special unit admission, and inclusion criteria. For instance, our cohort presented a high proportion of mild COVID-19 cases, which may explain the lower prevalence rate of encephalopathy.

Encephalopathy and delirium in patients with COVID-19 may be caused by a myriad of factors, such as metabolic, respiratory, and coagulation alterations caused either by the direct effects of SARS-CoV-2 on the brain, remote effects, or systemic inflammation affecting the blood-brain barrier.²² Older age, male sex, presence of comorbidities (hypertension, diabetes mellitus, kidney disease, coronary artery disease, malignancy, heart failure), smoking, and previous neurological history (cerebrovascular disease, dementia, epilepsy, movement disorders, CNS infection) were more frequent in the encephalopathy group compared to the no-encephalopathy group. These findings are congruent with those of 2 previous large-scale studies of COVID-19 patient cohorts.^{8,15} In the general acute medical setting, older age, male sex, and presence of cognitive disorder are among the known risk factors for encephalopathy.²³ The higher incidence of encephalopathy among elderly patients and those with history of neurological disorders may be explained by decreased cognitive reserve, making the brain vulnerable to such insults as hypoxia and other metabolic alterations.²⁴ Moreover, the majority of our patients in the encephalopathy group were elderly. Polypharmacy is also common in elderly people and can easily predispose to delirium, a feature of encephalopathy.²³ Furthermore, studies in elderly patients with dementia found that delirium is a common initial presentation of COVID-19 in this population, and is associated with a higher mortality rate.^{18,25}

Our findings showed that the adjusted HR for mortality among patients with encephalopathy was higher among patients with mild COVID-19 than among those with severe/critical COVID-19. The presence of encephalopathy may not have markedly contributed to the risk of mortality in patients with severe and critical COVID-19, as

other factors such as presence of underlying diseases and several complications like acute respiratory distress syndrome, acute kidney injury, shock, secondary infections, and arrhythmias were found to increase the risk of mortality among patients admitted to the ICU.^{26–28} The increased risk of mortality among patients with mild COVID-19 and encephalopathy suggests that encephalopathy may play a role as a prognostic marker.

Some results have shown that patients with encephalopathy present significantly higher rates of ICU admission than those without encephalopathy. ICU admissions, along with presentation of stupor or coma, have been shown in turn to be predictors of worse outcome at discharge,²⁹ with patients aged > 65 years having a markedly increased risk for persistent and new sequelae of various clinical conditions, including chronic respiratory failure, cardiac rhythm disorders, acute coronary syndrome, stroke, and kidney injury.³⁰ Thus, further studies on the follow up of elderly patients with encephalopathy may be prudent to explore long-term complications of COVID-19.

In the current study, no association was observed between length of ICU stay and encephalopathy. Several factors influence length of ICU stay, such as social and institutional factors and the presence of a specialized team at the ICU³¹; as these factors were not taken into consideration during our data collection, the lack of association cannot be fully explained by our study.

The limitations of the present study lie in the retrospective nature of the research, due to the inherent risks of recording bias. The onset of encephalopathy, its duration, and correlation with other events such as sepsis, strokes, seizures, and the notorious cytokine storm would likewise clarify the underlying mechanism better. No additional data on cerebrospinal fluid were recorded. Nevertheless, this was the first large-scale nationwide study of COVID-19 in the Philippines, providing valuable information on the incidence of encephalopathy and its associations with clinical outcomes. A prospective study to reduce recording bias may provide more accurate data and remove confounding variables affecting the outcomes of COVID-19 patients with encephalopathy.

Conclusion

Our study showed that encephalopathy was associated with COVID-19 severity, mortality, respiratory failure, ICU admission, and longer hospital stays. Further studies to determine specific risk factors for the development of encephalopathy in COVID-19 may help in improving the outcomes of patients admitted to hospital with COVID-19 in our setting.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the local institutional review boards (code) of: Asian Hospital and Medical Center, Muntinlupa City (2020-010-A); Baguio General Hospital and Medical Center (BGHMC), Baguio City (BGHMC-ERC-2020-13); Cagayan Valley Medical Center (CVMC), Tuguegarao City; Capitol Medical Center, Quezon City; Cardinal Santos Medical Center (CSMC), San Juan City (CSMC REC 2020-020); Chong Hua Hospital, Cebu City (IRB 2420-04); De La Salle Medical and Health Sciences Institute (DLSMHSI), Cavite (2020-23-02-A); East Avenue Medical Center (EAMC), Quezon City (EAMC IERB 2020-38); Jose R. Reyes Memorial Medical Center, Manila; Jose B. Lingad Memorial Regional Hospital, City of San Fernando, Pampanga; Dr. Jose N. Rodriguez Memorial and Sanitarium Hospital, Caloocan City; Lung Center of the Philippines (LCP), Quezon City (LCP-CT-010-2020); Manila Doctors Hospital, Manila (MDH IRB 2020-006); Makati Medical Center, Makati City (MMC IRB 2020-054); Medical Center Manila, Manila (MMERC 2020-09); Northern Mindanao Medical Center, Cagayan de Oro City (025-2020); Quirino Memorial Medical Center (QMMC), Quezon City (QMMC REB GCS 2020-28); Ospital ng Makati, Makati City; Philippine General Hospital, University of the Philippines Manila (2020-314-01 SJREB); Philippine Heart Center, Quezon City; Research Institute for Tropical Medicine, Muntinlupa City (RITM IRB 2020-16); San Lazaro Hospital, Manila; San Juan De Dios Educational Foundation Inc – Hospital, Pasay City (SJRIIB 2020-0006); Single Joint Research Ethics Board of the DOH, Philippines (SJREB-2020-24); Southern Isabela Medical Center, Santiago City (2020-03); Southern Philippines Medical Center (SPMC), Davao City (P20062001); St. Luke's Medical Center, Quezon City (SL-20116); St. Luke's Medical Center, Bonifacio Global City, Taguig City (SL-20116); Southern Philippines Medical Center, Davao City; The Medical City, Pasig City; University of Santo Tomas Hospital, Manila (UST-REC-2020-04-071-MD); University of the East Ramon Magsaysay Memorial Medical Center, Inc, Quezon City (0835/E/2020/063); Veterans Memorial Medical Center (VMMC), Quezon City (VMMC2020-025) and Vicente Sotto Memorial Medical Center, Cebu City (VSMC-REC-O-2020-048).

Informed consent statement

Informed consent was not necessary since the study design was a retrospective cohort study employing medical chart review. All data obtained were completely anonymized.

Submission declaration and verification

This manuscript has never been published in part and is not under consideration for publication elsewhere. All authors have read and agreed to the published version of the manuscript. If accepted, this manuscript will not be published elsewhere in the same form, in English or in any other language, including electronically, without the consent of the copyright holder.

Conflict of interest

None.

Data availability statement

Data not published within this article are available upon request from the corresponding author.

Statement on artificial intelligence and artificial intelligence-assisted technologies

During the preparation of this work the primary authors only used ChatGPT to translate the title, abstract, and keywords from English to Spanish. After using this tool/service, the primary authors reviewed and edited the Spanish translation of the title, abstract, and keywords and take full responsibility for the content of the publication.

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References

1. Collantes MEV, Espiritu AI, Sy MCC, Anlacan VMM, Jamora RDG. Neurological manifestations in COVID-19 infection: a systematic

- review and meta-analysis. *Can J Neurol Sci J Can Sci Neurol*. 2021;48:66–76.
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683.
3. Espiritu AI, Sy MCC, Anlacan VMM, Jamora RDG, Philippine CORONA Study Group Investigators. COVID-19 outcomes of 10,881 patients: retrospective study of neurological symptoms and associated manifestations (Philippine CORONA Study). *J Neural Transm Vienna Austria*. 2021;128:1687–703.
4. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. *Neurology*. 2020;95:e1060–70.
5. Eskandar EN, Altschul DJ, de la Garza Ramos R, Cezayirli P, Unda SR, Benton J, et al. Neurologic syndromes predict higher in-hospital mortality in COVID-19. *Neurology*. 2021;96:e1527–38.
6. Mahdizade Ari M, Mohamadi MH, Shadab Mehr N, Abbasi-moghaddam S, Shekartabar A, Heidary M, et al. Neurological manifestations in patients with COVID-19: a systematic review and meta-analysis. *J Clin Lab Anal*. 2022;36:e24403.
7. Slooter AJC, Otte WM, Devlin JW, Arora RC, Bleck TP, Claassen J, et al. Updated nomenclature of delirium and acute encephalopathy: statement of ten societies. *Intensive Care Med*. 2020;46:1020–2.
8. Frontera JA, Melmed K, Fang T, Granger A, Lin J, Yaghi S, et al. Toxic metabolic encephalopathy in hospitalized patients with COVID-19. *Neurocrit Care*. 2021;35:693–706.
9. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: a review. *J Med Virol*. 2021;93:206–22.
10. Pajo AT, Espiritu AI, Apor ADAO, Jamora RDG. Neuropathologic findings of patients with COVID-19: a systematic review. *Neurol Sci*. 2021;42:1255–66.
11. Dziegielewska C, Skead C, Canturk T, Webber C, Fernando SM, Thompson LH, et al. Delirium and associated length of stay and costs in critically ill patients. *Crit Care Res Pract*. 2021;2021:6612187.
12. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291:1753–62.
13. Salluh JIF, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ*. 2015;350:h2538.
14. Espiritu AI, Sy MCC, Anlacan VMM, Jamora RDG. The Philippine COVID-19 outcomes: a retrospective study of neurological manifestations and associated symptoms (the Philippine CORONA study): a protocol study. *BMJ Open*. 2020;10:e040944.
15. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol*. 2020;7:2221–30.
16. Garcez FB, Aliberti MJR, Poco PCE, Hiratsuka M, Takahashi S, de F, et al. Delirium and adverse outcomes in hospitalized patients with COVID-19. *J Am Geriatr Soc*. 2020;68:2440–6.
17. Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, et al. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care*. 2020;24:491.
18. Poloni TE, Carlos AF, Cairati M, Cutaia C, Medici V, Marelli E, et al. Prevalence and prognostic value of Delirium as the initial presentation of COVID-19 in the elderly with dementia: an Italian retrospective study. *EClinicalMedicine*. 2020;26:100490.
19. Pranata R, Huang I, Lim MA, Yonas E, Vania R, Kuswardhani RAT. Delirium and mortality in coronavirus disease 2019 (COVID-19) – a systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2021;95:104388.
20. Frontera JA, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Verneti P, et al. A Prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. *Neurology*. 2021;96:e575–86.
21. Shah VA, Nalleballe K, Zaghloleh ME, Onteddu S. Acute encephalopathy is associated with worse outcomes in COVID-19 patients. *Brain Behav Immun – Health*. 2020;8:100136.
22. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care*. 2020;24:176.
23. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. *Crit Care Clin*. 2008;24:657–722.
24. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911–22.
25. Bianchetti A, Rozzini R, Guerini F, Boffelli S, Ranieri P, Minelli G, et al. Clinical presentation of COVID19 in dementia patients. *J Nutr Health Aging*. 2020;24:560–2.
26. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, et al. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: a prospective, cohort, multicentre study. *Rev Esp Anestesiología Reanimación Engl Ed*. 2020;67:425–37.
27. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180:1–11.
28. Zangrillo A, Beretta L, Scandroglio AM, Monti G, Fominskiy E, Colombo S, et al. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. *Crit Care Resusc J Australas Acad Crit Care Med*. 2020;22:204–9.
29. Beghi E, Helbok R, Ozturk S, Karadas O, Lisnic V, Grosu O, et al. Short- and long-term outcome and predictors in an international cohort of patients with neuro-COVID-19. *Eur J Neurol*. 2022;29:1663–84.
30. Cohen K, Ren S, Heath K, Dasmariñas MC, Jubilo KG, Guo Y, et al. Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2022;376:e068414.
31. Toptas M, Sengul Samanci N, Akkoc İ, Yucetas E, Cebeci E, Sen O, et al. Factors affecting the length of stay in the intensive care unit: our clinical experience. *BioMed Res Int*. 2018;2018:9438046.