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Research article

Clinical outcomes of patients with seizure admitted for COVID-19: Findings from the Philippine CORONA study

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ABSTRACT

Objective: Seizure is one of the neurologic manifestations of coronavirus disease 2019 (COVID-19) infection. There are few studies focused on the outcome of hospitalized patients with COVID-19 and seizure.
Methods: This was a subgroup analysis of patients with seizure based on a nationwide, multicenter, retrospective study of COVID-19 patients admitted in 37 hospitals in the Philippines.
Results: A total of 10,881 patients with COVID-19 infection were included. Among these, 27 (0.2 %) patients had pre-existing seizure/epilepsy and 125 (1.1 %) had new-onset seizure. The patients with pre-existing seizure/epilepsy had a mean age of 49 years and majority were males (63.0 %). The patients with new-onset seizure had a mean age of 57 years and majority were males (60.5 %). Among patients with pre-existing seizure/epilepsy, there were no significant differences in the proportion of severe/critical COVID-19 ($p = 0.131$), all-cause mortality ($p = 0.177$), full/partial neurologic recovery ($p = 0.190$), ventilator use ($p = 0.106$), length of intensive care unit stay ($p = 0.276$), and length of hospitalization ($p = 0.591$). Patients with new-onset seizure were 2.65 times more likely to have severe/critical COVID-19 infection ($p < 0.001$), 3.12 times more likely to die ($p < 0.001$), and 3.51 times more likely to require a ventilator ($p < 0.001$) than those without new-onset seizure. New-onset seizure, however, was not significantly associated with full/partial neurologic recovery ($p = 0.184$) and prolonged length of hospitalization ($p = 0.050$).
Conclusion: Severe/critical COVID-19 infection, higher mortality rate, and use of a ventilator were significantly higher among patients with new-onset seizure but not among patients with pre-existing seizure/epilepsy.

1. Introduction

COVID-19 is a respiratory disease caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV2). It was first

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reported in December 2019 in China and later declared as a pandemic by the World Health Organization [1,2]. This disease has already affected the health care system of different nations, as well as their economy.

The clinical manifestations of COVID-19 infection are not just limited to the respiratory system. Various neurologic signs and symptoms can be the manifestation/s of COVID-19 infection. Some of these include seizure, cerebrovascular disease, altered mental status, headache, dizziness, olfactory and gustatory dysfunction, fatigue, sleep disorder, Guillain-Barre syndrome, movement disorder, myalgia, neuralgia, and dizziness [3–6]. A meta-analysis of the neurologic manifestations of COVID-19 showed that the prevalence of seizure is 0.5 % [4,7]. Seizure is focal in 50.3 %, generalized in 46.2 %, and unclassified in 3.5 % [8]. The seizure type in these patients are varied such as acute symptomatic seizure, breakthrough seizure in a previously controlled epilepsy, new-onset epilepsy, and/or status epilepticus, with a multi-factorial etiology [9–12]. The possible mechanisms of seizure generation by SARS-CoV2 are inflammation leading to neuronal necrosis, increased glutamate and decreased gamma-amino butyric acid (GABA), breakdown of the blood-brain barrier causing impaired neuronal homeostasis, hypoxia and/or ischemia, mitochondrial dysfunction, and electrolyte imbalances [12,13]. Patients with pre-existing epilepsy may also experience increased seizure frequency and lowered seizure threshold [14–16].

Although there are numerous published studies on seizure and COVID-19 infection, only a small fraction of these studies, excluding case reports and case series, focused on the outcome of hospitalized patients infected with SARS-CoV2 with concomitant seizure or epilepsy in terms of mortality, functional outcome, and duration of hospitalization [17–21]. Published data were from studies completed in the United States, Spain, Iran, and Turkey, with no study emanating from Southeast Asia on seizure and COVID-19 outcomes. Furthermore, in developing countries such as the Philippines where the healthcare system is different from developed nations, a more profound gap in seizure and epilepsy diagnosis and treatment is evident [22]. We therefore looked into the outcomes of COVID-19 patients with and without seizure in terms of mortality, neurologic outcome at discharge, use of a ventilator, length of stay in the hospital and intensive care unit (ICU).

2. Method

2.1. Study design and setting

This sub study was an analysis of patients with pre-existing and new-onset seizure from the data of the Philippine CORONA Study involving 10,881 patients [23]. This was a nationwide, multicenter, retrospective study involving hospitalized patients with COVID-19 from February 2020 to December 2020 in 37 major hospitals in the country [23]. The study obtained approval from the respective research ethics boards of all the participating sites (UPMREB Code: 2020-314-01 SJREB) and was registered in ClinicalTrials.gov (NCT04386083). The details about the research design, patient selection and enrollment, and data collection procedures were discussed in the published protocol [24].

2.2. Patient selection and sampling

Patients from the Philippine CORONA Study were included in this subgroup if they satisfied the inclusion criteria: (a) at least 19 years old, (b) COVID-19 confirmed by testing of the nasopharyngeal swab samples by real-time reverse transcription polymerase chain reaction (RT-PCR), (c) with clinical signs and symptoms of COVID-19 (respiratory and non-respiratory), and (d) with final disposition at the end of the study period (discharged or deceased). COVID-19 patients with pre-existing seizure/epilepsy and new-onset seizure were compared to those without pre-existing seizure/epilepsy and new-onset seizure, respectively. The seizure/epilepsy etiology, type, frequency, duration, treatment, and the presence of status epilepticus were not included in the Philippine CORONA Study data collection form. The presence of any past neurologic disorder was noted. The data collected were up to the time of discharge [23,24].

2.3. Outcomes

The outcomes of the study were COVID-19 severity (mild, severe, or critical), mortality, neurological recovery (full, partial improvement of neurological deficit, or no improvement of neurological deficit), use of a ventilator, duration of ventilator dependence (days from the start of assisted ventilation to cessation), ICU admission, length of ICU stay, and length of hospital stay. The outcomes of the patients who had no neurological deficit/s, who did not stay in the ICU, and who did not use the ventilator were also taken based on chart review.

Mild COVID-19 was defined as the presence of mild pneumonia or absence of pneumonia. Severe COVID-19 included the presence of dyspnea, respiratory rate >30 breaths/minute, oxygen saturation of <93 %, or >50 % lung involvement on imaging within 24–48 h of admission. Critical COVID-19 disease was defined as the presence of respiratory failure, shock, or multi-organ dysfunction. Full neurological recovery was considered if the patient had any neurological deficit during admission with complete resolution of that deficit at discharge. Partial improvement of neurological deficit was defined as the incomplete resolution of that deficit on discharge and no improvement of the neurological deficit was considered if the neurological deficit remained the same at discharge.

2.4. Statistical analysis

Baseline characteristics and clinical outcomes of the participants were summarized by descriptive statistics. Numerical variables were described as mean and standard deviation for the variables with normally distributed data, and median and interquartile range,

for non-normally distributed variables. Categorical variables were described as count and proportion. These different baseline characteristics and clinical outcomes were compared between the two groups: patients with seizure and patients without seizure. Significant differences in the mean/median/mean-rank of the different numerical variables between the two groups were determined by Student's *t*-test for the variables with normally distributed data, while Mann-Whitney *U* test was done for non-normally distributed variables. Heterogeneity of the proportions of the different categorical variables between the two groups were determined by chi-square test or Fisher exact test.

The association between seizure and the different individual dichotomous outcome variables of interest was determined by binary logistic regression. Survival analysis was also done for time-to-event data of mortality, ICU admission, and use of a ventilator. The time-to-event were right-censored on time-to-discharge as the exit from the time-at-risk among those who have not experienced the event, i.e., mortality, ICU admission, or respiratory failure, and during the hospital stay. The associations between seizure and the different time-to-event outcome variables of interest were determined by multivariable Cox proportional hazards regression. Multivariable regression analysis was also performed to adjust for age, comorbidities with hypertension, diabetes mellitus (DM), chronic cardiac disease, cerebrovascular disease, and COVID-19 severity at nadir. A cutoff of $p < 0.05$ identifies seizure as significant predictor of the different outcomes of interest. Kaplan-Meier curves were constructed to visualize the failure plot of the full cohort, and comparison between patients with versus without seizure.

Data analysis was performed using Stata 17. The normality of distribution of the variables were assessed by skewness and kurtosis test for normality and graphically by quantile-quantile plot. Significance level was set at $\alpha = 0.05$.

3. Results

A total of 10,881 patients with RT-PCR confirmed COVID-19 infection were included for analysis. Among these, 27 patients (0.2 %) had pre-existing seizure/epilepsy and 125 patients (1.1 %) had new-onset seizure.

3.1. Demographic and clinical profile

Among the patients with COVID-19 and pre-existing seizure, the mean age was 49 years, with males ($n = 17$, 63.0 %) comprising the majority. The most common comorbidities/risks were hypertension ($n = 13$, 48.2 %), smoking history ($n = 8$, 29.6 %), DM ($n = 6$,

Table 1
Clinicodemographic characteristics of the stratified according to seizure.

Clinical profile	With pre-existing seizure/ epilepsy ($n = 27$)	Without pre-existing seizure/ epilepsy ($n = 10,854$)	*p* value	With new-onset seizure ($n = 125$)	Without new-onset seizure ($n = 10,756$)	*p* value
Age[a]	49 (32)	52 (28)	0·086	57 (28)	52 (28)	0·056
Sex			0·305			0·099
Male	17 (63·0 %)	5763 (53·1 %)		75 (60·0 %)	5705 (53·1 %)	
Female	10 (37·0 %)	5089 (46·9 %)		49 (39·5 %)	5050 (46·9 %)	
Nationality			>0·999			>0·999
Filipino	27 (100·0 %)	10,762 (99·2 %)		125 (100·0 %)	10,664 (99·1 %)	
Others	0	92 (0·9 %)		0	92 (0·9 %)	
Body mass index[a,b]	25·19 (3·52)	24·98 (6·1)	0·741	23.5 (4·7)	25·0 (6·1)	0·017
Comorbidities/risks						
Smoking history	8 (29·6 %)	1018 (9·4 %)	<0·001	33 (26·4 %)	993 (9·2 %)	<0·001
Hypertension	13 (48·2 %)	3634 (33·5 %)	0·107	75 (60·0 %)	3572 (33·2 %)	<0·001
Diabetes mellitus	6 (22·2 %)	2185 (20·1 %)	0·787	42 (33·6 %)	2149 (20·0 %)	<0·001
Kidney disease	4 (14·8 %)	607 (5·6 %)	0·038	17 (13·6 %)	594 (5·5 %)	<0·001
Obesity[b]	1 (8·3 %)	764 (17·0 %)	0·426	3 (6·7 %)	762 (17·0 %)	0·065
Healthcare worker	3 (11·1 %)	873 (8·0 %)	0·558	6 (4·8 %)	870 (8·1 %)	0·179
Neurologic disease[c]						
Stroke	7 (25·9 %)	314 (2·9 %)	<0·001	21 (16·8 %)	300 (2·8 %)	<0·001
Others[d]	1 (3·7 %)	71 (0·7 %)	0·051	2 (1·6 %)	70 (0·7 %)	0·193
Therapeutics received						
Glucocorticoids	10 (37·0 %)	2834 (26·1 %)	0·197	58 (46·4 %)	2786 (25·9 %)	<0·001
Tocilizumab	0	1029 (9·5 %)	0·105	13 (10·4 %)	1016 (9·5 %)	0·717
Antiviral[e]	7 (25·9 %)	1895 (17·5 %)	0·305	35 (28·0 %)	1867 (17·3 %)	0·002
Antibacterial	24 (88·9 %)	8990 (82·8 %)	0·608	111 (88·8 %)	8903 (82·7 %)	0·076
Others[f]	12 (44·4 %)	3893 (35·9 %)	0·422	42 (33·6 %)	3863 (35·9 %)	0·592

[a] Data presented is in median (interquartile range).
[b] Only 4518 participants have body mass index data and corresponding obesity information. Obesity is defined as a body mass index of at least 25 (based on the World Health Organization definition for the Asia-Pacific).
[c] Neurologic disease is defined as a past history of neurologic disease.
[d] Includes dementia, movement disorder, headache, demyelinating disease, central nervous system infection, peripheral nerve disease, neuromuscular junction disorder, and myopathy.
[e] Includes chloroquine, hydroxychloroquine, convalescent plasma, systemic glucocorticoids, and tocilizumab.
[f] Includes remdesivir, lopinavir, and ritonavir.

Table 2
Association of having seizure with the different outcomes of interest.

Outcomes	Pre-existing seizure/epilepsy						New-onset seizure					
	Estimate[a]	95 % Confidence Interval	*p* value	Adjusted estimate[b]	95 % Confidence Interval	*p* value	Estimate[a]	95 % Confidence Interval	*p* value	Adjusted estimate[b]	95 % Confidence Interval	*p* value
Dichotomous outcomes												
Severe/critical COVID-19[c]	1·78	0·83, 3·78	0·136	2·18	0·94, 5·08	0·070	3·03	2·08, 4·40	<0·001	2·65	1·75.4·00	<0·001
Full/partial improvement of neurologic deficit/s	0·43	0·11, 1·63s	0·215	0·58	0·14, 2·45	0·454	0·50	0·30, 0·84	0·008	0·67	0·37, 1·21	0·184
All-cause mortality	1·89	0·80, 4·48	0·147	1·74	0·63, 4·81	0·286	4·49	3·15, 6·42	<0·001	3·12	1·99, 4·88	<0.001
Use of a ventilator	2·02	0·85, 4·79	0·109	1·48	0·52, 4·15	0·460	5·49	3.85, 7·83	<0·001	3·51	2·24, 5·50	<0·001
Prolonged duration of ventilator dependence (≥6 days)	0·25	0·06, 1·08	0·063	0·35	0·08, 1·58	0·173	0·20	0·11, 0·38	<0·001	0·34	0·17, 0·65	0·001
ICU admission	0·91	0·32, 2·64	0·867	0·57	0·18, 1·84	0·347	4·99	3·50, 7·11	<0·001	3·28	2·10, 5·11	<0·001
Prolonged length of hospital stay (≥15 days)	0·64	0·28, 1·47	0·295	0·60	0·26, 1·38	0·230	1·67	1·17, 2·37	0·005	1·44	1·00, 2·07	0·050
Time-to-event outcomes												
All-cause mortality	2·14	1·02, 4·49	0·045	1·81	0·86, 3·81	0·119	2·33	1·78, 3·04	<0·001	1·59	1·20, 2·09	0·001
ICU admission	0·98	0·37, 2·61	0·964	0·71	0·26, 1·89	0·488	3·81	2·95, 4·93	<0·001	2·13	1·63, 2·77	<0·001
Use of a ventilator	1·85	0·88, 3·89	0·103	1·27	0·60, 2·68	0·534	3·96	3·06, 5·13	<0·001	2·05	1·56, 2·68	<0·001

COVID-19 – coronavirus disease 2019; ICU – intensive care unit.

[a] Odds ratio for dichotomous outcomes, and hazard ratio for time-to-event outcomes.

[b] Adjusted for age, comorbidities with hypertension, diabetes mellitus, chronic cardiac disease, cerebrovascular disease, and COVID-19 severity at nadir.

[c] Adjusted only for age, and comorbidities with hypertension, diabetes mellitus, chronic cardiac disease, and cerebrovascular disease.

22.2 %), and kidney disease ($n = 4$, 14.8 %). There was a significantly higher proportion of previous stroke ($p < 0.001$), smoking history ($p < 0.001$), and kidney disease ($p = 0.038$) among those with pre-existing seizure/epilepsy (see Table 1).

Among those patients with new-onset seizure, the mean age was 57 years and males ($n = 75$, 60.5 %) comprised the majority. Hypertension ($n = 75$, 60.0 %) was the most common comorbidity, followed by DM ($n = 42$, 33.6 %), smoking history ($n = 33$, 26.4 %), and kidney disease ($n = 17$, 13.6 %). There was a higher proportion of lower body mass index ($p = 0.017$), smoking history ($p < 0.001$), hypertension ($p < 0.001$), DM ($p < 0.001$), kidney disease ($p < 0.001$), stroke ($p < 0.001$), and treatment with glucocorticoids ($p < 0.001$) and antiviral medications ($p = 0.002$) (see Table 1). Among 27 patients who had pre-existing seizure/epilepsy, 7 patients (25.9 %) developed seizure during hospitalization.

None of the patients with pre-existing seizure/epilepsy underwent lumbar puncture and electroencephalogram (EEG). Among those with new-onset seizure, 6 out of 125 (4.8 %) underwent lumbar puncture. One patient had both neutrophilia and lymphocytosis, one patient had lymphocytosis alone, four patients had elevated protein, and one patient had hypoglycorrhachia. Two out of 125 (1.6 %) patients with new-onset seizure had an EEG. One patient had a normal EEG result and the other patient had an isoelectric pattern on EEG (complete loss of cortical activity even with maximal amplification).

3.2. Clinical outcomes

After adjusting for age and comorbidities with hypertension, DM, chronic cardiac disease, and cerebrovascular disease, pre-existing seizure/epilepsy was not significantly associated with COVID-19 severity (adjusted odds ratio [OR] = 2.18, 95 % CI 0.94–5.08, $p = 0.070$). After adjusting for age, comorbidities with hypertension, DM, chronic cardiac disease, cerebrovascular disease, and COVID-19 severity at nadir, pre-existing seizure/epilepsy was not significantly associated with full/partial improvement of neurologic deficit/s (adjusted OR = 0.58, 95 % CI 0.14–2.45, $p = 0.454$), all-cause mortality (adjusted OR 1.74, 95 % CI 0.63–4.81, $p = 0.286$), use of a ventilator (adjusted OR = 1.48, 95 % CI 0.52–4.15, $p = 0.460$), prolonged duration of ventilator dependence (adjusted OR = 0.35, 95 % CI 0.08–1.58, $p = 0.173$), ICU admission (adjusted OR = 0.57, 95 % CI 0.18–1.84, $p = 0.347$), and prolonged length of hospitalization (adjusted OR = 0.60, 95 % CI 0.26–1.38, $p = 0.230$) (see Table 2).

After adjusting for age and comorbidities with hypertension, DM, chronic cardiac disease, and cerebrovascular disease, the patients with new-onset seizure were 2.65 times more likely to have severe/critical COVID-19 infection (95 % CI 1.75–4.00, $p < 0.001$), 3.12 times more likely to die (95 % CI 1.99–4.88, $p < 0.001$), and 3.51 times more likely to use a ventilator (95 % CI 2.24–5.50, $p < 0.001$) than those without new-onset seizure. COVID-19 patients with new-onset seizure also had a 66 % decrease in the odds of prolonged ventilator dependence (adjusted OR = 0.34, 95 % CI 0.17–0.65, $p = 0.001$), a 59 % increase in the hazards of mortality (adjusted hazard ratio [HR] = 1.59, 95 % CI 1.20–2.09, $p = 0.001$), a 113 % increase in the hazards of ICU admission (adjusted HR = 2.13, 95 % CI 1.63–2.77, $p < 0.001$), and a 105 % increase in the hazards of ventilator use (adjusted HR = 2.05, 95 % CI 1.56–2.68, $p < 0.001$). On the other hand, the patients with new-onset seizure were not significantly associated with full/partial improvement of neurologic deficit/s (adjusted OR = 0.67, 95 % CI 0.37–1.21, $p = 0.184$) and prolonged length of hospitalization (adjusted OR = 1.44, 95 % CI 1.00–2.07, $p = 0.050$) after adjusting for age and comorbidities with hypertension, DM, chronic cardiac disease, and cerebrovascular disease (see Table 2).

There was no sufficient evidence to conclude that there were significant differences in the proportion of the following outcomes

Table 3
Clinical outcomes of COVID-19 patients stratified according to having seizure.

Outcome	With pre-existing seizure/ epilepsy ($n = 27$)	Without pre-existing seizure/ epilepsy ($n = 10,854$)	p value	With new-onset seizure ($n = 125$)	Without new-onset seizure ($n = 10,756$)	p value
COVID-19 severity			0·131			<0·001
Severe/critical	14 (51·8 %)	4047 (37·7 %)		78 (64·5 %)	3983 (37·5 %)	
Mild/moderate	13 (48·2 %)	6677 (62·2 %)		43 (35·5 %)	6647 (62·5 %)	
All-cause mortality			0·177			<0·001
Mortality	7 (25·9 %)	1695 (15·6 %)		56 (44·8 %)	1646 (15·3 %)	
Survivor	20 (74·1 %)	9159 (84·3 %)		69 (55·2 %)	9110 (84·7 %)	
Neurologic outcomes[a]			0·190			0·007
Full/partial improvement	8 (72·7 %)	1631 (86·1 %)		68 (76·4 %)	1571 (86·5 %)	
Stable, no improvement	3 (27·3 %)	263 (13·9 %)		21 (23·6 %)	245 (13·5 %)	
Use of a ventilator			0·106			<0·001
Yes	7 (25·9 %)	1601 (14·8 %)		60 (48·0 %)	1548 (14·4 %)	
No	20 (74·1 %)	9253 (85·3 %)		65 (52·0 %)	9208 (85·6 %)	
Length of ICU stay[b,c]	19·5 (11·5)	15 (12)	0·276	15 (10·5)	15 (12)	0·996
Length of hospital stay[c]	12 (7)	13 (9)	0·591	15 (10)	13 (9)	0·059

COVID-19 – Coronavirus disease 2019; ICU – intensive care unit.
[a] Only 1905 participants have neurologic outcome data among the 2291 participants with neurologic presentation and/or complication.
[b] Among 1740 participants who have been admitted in the ICU.
[c] Data presented is median (interquartile range).

between patients with pre-existing seizure/epilepsy versus those without: severe/critical COVID-19 ($p = 0.131$), all-cause mortality ($p = 0.177$), full/partial neurologic recovery among patients with neurologic presentation at admission ($p = 0.190$), use of a ventilator ($p = 0.106$), length of ICU stay ($p = 0.276$), and length of hospital stay ($p = 0.591$) (see Table 3).

The patients with new-onset seizure had a significantly higher proportion of severe/critical COVID-19 infection ($p < 0.001$), all-cause mortality ($p < 0.001$), and use of a ventilator ($p < 0.001$) compared to those without new-onset seizure. COVID-19 patients with new-onset seizure had a significantly lower proportion of full/partial neurologic improvement ($p = 0.007$) than those without new-onset seizure. In terms of the length of ICU and hospitalization, there were no significant differences between patients with and without new-onset seizure ($p = 0.996$ and $p = 0.059$, respectively) (see Table 3). See Fig. 1A to F for the Kaplan-Meier plot of the patients with epilepsy or new-onset seizure in relation to all-cause mortality, respiratory failure, and ICU admission.

4. Discussion

Seizure is one of the neurologic manifestations of COVID-19 [5,6,8,9,12,15,25]. In an observational study, seizure occurred after a mean of 3.91 ± 5.07 days after the onset of general symptoms [20]. Among 2751 people with epilepsy (PWE) and COVID-19 infection, 8.6 % developed worsening of seizure frequency [26]. Among the different possible mechanisms of seizure in relation to SARS-CoV2 infection, inflammation from the infection played a major role. Other mechanisms were blood-brain barrier breakdown, hypoxia-ischemia, mitochondrial dysfunction, and electrolyte imbalance [12,13]. Neuropathologic studies also showed that perivascular infiltrates and microglial activation were seen in neuroinflammation [27].

In this study, the clinical profile and outcome of COVID-19 patients with and without pre-existing and new-onset seizure were analyzed and compared. Since these patients were admitted for COVID-19 infection, this can account for the large number of patients with severe or critical COVID-19 infection, including those with respiratory failure, unstable comorbid conditions, or those with more severe symptoms.

In this study, the patients with pre-existing epilepsy and new-onset seizure were older. Advanced age may account for the presence of more comorbidities, such as hypertension and previous stroke, which is a known risk factor for the development of epilepsy. With regards to new-onset seizure in COVID-19 patients, it is unclear if a history of previous stroke contributed to its pathogenesis or if the mechanism is solely from COVID-19 infection [25]. Ventilatory support was needed by 25.9 % of those who had pre-existing seizure and by 48.0 % of those with new-onset seizure. The higher rate of ventilator use in those with new-onset seizure coincided with a higher rate of severe/critical COVID-19 infection in these patients. It is fortunate that the majority of the patients had full or partial neurologic improvement (72.7 % with pre-existing seizure and 76.4 % with new-onset seizure). In a Spanish registry of COVID-19 patients with seizure, 75 % had favorable outcome, with resolution of seizure [20].

The mortality rate was not significantly higher in patients with pre-existing seizure/epilepsy in this study. This finding is similar to a study in Iran that included 82 PWE and a total of 37,968 patients with COVID-19. The Iranian study showed that PWE did not have a higher likelihood for intubation, ICU admission, and mortality [21]. Another study of a smaller sample size in Spain (21 PWE and 1537 patients with COVID-19) reported that epilepsy was associated with a higher fatality rate [19]. However, the smaller number of PWE and COVID-19 patients in this study may have affected the results and may make it difficult to draw an adequate association.

Patients with new-onset seizure had higher mortality rates than those with no new-onset seizure in this study, likely due to more severe COVID-19 infection. The shorter duration of ventilator use in these patients can be attributed to a shorter duration of

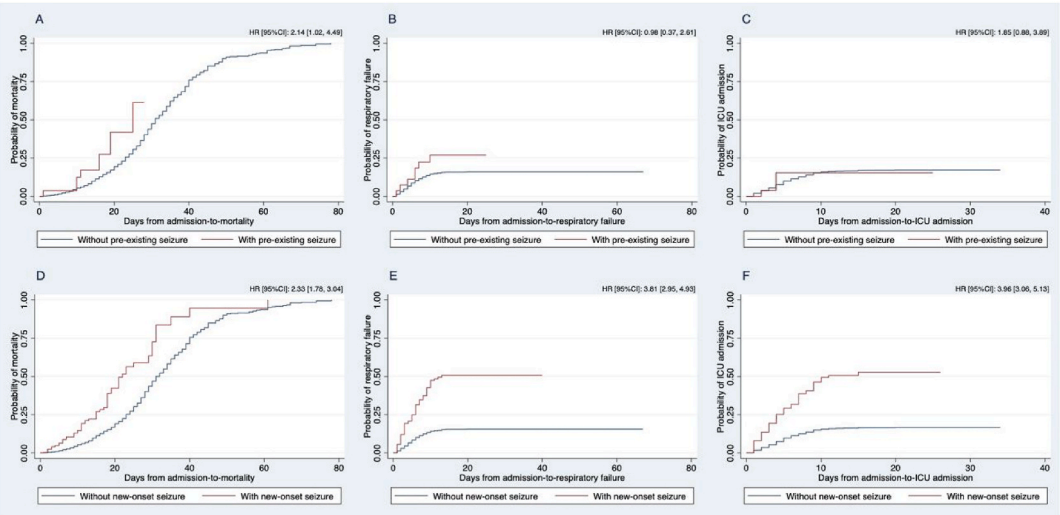

Fig. 1. Kaplan-Meier failure plot comparing COVID-19 patients with and without pre-existing seizure/epilepsy (A to C) with: (A) all-cause mortality, (B) respiratory failure, and (C) intensive care unit admission. The plot from D to F compares COVID-19 patients with and without new-onset seizure with the following: (D) all-cause mortality, (E) respiratory failure, and (F) intensive care unit admission.

hospitalization, a consequence of early mortality. The reported risk factors for mortality among COVID-19 patients with seizure were respiratory and cancer morbidities and an EEG done on the third week of COVID-19 evolution [17,28]. The identified biomarkers for mortality among COVID-19 patients with seizure were high peripheral neutrophil count, high platelet levels, high ferritin levels, low lymphocyte count, and low calcium levels [18]. For the EEG findings in these patients, the most frequent were generalized slow waves [28,29]. Periodic rhythmic activity, epileptiform discharges, and non-convulsive status epilepticus were also seen [29–31]. Unfortunately, in our study, only two patients (out of 125) with new-onset seizure had an EEG and only 6 patients underwent lumbar puncture. There was no mention about testing for cerebrospinal fluid (CSF) SARS-COV2 PCR. In a systematic review of CSF findings in COVID-19, 33 % had pleocytosis, 39 % had elevated protein, and 13 % had a positive SARS-CoV2 PCR [32].

Data on outcomes of patients including seizure recurrence after hospital discharge is limited. In a follow-up study in Iran, 28 patients admitted with seizure and COVID-19 were followed up after a mean of 87 days after discharge and eight of these patients had seizure recurrence [33]. Studies that explored long-term outcomes of hospitalized COVID-19 patients with seizure are still lacking.

This study showed that smoking history, stroke, hypertension, DM, and kidney disease were more commonly seen in COVID-19 patients with seizure than in those without seizure. The presence of these risk factors and/or comorbid conditions should be controlled and treated not just in this subgroup of patients but in other diseases as well. This study showed that the presence of pre-existing seizure/epilepsy among hospitalized patients with COVID-19 does not significantly increase the COVID-19 severity, mortality rate, use of a ventilator, duration of ventilator dependence, and length of ICU stay and hospital stay. However, the presence of new-onset seizure among these patients was associated with a significantly higher risk for more severe COVID-19 infection, mortality, and use of a ventilator. These findings were consistent with the other studies that reported a good outcome with no significant increase in mortality rate among PWE with COVID-19 patients and a higher mortality risk among COVID-19 patients with new-onset seizure [17,18,32]. Among deceased PWE who were infected with SARS-CoV2, the possible cause of death was related to the underlying comorbidities, which were all risk factors for severe COVID-19 infection [26]. In relation to these findings, the presence of seizure in a COVID-19 patient should be treated meticulously and comprehensively.

This study had several limitations. First of all, the dataset of this study was taken in 2020 from which the situation differed in terms of the COVID-19 variants, availability of the vaccinations, and the management of COVID-19 infection. All patients were hospitalized and none of them were isolated at home or in a facility outside of a hospital. Thus, non-hospitalized COVID-19 patients with seizure and their outcomes were not included in this study. EEG and CSF studies were not done in the most of these patients due to logistical problems. The sample size involving patients with seizure is also small, so the findings may not be generalizable to a larger population. The seizure/epilepsy type, etiology, frequency, duration, treatment, and the presence or absence of status epilepticus were also not included. The long-term outcomes of these patients were not determined since their outcome was limited to the time of discharge.

Despite these limitations, this study has several strengths. Aside from being the first cohort study about seizure in COVID-19 in Southeast Asia, this was a large, nationwide study. This study not only looked at the demographic data of the patients but also looked into the comorbid conditions of these patients that may have a relationship with their seizure. In terms of outcome, this study also included the duration of mechanical ventilation and neurologic outcomes in relation to the presence or absence of seizure.

It is recommended that a prospective study be conducted, which involves following-up a larger number of COVID-19 patients with seizure after several years, to determine the long-term effects of seizure on COVID-19 and vice versa. Baseline and repeat neuroimaging and EEG can also be performed in these patients.

5. Conclusion

The presence of pre-existing seizure/epilepsy among hospitalized patients with COVID-19 does not increase the COVID-19 severity, mortality rate, use of ventilator, and length of ICU stay and hospital stay. However, the presence of new-onset seizure among hospitalized patients with COVID-19 was associated with a higher risk for more severe COVID-19 infection, higher mortality rate, and use of a ventilator. A larger and longer prospective study examining the long-term outcomes of these patients is needed.

Ethical approval

Our protocol was approved and endorsed by the local institutional review boards (code): 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; University of the Philippines – Philippine General Hospital (UP-PGH), 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 (SJRIB 2020–0006); Single Joint Research Ethics Board of the Department of Health, 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

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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