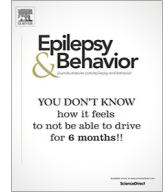




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Impact of COVID-19 on quality of life in people with epilepsy, and a multinational comparison of clinical and psychological impacts

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ABSTRACT

Background: This study aimed to determine the relationship among the clinical, logistic, and psychological impacts of COVID-19 on people with epilepsy (PWE), and the impact of COVID-19 on the quality of life.

Method: This is a cross-sectional anonymized web-based study on PWE, using an online questionnaire to assess the clinical, logistic, and psychological impacts of COVID-19, including Hospital Anxiety Depression Scale (HADS) and Quality of Life in Epilepsy Inventory (QOLIE-31).

Result: 461 patients were recruited, with a mean age of 39.21 ± 15.88 years, majority female (50.1%), with focal epilepsy (54.0%), and experienced seizures at least once yearly (62.5%). There were 13.0% experienced seizure worsening during COVID-19 period, which were associated with baseline seizures frequency ≥ 1 per month (32.0% vs. 6.2%, $p < 0.001$), worries of seizure worsening (18.0% vs. 10.9%, $p < 0.001$), difficulty to go emergency unit (24.4% vs. 10.4%, $p < 0.001$), AEDs ran out of stock (23.2% vs. 11.6%, $p < 0.05$), self-adjustment of AED dosages (26.4% vs. 11.3%, $p < 0.001$), inadequate sleep (22.4% vs. 9.2%, $p < 0.001$), and stress (23.4% vs. 10.1%, $p < 0.01$). Participants experiencing seizure worsening reported greater anxiety (8.10 ± 5.011 vs. 4.84 ± 3.989 , $p < 0.001$) and depression (6.05 ± 3.868 vs. 3.86 ± 3.589 , $p < 0.001$). Logistic regression showed baseline seizures frequency > 1 per month (OR, 14.10) followed by anxiety (OR, 3.90), inadequate sleep (OR, 0.37), and treated in UMMC (OR, 0.31) as the predictors for seizure worsening during COVID-19 period. Poorer total QOLIE-31 score was noted in those with seizure worsening (48.01 ± 13.040 vs. 62.15 ± 15.222 , $p < 0.001$). Stepwise regression highlighted depression as the main negative predictor for quality of life ($\beta = -0.372$, $p < 0.001$), followed by anxiety ($\beta = -0.345$, $p < 0.001$).

Conclusion: A significant number of PWE experienced seizure worsening during COVID-19 period, which was related to the clinical, logistic, and psychological factors. Quality of life was affected by the seizure worsening and the psychological stress.

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1. Introduction

Epilepsy is a chronic illness requiring regular monitoring of seizure control, antiepileptic drugs (AEDs) and its side effects, and psychosocial comorbidities [1]. Since the first reported case of coronavirus disease 2019 (2019-nCoV) in Wuhan, China on 8 December 2019, the outbreak has spread around the world [2]. In Malaysia, the government took stringent precautionary measures to combat the spread of this disease by implementing the movement restriction control order (MCO) on 18th March 2020 through mandatory social distancing and lockdown [3].

The complete restriction of movement and assembly resulted in postponement of healthcare visits in Malaysia, similarly in many

other countries. This unprecedented loss of access to healthcare is postulated to give rise to worsening seizure control and anxiety, which were reported in many countries in most continents, including China [4–6], Hong Kong [7], Pakistan [8], and Saudi Arabia [9] in Asia, Brazil [10] in South America, Spain [11,12] and Italy [13] in Europe, and United States of America [14]. However, most studies analyze mainly the direct impact of AEDs on the psychological and clinical consequences, but not the access to emergency and outpatient services.

Therefore, we aimed to determine the relationship among the clinical, logistic, and psychological impacts of COVID-19 on people with epilepsy (PWE) in Malaysia, which is an upper middle-income country located in southeast Asia, adopting the British public-health medical services. In addition, we also aimed to study the impact of COVID-19 on the quality of life in PWE. To the best of our knowledge, the impact of COVID-19 on the quality of life in PWE has never been reported before.

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2. Methodology

2.1. Sampling and framework

This is a cross-sectional anonymized web-based study involving 461 PWE, 18 years and above, can read English, Bahasa Malaysia, and Mandarin, with a diagnosis of epilepsy certified by neurologists, and were treated in adult neurology clinic in University Malaya Medical Centre (UMMC) or a member of the Malaysian Epilepsy Society (MES). MES is the national epilepsy society for PWE and their family members. Those who refused or unable to provide consent, or without a history of seizures were excluded. This study was approved by the University Malaya Medical Ethics Committee (MECID. No. 2020420–8539).

The recruitment was performed using convenience sampling. The invitation links to online questionnaires were sent via short messages (SMS), email or Facebook. Patients with epilepsy in the clinic were also approached physically. Participants have an option to leave their contact details at the end of the survey or to remain anonymous.

2.2. Measures

An online questionnaire was designed to assess the clinical, logistic, and psychological impacts of COVID-19 on PWE. Informed consent was obtained online prior to the study. Socio-demographic and clinical information were collected. The impacts of COVID-19 were assessed in 3 sections, included (1) clinical impact: seizure control, (2) logistic impact: access to clinic appointment, emergency services, and AED supply, and (3) psychological impact: assessed using validated Hospital Anxiety Depression Scale (HADS) and Quality of Life in Epilepsy Inventory (QOLIE-31). This questionnaire was sent to PWE from June 7 to July 5, 2020, 134 days after the first COVID-19 case was confirmed in Malaysia and 81 days since the implementation of MCO, with a reported 8, 663 cumulative cases as of July 5.

2.2.1. Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety Depression Scale (HADS) is used as a tool to measure anxiety and depression in patients with general medical condition [15]. It is a 14-item self-administered questionnaire consisting of two subscales, anxiety and depression. The subscale of anxiety focused on symptoms of generalized anxiety disorder and subscale of depression focused on anhedonia, and main symptoms of depression. Each item was scored on a response-scale with four alternatives ranging between 0 and 3. The responses were summed to obtain the total score for each subscale. The total score for each subscale were then categorized into normal (0–7), and abnormal – borderline (8–10) and definite (11–21). HADS was validated in epilepsy cohort, age 18 years and above, with high internal consistency reported for HAD-Anxiety (Cronbach's $\alpha = 0.88$) and HAD-Depression (Cronbach's $\alpha = 0.82$) [16].

2.2.2. Quality of Life in Epilepsy Inventory (QOLIE-31)

The QOLIE-31 has been widely cited as a reliable instrument (Cronbach's $\alpha = 0.93$) to assess epilepsy-related QOL [17]. It is a 31-item self-administered questionnaire clustered in seven subscales in the following domains: seizure worry (five items), emotional well-being (five items), energy/fatigue (four items), cognitive functioning (six items), medication effects (three items), social functioning (five items), and overall QOL (two items). The seven subscales generate a QOLIE-31 overall score representing the overall epilepsy-related quality of life. Each subscale and the overall score range from 0 to 100, with higher scores indicating better wellbeing.

2.3. Operational definition

Baseline seizure frequency was defined as the frequency of seizures in the previous 12 months before COVID-19 outbreak. Seizure control during COVID-19 period was determined based on the changes of seizure frequency, duration, or severity. Seizure worsening was defined with an increased in seizure frequency, duration, or severity.

2.4. Sample size calculation

The sample size was calculated to achieve an alpha level of 0.05 and a power of 0.80 in a two-tailed independent *t*-test. The effect size (Cohen's *d*) was assumed to be 0.35 to detect a low to medium effect. A minimum of 260 samples were needed to achieve these parameters.

2.5. Analyses and results

Statistical analysis using IBM® SPSS® Statistics software (version 25.0) was performed with significance level defined at 0.05. All demographic data were analyzed descriptively, with nominal data presented as frequencies and percentages and continuous data presented as means and standard variations. For continuous data, independent *t*-tests were used for group comparison. Multivariate logistic regression analysis was carried out to ascertain the significant predictors for seizure worsening during COVID-19 period. Variables associated with a $p < 0.05$ in the univariate analysis were entered in a forward stepwise multiple logistic regression model. Stepwise linear regression analysis was carried out to ascertain whether seizure control during COVID-19 period and the psychological factors predicted quality of life (QOLIE-31 score).

2.6. Multinational comparison on clinical and psychological impacts on epilepsy

A literature search was performed on recent studies reporting the clinical or psychological impacts of COVID-19 on people with epilepsy. The clinical impact was defined as the percentage of participants with either increased seizure frequency or worsening seizure control. Psychological impacts were determined by the percentages of participants who were screened positive for or reported anxiety and depression using various psychological scales. The Gross Domestic Product (GDP) per capita was accessed from the International Monetary Fund report in October 2020 [18].

3. Results

A total of 461 patients were included in this study, with a respondent rate of 64.8%. The mean age was 39.21 ± 15.88 years, and 50.1% were female, majority Chinese (45.1%), single (57.5%), with secondary education level or lower (55.5%), and 39.7% employed. The mean age of seizure onset was 20.85 ± 15.72 years. Majority had focal epilepsy (54.0%), experienced seizures at least once yearly (62.5%), with abnormal EEG (67.2%) and neuroimaging results (55.1%). A hundred ninety (41.2%) had tried at least 3 types of AEDs for seizure control while another 12.4% had epilepsy surgery. None of our patients or their care takers reported being infected with SARS-CoV-2 at the time of data collection (Table 1).

3.1. Clinical, logistic, and psychological impacts

There were 11.1% reported increased seizure frequency during COVID-19 period, 4.3% and 7.4% experienced longer seizure duration and severity, respectively. In total, 13.0% experienced seizure

Table 1
Sociodemographic and clinical characteristics of the participants, and the clinical, logistic, and psychological impacts of COVID-19 pandemic (N = 461).

	Mean ± Standard Deviation
Age (Year)	39.21 ± 15.88
Gender	N (%)
Male	230 (49.9)
Female	231 (50.1)
Race	
Malay	139 (30.2)
Chinese	208 (45.1)
Indian	103 (22.3)
Native	2 (0.4)
Others	9 (2.0)
Marital Status	
Single	265 (57.5)
Others	196 (42.5)
Highest Education Attained	
Postgraduate	15 (3.3)
Degree	115 (24.9)
A Level/STPM/Diploma	75 (16.3)
Secondary	194 (42.1)
Primary	31 (6.7)
No formal education	31 (6.7)
Employment Status	
Full time student	42 (9.1)
Employed full time	162 (35.1)
Employed part time	21 (4.6)
Full time house duties/Housewife	22 (4.8)
Retired	63 (13.7)
Unemployed	151 (32.8)
Clinical characteristics	
Frequency of seizures before COVID-19 outbreak	
No seizure for at least a year	173 (37.5)
Less than once a month	166 (36.0)
One or more seizures a month	122 (26.5)
Type of seizure	
Focal	249 (54.0)
Generalized	193 (41.9)
Unsure	19 (4.1)
EEG Results	
Abnormal	310 (67.2)
Normal	106 (23.0)
Unsure/Not done	45 (9.8)
CT scan/MRI Results	
Abnormal	254 (55.1)
Normal	138 (29.9)
Unsure/Not done	69 (15.0)
Types of medication tried (Before and Now)	
1	144 (31.2)
2	127 (27.5)
3 or more	190 (41.2)
Surgery to control seizure	
Yes	57 (12.4)
No	402 (87.2)
Unsure	2 (0.4)
Clinical impact	
Seizure Frequency	
More frequent	51 (11.1)
No change	115 (24.9)
Less frequent	79 (17.1)
No seizure	216 (46.9)
Seizure Duration	
Longer	20 (4.3)
No change	157 (34.1)
Shorter	63 (13.7)
No seizure	221 (47.9)
Seizure Severity	
More severe	34 (7.4)
No change	148 (32.1)
Less severe	56 (12.1)
No seizure	223 (48.4)
Seizure Worsening*	
Yes	60 (13.0)
No	401 (87.0)
Causes of seizures worsening	

(continued on next page)

Table 1 (continued)

	Mean ± Standard Deviation
Not enough sleep	125 (28.3)
Stress	107 (24.0)
Missed medication dosage	62 (14.1)
Inadequate medication supply	10 (2.3)
Fever	24 (5.5)
Physical tiredness	86 (19.5)
Diet	23 (5.2)
Unsure	76 (17.2)
Seizure no change	181 (40.2)
No seizure	18 (4.1)
Others;	13 (10.4)
Logistic Impact	
Difficulty re-schedule clinic appointments	
Strongly disagree	76 (16.5)
Disagree	106 (23.0)
Neutral	159 (34.5)
Agree	73 (15.8)
Strongly agree	47 (10.2)
Worries seizures get worse because my clinic appointments were postponed	
Strongly disagree	
Disagree	86 (18.7)
Neutral	103 (22.3)
Agree	133 (28.9)
Strongly agree	93 (20.2)
	46 (10.0)
Access to online or tele-consultation	
Never	284 (61.6)
Occasionally	57 (12.4)
Sometimes	69 (15.0)
Often	28 (6.1)
Always	23 (5.0)
Afraid to go to Emergency Unit	
Strongly disagree	93 (20.2)
Disagree	118 (25.6)
Neutral	117 (25.4)
Agree	80 (17.4)
Strongly agree	53 (11.5)
Difficulty to go to Emergency Unit	
Strongly disagree	105 (22.8)
Disagree	128 (27.8)
Neutral	142 (30.8)
Agree	59 (12.8)
Strongly agree	27 (5.9)
Understand need to go to Emergency Unit	
Yes	372 (80.7)
No	89 (19.3)
Adequately informed on what to do in the event of seizures	
Yes	363 (78.7)
No	98 (21.3)
Obtain supply of medications from	
University Malaya Medical Centre	407 (88.3)
Other university hospital	5 (1.1)
Ministry of Health Malaysia hospital or clinic	24 (5.2)
Private hospital or clinic	5 (1.1)
Private pharmacies	20 (4.3)
Difficult to obtain medications	
Strongly disagree	89 (19.3)
Disagree	135 (29.3)
Neutral	125 (27.1)
Agree	72 (15.6)
Strongly agree	40 (8.7)
Procedures to arrange for medication delivery via postage are complicated	
Strongly disagree	66 (14.3)
Disagree	106 (23.0)
Neutral	166 (36.0)
Agree	73 (15.8)
Strongly agree	50 (10.8)
Procedures to arrange for medication self-collection via “pick-and-go” or “drive-through” are complicated	
Strongly disagree	56 (12.1)
Disagree	96 (20.8)
Neutral	218 (47.3)
Agree	63 (13.7)
Strongly agree	28 (6.1)
Medications ran out of stock	
Strongly disagree	112 (24.3)

Table 1 (continued)

		Mean ± Standard Deviation
Disagree		167 (36.2)
Neutral		126 (27.3)
Agree		39 (8.5)
Strongly agree		17 (3.7)
Medications provided are always insufficient for the stated duration of supply		
Strongly disagree		116 (25.2)
Disagree		204 (44.3)
Neutral		88 (19.1)
Agree		38 (8.2)
Strongly agree		15 (3.3)
I have skipped my medications to avoid running out of supply		
Never		345 (74.8)
Rarely		50 (10.8)
Sometimes		50 (10.8)
Often		10 (2.2)
Always		6 (1.3)
I have adjusted the dose of my medications without consulting my doctor to avoid running out of supply during the COVID-19 outbreak		
Never		369 (80.0)
Rarely		39 (8.5)
Sometimes		32 (6.9)
Often		11 (2.4)
Always		10 (2.2)
Psychological Impact		
HADS-Anxiety	Normal	334 (72.5)
	Borderline	80 (17.4)
	Abnormal	47 (10.2)
HADS-Depression	Normal	374 (81.1)
	Borderline	55 (11.9)
	Abnormal	32 (6.9)

*Seizure worsening is defined as an increased in seizure frequency, duration, or severity.

worsening, with either an increase in seizure frequency, duration, or severity. The main perceived reasons for seizure worsening included inadequate sleep (28.3%), stress (24.0%), and physical tiredness (19.5%). In reverse, 12.1–17.1% of our patients experienced less frequent, shorter, or less severe seizures during the pandemic (Table 1).

One hundred twenty (26.0%) participants found it difficult to re-schedule clinic appointments while 139 worried that their seizure will worsen (30.2%). More than half (61.6%) of the respondents have never had any prior online or tele-consultation access. One hundred thirty-three patients (28.9%) were afraid of going to the emergency unit and 18.7% found it difficult to go to emergency unit during the COVID-19 and MCO period. Fifty-three (11.5%) had self-adjusted AED dosages to avoid running out of supply. Some reported difficulty to obtain their AEDs (24.3%), 14.3% skipped their AED doses to conserve their remaining supply and 15.9% ran out of AEDs. A significant number experienced abnormal levels of anxiety (27.6%) as well as depression (18.8%) (Table 1).

3.2. Factors related to seizure worsening during COVID-19 period

Seizure worsening was more frequently reported in those with baseline seizures frequency ≥ 1 per month (32.0%) as compared to others with no seizure for at least a year (2.3%) and < 1 per month (10.2%, $p < 0.001$). Seizure worsening was also reported in patients who tried at least 3 AEDs (21.1% vs. 8.3% with 1 AED or 6.3% with 2 AEDs, $p < 0.001$), worries of seizure worsening (18.0% vs. 10.9% with no worries at all, $p < 0.001$), difficulty to go emergency unit (24.4% vs. 10.4% with no difficulty, $p < 0.001$), AEDs ran out of stock (23.2% vs. 11.6%, $p < 0.05$), self-adjustment of AED dosages (26.4% vs. 11.3%, $p < 0.001$), and inadequate sleep (22.4% vs. 9.2%, $p < 0.001$) and stress (23.4% vs. 10.1%, $p < 0.01$). Less patients in our hospital (UMMC) reported seizure worsening as compared to

other hospitals (11.4% vs. 29.3%, $p < 0.01$). Participants experiencing seizure worsening reported greater anxiety (8.10 ± 5.011 vs. 4.84 ± 3.989 , $p < 0.001$) and depression (6.05 ± 3.868 vs. 3.86 ± 3.589 , $p < 0.001$) (Table 2).

A binary logistic regression analysis was conducted to investigate the predictors of seizure worsening. Among the 12 variables that correlated significantly with seizure worsening, 4 variables (stress as a precipitating factor, medication ran out of stock, difficulty to arrange self-pick-up, worries seizures get worse because of postponed clinic appointments) were excluded because of strong correlation with other independent variables. The full model containing all predictors was statistically significant, $\chi^2(8, N = 461) = 96.49$, $p < 0.001$. The model correctly classified 89.1% of cases. The strongest predictor for seizure worsening during COVID-19 period was baseline seizures frequency > 1 per month (OR, 14.10), followed by anxiety (OR, 3.90), inadequate sleep (OR, 0.37) and treatment at UMMC (OR, 0.31) (see Table 3).

3.3. Quality of life in epilepsy

Poorer total QOLIE-31 score was noted in those with seizure worsening (48.01 ± 13.040 vs. 62.15 ± 15.222 in those with no change or improve in seizure control, $p < 0.001$), similarly in all subscales except medication effects (Table 2).

Stepwise linear regression was conducted to determine whether seizure control predicted QOLIE-31 score in step 1, which explained 9% of the variance, $F(1, 453) = 46.8$, $p < 0.001$. Subsequent psychological factors (HADS anxiety and depression scores) were entered at Step 2, which further explained an additional 42% of the variance in predicting QOLIE-31 during COVID-19 period. All measures were statistically significant, $F(3, 451) = 158.4$, $p < 0.001$, with depression recording the highest beta value ($\beta = -0.372$, $p < 0.001$) (Table 4).

Table 2
Factors associated with seizure worsening during COVID-19 period (n = 461).

Factors	Seizure worsening during COVID-19		p-value	
	Yes (n = 60), n (%)	No (n = 400), n (%)		
Sociodemographic Characteristics				
Age (Years), Mean ± SD	37.18 ± 15.79	39.51 ± 15.91	NS	
Gender				
	Male (n = 230)	30 (13.0)	200 (87.0)	NS
	Female (n = 231)	30 (13.0)	201 (87.0)	
Race				
	Malay (n = 139)	21 (35.0)	118 (29.3)	NS
	Chinese (n = 208)	25 (41.7)	183 (45.8)	
	Indian (n = 103)	11 (18.3)	92 (23.0)	
	Native (n = 1)	1 (1.7)	1 (0.3)	
	Others (n = 7)	2 (3.3)	7 (1.8)	
Marital Status				
	Single (n = 265)	38 (14.3)	227 (85.7)	NS
	Others (n = 196)	22 (11.2)	174 (88.8)	
Education				
	Secondary or below (n = 256)	36 (14.1)	220 (85.9)	NS
	Tertiary (n = 205)	24 (11.7)	181 (88.3)	
Employment				
	Employed (n = 183)	20 (10.9)	163 (89.1)	NS
	Others (n = 278)	25 (16.6)	126 (83.4)	
Clinical characteristics				
Age of onset (Years), Mean ± SD	17.78 ± 14.00	21.34 ± 15.93	NS	
Seizure frequency before COVID-19				
	No seizure for at least a year (n = 173)	4 (2.3)	169 (97.7)	0.000
	Less than once a month (n = 166)	17 (10.2)	149 (89.8)	
	One of more seizure a month (n = 122)	39 (32.0)	83 (68.0)	
Seizure type				
	Focal (n = 249)	39 (15.7)	210 (84.3)	NS
	Others (n = 212)	21 (9.9)	191 (90.1)	
EEG				
	Abnormal (n = 310)	46 (14.8)	264 (85.2)	NS
	Others (n = 151)	14 (9.3)	137 (90.7)	
Imaging				
	Abnormal (n = 254)	33 (13.0)	221 (87.0)	NS
	Others (n = 207)	27 (13.0)	180 (87.0)	
No. of AEDs				
	1 (n = 144)	12 (8.3)	132 (91.7)	0.000
	2 (n = 127)	8 (6.3)	119 (93.7)	
	3 or more (n = 190)	40 (21.1)	150 (78.9)	
Surgery				
	Yes (n = 57)	6 (10.5)	51 (89.5)	NS
	Others (n = 404)	54 (13.4)	350 (86.6)	
Hospital				
	UMMC (n = 420)	48 (11.4)	372 (88.6)	0.003
	Others (n = 41)	12 (29.3)	29 (70.7)	
Triggers				
Reason for seizure worsening				
	Stress (n = 107)	25 (23.4)	82 (76.6)	0.001
	Inadequate sleep (n = 125)	28 (22.4)	97 (77.6)	0.000
	Missed AEDs (n = 62)	5 (8.1)	57 (91.9)	NS
	Inadequate AEDs (n = 10)	3 (30.0)	7 (70.0)	NS
	Fever (n = 24)	2 (8.3)	22 (91.7)	NS
	Physical tiredness (n = 86)	16 (18.6)	70 (81.4)	NS
	Diet (n = 23)	4 (17.4)	19 (82.6)	NS
Clinic Appointment				
Difficulty to reschedule clinic appointments				
	Yes (n = 120)	21 (17.5)	99 (82.5)	NS
	No (n = 182)	19 (10.4)	163 (89.6)	
Worries seizures get worse because of postponed clinic appointments				
	Yes (n = 139)	25 (18.0)	114 (82.0)	0.001
	No (n = 322)	35 (10.9)	287 (89.1)	
Access to online or tele-consultation				
	Yes (n = 341)	20 (16.7)	100 (83.3)	NS
	No (n = 120)	40 (11.7)	301 (88.3)	
Emergency unit				
Afraid to go to emergency unit				
	Yes (n = 133)	19 (14.3)	114 (85.7)	NS
	No (n = 211)	22 (10.4)	189 (89.6)	
Difficulty to go to emergency unit				
	Yes (n = 86)	21 (24.4)	65 (75.6)	0.000
	No (n = 375)	39 (10.4)	336 (89.6)	
Understand need to go to emergency unit				
	Yes (n = 372)	47 (12.6)	325 (87.4)	NS
	No (n = 89)	13 (14.6)	76 (85.4)	
Knowledge on what to do during seizures				
	Yes (n = 363)	47 (12.9)	316 (87.1)	NS
	No (n = 98)	13 (13.3)	85 (86.7)	
Medication Supply				
Pay for your own AEDs				
	Yes, fully (n = 191)	23 (12.0)	168 (88.0)	NS
	Yes, partially (n = 187)	21 (11.2)	166 (88.8)	
	No, fully subsidized (n = 83)	16 (19.3)	67 (80.7)	
Difficult to get AEDs				
	Yes (n = 112)	20 (17.9)	92 (82.1)	NS
	No (n = 224)	24 (10.7)	200 (89.3)	
Difficult to arrange AED delivery				
	Yes (n = 123)	21 (17.1)	102 (82.9)	NS
	No (n = 172)	19 (11.0)	153 (89.0)	
Difficult to arrange self-pick-up				
	Yes (n = 91)	18 (19.8)	328 (88.6)	0.016
	No (n = 370)	42 (11.4)	138 (91.4)	
AEDs ran out of stock				
	Yes (n = 56)	13 (23.2)	43 (76.8)	0.037
	Others (n = 405)	47 (11.6)	358 (88.4)	
Insufficient AED supply				
	Yes (n = 53)	8 (15.1)	45 (84.9)	NS
	No (n = 320)	41 (12.8)	279 (87.2)	
Skipped AEDs				
	Yes (n = 66)	12 (18.2)	54 (81.8)	NS
	Others (n = 395)	48 (12.2)	347 (87.8)	

Table 2 (continued)

Factors		Seizure worsening during COVID-19		p-value
		Yes (n = 60), n (%)	No (n = 400), n (%)	
Self-adjusted AED dosage	Yes (n = 53) Others (n = 408)	14 (26.4) 46 (11.3)	39 (73.6) 362 (88.7)	0.004
Psychological Scales		Mean ± SD		
HADS	Anxiety score	8.10 ± 5.011	4.84 ± 3.99	0.000
	Depression score	6.05 ± 3.87	3.86 ± 3.59	0.000
QOLIE -31	Overall Score	48.01 ± 13.04	62.15 ± 15.22	0.000
	- Seizure worry	29.72 ± 23.71	49.17 ± 27.45	0.000
	- Overall Quality of Life	56.25 ± 16.26	69.72 ± 17.47	0.000
	- Emotional Well-being	56.07 ± 17.04	66.76 ± 17.38	0.000
	- Energy	44.42 ± 14.99	59.36 ± 17.22	0.000
	- Cognitive	47.71 ± 21.87	61.12 ± 22.74	0.000
	- Medication Effects	52.26 ± 11.78	54.35 ± 12.96	NS
	- Social Function	45.55 ± 20.19	62.68 ± 22.65	0.000

NS, Not significant; *UMMC, University Malaya Medical Centre.

Table 3

Logistic regression model for predictors of seizure worsening during COVID-19 period.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI	
							Lower	Upper
Seizure frequency before COVID-19: ≥1 seizure a month	2.65	0.58	20.52	1	0.00	14.10	4.49	44.32
HADS (Anxiety): abnormal	1.36	0.41	11.23	1	0.00	3.90	1.76	8.64
Difficulty to go to emergency unit	0.57	0.38	2.26	1	0.13	1.77	0.84	3.74
Self-adjusted AED dosage	0.37	0.44	0.71	1	0.40	1.45	0.61	3.45
No. of AEDs: 3 or more	0.31	0.44	0.50	1	0.48	1.37	0.57	3.26
HADS (Depression): abnormal	-0.23	0.44	0.28	1	0.60	0.79	0.34	1.87
Reason for seizure worsening: Inadequate sleep	-1.00	0.35	8.16	1	0.004	0.37	0.19	0.73
Hospital: UMMC	-1.16	0.47	6.10	1	0.014	0.31	0.13	0.79

*CI, Confidence interval; UMMC, University Malaya Medical Centre.

Table 4

Stepwise regression analyses in predicting QOLIE-31 (N = 461).

	B	SE B	Beta	p	95% CI
Model A: Seizure control only (adjusted R ² = 0.094)					
Seizure Control	-14.233	2.082	-0.306	0.000	-18.324 to -10.143
Model A: Seizure control and psychological factors (adjusted R ² = 0.509)					
Seizure Control	-6.661	1.583	-0.143	0.000	-9.772 to -3.549
HADS Anxiety	-1.265	0.181	-0.345	0.000	-1.620 to -0.910
HADS Depression	-1.577	0.206	-0.372	0.000	-1.982 to -1.172

3.4. Multinational comparison of clinical and psychological impacts

Seizure worsening was reported in 8.6–29.5% of the respondents in various countries, highest in Saudi Arabia, followed by Spain and USA, Italy, China, and Malaysia. The anxiety rate ranged from 9.4 to 60.5% (highest in Italy), and depression rate from 8.6 to 46.9% (highest in Brazil and Belgium); the rates in Malaysia were within the range. Higher anxiety and depression rates (>30%) were reported in countries with >30,000 COVID-19 cases per 1 million population, including Brazil, Belgium, Spain, and Italy (Table 5).

4. Discussion

In this Malaysian nationwide study, 13.0% of the participants reported worsening of their seizure control (13.0%), 27.6% experienced anxiety, and 18.8% depression. Seizure worsening was related to clinical (uncontrolled pre-COVID seizure control and number of AEDs), logistic (difficult access to emergency, postponed clinic appointment, inadequate AED supply and self-adjustment of AEDs), and psychological (inadequate sleep and anxiety) factors. This led to poorer quality of life among PWE.

In Malaysia, seizure worsening was reported in 13% of the respondents, compatible with China but lower than the European countries and Saudi Arabia [4,6,9–13]. As shown in Table 5, the rates were higher in countries with higher percentage of COVID-19 cases, similar to the rates of anxiety and depression. These differences might also be related to the cultural differences in these countries, which influence the national policy and individual reaction toward the pandemic, but also can be disease specific [20]. As a comparison, we found different patterns in cancer studies during the pandemic, in which the rates of depression and anxiety were lower in Malaysia but not in China, whereas for European countries the rates were high but not in USA [21–24]. Stress or anxiety was commonly associated with seizure worsening [4–6,9,11], but not depression. In our study, though depression was associated with seizure worsening in univariate analysis, the association was not significant in multivariate analysis. This supports the need to screen for psychological distress routinely especially during COVID-19 pandemic.

Many studies reported logistic issues among PWE especially on the access and adjustment of AEDs [4,5,10,11], and clinic postponement [13]. It was postulated that these logistic issues may be the

Table 5
Multinational comparison of the clinical and psychological impacts of COVID-19 on people with epilepsy.

Countries	Total COVID-19 cases [19]	Cases per 1 million people	Deaths	GDP per capita	Seizure worsening, %	Anxiety, % (scale)	Depression, % (scale)
Malaysia	86,618	2,646	422	10,192	13.0	27.6 (HADS)	18.8 (HADS)
Brazil,	6,970,034	32,981	182,799	6,450	-	50.4 (HADS)	39.8 (HADS)
Belgium [10]	611,422	53,054	18,178	43,814			46.9 (PHQ-9)
Spain [11]	1,762,212	37,414	48,401	26,832	27.0	42	35
Spain [12]	1,762,212	37,414	48,401	26,832	9.8	26.7	8.6
Saudi Arabia [9]	360,155	10,525	6,069	19,587	29.5	-	-
Italy [13]	1,870,576	31,050	65,857	30,657	18.0	60.5 (GAD-7)	34.8 (BDI-II)
China [4]	86,770	62	4,634	10,839	17.7	30.2 ¹	-
Wuhan [5]	86,770	62	4,634	10,839	8.6	9.4 (GAD-7)	13.0 (PHWQ-9)
Chengdu [6]	86,770	62	4,634	10,839		13.1 (K-6) ²	
USA [14]	16,766,932	50,877	303,895		27	-	-

¹ Aggravated psychological disorder; ² Six-item Kessler Psychological Distress Scale.

cause of seizure worsening, but only AED issues (dose adjustment and supply) were reported as a factor for seizure control during COVID-19 period [5,11]. In our study, seizure worsening was shown to be related to access of all related healthcare services including emergency, outpatient, and pharmacy services. Consequently, about 10% of the respondents adjusted their dose to avoid depletion of their AEDs and this was associated with seizure worsening, thus should be discouraged. In response to the logistic issues, immediate measures were established in our hospital (UMMC) to allow patient's online access to the epilepsy team, pharmacy, and registration counter virtually. These measures may not be widely available in other hospitals during the early phase of the pandemic, which possibly explain more patients with seizure worsening in these hospitals.

During this pandemic, some patients (12–17%) experienced seizure improvement during the pandemic. This could be attributed to less provoking factors such as sleep deprivation and work stress in these patients, during the confinement period [11–13].

Quality of life in PWE was affected by seizure worsening during COVID-19 period, which was expected. However, the regression analysis in our study showed a higher impact of psychological stress, including both anxiety and depression, on the quality of life.

4.1. Implications

This study showed that the rights and needs of patients with chronic illness have not been silenced by the COVID-19 pandemic, and the need for the Health Authorities to re-organize the healthcare services to ensure continuity of care.

For some patients, delayed medical attention from the fear of contracting COVID-19 might have life-threatening consequences. Therefore, it is vital for us to understand and address their needs in a timely manner. A balance must be achieved between the required safety measures to prevent further spread of this virus and adequate care to patients with chronic illnesses [25]. As an alternative, telemedicine was frequently discussed and was shown to be practical and effective [26]. Epilepsy Electronic Patient Portal was also proposed to improve seizure care [27]. Another suggestion would be to allocate staggered clinic hours to prevent overcrowding while remaining available to those in need.

Further research is warranted to help design platform that caters to the diversified communities and countries, especially in the resource limited areas while reducing the negative impact of COVID-19. Algorithms should be designed to prevent sudden loss of access to healthcare in the event of a public health emergency.

4.2. Limitations

As the web-based study was conducted in urban and semi-rural areas, the findings may not be representative of the rural or underprivileged settings with no access to internet. Future studies involving these underprivileged communities should be conducted to assess their continuity of care in a resource-limited driven setting.

5. Conclusion

A significant number of PWE experienced seizure worsening during COVID-19 period, which was related to the clinical, logistic, and psychological factors. Quality of life was affected by seizure worsening and psychological stress. This study highlights the impact of the COVID-19 faced by people with epilepsy and the importance to understand their needs.

Author contributions

MY designed the project, wrote the protocol, obtained the data, performed the statistical analysis, interpreted the data, and drafted the manuscript. KS designed the study, reviewed the study protocol, supervised the execution, and coordinated the data analysis plan. SL reviewed the study protocol, supervised the execution, and interpreted the data. All authors reviewed, revised, and approved the manuscript.

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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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