The impact of COVID-19 on people with epilepsy is not over, a longitudinal study

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Abstract

Background: Despite the shift of the COVID-19 era, the post-pandemic impacts on healthcare for people with epilepsy (PWE) remain unknown. This study aimed to determine the clinical, logistic, and psychological impacts of the COVID-19 pandemic during and after COVID-19 containment measures. *Method:* This is a longitudinal study over two years. Clinical and psychological outcomes of COVID-19 were assessed with the Hospital Anxiety Depression Scale (HADS) and Quality of Life in Epilepsy Inventory (QOLIE-31). *Result:* A total of 239 patients were recruited, with a mean age of 38.32 ± 14.16 years, and 51.5% were male. Seventy-nine (33.1%) were previously infected with COVID-19. As compared to during the COVID-19 pandemic, the percentage of patients who reported seizure worsening (13.0%) remained the same after the pandemic. The main reasons associated with seizure worsening include baseline seizure frequency ≥ 1 per month (54.8%), stress (61.3%) and fatigue (48.4%), despite more accessible clinic appointments (49.4%), medication supply (67.8%) and emergency units (62.8%). Psychologically, after the COVID-19 pandemic, PWE reported similar anxiety (4.65 ± 4.46 vs. 4.78 ± 3.72, $p=0.715$) and depression scores (3.81 ± 3.97 vs. 3.86 ± 3.52, $p=0.869$) than during the pandemic. Despite improvement in clinical and logistics factors, PWE experiences worsening in quality of life (57.44 ± 15.41 vs. 61.70 ± 15.05, $p=<.001$), especially in the emotional well-being, cognitive, medication effects, and social function subscales.
Conclusion: Despite the improvement in clinical and medication access in the post-COVID-19 era, the challenges and consequences of the pandemic remained, without an improvement in seizure control and psychological well-being, and worsening quality of life.

Keywords: COVID-19, epilepsy, anxiety, depression

INTRODUCTION

Since the spread of the coronavirus disease-19 (COVID-19) virus in January 2020, the pandemic has caused extreme ramifications across global platforms disabling healthcare systems and economies with a recorded 673 million total infections and 6.86 million deaths.[1] However, the transition of COVID-19 to the endemic phase led to the relaxation of the nationwide lockdown. The ease of restrictions could be attributed to the implementation success of various measures including social distancing with hand hygiene, mass COVID-19 vaccinations uptake, and strict adherence to quarantine regulations.[2]

With the shift of the COVID-19 era, the experiences and challenges associated also changed. During the COVID-19 pandemic, patients with chronic illnesses, especially epilepsy, were faced with a multitude of problems that arose from healthcare barriers. People with epilepsy (PWE) found it difficult to engage with healthcare services or obtain medication supplies and faced stressors from job insecurity and financial constraints resulting in seizure worsening.[3] Self-isolation for a prolonged duration could also be detrimental to their mental health.

Although eased lockdown measures mark the beginning of an epoch, the influence of these post-pandemic-induced changes in healthcare delivery remains unknown towards PWE. In previous literature, PWE was known to show a pattern of vulnerability associated with poor COVID-19 outcomes.[4] The relationship between epilepsy care and post-COVID-19 was not well

explored. Therefore, we aim to determine the clinical, logistics, and psychological impacts resulting from the aftermath of the COVID-19 pandemic on PWE. In addition, we also aimed to compare the differences between psychological outcomes of the same cohort measured during and after two years of COVID-19 containment measures. A detailed understanding of these factors would provide important clues for the continued provision of epilepsy care.

METHODS

This is a longitudinal study consisting of three phases, Phase 1[3] started at the beginning of the COVID pandemic (2020), Phase 2[5] with early physical consultation, and Phase 3 at 2 years after the pandemic. This is Phase 3, recruiting a total of 239 patients, 18 years and above, treated at the University Malaya Medical Centre (UMMC) with a participation rate of 85%. Those who refused or were unable to provide consent, or without a history of seizures were excluded. This recruitment was conducted from 9 April 2022 for six months, 2 years after the first COVID-19 case was confirmed in Malaysia and 99 days since the end of the lockdown. The invitation links to online questionnaires were sent via short messages (SMS), email, or Facebook. The epilepsy patients in the clinic were also approached physically. This study was approved by the University Malaya Medical Ethics Committee (MECID. No. *2020420-8539)*, and written consent was obtained.

Measurements

The questionnaire comprised of structured questions on demographic data, clinical, logistic, and psychological impacts of the COVID-19 pandemic. The impacts of COVID-19 were assessed in 3 sections, including (1) clinical impact: seizure control and COVID-19 infections, (2) logistic impact: access to clinic appointments, telemedicine services, emergency services, and AEDs supply, and (3) psychological impact: assessed using validated Hospital Anxiety Depression Scale (HADS) and Quality of Life in Epilepsy Inventory (QOLIE-31).

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety Depression Scale (HADS) is used as a tool to measure anxiety and depression in patients with general medical conditions.[6] 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 the subscale of depression focused on anhedonia and the main symptoms of depression. Each item is scored on a response scale with four alternatives ranging between 0 and 3. The responses are summed to obtain the total score for each subscale. The total score for each subscale was then categorized into normal (0-7), abnormal - borderline (8-10), and definite (11- 21). HADS was validated in the 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 $\alpha = 0.82$).[7]

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.[8] 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 well-being.

Operational definition

Baseline seizure frequency was defined as the frequency of seizures in the previous 12 months before the COVID-19 outbreak. Seizure control after the COVID-19 period was determined based on the changes in seizure frequency, duration, or severity. Seizure worsening after the COVID-19 pandemic was defined by an increase in seizure frequency, duration, or severity, as reported in our phase 1[3] and 2[5] study.

Analyses and results

Statistical analysis using *IBM® SPSS® Statistics software (version 25.0) was performed with a 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 comparison of the psychological measures between the pre- and post-COVID-19 pandemic, one-way repeated measures ANOVA were used to determine the significance of the differences.

RESULTS

Sociodemographic characteristics and recruitment process

In Phase 1[3], 461 participants were enrolled in the study, and 312 patients in Phase 2[5]. In this study (Phase 3), a total of 239 patients were recruited, with a mean age of 38.32±14.16 years and 51.5% were male, of which 115 also participated in Phase 1.

The majority were Chinese (51.1%), single (54.8%), with tertiary education (58.6%), and 46.9% employed had focal epilepsy (71.5%), experienced seizures at least once yearly (59.0%), with abnormal EEG (66.9%) and neuroimaging results (59.0%). Seventy-five (31.4%) had tried at least 3 types of AEDs for seizure control while another 13.8% had epilepsy surgery. Seventy-nine (33.1%) were previously infected with SARS-CoV-2 at the time of data collection. (Table 1)

Clinical, logistics, and psychological outcomes of COVID-19

As compared to during the COVID-19 pandemic, the percentage of patients who reported seizure worsening (13.0%) remained the same after the pandemic, with 9.6% reporting more frequent, 5.9% longer, and 6.3% more severe seizures. The main reasons associated with seizure worsening after COVID-19 include stress (40.6%), inadequate sleep (38.5%) and fatigue (28.5%). More patients missed their medication dosages after COVID-19 (25.1%) than during the pandemic (14.1%). (Table 1)

After the COVID-19 pandemic, patients find it easier to reschedule their clinic appointments (49.4% vs. 39.5% during the COVID-19 pandemic, $p < 0.001$). The majority were less worried about postponed appointments (50.2% vs. 41.0%, $p < 0.001$). There were fewer patients afraid (14.2% vs. 28.9%, $p < 0.001$) and more accessible to the emergency unit (62.8% vs. 50.6%, $p < 0.001$). Medications were also easier to obtain (67.8% vs. 48.6%, $p < 0.001$), and the patients were less likely to encounter out-of-stock (strongly disagree, 46.9% vs. 24.3% during the COVID-19 pandemic, $p < 0.001$) or insufficient supply of medications (strongly disagree, 45.6% vs 25.2%, $p < 0.001$). (Table 1)

Table 1: Sociodemographic and clinical characteristics comparison between the participants during (N=461) and after (N=239) COVID-19 pandemic

During (N=461) The year 2020	COVID-19 Pandemic		
	During (N=461) Year 2020	After (N=239), Year 2022	p
Age (Year), Mean±SD	39.21±15.88	38.32±14.16	-
N (%)			
Gender			
• Male	230 (49.9)	123 (51.5)	NS
• Female	231 (50.1)	116 (48.5)	
Race			
• Malay	139 (30.2)	67 (28.0)	
• Chinese	208 (45.1)	123 (51.5)	
• Indian	103 (22.3)	43 (18.0)	NS
• Native	2 (0.4)	1 (0.4)	
• Others	9 (2.0)	5 (2.0)	
Marital Status			
• Single	265 (57.5)	131 (54.8)	NS
• Others	196 (42.5)	108 (45.2)	
Highest Education Attained			
• Postgraduate	15 (3.3)	15 (6.3)	
• Degree	115 (24.9)	71 (29.7)	
• Post-secondary	75 (16.3)	54 (22.6)	0.004
• Secondary	194 (42.1)	72 (30.1)	
• Primary	31 (6.7)	8 (3.3)	
• No formal education	31 (6.7)	19 (7.9)	

Employment Status			
• Full-time student	42 (9.1)	24 (10.0)	
• Employed full-time	162 (35.1)	98 (41.0)	
• Employed part-time	21 (4.6)	14 (5.9)	NS
• Full-time house duties/Housewife	22 (4.8)	13 (5.4)	
• Retired	63 (13.7)	22 (9.2)	
• Unemployed	151 (32.8)	60 (25.1)	
Past-COVID infection			
• Yes	-	79 (33.1)	-
• No		160 (66.9)	
Clinical characteristics			
Frequency of seizures before COVID-19 outbreak			
• No seizure for at least a year	173 (37.5)	93 (38.9)	
• Less than once a month	166 (36.0)	72 (30.1)	NS
• One or more seizures a month	122 (26.5)	69 (28.9)	
• Seizure started during COVID outbreak	-	5 (2.1)	
Type of seizure			
• Focal	249 (54.0)	171 (71.5)	
• Generalized	193 (41.9)	56 (23.4)	0.000
• Unsure	19 (4.1)	12 (5.0)	
EEG Results			
• Abnormal	310 (67.2)	160 (66.9)	
• Normal	106 (23.0)	45 (18.8)	NS
• Unsure/Not done	45 (9.8)	34 (14.2)	
CT scan/MRI Results			
• Abnormal	254 (55.1)	141 (59.0)	
• Normal	138 (29.9)	51 (21.3)	0.033
• Unsure/Not done	69 (15.0)	47 (19.7)	
Types of medication tried (Before and Now)			
• One	144 (31.2)	65 (27.2)	
• Two	127 (27.5)	99 (41.4)	0.001
• Three or more	190 (41.2)	75 (31.4)	
Surgery to control seizure			
• Yes	57 (12.4)	33 (13.8)	NS
• No	402 (87.2)	206 (86.2)	
Seizure control in the past 3 months			
• Seizure frequency			
• More frequent	51 (11.1)	23 (9.6)	
• No change	115 (24.9)	45 (18.8)	0.001
• Less frequent	79 (17.1)	72 (30.1)	
• No seizures	216 (46.9)	99 (41.4)	
Seizure duration			
• Longer	20 (4.3)	14 (5.9)	
• No change	157 (34.1)	62 (25.9)	0.001
• Shorter	63 (13.7)	59 (24.7)	
• No seizures	221 (47.9)	104 (43.5)	
Seizure severity			
• More severe	34 (7.4)	15 (6.3)	
• No change	148 (32.1)	60 (25.1)	0.000
• Less severe	56 (12.1)	60 (25.1)	
• No seizures	223 (48.4)	104 (43.5)	

Factors associated with seizure worsening			
• Inadequate sleep	125 (28.3)	92 (38.5)	0.001
• Stress	107 (24.0)	97 (40.6)	0.000
• Missed medication dosages	62 (14.1)	60 (25.1)	0.000
• Inadequate medication supply	10 (2.3)	7 (2.9)	NS
• Fatigue	86 (19.5)	68 (28.5)	0.002
• Diet	23 (5.2)	19 (7.9)	NS
• Unsure	76 (17.2)	27 (11.3)	0.04
Clinical outcome			
Seizure Worsening*			
• Yes	60 (13.0)	31 (13.0)	NS
• No	401 (87.0)	208 (87.0)	
Logistic impact			
Difficulty re-schedule clinic appointments			
• Strongly disagree	76 (16.5)	85 (35.6)	
• Disagree	106 (23.0)	33 (13.8)	
• Neutral	159 (34.5)	59 (24.7)	0.000
• Agree	73 (15.8)	26 (10.9)	
• Strongly agree	47 (10.2)	36 (15.1)	
Worries seizures get worse because my clinic appointments were postponed			
• Strongly disagree	86 (18.7)	86 (36.0)	
• Disagree	103 (22.3)	34 (14.2)	0.000
• Neutral	133 (28.9)	68 (28.5)	
• Agree	93 (20.2)	28 (11.7)	
• Strongly agree	46 (10.0)	23 (9.6)	
Afraid to go to the Emergency Unit			
• Strongly disagree	93 (20.2)	104 (43.5)	
• Disagree	118 (25.6)	43 (18.0)	
• Neutral	117 (25.4)	58 (24.3)	0.000
• Agree	80 (17.4)	19 (7.9)	
• Strongly agree	53 (11.5)	15 (6.3)	
Difficulty to go to Emergency Unit			
• Strongly disagree	105 (22.8)	98 (41.0)	
• Disagree	128 (27.8)	52 (21.8)	
• Neutral	142 (30.8)	56 (23.4)	0.000
• Agree	59 (12.8)	17 (7.1)	
• Strongly agree	27 (5.9)	16 (6.7)	
Understand the need to go to the Emergency Unit			
• Yes	372 (80.7)	197 (82.4)	NS
• No	89 (19.3)	42 (17.6)	
Adequately informed on what to do in the event of seizures			
• Yes	363 (78.7)	200 (83.7)	NS
• No	98 (21.3)	39 (16.3)	
Obtain a supply of medications from			
• University Malaya Medical Centre	407 (88.3)	207 (86.6)	
• Other university hospitals	5 (1.1)	4 (1.7)	
• Ministry of Health Malaysia hospital or clinic	24 (5.2)	14 (5.9)	NS
• Private hospital or clinic	5 (1.1)	4 (1.7)	
• Private pharmacies	20 (4.3)	10 (4.2)	

Difficult to obtain medications			
• Strongly disagree	89 (19.3)	110 (46.0)	
• Disagree	135 (29.3)	52 (21.8)	
• Neutral	125 (27.1)	41 (17.2)	0.000
• Agree	72 (15.6)	17 (7.1)	
• Strongly agree	40 (8.7)	19 (7.9)	
Procedures to arrange for medication delivery via postage are complicated			
• Strongly disagree	66 (14.3)	81 (33.9)	
• Disagree	106 (23.0)	39 (16.3)	
• Neutral	166 (36.0)	77 (32.2)	0.000
• Agree	73 (15.8)	18 (7.5)	
• Strongly agree	50 (10.8)	24 (10.0)	
Procedures to arrange for medication self-collection via "pick-and-go" or "drive-through" are complicated			
• Strongly disagree	56 (12.1)	72 (30.1)	
• Disagree	96 (20.8)	43 (18.0)	
• Neutral	218 (47.3)	77 (32.2)	0.000
• Agree	63 (13.7)	23 (9.6)	
• Strongly agree	28 (6.1)	24 (10.0)	
Medications ran out of stock			
• Strongly disagree	112 (24.3)	112 (46.9)	
• Disagree	167 (36.2)	44 (18.4)	
• Neutral	126 (27.3)	49 (20.5)	0.000
• Agree	39 (8.5)	23 (9.6)	
• Strongly agree	17 (3.7)	11 (4.6)	
Medications provided are always insufficient for the stated duration of supply			
• Strongly disagree	116 (25.2)	109 (45.6)	
• Disagree	204 (44.3)	54 (22.6)	
• Neutral	88 (19.1)	36 (15.1)	0.000
• Agree	38 (8.2)	22 (9.2)	
• Strongly agree	15 (3.3)	18 (7.5)	
I have skipped my medications to avoid running out of supply			
• Never	345 (74.8)	179 (74.9)	
• Rarely	50 (10.8)	27 (11.3)	
• Sometimes	50 (10.8)	20 (8.4)	NS
• Often	10 (2.2)	8 (3.3)	
• Always	6 (1.3)	5 (2.1)	
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)	177 (74.1)	
• Rarely	39 (8.5)	21 (8.8)	
• Sometimes	32 (6.9)	20 (8.4)	NS
• Often	11 (2.4)	10 (4.2)	
• Always	10 (2.2)	11 (4.6)	
Psychological Impact			
HADS-Anxiety Normal	334 (72.5)	180 (75.3)	
Borderline	80 (17.4)	27 (11.3)	NS
Abnormal	47 (10.2)	32 (13.4)	
HADS-Depression Normal	374 (81.1)	196 (82.0)	
Borderline	55 (11.9)	26 (10.9)	NS
Abnormal	32 (6.9)	17 (7.1)	

*Seizure worsening was defined by an increase in seizure frequency, duration, or severity. NS, not significant.

Table 2: Factors associated with seizure worsening after COVID-19 pandemic (N=239)

Factors		Seizure worsening after COVID-19		p	Previous COVID-19 infection		p
		Yes (n=31), n (%)	No (n=208), n (%)		Yes (n=79), n (%)	No (n=160), n (%)	
Sociodemographic Characteristics							
Age (Years), Mean±SD		36.94±12.37	38.43±14.46	NS	35.51±12.23	39.71±14.87	0.03
Gender	Male (n=123)	13 (41.9)	110 (52.9)	NS	39 (49.4)	84 (52.5)	NS
	Female (n=116)	18 (58.1)	98 (47.1)		40 (50.6)	76 (47.5)	
Race	Malay (n=67)	10 (32.3)	57 (27.4)	NS	26 (32.9)	41 (25.6)	NS
	Chinese (n=123)	15 (48.4)	108 (51.9)		36 (45.6)	87 (54.4)	
	Indian (n=43)	37 (17.8)	37 (17.8)		28 (17.5)	28 (17.5)	
	Native (n=1)	0 (0.0)	1 (0.5)		1 (1.3)	0 (0.0)	
	Others (n=5)	0 (0.0)	5 (2.5)		1 (1.3)	4 (2.6)	
Marital Status	Single (n=131)	16 (51.6)	115 (55.3)	NS	45 (57.0)	86 (53.8)	NS
	Others (n=108)	15 (48.4)	93 (44.7)		34 (43.0)	74 (46.3)	
Education	Secondary or below (n=99)	8 (25.8)	91 (43.8)	NS	29 (36.7)	70 (43.8)	NS
	Tertiary (n=140)	23 (74.2)	117 (56.3)		50 (63.3)	90 (56.3)	
Employment	Employed (n=120)	16 (51.6)	104 (50.0)	NS	48 (60.8)	72 (45.0)	0.028
	Others (n=119)	15 (48.4)	104 (50.0)		31 (39.2)	88 (55.0)	
Post-COVID infection	Yes (n=79)	18 (58.1)	66 (31.7)	0.004	-	-	-
	No (n=160)	13 (41.9)	142 (68.3)				
Clinical characteristics							
Seizure frequency before COVID-19	No seizure for at least a year (n=93)	5 (16.1)	88 (42.3)	0.003	27 (34.2)	66 (41.3)	NS
	Less than once a month (n= 72)	9 (29.0)	63 (30.3)		31 (39.2)	41 (25.6)	
	One or more seizures a month (n= 69)	17 (54.8)	52 (25.0)		20 (25.3)	49 (30.6)	
	Seizure started during the COVID outbreak (n=5)	0 (0.0)	5 (2.4)		1 (1.3)	4 (2.5)	
Seizure type	Focal (n= 171)	21 (67.7)	150 (72.1)	NS	56 (70.9)	115 (71.9)	NS
	Others (n= 68)	10 (32.3)	58 (27.9)		23 (29.1)	45 (28.1)	
EEG	Abnormal (n=160)	21 (67.7)	139 (66.8)	NS	54 (68.4)	106 (66.3)	NS
	Others (n=79)	10 (32.3)	69 (33.2)		25 (31.6)	54 (33.8)	
Imaging	Abnormal (n=141)	18 (58.1)	123 (59.1)	NS	46 (58.2)	95 (59.4)	NS
	Others (n= 98)	13 (41.9)	85 (40.9)		33 (41.8)	65 (40.6)	

No. of AEDs	1 (n=65)	7 (22.6)	58 (27.9)		19 (24.1)	46 (28.8)	
	2 (n=99)	16 (51.6)	83 (39.9)	NS	37 (46.8)	62 (38.8)	NS
	≥3 (n=75)	8 (25.8)	67 (32.2)		23 (29.1)	52 (32.5)	
Surgery	Yes (n=33)	5 (16.1)	28 (13.5)	NS	9 (11.4)	24 (15.0)	NS
	No (n=206)	26 (83.9)	180 (86.5)		70 (88.6)	136 (85.0)	
Hospital	UMMC (n=218)	30 (96.8)	188 (90.4)	NS	71 (89.9)	147 (91.9)	NS
	Others (n=21)	1 (3.2)	20 (9.6)		8 (10.1)	13 (8.1)	
Triggers							
Reason for seizure worsening	Stress (n=97)	19 (61.3)	78 (37.5)	0.018	27 (34.2)	70 (43.8)	NS
	Inadequate sleep (n=92)	15 (48.4)	77 (37.0)	NS	29 (36.7)	63 (39.4)	NS
	Physical tiredness (n=68)	15 (48.4)	53 (25.5)	0.017	27 (34.2)	41 (25.6)	NS
	Missed AEDs (n=60)	9 (29.0)	51 (24.5)	NS	19 (24.1)	41 (25.6)	NS
	Diet (n=19)	6 (19.4)	13 (6.3)	0.023	7 (8.9)	12 (7.5)	NS
	Inadequate AEDs (n=7)	4 (12.9)	3 (1.4)	0.006	2 (2.5)	5 (3.1)	NS
Clinic Appointment							
Difficulty to reschedule clinic appointment	Yes (n=62)	15 (48.4)	47 (22.6)	0.004	24 (30.4)	38 (23.8)	NS
	No (n=177)	16 (51.6)	161 (77.4)		55 (69.6)	122 (76.3)	
Worries seizures get worse because of postponed clinic appointment	Yes (n=51)	11 (35.5)	40 (19.2)	NS	17 (21.5)	34 (21.3)	NS
	No (n= 188)	20 (64.5)	168 (80.8)		62 (78.5)	126 (78.8)	
Access to online or tele-consultation	Yes (n=83)	15 (48.4)	68 (32.7)	NS	30 (38.0)	53 (33.1)	NS
	No (n=156)	16 (51.6)	140 (67.3)		49 (62.0)	107 (66.9)	
Emergency unit							
Afraid to go to the emergency unit	Yes (n=34)	8 (25.8)	26 (12.5)	NS	9 (11.4)	25 (15.6)	NS
	No (n=205)	23 (74.2)	182 (87.5)		70 (88.6)	135 (84.4)	
Difficulty to go to the emergency unit	Yes (n=33)	9 (29.0)	24 (11.5)	0.021	9 (11.4)	24 (15.0)	NS
	No (n=206)	22 (71.0)	184 (88.5)		70 (88.6)	136 (85.0)	
Understand the need to go to the emergency unit	Yes (n=197)	23 (74.2)	174 (83.7)	NS	64 (81.0)	133 (83.1)	NS
	No (n=42)	8 (25.8)	34 (16.3)		15 (19.0)	27 (16.9)	

Knowledge of what to do during seizures	Yes (n=201)	24 (77.4)	177 (85.1)	NS	70 (88.6)	131 (81.9)	NS
	No (n=38)	7 (22.6)	31 (14.9)		9 (11.4)	29 (18.1)	
Medication Supply							
Difficult to get AEDs	Yes (n=36)	6 (19.4)	30 (14.4)	NS	15 (19.0)	21 (13.1)	NS
	No (n=203)	25 (80.6)	178 (85.6)		64 (81.0)	139 (86.9)	
Difficult to arrange AED delivery	Yes (n=42)	8 (25.8)	23 (74.2)	NS	15 (19.0)	27 (16.9)	NS
	No (n=197)	30 (16.3)	174 (83.7)		64 (81.0)	133 (83.1)	
Difficult to arrange self-pick-up	Yes (n=47)	8 (25.8)	39 (18.8)	NS	16 (20.3)	31 (19.4)	NS
	No (n=192)	23 (74.2)	169 (81.3)		63 (79.7)	129 (80.6)	
AED ran out of stock	Yes (n=34)	6 (19.4)	28 (13.5)	NS	10 (12.7)	24 (15.0)	NS
	Others (n=205)	25 (80.6)	180 (86.5)		69 (87.3)	136 (85.0)	
Insufficient AEDs supply	Yes (n=163)	21 (67.7)	142 (68.3)	NS	58 (73.4)	105 (65.6)	NS
	No (n=76)	10 (32.3)	66 (31.7)		21 (26.6)	55 (34.4)	
Skipped AEDs	Yes (n= 13)	2 (6.5)	11 (5.3)	NS	5 (6.3)	8 (5.0)	NS
	Others (n=226)	29 (93.5)	197 (94.7)		74 (93.7)	152 (95.0)	
Self-adjusted AEDs dosage	Yes (n= 21)	2 (6.5)	19 (9.1)	NS	8 (10.1)	13 (8.1)	NS
	Others (n=218)	29 (93.5)	189 (90.9)		71 (89.9)	147 (91.9)	
Psychological Scales							
		Mean±SD		p	Mean±SD		p
HADS	Anxiety score	8.42±5.11	4.57±4.52	0.000	5.05±4.69	5.08±4.83	NS
	Depression score	6.90±5.19	3.57±3.59	0.000	4.01±3.92	4.03±4.00	NS
QOLIE -31	Overall Score	44.92±18.66	59.58±15.94	0.000	58.09±17.82	57.47±16.64	NS
	Seizure worry	31.14±26.16	49.20±28.38	0.000	47.58±29.47	46.51±28.41	NS
	Overall Quality of Life	56.61±22.77	70.50±17.46	0.000	68.64±18.65	68.73±18.89	NS
	Emotional Well-being	57.94±19.70	66.31±18.65	0.021	65.62±19.55	65.03±18.71	NS
	Energy	47.26±17.74	58.58±19.56	0.003	56.39±19.69	57.47±19.71	NS
	Cognitive	39.52±22.80	57.79±22.70	0.000	56.87±25.80	54.70±22.30	NS
	Medication Effects	39.96±30.76	47.58±28.26	NS	43.84±31.49	47.95±27.14	NS
	Social Function	39.42±24.11	55.84±23.50	0.000	54.04±26.62	53.54±22.96	NS

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

Factors associated with seizure worsening after COVID-19 pandemic

Seizures worsening after the COVID-19 pandemic were more frequently associated with baseline seizure frequency ≥1 per month (54.8%) than patients with no seizure for at least a year (16.1%) and <1 per month (29.0%, *p*<0.01). Reasons associated with seizure worsening included stress (61.3% vs. 37.5%, *p*<0.05), physical tiredness (48.4% vs. 25.5%, *p*<0.05), diet (19.4% vs. 6.3%,

$p<0.05$) and previous COVID infection (58.1% vs 31.7%, $p<0.01$). Inadequate AEDs (12.9% vs. 1.4%, $p<0.01$), difficulty in rescheduling clinic appointments (48.4% vs. 22.6% with no difficulty, $p<0.01$) and going to the emergency unit (29.0% vs. 11.5% with no difficulty, $p<0.05$) were also associated with seizure worsening after the COVID-19 pandemic. Psychologically, patients experiencing seizure worsening reported greater anxiety (8.42±5.11 vs. 4.57±4.52, $p<0.001$), depression (6.90±5.19 vs. 3.57±3.59, $p<0.001$), and lower quality of life (QOLIE-31) scores (44.92±18.66 vs. 59.58±15.94, $p<0.001$). (Table 2) Patients with previous COVID-19 infection did not experience any differences in seizure control, logistic issues, or psychological well-being from those without.

Changes in psychological impact during and after COVID-19 pandemic

A total of 115 responded to the survey in both Phases 1 (during) and 3 (after the pandemic). In comparison to those during the COVID-19 pandemic, these patients reported no change in anxiety (4.65±4.46 vs. 4.78±3.72 during COVID-19, $p=0.715$) and depression scores (3.81±3.97 vs. 3.86±3.52, $p=0.869$) after the pandemic. Overall quality of life declined after the pandemic (57.44±15.41 vs. 61.70±15.05 during the pandemic, $p=<.001$). On subscale analysis, the decline involved emotional well-being, cognitive, medication effects, and social function. (Table 3)

DISCUSSION

In this study, conducted two years after Phase 1[3], overall seizure control after the COVID-19 pandemic remains the same. However, a significant percentage of patients with worsening seizures (13%) postulated to result from heightened post-pandemic challenges that remain or emerge with eased lockdown measures. The seizure worsening was shown to be related to stress and fatigue, likely related to post-pandemic economic and psychosocial challenges. The pandemic negative effect on sleep quality, psychological distress, and anhedonia were also reported in this Italian longitudinal study.[9] Increased smoking activities and alcohol consumption associated with socializing could also result in worsening seizure control.[9] In particular, a noteworthy 58% of PWE reported seizure worsening had COVID-19 infections postulated due to the reduced seizure threshold associated with symptomatic illnesses such as fever and respiratory tract infections. The rate of hospital admissions for PWE with COVID-19 was also higher than in general populations.[10]

Similarly, in studies published during the height of the pandemic, seizure worsening was reported in patients with poorer baseline seizure control baseline seizure frequency ≥1 per month.[11,12] Some studies have also reported reasons behind the exacerbation of seizure control, regardless of COVID-19 infection, including epilepsy severity, medications polytherapy, sleep disorders, social factors, and mental stress

Table 3: Psychological outcome comparison during and after COVID-19 pandemic (N=115)

Time period	COVID-19 Pandemic, (Mean±SD)		Wilks' Lambda	F	Effect Size	p
	During (Phase 1)	After (Phase 3)				
Anxiety	4.78±3.72	4.65±4.46	.999	.134	.001	0.715
Depression	3.86±3.52	3.81±3.97	1.000	.027	.000	0.869
Overall Score	61.70±15.05	57.44±15.41	.905	11.929	.095	<.001
– Seizure worry	47.54±28.00	47.61±28.21	1.000	.001	.000	0.975
– Overall Quality of Life	69.70±17.84	68.83±17.20	.998	.270	.002	0.604
– Emotional Well-being	70.50±16.56	66.50±17.30	.944	6.716	.056	0.011
– Energy	60.17±17.70	58.26±18.90	.990	1.172	.010	0.281
– Cognitive	59.50±21.93	54.50±21.48	.927	8.984	.073	0.003
– Medication Effects	55.42±13.30	45.77±29.46	.894	13.485	.106	<.001
– Social Function	60.10±23.20	52.10±23.95	.892	13.797	.108	<.001

in general.[11-14] However, in this era, the focus of these reasons shifted mainly onto stress and fatigue possibly due to workplace competition and rectifying the economic consequences suffered during the pandemic. The change from a flexible work environment often practiced during the pandemic to an onsite and fixed workplace often causes PWEs to struggle with traffic congestion, overtime, and work commitments.

Notably, the similar seizure control could be attributed to the balance between the improvement of logistics factors and the deterioration of psychological factors. The accessibility of current clinic appointments, and emergency and medication supply services were in stark contrast to the pandemic, in which epilepsy care was negatively impacted with restriction to aforementioned services.[11-14] A small percentage (9.0%) of patients reported difficulty rescheduling their clinic appointments postulated due to increased patient load in outpatient clinics. Despite 67.8% of patients agreeing that medications were easier to obtain, more patients missed their medications after COVID-19 (25.1%) than before (14.1%). The increase in patient load and poorer medication adherence might offset the positive impact of medical care and medication accessibility.

In comparison, among the 115 patients who participated in both during and after the pandemic studies, the anxiety and depression scores remained the same, and the quality of life declined. These could be attributed to challenges that remained or emerged after the COVID-19 pandemic such as economic, work, and psychosocial issues. In line with an Italian study, patients were still negatively affected in terms of sleep quality and psychological stress after the pandemic without affecting their seizure control suggesting that the COVID-19 pandemic had more long-term neuropsychological than clinical effects.[9] COVID-19 pandemic has its own global catastrophic risks (GCRs), that are endanger human well-being worldwide physically and psychologically.[15] Some may develop depression and anxiety secondary to the losses and threats incurred by GCRs, and the impacts may persist in the post-pandemic era, as shown in this study. Thus, positive coping strategies, either religious or non-religious, should be advocated among people with epilepsy.[16,17]

The limitation of this study was that the web-based study was conducted in urban and semi-rural areas. Therefore, our results might not be reflective of patients from rural or underprivileged settings with no access to the Internet. Future studies involving these underprivileged communities should be conducted to explore and reduce the negative impacts of the pandemic.

The implications of this study was that compared to previous reports studying the impact of COVID-19 on PWE, our study suggested that the challenges and consequences of the pandemic remained based on a longitudinal study design. Extra efforts should be made to address the long-term impact of the COVID-19 pandemic on people with epilepsy to achieve a better quality of life.

In conclusion, despite the improvement in clinical and medication access in the post-COVID-19 era, the reduction of COVID-19 infection rates, and the lifting of lockdown measures, the battle with COVID-19 is far from over. The challenges and consequences of the pandemic remained, without an improvement in seizure control and psychological well-being, and worsening quality of life. If left unaddressed, these issues will widen the treatment gap, affecting the lives of PWE.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. COVID-19 Worldwide Infection and Mortality Report. 2022. (https://news.google.com/covid19/map?hl=en-MY&mid=%2Fm%2F02j71&gl=MY&ceid=MY%3Aen).
2. Hippisley-Cox J, Coupland CA, Mehta N, *et al*. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. *BMJ* 2021;374:n2244. DOI:10.1136/bmj.n2244.
3. Koh MY, Lim KS, Fong SL, Khor SB, Tan CT. Impact of COVID-19 on quality of life in people with epilepsy, and a multinational comparison of clinical and psychological impacts. *Epilepsy Behav* 2021;117:107849. DOI:10.1016/j.yebeh.2021.107849.
4. Siahaan YMT, Ketaren RJ, Hartoyo V, Hariyanto TI. Epilepsy and the risk of severe coronavirus disease 2019 outcomes: A systematic review, meta-analysis, and meta-regression. *Epilepsy Behav* 2021;125:108437. DOI:10.1016/j.yebeh.2021.108437.
5. Koh MY, Lim KS, Fong SL, Khor SB, Tan CT. Impact of COVID-19 pandemic on people with epilepsy: An interventional study using early physical consultation. *Epilepsy Behav* 2021;122:108215. DOI:10.1016/j.yebeh.2021.108215.

6. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:69-77. DOI:10.1016/s0022-3999(01)00296-3.

7. Goldstein LH, Holland L, Soteriou H, Mellers JD. Illness representations, coping styles and mood in adults with epilepsy. *Epilepsy Res* 2005;67:1-11. DOI:10.1016/j.eplepsyres.2005.06.008.

8. Vickrey B, Perrine K, Hays R, Hermann B, Cramer J, Meador K. Quality of Life in Epilepsy QOLIE-31 (version 1.0). Santa Monica, CA: RAND 1993.

9. Sammarra I, Martino I, Caligiuri ME, *et al*. The impact of one-year COVID-19 containment measures in patients with mesial temporal lobe epilepsy: A longitudinal survey-based study. *Epilepsy Behav* 2022;128:108600. DOI:10.1016/j.yebeh.2022.108600.

10. Muccioli L, Zenesini C, Taruffi L, *et al*. Risk of hospitalization and death for COVID-19 in persons with epilepsy over a 20-month period: The EpiLink Bologna cohort, Italy. *Epilepsia* 2022;63:2279-89. DOI:10.1111/epi.17356.

11. Neshige S, Aoki S, Takebayashi Y, *et al*. A longitudinal seizure outcome following the COVID-19 pandemic in 2020 and 2021: Transient exacerbation or sustainable mitigation. *J Neurol Sci* 2022;434:120100. DOI:10.1016/j.jns.2021.120100.

12. Huang S, Wu C, Jia Y, *et al*. COVID-19 outbreak: The impact of stress on seizures in patients with epilepsy. *Epilepsia* 2020;61:1884-93. DOI:10.1111/epi.16635.

13. Assenza G, Lanzone J, Brigo F, *et al*. Epilepsy care in the time of COVID-19 pandemic in Italy: Risk factors for seizure worsening. *Front Neurol* 2020;11:737. DOI:10.3389/fneur.2020.00737.

14. Mostacci B, Licchetta L, Cacciavillani C, *et al*. The impact of the COVID-19 pandemic on people with epilepsy. An Italian survey and a global perspective. *Front Neurol* 2020;11:613719. DOI:10.3389/fneur.2020.613719.

15. Bostrom N, Cirkovic MM. Global catastrophic risks: Oxford University Press; 2011.

16. Francis B, Ken CS, Han NY, *et al*. Religious coping during the COVID-19 pandemic: Gender, occupational and socio-economic perspectives among Malaysian frontline healthcare workers. *Alpha Psychiatry* 2021;22:194-9. DOI:10.5152/alphapsychiatry.2021.21185.

17. Counted V, Pargament KI, Bechara AO, Joynt S, Cowden RG. Hope and well-being in vulnerable contexts during the COVID-19 pandemic: does religious coping matter? *J Positive Psychology* 2020;17:70-81. DOI:10.1080/17439760.2020.1832247.