Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correlation of Seizure Increase and COVID-19 Outbreak in Adult Patients with Epilepsy: Findings and Suggestions from a Nationwide Multi-centre Survey in China

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ABSTRACT

Objectives: To investigate the impact of the COVID-19 outbreak on the behaviours, mental health and seizure control of adult patients with epilepsy (PWE) and to identify the correlation of seizure increase and the COVID-19 outbreak to guide the medical care of individuals with epilepsy during a public health crisis.
Methods: This study was conducted at 28 centres from February 2020 to April 2020. Participants filled out a 62-item online survey including sociodemographic, COVID-19-related, epilepsy-related and psychological variables and were divided into two groups based on whether their seizure frequency increased during the COVID-19 pandemic. Chi-square tests and t-tests were used to test differences in significant characteristics. Multiple logistic regression analyses were used to identify risk factors for seizure worsening.

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Results: A total of 1,237 adult PWE were enrolled for analysis. Of this sample, 31 (8.33%) patients experienced an increase in seizures during the pandemic. Multivariate logistic regression suggested that feeling nervous about the pandemic ($P < 0.05$), poor quality of life ($P = 0.001$), drug reduction/withdrawal ($P = 0.032$), moderate anxiety during the COVID-19 outbreak ($P = 0.046$) and non-seizure free before the COVID-19 outbreak ($P < 0.05$) were independently related to seizure increase during the pandemic.
Conclusions: During the COVID-19 pandemic, PWE with poor quality of life and mental status, as well as AED reduction/withdrawal, were more likely to experience seizure increase. This observation highlights the importance of early identification of the population at high risk of seizure worsening and implementation of preventive strategies during the pandemic.

1. Introduction

The coronavirus disease 2019 (COVID-19) broke out in Wuhan, China, quickly sweeping the world, infecting more than 127 million people, and killing 2,796,561 by Mar 28th, 2021, according to reports from the WHO (https://www.who.int/zh/emergencies/diseases/novel-coronavirus-2019). To lower the risk of disease transmission, most countries took active and effective measures. The national security strategy for COVID-19 in China shifted to so-called wartime control measures from Jan 23rd to April 8th, putting cities on lockdown and affecting an estimated 760 million individuals [1]. Most hospitals and private clinics were shut down for over a month except for fever clinics and emergencies. Many patients with chronic diseases stopped taking drugs due to the long-term closure of outpatient clinics and/or fear of visiting hospitals and pharmacies. Noncompliance became a major concern in the management of chronic diseases, including epilepsy, as irregular consumption and sudden withdrawal of antiepileptic drugs (AEDs) are risk factors for seizures [2], status epilepticus [3] and sudden unexpected death [4, 5]. Therefore, it was possible that the COVID-19 pandemic would increase the risk of irregular medication and AED withdrawal, therefore affecting seizure control in patients with epilepsy (PWE).

PWE are also vulnerable to mental health problems [6, 7]. The overwhelming information about COVID-19, usually described as a potentially fatal disease, has perpetuated the sense of stress, anxiety, depression and fear among the public. Those in quarantine might experience boredom, loneliness, and anger. Furthermore, symptoms such as fever, hypoxia, and cough could lead to worsening anxiety and mental distress. Therefore, the National Health Commission of China released the notification of basic principles for emergency psychological crisis interventions for 2019-nCoV pneumonia on Jan 26th, 2020 [8]. Further, mental health care has been recommended for patients infected with COVID-19 and medical workers facing possible infection on the job, but interventions have been underaddressed for those with other diseases and difficulties accessing medical care.

To date, epidemiological data on the prevalence of confirmed or suspected COVID-19, seizure control conditions, mental health problems and psychiatric morbidity in PWE during the COVID-19 pandemic are limited; therefore, how best to respond to challenges for PWE during the pandemic is unknown. In this multi-centre study, we retrospectively investigated COVID-19 perception, epilepsy-related conditions and mental health in adult PWE using an integrated scale. Our aim is to clarify whether and how the COVID-19 pandemic affects behaviours and seizure control in PWE to develop coping strategies.

2. Materials and methods

2.1. Study population

The multi-centre study was conducted in 28 public hospitals in 13 mainland China provinces. Patients who were previously diagnosed in an epilepsy outpatient clinic and wanted to interact with their centres were voluntarily registered in the social media group at each centre. Patients were regularly followed in the outpatient clinics and frequently consulted their doctors through WeChat. The cross-sectional survey was conducted from February 2020 to April 2020. A questionnaire was uploaded to "Questionnaire Star", and a free open-access online link (https://www.wjx.cn/jq/59056765.aspx) was delivered to each subject via WeChat. We took a series of measures to ensure the response rate, including publicity and education, free outpatient follow-up, gifts (a diary or portable medicine box), encouraging family members' assistance if patients could not finish the questionnaire independently, etc. Finally, 1,719 (92.8%) patients completed the online questionnaire.

2.2. Survey

The 62-item questionnaire involved sociodemographic characteristics, COVID-19 perception, epilepsy-related condition, psychological status and sleep quality.

Perceptions of COVID-19 were measured by 10 items involving COVID-19 infection, exposure, symptoms, attitudes to COVID-19 and government actions. Epilepsy-related condition was measured by 22 items (i.e., course, seizure type, frequency, use of AEDs, way to purchase AEDs, access to doctors).

Mental status was evaluated by the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder Scale (GAD-7) [9-12]. A total PHQ-9 score shows different levels of depression status: 0 to 4 indicates no depression, 5 to 9 indicates mild depression, 10 to 14 indicates moderate depression, 15 to 19 indicates moderately severe depression, and 20 to 27 indicates severe depression. The GAD-7 is a seven-item scale with a total score classified as mild (5–9), moderate (10–14), and severe ($\geq$15) anxiety. Sleep quality in the past month was assessed by the Pittsburgh Sleep Quality Index (PQSI), which consists of seven components (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction) [13]. A total score of ≤ 5 indicates good sleep quality, while a score of > 5 indicates poor sleep quality [14].

The definition of "before the COVID-19 outbreak" is three months before Jan 20th, 2020, the day when Dr. Nanshan Zhong officially announced human-to-human transmission of coronavirus on Chinese official media; "during the COVID-19 outbreak" is the period from Jan 20th, 2020 to online investigation.

In addition to the questionnaire, participants' medical records were reviewed, and each participant received a telephone interview for further confirmation of key information, including COVID-19 infection/exposure, seizure type, seizure frequency, etc. Seizures were classified into generalised, focal and unclassified types based on their history by two experienced neurologists using the 2017 classification of epileptic seizures from the International League against Epilepsy (ILAE) [15]. For patients who answered the questionnaire with assistance, subjective issues, including depression and anxiety, were reassessed by investigators.

2.3. Grouping

Patients were divided into the following two groups for comparison of the impact of the COVID-19 outbreak on seizure control: (1) "with seizure increase" and (2) "without seizure increase". To reduce bias,

participants were only required to fill out seizure frequency per month before and during the COVID-19 outbreak (PWE registered in our social media group were required to keep seizure diaries. For this online investigation, patients retrospectively reported the seizure frequency according to their diaries). Taking into consideration the natural fluctuation of seizure attacks, only patients who had a $\geq$ 50% increase in self-reported seizure frequency during the COVID-19 outbreak compared to seizure frequency before the outbreak were defined as PWE with seizure increase.

2.4. Ethics approval

This study was approved by the Ethics Committee of Xiangya Hospital, Central South University and conformed with the World Medical Association Declaration of Helsinki. Online informed consent to participate was obtained from all participants.

2.5. Quality control

The quality in our study was assured by the following measures: 1) only hospitals with clinical and research capabilities were selected as subcentres; 2) the research plan was discussed with each centre in the early stages of the project in order to predict problems and devise countermeasures; 3) quality control staff from each subcentre were required to check and upload data and report progress on schedule; and 4) a chief quality control manager was placed in charge of the overall data quality and reported directly to the principle investigator on schedule.

2.6. Statistical analysis

Demographic information, COVID-19 perception, epilepsy-related condition, and mental health were compared between PWE with/without seizure increase.

Distributions (frequencies, percentage) were used to describe the overall sample. Chi-square tests (for ordinal categorical variables) and independent sample t-tests (for continuous variables) were used to detect differences in significant characteristics.

When the above variables between PWE with/without seizure increase were significantly different, they were included in an established binary logistic regression equation and set as independent variables, whereas PWE with or without seizure increase was set as a dependent variable.

The analyses were performed with SPSS 26.0 software for Windows (SPSS Inc., Chicago, IL, United States). Significance was set at $P < 0.05$.

3. Results

3.1. Demographic findings

In all, 1,719 PWE from 28 medical centres participated in the present study. Four hundred eighty-two patients who (1) were younger than 18 years, (2) submitted incomplete or unreliable answers (unreasonable answers of age, course, etc., unreachable phone number), and (3) had a history of psychological diseases before the COVID-19 outbreak or experience of other stressful life events were excluded. The remaining 1,237 PWE were enrolled for further analysis. Demographic characteristics are presented in Table 1.

3.2. COVID-19 exposure and perception

Of the 1,237 subjects, 37 (3.0%) had an exposure history (35 [2.8%] Wuhan travel/residence history and 2 [0.2%] contact history of COVID-19 patients). One hundred (8.1%) subjects claimed COVID-19-related symptoms, and nine (0.7%) were diagnosed with COVID-19 by nucleic acid tests. Nearly all (99.6%, 1,232/1,237) subjects showed varying degrees of concern about the pandemic, and 84.1% (1,040/1,237) had worries of being infected. The majority (66.1%, 818/1,237) of patients thought that the COVID-19 information was explicit, while fewer patients (10.3%, 127/1,237) regarded the information as chaotic. All patients received COVID-19 information through the following channels: internet (91.8%, 1,135/1,237), television (59.8%, 740/1,237), friends and relatives (30.3%, 375/1,237), broadcasting (14.1%, 174/1,237) and newspaper (4.6%, 57/1,237). Most patients believed the pandemic could be controlled (84.5%, 1,045/1,237) and adhered to local preventive policies (99.4%, 1,230/1,237).

Table 1
Comparison of PWE without seizure increase and PWE with seizure increase in demographic characteristics and COVID-19 exposure

Variables	PWE without seizure increase (n=1134)	PWE with seizure increase (n=103)	*P* value
Gender			0.790
Female	557 (49.1%)	52 (50.5%)	
male	577 (50.9%)	51 (49.5%)	
Age	33.18±12.07	34.56±11.65	0.254
Education			0.072
<High school	349 (30.8%)	43 (41.7%)	
High school or equivalent	281 (24.8%)	22 (21.4%)	
Higher professional or university	504 (44.4%)	38 (36.9%)	
Living state			0.332
On leave at home	91 (8.0%)	8 (7.8%)	
Work in workplace	244 (21.5%)	15 (14.6%)	
Work at home	163 (14.4%)	15 (14.6%)	
Study at school	24 (2.1%)	2 (1.9%)	
Home quarantine	605 (53.4%)	61 (59.2%)	
Hospital treatment	7 (0.6%)	2 (1.9%)	
COVID-19 exposure[a]			0.726
No	1099 (96.9%)	101 (98.1%)	
Yes	35 (3.1%)	2 (1.9%)	
COVID-19 related symptoms			
Yes	83 (7.3%)	17 (16.5%)	0.001**
No	1051 (92.7%)	86 (83.5%)	
COVID-19 infection			0.168
Yes	7 (0.6%)	2 (1.9%)	
No	1127 (99.4%)	101 (98.1%)	

[a] PWE with the following history were considered to have COVID-19 exposure: (1) Wuhan travel or residence history; (2) confirmed or suspicious patients contact history. *P<0.05, ** P<0.01.

3.3. Epilepsy-related characteristics

Of the 1,237 subjects, 571 (46.2%) presented with generalised seizures, 622 (50.3%) focal and 44 (3.6%) unclassified. Before the COVID-19 outbreak, 632 (51.1%) subjects were treated with AED monotherapy, and 548 (44.3%) subjects were treated with two or more AEDs for seizure control; 473 (40.1%) subjects were seizure free, 594 (48.0%) subjects reported a reduction in seizure frequency, and 161 (13.0%) subjects reported no reduction in seizure occurrence. During the COVID-19 outbreak, 46 (3.7%) subjects added drug types or dosages, and 23 (1.9%) subjects reduced or replaced medication. Four (0.3%) subjects stopped taking medication.

The majority (61.6%) of subjects worried about seizure attacks during the COVID-19 outbreak. Nearly half (48.8%, 603/1,237) of the subjects showed varying degrees of worry about the pandemic's impact on seizure control. Of these, the greatest concerns were difficulty in purchasing AEDs (61.0%, 368/603), difficulty in visiting the outpatient department (60.9%, 367/603) and difficulty in receiving prompt treatment for seizures (35.3%, 213/603). Assuming that participants would experience seizure attacks during the COVID-19 outbreak, 480 (38.8%) subjects would prefer to continue with the original prescription, and 250 (20.2%) subjects would prefer to consult online due to loss of contact

with outpatient doctors. Only 322 (26.0%) subjects reported that they would go to emergency rooms.

3.4. Mental health

Based on the GAD-7 scale, 269 of 1,237 subjects had mild anxiety, 75 had moderate anxiety and 32 had severe anxiety. The remaining 861 subjects were identified with no anxiety. Similarly, the PHQ-9 scale detected 268 subjects with mild, 110 moderate, 48 moderately severe and 37 severe depression. The remaining 774 subjects were defined as having no depression. According to the PSQI scale (cut-off > 5), 701 subjects were poor sleepers, while the other 536 subjects had good sleep quality.

3.5. Characteristics of patients with seizure increase

During the outbreak, 103 patients (8.3%) reported an increase in seizure frequency and were classified as "PWE with seizure increase", while the remaining 1,134 subjects were classified as "PWE without seizure increase". A comparison between the two groups is presented in Tables 1-4. As shown in Table 1, there was no significant difference between PWE with/without seizure increase in demographic characteristics, including sex, age, education, living state, COVID-19 exposure history and COVID-19 infection. However, PWE with seizure increase had a higher percentage of COVID-19-related symptoms than PWE without seizure increase (8.1% v.s. 7.3%, $P < 0.001$). Table 2 suggests that compared with the PWE without a seizure increase group, PWE with seizure increase were more susceptible to feeling nervous about the pandemic ($P < 0.001$) and had poorer quality of life during the COVID-19 outbreak ($P < 0.001$). For epilepsy-related characteristics, PWE with seizure increase had a significantly higher percentage of uncontrolled epilepsy ($P < 0.001$), AED polytherapy before the COVID-19 outbreak ($P < 0.01$) and medication alterations during the COVID-19 outbreak ($P < 0.001$). Meanwhile, a significantly higher proportion of PWE with seizure increase worried about seizure attacks ($P < 0.001$) and the pandemic's impact on seizure control ($P < 0.001$) during the COVID-19 outbreak (Table 3). PWE with seizure increase also had higher scores for

Table 2
Comparison of PWE with/without seizure increase in COVID-19 perception

Variables	PWE without seizure increase (n=1134)	PWE with seizure increase (n=103)	*P* value
Concern about COVID-19			0.377
None	5 (0.4%)	0 (0.0%)	
A little	66 (65.1%)	5 (4.9%)	
Medium	149 (13.1%)	7 (6.8%)	
Fairly much	406 (35.8%)	41 (39.8%)	
Very much	508 (44.8%)	50 (48.5%)	
Feelings of the COVID-19 information			0.456
Very chaotic	27 (2.4%)	6 (5.8%)	
Fairly chaotic	87 (7.7%)	7 (6.8%)	
Neutral	270 (23.8%)	22 (21.4%)	
Fairly explicit	473 (41.7%)	44 (43.0%)	
Very explicit	277 (24.4%)	24 (23.3%)	
Worries of being infected			0.136
None	184 (16.2%)	13 (12.6%)	
A little	354 (31.2%)	24 (23.3%)	
Medium	128 (11.3%)	17 (16.5%)	
Fairly much	237 (20.9%)	21 (20.4%)	
Very much	231 (20.4%)	28 (27.2%)	
Feel nervous about the pandemic			0.000***
Totally disagree	305 (26.9%)	10 (9.7%)	
Fairly disagree	222 (19.6%)	16 (15.5%)	
Neutral	390 (34.4%)	45 (43.7%)	
Fairly agree	146 (12.9%)	19 (18.4%)	
Totally agree	71 (6.3%)	13 (12.6%)	
Quality of life during the COVID-19 pandemic			0.000***
Very good	329 (29.0%)	15 (14.6%)	
Fairly good	539 (47.5%)	29 (28.2%)	
Neutral	248 (21.9%)	41 (39.8%)	
Poor	18 (1.6%)	18 (17.5%)	

*** $P<0.001$.

Table 3
Comparison of PWE with/without seizure increase in epilepsy-related condition

Variables	PWE without seizure increase (n=1134)	PWE with seizure increase (n=103)	*P* value
Epilepsy course (month)	101.89±97.77	119.38±101.39	0.095
Seizure type			0.867
Generalised seizures	526 (46.4%)	45 (43.7%)	
Partial seizures	568 (50.1%)	54 (52.4%)	
Unidentified	40 (3.5%)	4 (3.9%)	
Seizure control before the COVID-19 outbreak			0.000***
No seizure	476 (42.0%)	6 (5.8%)	
Seizure reduction > 90%	289 (25.5%)	20 (19.4%)	
Seizure reduction ≥50%	140 (12.3%)	26 (25.2%)	
Seizure reduction < 50%	104 (9.2%)	15 (14.6%)	
No reduction	125 (11.0%)	36 (35.0%)	
Number of doses missing before the COVID-19 outbreak			0.184
0	904 (79.7%)	79 (76.7%)	
1-2 doses/week	200 (17.6%)	18 (17.5%)	
≥3 doses/week	30 (2.6%)	6 (5.8%)	
Number of doses missing during the COVID-19 outbreak			
1.000			
0	904 (79.7%)	83 (80.6%)	
1-2 doses/week	191 (16.8%)	17 (16.5%)	
≥3 doses/week	39 (3.4%)	3 (2.9%)	
Number of AEDs before the COVID-19 outbreak			0.006**
1	584 (51.5%)	38 (36.9%)	
2	372 (32.8%)	37 (35.9%)	
3	95 (8.4%)	15 (14.6%)	
>3	31 (2.7%)	8 (7.8%)	
Never took AEDs	33 (2.9%)	4 (3.9%)	
Stop medication	19 (1.7%)	1 (1.7%)	
Medication alteration during the COVID-19 outbreak			0.000***
None	1077 (95.0%)	86 (83.5%)	
Increase	38 (3.4%)	10 (9.7%)	
Reduction/withdrawal	19 (1.7%)	7 (6.8%)	
Worry about seizure attack during the COVID-19 outbreak			0.000***
None	478 (40.9%)	14 (13.6%)	
A little	399 (35.2%)	30 (29.1%)	
Medium	72 (6.3%)	8 (7.8%%)	
Fairly much	111 (9.8%)	22 (21.4%)	
Very much	88 (7.8%)	29 (28.2%)	
Worry about the pandemic's impact on seizure control			0.000***
None	606 (53.4%)	30 (29.1%)	
A little	321 (28.3%)	32 (31.1%)	
Medium	54 (4.8%)	7 (6.8%)	
Fairly much	87 (7.7%)	12 (8.2%)	
Very much	66 (5.8%)	22 (21.4%)	

** $P<0.01$, *** $P<0.001$.

anxiety ($P < 0.001$) and depression ($P < 0.001$) and poorer sleep quality ($P < 0.001$) (Table 4).

3.6. Multiple logistic regression analysis

Forward stepwise multiple logistic regression analysis was used to further identify the correlation of increased self-reported seizure frequency and COVID-19 outbreak (Table 5). We observed factors such as nervous about the pandemic: fairly disagree (OR = 2.471, $P = 0.049$, 95% CI = 1.003~6.085), neutral (OR = 2.279, $P = 0.045$, 95% CI = 1.019~5.095), fairly agree (OR = 3.195, $P = 0.016$, 95% CI = 1.240~8.084). Participants reported a fairly poor quality of life during the pandemic (OR = 5.387, $P = 0.001$, 95% CI = 1.970~14.735), seizure reduction > 90% before the COVID-19 outbreak (OR = 4.006, $P = 0.005$, 95% CI = 1.516~10.584), seizure reduction ≥ 50% before the COVID-19 outbreak (OR = 9.577, $P = 0.000$, 95% CI = 2.628~25.284), seizure reduction < 50% before the COVID-19 outbreak (OR = 5.418, $P = 0.002$, 95% CI = 1.858~15.799), no seizure reduction before the COVID-19 outbreak (OR=12.670, $P = 0.000$, 95% CI = 4.755~33.760), drug reduction/withdrawal during the pandemic (OR = 3.317, $P = 0.032$, 95% CI = 1.107~9.936) and moderate anxiety (OR = 2.433, $P = 0.046$, 95% CI = 1.015~5.832) were presented as risk factors. For the number of AEDs before the COVID-19 outbreak, stopping medication (OR = 0.053, $P = 0.023$, 95% CI = 0.004~0.667), one AED (OR = 0.147, $P = 0.006$, 95% CI = 0.037~0.584), and two AED$_S$ (OR = 0.141, $P = 0.006$, 95% CI = 0.034~0.577) were protective factors. Since the two groups of PWE did not differ in background factors such as gender, age, educational level and living state, the logistic regression analyses were not adjusted.

4. Discussion

The COVID-19 pandemic has proven to affect the management of chronic diseases, including cancer, diabetes mellitus and cardiovascular disease [16-18]. It is therefore foreseeable that COVID-19 would likely result in stress in PWE. In our study, a minority (8.3%) of PWE experienced seizure worsening during the COVID-19 outbreak, similar to observations from a single-centre, cross-sectional study in Wuhan and its surrounding cities (8.6%) [19] and lower than two foreign surveys (18-29.5%) [20, 21]. The variation could possibly be explained by: 1) difference in infection rates (much higher in US, Europe) and access to medical supplies; 2) difference in definition of seizure increase (self--reported or unbiased calculated); and 3) difference in timings of survey.

Table 4
Comparison of PWE without seizure increase and PWE with seizure increase in mental health

Variables	PWE without seizure increase (n=1134)	PWE with seizure increase (n=103)	*P* value
GAD-7			0.000***
0-4 (No anxiety)	819 (72.2%)	42 (40.8%)	
5-9 (Mild anxiety)	237 (20.9%)	32 (31.3%)	
10-14 (Moderate anxiety)	55 (4.9%)	20 (19.4%)	
≥15 (Severe anxiety)	23 (2.0%)	9 (8.7%)	
PHQ-9			0.000***
0-4 (No depression)	738 (65.1%)	36 (35.0%)	
5-9 (Mild depression)	238 (21.0%)	30 (29.1%)	
10-14 (Moderate depression)	94 (8.3%)	16 (15.5%)	
15-19 (Moderately severe depression)	38 (3.4%)	10 (9.7%)	
20-27 (Severe depression)	26 (2.3%)	11 (10.7%)	
PSQI			0.000***
≤5 (good)	514 (45.3%)	22 (21.4%)	
>5 (poor)	620 (54.7%)	81 (78.6%)	

*** $P<0.001$.

Table 5
Predictors of seizure increase during the COVID-19 outbreak

Variables	B	OR (95%CI) value	P value
Constant	-2.399		0.000
COVID-19 related symptoms	0.243	1.275 (0.647~2.514)	0.482
Feel nervous about the pandemic			
Totally disagree		1.000 (reference)	
Fairly disagree	0.905	2.471 (1.003~6.085)	0.049*
Neutral	0.824	2.279 (1.019~5.095)	0.045*
Fairly agree	1.150	3.159 (1.240~8.048)	0.016*
Totally agree	0.765	2.148 (0.739~6.243)	0.160
Quality of life during the COVID-19 outbreak			
Very good		1.000 (reference)	
Fairly good	-0.436	0.647 (0.319~1.310)	0.226
Neutral	0.070	1.072 (0.512~2.246)	0.853
Fairly poor	1.684	5.387 (1.970~14.735)	0.001**
Worry about seizure attack during the COVID-19 outbreak			
None		1.000 (reference)	
A little	0.147	1.159 (0.544~2.469)	0.703
Medium	0.674	1.962 (0.671~5.735)	0.218
Fairly much	0.720	2.054 (0.841~5.013)	0.114
Very much	0.941	2.564 (0.969~6.781)	0.058
Worry about the pandemic's impact on seizure control			
None		1.000 (reference)	
A little	0.121	1.129 (0.602~2.118)	0.706
Medium	-0.497	0.609 (0.194~1.907)	0.394
Fairly much	-0.528	0.590 (0.238~1.462)	0.255
Very much	-0.032	0.968 (0.381~2.458)	0.946
Seizure control before the COVID-19 outbreak			
No seizure		1.000 (reference)	
Seizure reduction >90%	1.388	4.006 (1.516~10.584)	0.005**
Seizure reduction≥50%	2.259	9.577 (2.628~25.284)	0.000***
Seizure reduction <50%	1.690	5.418 (1.858~15.799)	0.002**
No reduction	2.539	12.670 (4.755~33.760)	0.000***
Number of AEDs before the COVID-19 outbreak			
Never took AEDs		1.000 (reference)	
Stop medication	-2.943	0.053 (0.004~0.667)	0.023*
1	-1.920	0.147 (0.037~0.584)	0.006**
2	-1.962	0.141 (0.034~0.577)	0.006**
3	-1.498	0.224 (0.049~1.016)	0.052
>3	-1.519	0.219 (0.042~1.141)	0.071
Medication alteration during the COVID-19 outbreak			
None		1.000 (reference)	
Increase	0.646	1.908 (0.806~4.513)	0.141
Reduction/withdrawal	1.199		0.032*

(continued on next page)

Table 5 (*continued*)

Variables	B	OR (95%CI) value	P value
		3.317 (1.107~9.936)	
GAD-7			
0-4 (No anxiety)		1.000 (reference)	
5-9 (Mild anxiety)	0.380	1.462 (0.780~2.740)	0.236
10-14 (Moderate anxiety)	0.889	2.433 (1.015~5.832)	0.046*
≥15 (Severe anxiety)	0.519	1.680 (0.489~5.777)	0.410
PHQ-9			
0-4 (No depression)		1.000 (reference)	
5-9 (Mild depression)	-0.037	0.964 (0.496~1.871)	0.913
10-14 (Moderate depression)	-0.079	0.954 (0.390~2.188)	0.857
15-19 (Moderately severe depression)	-0.046	1.003 (0.322~2.835)	0.935
20-27 (Severe depression)	-0.053	0.948 (0.304~3.138)	0.969
PSQI	0.361	1.435 (0.777~2.648)	0.248

* $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Our study shows that feeling nervous about the pandemic, moderate anxiety, poor quality of life, drug reduction/withdrawal during the COVID-19 outbreak, and seizure activity before the COVID-19 outbreak were independently related to seizure increase. This is not the first time public health emergencies have adversely affected seizure control. A retrospective single-centre study in Taiwan interviewed PWE regarding their epileptic seizures before, during, and after the 2003 severe acute respiratory syndrome (SARS) outbreak. It revealed that 21.6% of subjects stopped taking medication during the outbreak, and AED withdrawal produced a significant increase in seizure frequency [22]. The single-centre study in Wuhan suggested that exposure history to COVID-19, uncontrolled seizures after AED therapy, seizure frequency of two or more times per month before the outbreak, change of AED regimen during the outbreak, and worry about the adverse effect of the outbreak on overall seizure-related issues were risk factors for increased seizures [19]. A national survey in Italy attributed seizure worsening to the number of AEDs and the severity of sleep disorders [20]. A cross-sectional study conducted in Saudi Arabia reported that higher baseline seizure frequency, more AEDs, noncompliance, an increase in self-reported stress, and sleep changes were significantly associated with an increase in seizure frequency during the pandemic [21]. These findings are important in the early identification of PWE at high risk of seizure recurrence and the development of preventive strategies during public health outbreaks.

In our study, the majority of patients showed varying degrees of concern about the pandemic and worried about becoming infected. Because of the lack of a control cohort, we were not able to conclude that these findings are specific to epilepsy. In fact, the panic is widespread in the general population and among patients with other diseases during the COVID-19 pandemic [17, 18]. Anxiety and depressive disorders are common and disabling comorbidities in PWE [23, 24]. In the present study, the prevalence of depression and anxiety among all patients was 37.4% and 30.4%, respectively, higher than that in patients from Wuhan using the same self-reported scales [19], and may be partially attributed to the difference in cut-off points set for diagnosis by these two studies. In our study, moderate anxiety was found to be responsible for seizure increase, in accordance with the findings from a cross-sectional case--control study in Southwest China that PWE showed significantly higher psychological distress than healthy controls [25]. During the COVID-19 outbreak, individuals were inundated with information rumours, and sensational news headlines and images. These factors may have added anxiety and fear to these situations. Similarly, in the early phase of the SARS outbreak, a range of psychiatric morbidities, including persistent depression, anxiety, panic attacks, psychomotor excitement, psychotic symptoms, delirium, and even suicide, were reported [26, 27]. History reminds health authorities and the public to provide mental health interventions to those who are in need. The National Health Commission of China issued guidelines to promote psychological crisis intervention for patients, medical staff and medical observers during the COVID-19 outbreak. The Chinese government has worked to raise public awareness of prevention and protection by providing daily monitoring and accurate updates on active coronavirus cases on websites and social media. An increasing number of psychologists and psychiatrists use the Internet and social media (such as WeChat, Weibo, etc.) to share strategies to deal with psychological stress. However, most attention has been given to the mental health of COVID-19 patients and medical professionals [28, 29]. Our study adds new evidence that the mental health and management of patients with chronic diseases also need special attention.

Determining sleep disorders in PWE is essential, as poor sleep quality is associated with the frequency of seizures and symptoms of fatigue, daytime sleepiness, and depression [30]. It has been reported that sleep disorders are more common in PWE (34-42.7%) [30, 31] than in the general population (8-18%) [32]. Our study found that 56.7% had poor sleep quality, even higher than the prevalence in the literature, indicating an adverse effect of the COVID-19 outbreak on the sleep quality of PWE. Although sleep quality was not presented as an independent risk factor for seizure increase, it is undoubtedly an important component of quality of life, which was negatively correlated with self-reported seizure frequency during the COVID-19 outbreak; therefore, maintaining good sleep is critical in seizure control.

The Centers for Disease Control and Prevention (CDC) has suggested that some neurological diseases, such as epilepsy, might be a risk factor for COVID-19, partly due to the increased rate of comorbidities [33]. However, information from countries, such as China, Italy, and the United States, fails to demonstrate that PWE are more susceptible to the virus, nor are they more likely to have severe COVID-19 manifestations. Accordingly, of the 1,237 patients who fulfilled the inclusion criteria in our study, only nine reported COVID-19 infection. Nevertheless, a cross-sectional observational study in Spain revealed that patients with active epilepsy had a higher COVID-19 cumulative incidence and fatality during hospitalisation compared to the population without epilepsy [34]. Larger samples are needed to further illustrate the incidence of COVID-19 in PWE.

Our study has several limitations. Although we included 28 medical centres covering different districts of China, including Wuhan, our cohort was relatively small in size. Considering that participants in this investigation were volunteers from the social media group of each subcentre, our sample was more likely to represent those patients with good compliance rather than the whole epilepsy population. Regional population prevalence and objective knowledge of COVID-19 infection was different from one city to the next, and the cities in this study each had a small sample size. Taking Wuhan as an example, only 30 patients participated in the online investigation. This made data comparison among cities difficult. Moreover, the retrospective nature and questionnaire-based design of this study was prone to induce recall bias and misidentification of seizure attacks. However, to reduce bias, we conducted additional telephone interviews with all participants to confirm their seizure types and frequency. Patients on the platform were required to keep seizure diaries, which further ensured accuracy.

Conclusions

In conclusion, the present study shed light on how the COVID-19 crisis affected seizure control regarding the behavioural and psychological responses of PWE to the pandemic. During public health outbreaks, healthcare professionals should focus on the mental health and medication adherence of PWE. Practical guidance and psychological

assistance are suggested to prevent noncompliance with drug protocols and seizures.

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Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

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