

# Depression in patients with epilepsy during the COVID-19 pandemic based on longitudinal self-reporting

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## ABSTRACT

**Objective.** The current study screened major depression in people with epilepsy (PWE) during the epidemic of the novel coronavirus-related disease COVID-19, in order to identify whether the outbreak generated negative psychological impact on PWE.

**Methods.** A Chinese version of the Neurological Disorders Depression Inventory for Epilepsy (C-NDDI-E), a self-reporting depression inventory, was applied for rapid detection of major depression. Assessment was carried out online during three different periods (prior to, during, and after the outbreak of COVID-19), with the aim of identifying changes in prevalence of depression and associated risk factors.

**Results.** A total of 158 PWE were recruited into the study (48.7% female). The questionnaire completion rates were 94.3% and 70.9% during and after the outbreak, respectively. The prevalence of depression prior to the epidemic, as the baseline, was 34.8% and increased to 42.3% during the period of the epidemic. Towards the end of the outbreak, the prevalence declined towards the baseline (36.6%). Factors such as living alone (OR = 4.022, 95% CI: 1.158-13.971, P = 0.028) and active seizures before the epidemic (OR = 2.993, 95% CI: 1.197-7.486, P = 0.019) were associated with depression during the epidemic. Monotherapy appeared to be protective against depression (OR = 0.105, 95% CI: 0.047-0.235, P < 0.001).

**Significance.** Our results suggest that the pandemic exerts negative influence on PWE's mental health. Depression is one of the common psychological disorders that needs greater attention during this extraordinary period.

**Key words:** COVID-19; depression; epilepsy

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Epilepsy is one of the most common chronic neurological disorders and affects over 70 million people globally [1]. Depression is documented to be highly prevalent in epilepsy, with reported lifetime prevalence at around 13% [2]. Comorbid depression is associated with poorer quality of life in people with epilepsy (PWE) [3] and may exacerbate epileptic seizures, leading to worse prognosis and greater adverse effects due to antiepileptic drugs (AEDs). Additionally,

psychological disorders have been shown to be a risk factor associated with a higher suicide rate in PWE compared with the general population [4]. The outbreak of the novel coronavirus (COVID-19) pandemic first started in China at the end of 2019 [5], and spread extensively across the world, leading to an unprecedented global public health crisis. Previous research has demonstrated that an epidemic can lead to profound psychosocial problems [6].

More recent studies from China have demonstrated a psychological burden (e.g., burnout and depression) in health care workers and the general population during the COVID-19 epidemic [7, 8]. Based on the above evidence, we speculate that an impact of the epidemic on mental health would be apparent among PWEs. Therefore, we initiated the present study to better understand the mental state of PWEs during the COVID-19 epidemic.

## Methods

### Study design

The current study was designed to longitudinally observe depression episodes at three different periods (before, within and after the outbreak of the COVID-19 in China). Ethics approval was obtained from the institutional review board of our hospital.

### Study areas and participants

This study was deployed in an academic, tertiary referral, epilepsy centre in western China. All participants, derived from our database, were previously diagnosed with epilepsy and receiving AED treatment. In order to observe the changes in mood status during different phases of the outbreak, we enrolled PWE according to the following criteria:

- disease duration of over three months;
- completion of an assessment of depression using the Chinese version of the Neurological Disorders Depression Inventory for Epilepsy (C-NDDI-E) within two months prior to the outbreak;
- age 18–60 years;
- competence in using smartphones and responding to online questionnaires;
- consent to participate.

The exclusion criteria were severe intellectual and developmental impairment, illiteracy or mental incompetence, neurological disease, psychosis, or other severe medical conditions (e.g., tumours, fractures). In total 158 participants who were selected from our registry met the criteria and were enrolled in the study.

### Procedures

Given that the epidemic in China started to become evident on January 23<sup>rd</sup> and seemed to be under control in March 2020 (WHO.<https://covid19.who.int/region/wpro/country/cn>), we set the time interval from January 23<sup>rd</sup> to March 31<sup>st</sup>, 2020, as the “epidemic

period.” In addition, we defined a previous two-month period prior to January 23<sup>rd</sup> as the “pre-epidemic period” and a two-month period after March 31<sup>st</sup> as the “post-epidemic period”. The present study was conceptualized and implemented at the end of February. All potential candidates were approached by one of our investigators via telephone contact or WeChat (which is one of the leading Chinese multipurpose messaging and social media Apps) in advance and were invited to participate from 1<sup>st</sup> to 7<sup>th</sup> of March. Eligible participants were informed that their participation was completely voluntary and that all the answers were guaranteed to be confidential. Incentives were not provided for participation. If the interviewee consented to participate, the online C-NDDI-E was then forwarded to the participant through an online survey platform (‘SurveyStar’, Changsha Ranxing Science and Technology, Shanghai, China). All participants were asked to complete the electronic C-NDDI-E and other questions within seven days. In the pre-epidemic period, the C-NDDI-E score was considered as the baseline. In the epidemic period, we forwarded the C-NDDI-E to participants immediately after eligible PWE consented to participate (1<sup>th</sup> to 7<sup>th</sup> of March). In the post-epidemic period, C-NDDI-E was dispatched to participants on 30<sup>th</sup> of May. Afterwards, we compiled our respondents’ response for analysis.

### Data collection

Demographic and clinical data were documented in our registered database. The data included age, gender, living alone, marital status, occupation, education level, frequency and type of seizures, disease course, age at onset, AED therapy regimen.

The C-NDDI-E was developed and validated as a rapid screening/detection instrument for depression in PWE [9, 10], and consists of six self-rating items to investigate symptoms of depression over the previous two weeks. The questionnaire avoids items associated with AED adverse effects or the nature of epilepsy itself (e.g., somnolence or memory problems). The six items are:

- everything is a struggle;
- nothing I do is right;
- feel guilty;
- i’d be better off dead;
- frustrated;
- and difficulty finding pleasure.

For each item, a 4-point scale from “never” to “always/often”, corresponding to a score of one to four in ascending order, was applied for grading. A higher score indicates a higher risk of major depression. Based on the original study for this inventory, scores greater than 15 were suggested to show a significant possibility of depressive episode (with a sensitivity of 0.81 and a specificity

of 0.90) [9]. For Chinese PWE, a cut-off point of > 12 is suggested, which was validated with a sensitivity of 0.926 and specificity of 0.804 [10]. In the present study, a cut-off score of CNDDI-E > 12 was used to determine depressive episodes. Item 4 was used to screen suicidality, with a cut-off score set at > 2 [11].

## Statistics

The analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Depression prevalence and C-NDDI-E score were documented at different stages of the epidemic. In addition, demographic and clinical variables were compared between PWE who were depressed and not depressed. Categorical variables were assessed using  $\chi^2$ , corrected  $\chi^2$ , Fisher exact test or Mann-Whitney test. A binary logistic regression model was performed for multivariable analyses of the risk factors of depression in the epidemic. In the model, each variable with a p value of < 0.05 (based on the univariate analysis) was entered into the final model. A Forward conditional method was conducted. Odds ratios

(OR) and 95% confidence intervals (CI) were calculated. A p value of <0.05 was considered statistically significant.

## Results

### Demographics and clinical characteristics

A total of 158 PWEs were recruited into the study (77 female; 48.7%). The questionnaire completion rates were 94.3% and 70.9% during epidemic and post-epidemic periods, respectively. During follow-up, no suicide was reported. *Table 1* illustrates the demographic and clinical features during the baseline period. The median age of the participants was 26 years old with inter quartile range (IQR) 20–38 years old. Fifty-five out of 158 (34.8%) participants were found to be depressed during the pre-epidemic period according to the criteria of C-NDDI-E. A higher percentage (63.6%) of women was found in the depression group ( $p=0.006$ ). PWE with active seizures tended to be depressed ( $p < 0.001$ ). Patients taking more than one type of AED seemed more likely to develop depression ( $p < 0.001$ ). For more details, see *table 1*.

▼ **Table 1.** Baseline data for demographics and clinical characteristics of participants during the pre-epidemic period.

	Total (n=158)	PWE without depression (n=103)	PWE with depression (n=55)	P value
Age, years, median (IQR)	26 (20–38)	26 (21–39)	25 (19–36)	0.948
Female (n, %)	77 (48.7)	42 (40.8)	35 (63.6)	0.006
Education level (n, %)				
Middle school or below	52 (32.9)	34 (33.0)	18 (32.3)	
High school	43 (27.2)	27 (26.2)	16 (29.1)	0.919
College or above	63 (39.9)	42 (40.8)	21 (38.2)	
Residency (urban area, n, %)	113 (71.5)	70 (68.0)	43 (78.2)	0.175
Employed (n, %)	95 (60.1)	65 (63.1)	30 (54.5)	0.295
Currently married or partnered (n, %)	76 (48.1)	53 (51.5)	23 (41.8)	0.248
Living alone (n, %)	14 (8.8)	7 (6.8)	7 (12.7)	0.339 <sup>b</sup>
Disease duration, years, median (IQR)	3.2 (0.3–4.1)	3.1 (0.3–4.3)	3.3 (0.5–3.7)	0.914
Seizure type* (n, %)				
Focal	118 (74.7)	71 (68.9)	47 (85.5)	
Generalized	44 (27.8)	25 (24.3)	19 (34.5)	0.878
Unknown	19 (12.0)	12 (11.7)	7 (12.7)	
Monotherapy	107 (67.7)	85 (82.5)	22 (40.0)	<0.001
Active seizure in the past 3 months before the epidemic period	38 (24.1)	15 (14.6)	23 (41.8)	<0.001

\* Both focal and generalized seizures occurred in some individuals. <sup>b</sup> Corrected; chi-square.

▼ **Table 2.** The characteristics of depression among PWEs during different periods of the COVID-19 epidemic.

	Pre-epidemic (n=158) n (%)	Epidemic (n=149) n (%)	Post-epidemic (n=112) n (%)	P value
Depression	45 (34.8)	63 (42.3)	41 (36.6)	0.040
Depression with suicide risk	15 (9.5)	18 (12.1)	11 (9.8)	0.733
New cases with depression	/	30 (20.1)	10 (8.9)	0.013
Treated with antidepressants	13 (8.2)	25 (16.7)	30 (26.8)	<0.001
With remission of depression	/	8/45 (17.8)	15/63 (23.8)	0.095
With depression lost to follow-up	/	4/45 (8.9)	17/63 (27.0)	0.002

### The prevalence of depression among PWE during the epidemic

Table 2 depicts the changing trends of the prevalence of depression among PWE. The prevalence of depression prior to the pandemic, as the baseline, was 34.8% (n=55) and increased to 42.3% (n=63) during the period of the pandemic, declining towards the baseline (n=41, 36.6%) towards the end of the epidemic. Among those depressed, 12.1% exhibited suicidality during the epidemic period, which is higher than that during the pre- and post-epidemic period, at 9.5% and 9.8%, respectively, although no statistical difference was revealed. Note that 30 (20.1%) new cases with depression were observed during the epidemic period, which contributed to approximately half of the population with depression during this period.

### Risk factors for developing depression during the epidemic

The factors for developing depression during the outbreak are elaborated on in more detail in table 3. During the epidemic and post-epidemic period,

two factors were associated with the development of depression. These were living alone (epidemic: OR 4.022, 95% CI 1.158–13.971; post-epidemic: OR 3.835, 95% CI 1.066–13.794) and active seizures before the epidemic (epidemic: OR 2.993, 95% CI 1.197–7.486; post-epidemic: OR 3.125, 95% CI 1.168–8.381). Monotherapy appeared to be protective against depression (epidemic: OR 0.105, 95% CI 0.047–0.235; post-epidemic: OR 0.194, 95% CI 0.079–0.479). Note that living alone did not appear to be a risk factor for developing depression during the pre-epidemic period.

### Discussion

The present longitudinal observation confirms our speculation that the pandemic exerted negative influence on mental health of PWE. To our knowledge, epilepsy coexisting with psychological disorders, such as depression, is common [12]. Two previous studies in our area have identified a high prevalence of depressive episodes in PWE, based on rapid detection using C-NDDI-E [10, 13]. Our findings not only provide information on the mental status of PWE during the epidemic, but also contribute

▼ **Table 3.** Risk factors of depression in PWE during different periods of the COVID-19 epidemic.

Risk factor	Pre-epidemic		Epidemic		Post-epidemic	
	OR	95% CI	OR	95% CI	OR	95% CI
Living alone			4.022	1.158–13.971	3.835	1.066–13.794
Monotherapy	0.121	0.054–0.271	0.105	0.047–0.235	0.194	0.079–0.479
Active seizure in the past 3 months before the epidemic period	5.254	2.191–12.597	2.993	1.197–7.486	3.125	1.168–8.381

Factors with p<0.05 remained in the final model.

to the understanding of the risk factors associated with depression. Therefore, subsequent measures against depression should be established for prevention and treatment accordingly.

In our study, the high rate of responders was probably due to the fact that these were registered patients, who voluntarily participated with good medical adherence. The first follow-up visit was scheduled immediately after obtaining consent from the participants, and it is reasonable to assume therefore that this would lead to a high completion rate of the questionnaire. During the epidemic, PWE in our cohort were able to receive medical aid and counselling via either virtual visits or normally via the clinic [14]. Hence a high retention rate of participants was achieved during the second follow-up period.

During the non-epidemic period, the prevalence rate of depression among PWE was previously reported to be 26.7–29.9% [10, 13] which is lower than that in our study (34.8%). However, reported prevalence rates of depression among PWE range between 10–50% depending on sample characteristics and other methodological factors [15]. A recent meta-analysis indicated a pooled prevalence of depression of 22.8% among the general population during the COVID-19 pandemic [16]. A recent survey using the Kessler Psychological Distress Scale revealed an increased level of non-specific psychological distress (including symptoms of anxiety and depression) in PWE compared to controls during the COVID-19 epidemic [17]. In contrast, our study, with the benefit of longitudinal data, demonstrates an elevated prevalence rate of depression during the epidemic, indicating that the COVID-19 pandemic has the potential to significantly affect mental health. Given the fact that prevalence of depression in PWE is higher than that in the general population, controls for cross-sectional comparison were not included in the present study. Note that in our study, there was a trend for prevalence of depression to return to baseline (pre-epidemic period), suggesting that a small number of PWE experienced a short-term period of depression during the epidemic, which may spontaneously recover as the epidemic mitigates. According to our clinical practice, all PWE who reveal severe psychological symptoms are required to consult a psychologist. However, we were unable to trace corresponding psychological treatment to these PWE due to limited resources. As a consequence, we are unable to determine the cause of the depression.

With respect to risk factors associated with the development of depression among PWE, published papers provide emerging evidence that seizure frequency, social support, annual income, female gender, unmarried status, disease course and focal impaired awareness

seizure are associated with depression [13, 18]. Consistent with this evidence, our results reveal that living alone and active seizures before the epidemic are two independent risk factors associated with the development of depression during the epidemic. It is reasonable to assume that living alone, as a new factor, would increase the risk of psychological problems, especially during the epidemic, as social distancing and movement restrictions are imposed. In contrast, monotherapy, which probably indicates non-refractory epilepsy, is less likely to be associated with depression.

## Limits and strength

Our study has several limitations. First, we skewed our selection to a small sample with certain conditions (e.g., registered patients only, those with C-NDDI-E scores, PWE who were capable of using electronic devices, excluding digital literacy), which does not represent the whole population. Second, a further bias effect was due to the nature of self-reporting, which may introduce information bias. Third, this study did not include healthy controls, thus we do not know whether the prevalence of depression was higher in PWE compared to the general population at the time of the epidemic (no data on C-NDDI-E scores from healthy controls were available before the epidemic). Fourth, the diagnosis of depression was not based on a structured psychiatric interview, which may affect diagnostic accuracy. Nevertheless, we believe that our findings provide useful information on the impact of the epidemic on the mood of PWE.

## Conclusion

The outbreak of COVID-19 has had a negative impact on the mental status of PWE, resulting in an increased prevalence of depression. Although the depression among PWE seems to spontaneously remit, appropriate immediate preventative interventions are essential in order to enhance the psychological resilience and wellbeing of PWE. ■

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None of the authors have any conflict of interest to declare.

### Data availability.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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