A longitudinal seizure outcome following the COVID-19 pandemic in 2020 and 2021: Transient exacerbation or sustainable mitigation

Shuichiro Neshige [a,b,*], Shiro Aoki [a], Yoshiko Takebayashi [a], Takeo Shishido [a], Yu Yamazaki [a], Koji Iida [b,c], Hirofumi Maruyama [a,b]

[a] Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Graduate School of Biomedical and Health Sciences, Japan
[b] Epilepsy Center, Hiroshima University Hospital, Japan
[c] Department of Neurosurgery, Hiroshima University, Graduate School of Biomedical and Health Sciences, Japan

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ABSTRACT

Objective: To study the longitudinal seizure outcomes of people with epilepsy (PWE) following the acute and chronic phases of the coronavirus disease 2019 (COVID-19) pandemic.
Methods: Consecutive PWE who were treated at the epilepsy center of Hiroshima University Hospital between 2018 and 2021 were enrolled. We evaluated the incidence of seizure frequency increase or decrease following the pandemic during observational periods in 2020 and 2021. Data between 2018 and 2019 were used as a control set. The sustainability of the altered seizure frequency condition was evaluated throughout the study period. We analyzed the clinical, psychological, and social factors associated with PWE with seizure exacerbation or amelioration.
Results: Among the 223 PWE who were evaluated (mean age 37.8 ± 16.3 years), seizure frequency increased for 40 (16.8%) and decreased for 34 (15.2%) after the pandemic began. While seizure exacerbation tended to be a transient episode during 2020, seizure amelioration was likely to maintain excellent status over the observation periods; the sustainability of the altered seizure frequency condition was more prominent for amelioration than exacerbation ($p < 0.001$). Seizure exacerbation was significantly associated with "no housemate" (odds ratio [OR] 3.37; $p = 0.045$) and "comorbidity of insomnia" (OR 5.80; $p = 0.004$). Conversely, "structural abnormality of MRI" (OR 2.57; $p = 0.039$) and "two-generation householding" (OR 3.70; $p = 0.004$) were independently associated with seizure amelioration.
Conclusion: This longitudinal observation confirmed that seizure exacerbation and amelioration emerged during the COVID-19 pandemic. The COVID-19 pandemic has shed light on the stark difference that social support systems can make on outcomes for PWE.

1. Introduction

The novel coronavirus disease 2019 (COVID-19) has had a tremendous impact on medical care worldwide [1] including clinical epilepsy practice [2]. This influence remains ongoing and threatens people with epilepsy (PWE), and the spread of COVID-19 causes mental health disturbance and seizure exacerbation [3–6]. However, the longitudinal outcome for PWE in terms of seizures since the onset of the pandemic is yet unknown.

During the acute phase of the pandemic, PWE were threatened both directly, by the pandemic (infection-related illness) and indirectly by the infodemic impact (socio-economic and psychological stress) on individuals [7]. Rapid and dynamic social changes caused substantial mental health impairment, leading to worsened seizures among PWE [8]. As PWE are sensitive to dramatic changes in social situations [9], seizure management may have been negatively impacted. However, more than a year has passed since the COVID-19 pandemic began and it is now in the chronic phase. Multiple medical guidelines and recommendations have addressed the current issues in clinical epilepsy practice [10,11]. Of particular interest are new approaches, such as telemedicine, that have also been promoted in clinical practice [12]. As the medical environment surrounding PWE is currently changing,

seizure outcomes can also change in the medium- to long-term during the pandemic. Thus, it is crucial to examine the long-term seizure outcome of PWE during the ongoing COVID-19 pandemic.

Changing social and lifestyle conditions are assumed to be burdensome for some PWE, given that health inequalities for PWE are associated with social deprivation [13]. However, during the chronic phase of the pandemic, other PWE may have found the new normal lifestyle relatively easy to accept, as PWE might gradually adapt to their new lifestyle, as previously observed among individuals other than PWE [14]. Therefore, this study aimed to elucidate longitudinal seizure outcomes as of the beginning of the pandemic to identify the features of PWE who were vulnerable to increased seizures or who adapted well to the new normal life. Given the diversity of PWE, the mental, social, and epilepsy-related factors will discriminate the long-term seizure outcomes between exacerbation and amelioration. We believe that this exploration will be informative for new risk management strategies in clinical epilepsy practice in advance of future pandemics that will inevitably entail dynamic social changes.

2. Methods

2.1. Patients and study protocol

We prospectively evaluated PWE who visited the epilepsy center in the Division of Neurology at Epilepsy Center in Hiroshima University Hospital from 2018 to 2021. Hiroshima University Hospital is located in Hiroshima City, with a population of approximately 1.19 million, an ordinance-designated city in western Japan. Our comprehensive epilepsy center, accredited by the Japanese Epilepsy Society, is the largest in Hiroshima prefecture. Thus, our center represents a typical profile of epileptology that treats all kinds of epilepsy including drug-resistant

epilepsy. This study was approved by the Ethics Committee of the Hiroshima University Hospital (No. E-2285 and E-2441). All patients provided informed consent to participate.

Based on the spikes of infections during the pandemic in Japan, the present study comprised the following three observational periods: a 6-month "pre-pandemic period" (between April 2019 and September 2019, as the baseline data), a 6-month "pandemic period in 2020" (between April and October 2020, the 6-months after the pandemic started in Japan), and a 6-month "pandemic period in 2021" (between March and August 2021, the 6-months after the end of the second pandemic wave in Japan; Fig. 1). The peak number of infections of the first to fifth waves of the COVID-19 pandemic in Japan are shown in Fig. 1. With each consecutive pandemic wave far more people were infected with COVID-19; the fifth wave displayed the highest peak during which more than 24,000 people were infected with COVID-19 daily in Japan (https://graphics.reuters.com/world-coronavirus-tracker-and-maps/ja/countries-and-territories/japan/). Thus, the impact of the pandemic period in 2021, in terms of the number of individual infected, was more substantial than that in 2020. We also used a 6-month "reference period" (between September 2018 and March 2019) that preceded the pre-pandemic period to determine the eligibility of PWE.

2.2. Inclusion and exclusion criteria

PWE were eligible if their medical history, including their seizure type and frequency data, were available for all the observation periods. Additionally, to investigate the pandemic's impact on the change in seizure frequency, we included only PWE who experienced no increase in seizure frequency before the onset of the pandemic. More specifically, we excluded PWE who already had ≥50% increase or decrease in seizure
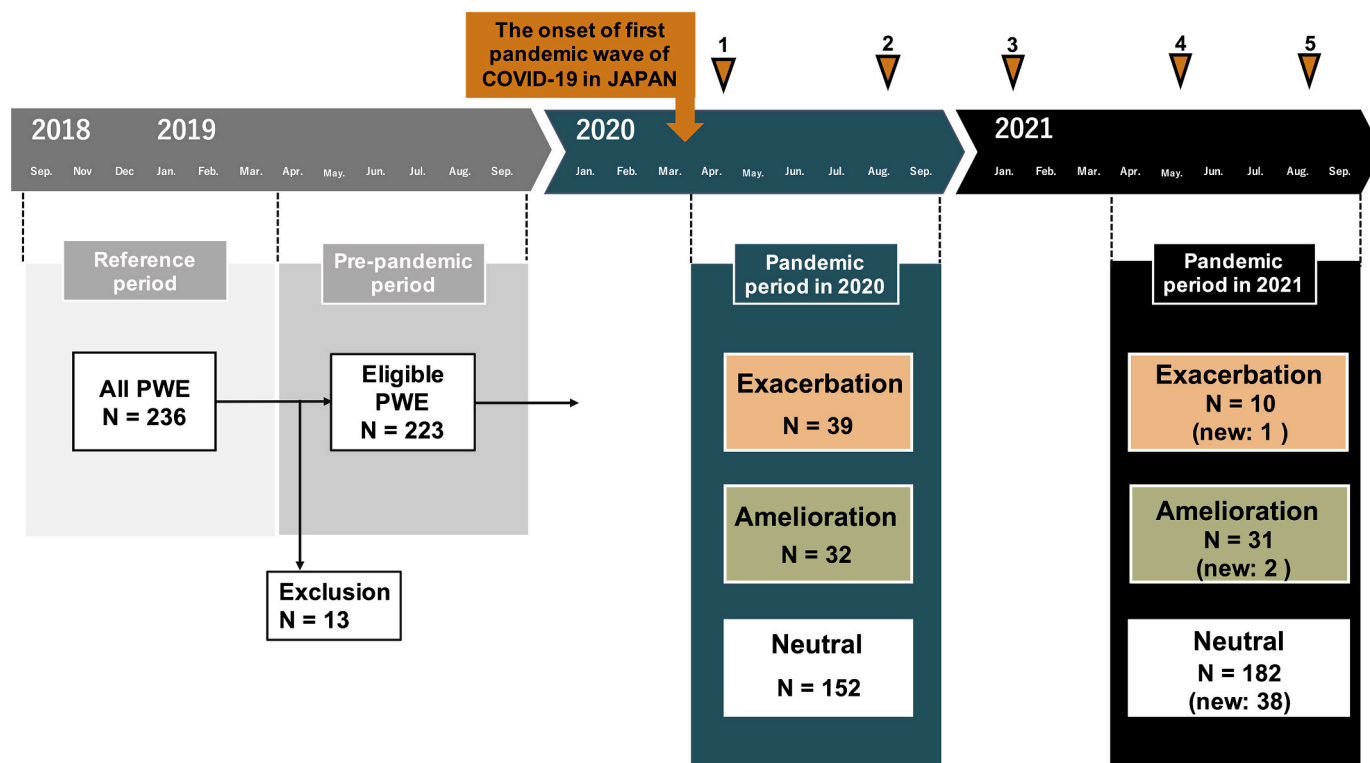
Fig. 1. Study protocol and seizure outcomes.
Four observational periods are shown before and after the onset of the COVID-19 pandemic. We determined the eligibility of PWE during the pre-pandemic period using data from the reference and pre-pandemic periods. We used the pandemic period in 2020 and 2021 to assess seizure outcomes. Seizure frequency change during these two periods was calculated based on baseline data (the pre-pandemic period). Yellow arrowheads indicate peaks of the 1st to 5th waves of COVID-19 pandemic-infected people in Japan. The number of PWE who experienced seizure exacerbation, amelioration, or neutrality are shown for each pandemic period. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

frequency during "the pre-pandemic period" compared with "the reference period" (Fig. 1). We also excluded PWE with a history of unstable psychosis or alcoholism. In view of the potential for inaccurate seizure measurement, patients with dementia or learning disabilities were also excluded; however, those PWE were included if the precise seizure frequency data were available from the caregivers. Additionally, PWE who underwent any epilepsy-related surgery during the study periods were excluded.

2.3. Clinical, social, economic, and psychological parameters

We investigated the clinical data associated with epilepsy (seizure type, epilepsy classification, seizure frequency, and medication). Seizure frequency was evaluated based on patient-reported seizure counts and patients' seizure calendars during each study period. Unprovoked habitual seizure data were used for evaluation. If a participant experienced multiple seizure types, we used the most harmful and frequent seizure type to calculate seizure frequency. When PWE had a focal impaired awareness seizure (FIAS) and focal to bilateral tonic-clonic seizure (FBTCS), the frequency of the two seizures was calculated as a combined total if the FBTCS was considerable a secondary event from the FIAS. Conversely, if the patient had different seizure types that appeared independently (such as focal awareness seizure [FAS] and FIAS, or two types of FAS), we calculated seizure frequency for each type. For example, if PWE exhibited emotional seizures (once per month) and auditory seizures (once per several days), the auditory seizure was used for the analysis. If a daily FAS was more harmful than a yearly FIAS that appeared independent from the FAS, we used the FAS's seizure frequency data for the analysis. Besides, psychogenic non-epileptic seizures (PNESs), or so-called dissociative seizures, were not counted together with true epileptic seizures. The incidence of PNES was assessed only for PWE, whose PNES was confirmed by video electro-encephalography (EEG) examination before the study. Provoked seizure data, such as an antiepileptic drug (AED) withdrawal seizure or acute symptomatic seizure, were not included in this evaluation. Seizure frequency reduction following medication changes was also not counted.

Magnetic resonance imaging (MRI) and EEG findings were used as the baseline data for each patient. We also investigated epilepsy comorbidities and etiology based on the International League Against Epilepsy classification [15,16]. The prevalence of comorbidities such as insomnia and depression was reviewed based on the interview sheet completed at the first visit and the participants' medical records and treatment histories.

We reviewed data on patients' life histories, including occupation. As people were required to "remain home" during the COVID-19 pandemic, the participants' living situations were considered important social background factors and were thus categorized according to whether the PWE lived alone, with their parents in a two-generation household, or with their parents and grandparents or more family members in a multigeneration household. Regarding socio-economic factors, we assessed changes in income level, work style (e.g., telecommuting), and lifestyle (e.g., whether PWE had to provide daycare for their children) due to social changes after the onset of the pandemic. To evaluate changes in psychological distress during the pandemic, we assessed the scores of a short screening scale, the six-item Kessler Psychological Distress Scale (K-6) [17,18], for the pre-pandemic and pandemic periods in 2020.

2.4. Data analyses

The primary outcome measure was habitual seizure frequency change during the pandemic period in 2020 and 2021. The change in seizure frequency was calculated relative to baseline pre-pandemic period data. We classified the frequency change into the following three categories for each pandemic period in 2020 and 2021: amelioration ($\geq$50% seizure reduction), neutral, or exacerbation ($\geq$50% seizure increase).

The secondary outcome measure was the sustainability of seizure conditions. When PWE exhibited exacerbation or amelioration during the pandemic period in 2020, we investigated whether the altered conditions returned to the baseline level or were sustained until the end of the study period. We then compared the proportion of sustainability between PWE with exacerbation and amelioration.

Lastly, we performed univariate analysis to identify features of PWE who exhibited seizure exacerbation or amelioration throughout the study period. PWE who exhibited seizure exacerbation in either 2020 or 2021 was defined as "exacerbation group." PWE who exhibited seizure amelioration in either 2020 or 2021 was defined as the "amelioration group." The statistical significance of the intergroup differences was determined using a Fisher exact test for categorical variables, while an unpaired Student's *t*-test was used for continuous variables.

Finally, significant variables ($p < 0.05$) in the univariate analysis were selected for subsequent logistic regression analysis. If the number of significant variables found in the univariate analysis was relatively large, given the number of PWE analyzed in the multivariate analyses, we selected the variables according to the strength of their statistical significance (in order of decreasing *p*-value). We also considered variables based on their potential internal correlations. For example, as the baseline seizure frequency and current number of AEDs could be correlated, we selected only the seizure frequency for the analysis. The same selections were applied for the variables between the K-6 score in 2019 and 2020 and the comorbidity of depression and insomnia. We used the likelihood ratio test to calculate odds ratios (ORs). A paired *t*-test was used to compare the incidence of seizure exacerbation or amelioration between the pandemic period of 2020 and 2021. All statistical analyses were conducted using JMP software (JMP Pro version 14; SAS Institute, Cary, NC, USA).

3. Results

Of the consecutive 236 PWE initially enrolled, 223 PWE were eligible (Fig. 1); 125 were male (56.1%), and the mean age was 37.8 $\pm$ 16.3 years (Table 1). The mean disease duration was 12.1 $\pm$ 12.5 years; before the onset of the COVID-19 pandemic in 2020, there were 27 (12.1%) PWE within 2 year of onset and 99 (44.4%) whose disease duration was more than 10 years. The majority of epilepsy classifications were focal epilepsy, among which the highest was temporal lobe epilepsy (28.7%). Approximately one-third of the patients experienced at least one bilateral or focal to bilateral tonic-clonic seizure. In contrast, 30 PWE (13.5%) experienced PNES. Baseline habitual seizure frequency was variable and the mean number of current AEDs used was 1.97 $\pm$ 1.28. Occupation and living situations also varied. No PWE was infected with COVID-19 during the study period.

Thirty-nine PWE (17.5%) exhibited seizure exacerbation during the pandemic period in 2020 (Fig. 1). Of those, the seizure frequency returned to the baseline for 29/39 PWE (76.9%) by the onset of the pandemic period in 2021. The remaining 10 PWE (23.1%) were still in an exacerbated condition by 2021. Namely, most of the exacerbations that emerged in 2020 were transient episodes of PWE in view of the longitudinal observation. In addition, there was only one PWE (0.5%) who newly exhibited seizure exacerbation in 2021. Thus, a total of 40 PWE (17.9%) experienced exacerbation in either 2020 or 2021 (exacerbation group). The proportion of PWE who newly experienced seizure exacerbation was significantly higher during the pandemic period in 2020 than in 2021 (17.5 vs. 0.5%, $p < 0.001$).

In contrast, 32 PWE (14.3%) exhibited seizure amelioration during the pandemic period in 2020 (Fig. 1). Of those, a few PWE (n = 3/32, 9.4%) reported that their seizure frequency returned to the baseline until the end of the 2021 period. Thus, the majority (n = 29/32, 90.6%) succeeded in maintaining their ameliorated condition over the year. In addition, two patients newly exhibited seizure amelioration during the pandemic period in 2021.

The probability of PWE for whom seizure frequency changed in 2020

Table 1
Clinical characteristics of patients with epilepsy.

	Epilepsy patients (n = 223)
Age, years (mean ± SD)	37.8 ± 16.3
Onset age, years (mean ± SD)	25.7 ± 18.3
Sex, male (n, %)	125 (56.1)
Epilepsy classification (n, %)	
Generalized epilepsy	74 (33.2)
Focal epilepsy	121 (54.3)
- Temporal lobe epilepsy	64 (28.7)
- Frontal lobe epilepsy	40 (17.9)
Unclassified	28 (12.6)
Seizure type (n, %)	
- FAS	57 (25.6)
- FIAS	84 (37.7)
- Myoclonus	26 (11.7)
- Focal to bilateral tonic–clonic seizure	61 (27.4)
- Bilateral tonic–clonic seizure	68 (30.5)
- PNES	30 (13.5)
Seizure frequency (n, %)	
- Weekly or more	29 (13.0)
- Monthly	81 (36.3)
- Yearly or less	113 (50.7)
Number of AEDs (mean ± SD)	1.97 ± 1.28
Drug-resistant epilepsy (n, %)	42 (18.8)
Occupation (n, %)	
- Blue-collar worker	22 (9.9)
- Office worker	32 (14.4)
- Service industry	24 (10.8)
- Medical staff	12 (5.4)
- Self employed	3 (1.4)
- Housewife	16 (7.2)
- Student	38 (17.0)
- Unemployed	74 (33.2)
Living situation (n, %)	
- No housemate	37 (16.6)
- Couple	35 (15.7)
- Two-generation household	123 (55.2)
- Three-generation household	17 (7.6)
- Personal care home	10 (4.5)
- With child (<6 years)	34 (15.2)

AED, anti-epileptic drug; FAS, focal awareness seizure; FIAS, focal impaired awareness seizure; PNES, psychiatric non-epileptic seizure; SD, standard deviation.

Table 2
Differences in clinical and social characteristics between patients with or without seizure exacerbation.

	Exacerbation group (n = 40)	Non-exacerbation group (n = 183)	p Value
Age, years (mean ± SD)	38.4 ± 15.3	37.7 ± 16.7	0.79
Onset age, years (mean ± SD)	25.6 ± 12.7	25.7 ± 19.3	0.97
Sex, male (n, %)	22 (55.0)	102 (55.7)	0.86
Epilepsy classification, (n, %)			
- Generalized	11 (27.5)	63 (34.4)	0.46
- Focal	21 (52.5)	100 (54.6)	0.86
Temporal lobe epilepsy, (n, %)	9 (22.5)	55 (30.1)	0.44
Seizure type, (n, %)			
- FAS	8 (20.0)	49 (26.8)	0.37
- FIAS	14 (35.0)	70 (38.3)	0.86
- Myoclonic seizure	7 (17.5)	19 (10.4)	0.27
- FBTCS	14 (35.0)	47 (25.7)	0.21
- PNES	16 (40.0)	14 (7.7)	**<0.001**
Frequent seizure, monthly or more at baseline (n, %)[a]	28 (70.0)	82 (44.8)	**0.005**
AED, number (n, %)	2.15 (1.56)	1.93 (1.21)	0.34
EEG (n, %)			
- Background slow	6 (15.0)	29 (15.8)	1.00
- Spike	16 (40.0)	95 (51.9)	0.17
- Focal slow	18 (45.0)	100 (54.6)	0.30
- Photosensitivity	5 (12.5)	13 (7.1)	0.33
MRI, structural abnormality (n, %)	10 (25.0)	73 (39.9)	0.10
Comorbidity (n, %)			
- ADHD/ASD	4 (10.0)	11 (6.0)	0.32
- Depression or anxiety	13 (32.5)	13 (7.1)	**<0.001**
- Insomnia	18 (45.0)	16 (8.7)	**<0.001**
- Headache	3 (7.5)	17 (9.3)	1.00
- Learning difficulty	14 (35.0)	44 (24.0)	0.16
- Neurodegenerative	2 (5.0)	6 (3.3)	0.64
Living situation, (n, %)			
- No housemate	14 (35.0)	24 (13.1)	**0.002**
- A couple	5 (12.5)	30 (16.4)	0.64
- Two-generation household	16 (40.0)	107 (58.5)	**0.037**
- Three-generation household	3 (7.5)	14 (7.7)	1.00
- Personal care home	2 (5.0)	8 (4.4)	1.00
- With child (<6 years)	5 (12.5)	29 (15.9)	0.81
Life work change (n, %)[a]			
- Need to provide childcare	2 (5.0)	12 (7.8)	1.00
- Income decrease by >10%	2 (6.3)	5 (3.2)	0.34
- Teleworking	10 (25.0)	26 (14.7)	0.16
K-6 score (mean ± SD)			
- Pre-pandemic period	23.4 ± 5.5	25.5 ± 6.0	0.086
- Pandemic period in 2020	20.0 ± 6.3	25.5 ± 5.5	**<0.001**

ADHD/ASD, attention deficit hyperactive disorder/autism spectrum disorder; AED, anti-epileptic drug; FAS, focal awareness seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure, PNES, psychiatric non-epileptic seizure; SD, standard deviation.

[a] Data were available for 172 PWE for Need to care child, 180 for income decrease, and 181 for teleworking.

returned to the baseline level was significantly higher among PWE with exacerbation in 2020 than in those with amelioration in 2020 (n = 10/39; 23.1% vs. n = 29/32; 90.6%, $p < 0.001$). Some PWE in the amelioration group reported that increased opportunities to telework provided more time to organize their schedule or more time for sleep; teleworking reduced the stress of commuting to work.

Table 2 shows that seizure exacerbation in 2020 or 2021 (exacerbation group) was significantly associated with PNES ($p < 0.001$), high seizure frequency at the baseline ($p = 0.005$), comorbidity of depression ($p < 0.001$) and insomnia ($p < 0.001$), and living situation of no housemate ($p = 0.002$). Two-generation household living situation was negatively associated with seizure exacerbation ($p = 0.037$). Multivariate logistic regression analysis revealed that "no housemate" (OR 3.37; 95% confidence interval [CI] 1.03–11.08; $p = 0.045$) and "comorbidity of insomnia" (OR 5.80; 95% CI 1.74–19.25; $p = 0.004$) were independently associated with exacerbation group (Table 3).

Table 4 shows that seizure amelioration in 2020 or 2021 was significantly associated with high seizure frequency at baseline ($p = 0.003$), higher numbers of administered AEDs ($p = 0.004$), EEG findings of spikes ($p = 0.039$) and focal slows ($p < 0.001$), structural abnormality of MRI ($p = 0.004$), and living situation of two generation household ($p = 0.008$). In contrast, "no housemate" living situation was inversely associated with the seizure amelioration ($p = 0.013$). Additionally, epilepsy classification, occupation, and psychological stress did not differ significantly. Subsequent multivariate logistic regression analysis revealed that "structural abnormality of MRI" (OR 2.57; 95%CI 1.05–6.30; $p = 0.039$) and "two-generation household" (OR 3.70; 95%CI 1.53–8.96; $p = 0.004$) were independently associated with amelioration (Table 5).

4. Discussion

The present longitudinal observational study confirmed that both seizure exacerbation and amelioration were experienced by PWE during the first five waves of the COVID-19 pandemic in 2020 and 2021. We also identified that the phenotypes and social backgrounds differed significantly between PWE who experienced exacerbation and those

Table 3
Multivariate analysis of factors associated with seizure exacerbation.

	OR	95%CI	*p* Value
No housemate	3.37	1.03–11.08	**0.045**
Comorbidity of depression or insomnia	5.80	1.74–19.25	**0.004**

Multivariate analyses were performed using the following factors: high seizure frequency, PNES, comorbidity of depression or insomnia, no housemate, and K-6 score during 2021. We combined the comorbidities of depression and insomnia into a single variable because of their internal correlation. There should also be a correlation between the K-6 score in the pre-pandemic period and the pandemic period in 2020.

Table 4
Differences in clinical and social characteristics between patients with or without seizure amelioration.

	Amelioration (*n* = 34)	Non-amelioration (n = 189)	*p* Value
Age, years (mean ± SD)	38.4 ± 14.6	37.7 ± 16.7	0.81
Onset age, years (mean ± SD)	29.3 ± 17.3	25.1 ± 18.4	0.22
Sex, male (n, %)	19 (55.9)	107 (56.6)	1.00
Epilepsy classification, (n, %)			
- Generalized	11 (32.4)	63 (33.3)	0.40
- Focal	21 (61.7)	100 (52.9)	
Temporal lobe epilepsy, (n, %)	14 (41.2)	50 (26.4)	0.10
Seizure type (n, %)			
- FAS	12 (35.3)	45 (23.8)	0.20
- FIAS	19 (55.9)	65 (34.4)	0.021
- Myoclonic seizure	1 (2.9)	25 (13.2)	0.14
- FBTCS	8 (23.5)	53 (28.0)	0.41
- PNES	3 (8.8)	27 (14.3)	0.59
Frequent seizure, monthly or more at baseline (n, %)	25 (73.5)	85 (45.0)	**0.003**
AED, number (n, %)	2.56 (1.52)	1.87 (1.21)	**0.004**
EEG (n, %)			
- Background slow	9 (26.5)	26 (13.8)	0.073
- Spike	23 (67.7)	89 (47.1)	**0.039**
- Focal slow	27 (79.4)	91 (48.1)	**<0.001**
- Photosensitivity	1 (2.9)	17 (9.0)	0.32
MRI, structural abnormality (n, %)	21 (61.8)	62 (32.8)	**0.004**
Comorbidity (n, %)			
- ADHD/ASD	1 (2.9)	14 (7.4)	0.48
- Depression or anxiety	3 (8.8)	23 (12.2)	0.77
- Insomnia	5 (14.7)	29 (15.3)	1.00
- Headache	4 (11.8)	16 (8.5)	0.52
- Mental retardation	8 (23.5)	50 (26.5)	0.83
- Neurodegenerative	1 (2.9)	7 (3.7)	1.00
Living situation (n, %)			
- No housemate	1 (2.9)	37 (19.6)	**0.013**
- A couple	5 (14.7)	30 (15.9)	1.00
- Two-generation household	26 (76.5)	97 (51.3)	**0.008**
- Three-generation household	2 (5.9)	15 (7.9)	1.00
- Personal care home	0 (0)	10 (5.3)	0.37
- With child (<6 years)	10 (29.4)	24 (12.7)	0.019
Life work change[a]			
- Need to provide child care	3 (9.7)	12 (7.7)	0.72
- Income decrease by >10%	0 (0)	7 (4.5)	0.60
- Teleworking	5 (15.2)	31 (16.9)	1.00
K-6 score (mean ± SD)			
- Pre-pandemic period	23.9 ± 6.0	25.4 ± 5.9	0.24
- Pandemic period in 2020	24.8 ± 4.9	24.4 ± 6.3	0.76

[a] Data were available for 172 PWE for Need to provide child care, 180 for income decrease, and 181 for teleworking.

who experienced amelioration. Additionally, the final seizure outcome, namely, the sustainability of seizure condition after seizure frequency change during the pandemic, also differed between groups. As the longitudinal outcome highly relies heavily on the differences in socio-clinical background, our findings will help clinicians provide better medical and social care management for PWE when they face with the

Table 5
Multivariate analysis of factors associated with seizure amelioration.

	OR	95%CI	*p* Value
MRI, structural abnormality	2.57	1.05–6.30	**0.039**
Two-generation household	3.70	1.53–8.96	**0.004**

We performed multivariate analyses using the following factors: seizure frequency, EEG abnormalities in spike or focal slow, MRI abnormality, and two-generation household. We did not adopt the number of AEDs because it likely had a correlation with high seizure frequency.

next dynamic social change.

4.1. Exacerbation risks and amelioration chances

The spread of COVID-19 infections has had a major impact on epilepsy care and the circumstances of PWE [11], i.e., there were 1) some barriers for PWE in visiting a hospital or receiving appropriate medical care, 2) reductions in supplies of AEDs, or 3) postponing or canceling neurophysiological examinations [19–21]. Thus, it is not surprising that complex environmental changes due to the pandemic can alter the seizure outcome of PWE. The incidence of seizure exacerbation following the pandemic observed here was similar to that of a recent report that investigated a large number of PWE [22]. We observed that the exacerbation group was significantly associated with PNES, psychological comorbidities, high seizure frequency at baseline, and high stress levels, also consistent with recent studies [11,23–25]. Additionally, exacerbation was highly associated with the "no housemate" living situation, which is associated with a risk of health inequalities and social deprivation during the pandemic [13].

Of note, our results also confirmed that seizure amelioration was experienced by 15.2% of enrolled PWE during the COVID-19 pandemic. The incidence was similar between PWE with exacerbation and improvement among our population. Amelioration tended to be associated with factors related to the phenotype of medically refractory focal epilepsy (high seizure frequency at baseline, a greater number of AEDs used. Additionally, the living situation of a "two-generation household" was strongly associated with amelioration. These findings collectively suggest that seizure exacerbation likely emerged for PWE with a high risk of psychological distress; in contrast, PWE who do not have such risk factors could achieve seizure amelioration, even during the ongoing COVID-19 pandemic. Interestingly, even patients with drug-resistant epilepsy may experience a reduction in seizure frequency without medication change. Our results also suggest that the likelihood of such amelioration may be promising if patients have solid, familial support. It appears that the COVID-19 pandemic has shed light on the stark difference that social support systems can make on outcome for PWE.

4.2. Seizure worsening in view of the longitudinal data

A follow-up investigation has recently been reported only for patients with COVID-19 infection presenting with seizures during the acute phase [26]. Conversely, the present study is the first to report the longitudinal seizure outcome in terms of worsening or amelioration related to the COVID-19 pandemic in PWE who were not infected with COVID-19. The present study evaluated data of only PWE whose seizure frequency during the pre-pandemic period remained stable relative to that during a 6-month period before the pre-pandemic period (reference period). Thus, the present longitudinal data on seizure frequency was reasonable to understand the impact of COVID-19 on seizures. Most seizure exacerbations following the pandemic were transient in the present study. This finding may contradict the evidence that PWE are sensitive to a dramatic social change due to the pandemic [9]. However, even if PWE had a psychological risk, we considered that they could have gradually adapted to ongoing social change and the new normal lifestyle [27]. Such habituation might be key for PWE during the long-

term chronological change in the pandemic. In general, if PWE's condition worsens during the turbulent, acute pandemic phase, it is vital to rapidly provide social support, robust education for epilepsy self-management, and promote multiple techniques, such as telemedicine [28]. This rapid response is ideal because seizure exacerbation can affect PWE's quality of life [23]. Further, our results are also informative for treating PWE moving forward, assuming that the increased seizure frequency will return to the baseline level. Our findings also highlight the substantial importance of strengthening social welfare support for PWE that was likely absent among PWE who experienced deterioration at baseline.

4.3. Underlying factors of seizure amelioration

Although it is not common in clinical practice that seizure frequency decreases without medication changes, our study demonstrated that 14.3% of PWE reported seizure amelioration after the COVID-19 pandemic began. Furthermore, seizure amelioration was substantially sustainable, even 1 year after the pandemic began. Adjunction of psychosocial functioning to conventional medication is an essential treatment strategy for epilepsy [29]. Thus, as observed for PWE with seizure exacerbation, it is conceivable that PWE with seizure amelioration also experienced the opportunity to adapt to the social change. Alternatively, a new normal lifestyle might be neutral for a particular PWE. They may appreciate online communication more than face-to-face communication, as multiple PWE reported in the present study, and people's behavioral change following the gradual reduction in the repeated state of emergency in Japan [30]. Such chronological habituation along with a substantial seizure reduction could be highlighted only from the present long-term observation, rather than previous studies that investigated only the acute phase of the pandemic [3,31]. One of the factors most strongly associated with amelioration was the "two-generation household" living situation in the present study. Thus, extensive familial, social support is crucial during the ongoing pandemic. This speculation was supported by our findings that the exacerbation and amelioration groups had essentially opposite backgrounds in their living situations ("no housemate" vs. "two-generation household"). Therefore, an excellent sustainable seizure outcome may be feasible when there is conformity with the ongoing lifestyle, in addition to substantial social support.

4.4. Limitations

Some limitations to the current study warrant notation. First, the present study lacked a control group. Thus, it was difficult to establish the causality between the pandemic and seizure frequency change. However, as PWE could not be randomized during the pandemic, we used the control data (reference data), i.e., seizure frequency data between 2018 and 2019 when the pandemic had not yet started were used as control data. Second, the number of COVID-19 infected people was relatively small in Japan compared to other countries that experienced the greatest impact due to the pandemic; however, the probability of seizure exacerbation was almost similar to that in these countries [3,4]. Differences in the state of emergency declaration and vaccination strategy also should be noted when generalizing our results to different regions [32]. Third, although we investigated several social factors such as living situation, work change, occupation, and income change, other potentially influential variables, such as travel patterns, physical activity levels, and use of social network services, were not incorporated. In this regard, we have not investigated clinical epilepsy practice changes during the pandemic or the use of telemedicine, which has become widely used since 2020 [33,34]. Lastly, although we did not use data for seizure frequency reduction following medication change, we could not remove the indirect or remote medication effects. Additionally, with regard to seizure count, the self-reporting design might be a limitation [35].

5. Conclusion

Our longitudinal observation revealed that some PWE experienced worsening seizures after the onset of the COVID-19 pandemic, while others achieved seizure relief. The majority of those with worsening returned to baseline conditions within a year. Conversely, those who experienced amelioration were able to maintain favorable outcomes. The between-group differences included not only differences in the presence of psychological risks, but also extensive social support at baseline. Our results may inspire future interventions that should be tailored to the patient's background, while also considering the long-term outlook when facing changes in social conditions.

Statement of ethics

This study was approved by the Ethics Committee of the Hiroshima University Hospital (No. E-2285 and E-2441).

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

Supplemental data

None.

Author contributions

- Shuichiro Neshige; design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
- Shiro Aoki; interpreted the data; revised the manuscript for intellectual content
- Yoshiko Takebayashi; analyzed and interpreted the data
- Takeo Shishido; conceptualized study; interpreted the data
- Yu Yamazaki; conceptualized study; interpreted the data
- Koji Iida; conceptualized study; interpreted the data
- Hirofumi Maruyama; revised the manuscript for intellectual content

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