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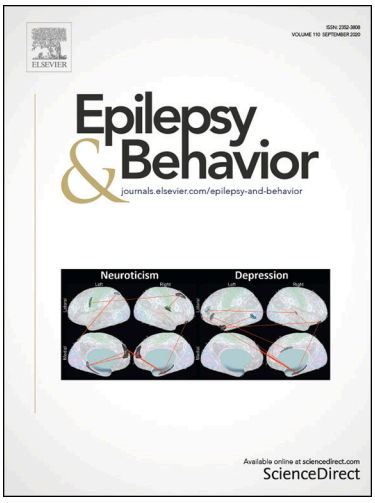

COVID-19 vaccination hesitancy and safety among adult people with epilepsy in eastern China

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COVID-19 vaccination hesitancy and safety among adult people with epilepsy in eastern China

Running Head: The hesitancy and safety of COVID-19 vaccine

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COVID-19 vaccination hesitancy and safety among adult people with epilepsy in eastern China

Abstract

Objective: This study assesses the hesitancy and safety of vaccination administration for novel 2019 Coronavirus Disease (COVID-19) among adult people with epilepsy (PWE).

Methods: We recruited adult PWE who visited the outpatient epilepsy clinic from Aug 2021 to Feb 2022. We administered a structured questionnaire and a face-to-face interview regarding demographic factors, epilepsy characteristics, and relevant vaccine issues to all patients. Factors related to receiving a vaccine and epilepsy-related events after vaccination were then analyzed.

Results: A total of 501 PWE were surveyed; 288 were unvaccinated and 213 were vaccinated. Patients without jobs (OR: 0.59; 95% CI: 0.37-0.95, $p = 0.03$) were less likely to receive the vaccine compared to students or those with jobs. Other factors associated with vaccination were a higher number of anti-seizure medications (OR: 0.72; 95% CI: 0.55-0.95, $p = 0.02$) and a lower pre-vaccine seizure frequency (OR: 2.21; 95% CI: 1.06-4.59, $p = 0.03$). Of the 213 vaccinated patients, 10 (4.70%) reported at least one local and/or systemic side effect. Most patients (92.50%) did not report worse seizures within one month of vaccination. Poor ASM adherence (OR: 15.06; 95% CI: 1.75-129.87, $p = 0.01$) and fatigue/stimulant drinks such as caffeine (OR: 50.59; 95% CI: 7.57-337.94, $p < 0.01$) were significantly associated with seizure worsening within one month of receiving the COVID-19 vaccination.

Conclusion: Almost two-fifths of patients with adult PWE have received a COVID-19 vaccine. Attention should be paid to educating epilepsy patients without jobs on the significance and safety of the vaccine. There was a low risk of seizure worsening in the short term after vaccination in PWE.

Keywords: COVID-19 vaccine; adult; people with epilepsy; seizure worsening

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Introduction

Coronavirus disease 2019 (COVID-19) led to a worldwide pandemic in December 2019 and has since tremendously impacted public health, especially for people with epilepsy (PWE)[1, 2]. It is well established that PWE have a higher cumulative COVID-19 incidence rate and a higher risk of mortality compared to the general population[2]. A mass immunization program is considered the best method of slowing the pandemic, and the COVID-19 vaccine is safe for the vast majority of people[3-6], though there are some post-vaccination cases of demyelinating diseases, cerebral venous sinus thrombosis, and seizures among healthy people without epilepsy[7-9]. While there are a limited number of PWE in studies with COVID-19 vaccines [4, 5, 10-12] and a lack of emphasis on seizure worsening, the International League Against Epilepsy (ILAE) still recommended that PWE should get vaccinated. However, many PWE have been hesitant to get vaccinated[3, 10-15].

To better outline this issue, this study aims to evaluate the safety of the vaccine and the causes of vaccination hesitancy among PWE.

Materials and methods

Study Design and participants

This is a cross-sectional observational study assessing COVID-19 vaccination in adult patients diagnosed with chronic epilepsy based on the ILAE classification[16, 17]. Included in the study are all individuals with epilepsy aged 18 years or older who visited our outpatient clinic between 27th Aug 2021 and 22nd Feb 2022. Questionnaires were administered through face-to-face interviews by trained investigators. All participants were asked to voluntarily complete the questionnaire by themselves or with the help of the interviewers if they had difficulty reading or writing. This study was approved by the institutional review board ethical guidelines of the Second Affiliated Hospital of Zhejiang University (SAHZU).

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The questionnaire can be summarized in three parts: (1) COVID-19 vaccination status and, if vaccinated, information on the vaccine type, date of vaccination, general adverse effects (injection site pain, fever, fatigue, headache, diarrhea, etc.), and adverse effects (change in seizure frequency, new seizure types, and status epilepticus); (2) for unvaccinated patients, reasons for not being vaccinated including sociodemographic and epilepsy-specific factors; and (3) for unvaccinated patients, attitudes about future vaccination (willingness to be vaccinated, hesitation to be vaccinated, and refusal to be vaccinated).

The following sociodemographic data were obtained: age, gender, level of education, children, occupation, and marital status. Possible occupations were as follows: employed, student, and unemployed (including stay-at-home parents, retirees, or other). Epilepsy characteristics were also collected, including seizure onset, epilepsy duration, seizure type, drug-resistant epilepsy, seizure frequency, history of bilateral tonic-clonic seizures (BTCS), anti-seizure medications (ASMs), and magnetic resonance imaging (MRI) and scalp electroencephalography (EEG) findings. Epilepsy was diagnosed according to the ILAE 2017 definition[16, 17], which was classified as focal, generalized, or unknown. Drug-resistant epilepsy was defined as patients who were not seizure-free in the previous 12 months despite having received adequate-dose treatments of two or more ASMs[18]. Seizure frequency before vaccination was categorized as a grading variable, with options of at least 1 year seizure-free, at least once per year, once every month, and once every week[3]. Seizure changes were recorded from the first day to one month of vaccination. Postvaccine fever was defined as a temperature > 37.3°C within 7 days after vaccination.

Statistical Analysis

The acquired data were presented as the median (interquartile range) using SPSS statistical analysis software (version 23). A nonparametric Mann-

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Whitney U test was used to compare group differences on continuous variables. Categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test. Univariate analysis results were entered into a multivariable binary logistic regression model with a statistical significance of $p \leq 0.05$. A stepwise logistic regression analysis was applied to determine unique related factors between several variables related to worsening seizures after vaccination, with a statistical significance of $p < 0.05$. The odds ratio (OR) and 95% confidence interval (CI) were also calculated for each parameter.

Results

Cohort Characteristics

A total of 501 patients were enrolled in this study (213 vaccinated and 288 non-vaccinated). Fig. 1 shows the detailed age distribution in the study. Over half of those who participated in this study were aged 30 years or younger both in the enrolled cohort and the vaccinated subgroup. There was no significant difference in age distribution between the whole group and the vaccinated subgroup. None previously. Fatigue and pain at the injection site were the most common side effects, followed by diarrhea, headache, and chest tightness. Fever was only reported by one person on the day after the first injection.

The clinical features of vaccinated and unvaccinated patients are shown in Table 1. Level of education (≧ high school), job status, pharmacoresistant epilepsy, seizure frequency, history of BTCS within one year, number of seizure types, number of ASMs, and MRI findings were set as independent variables in the logistic regression. The results found that the median number of ASMs (OR 0.72, 95% CI 0.55-0.95, $p = 0.02$) and unemployed patients (OR 0.59, 95% CI 0.37-0.95, $p = 0.03$) were negatively associated with being vaccinated while a seizure frequency of less than once a year (OR 2.21, 95% CI 1.06-4.59, $p = 0.03$) was significantly associated with being vaccinated (Table 2). 56.30% of the vaccinated patients experienced at least six seizure-free months after ASM

therapy, which was higher than (29.50%) in the unvaccinated group ($p < 0.01$, Figure 2) and similar to the results after 12 months (46.90% vs. 23.60%, $p < 0.01$).

Of the 288 unvaccinated patients, 108 (37.50%) were willing to receive the COVID-19 vaccine within the following six months. The main reasons for refusing or hesitance about the COVID-19 vaccine were fear of vaccine safety and fear of seizure worsening, followed by other co-existing diseases, pregnancy, history of severe allergies, breastfeeding, and planning to become pregnant (Table 3). A significant association was found between unwillingness to receive the COVID-19 vaccine and fear of worsening seizures ($p = 0.01$).

In the vaccinated group, 16 patients (7.50%) experienced typical seizure worsening within 1-month post-vaccination, including 8 patients after receiving the first dose, 7 after the second dose, and 1 after the third dose. No episode of status epilepticus was reported. Among them, we found that there were 11 patients whose therapy changed after vaccination (7 with starting ASM therapy; 3 with increased their ASMs dose; 1 with the addition of a new ASM). Univariate analysis found late seizure onset ($p = 0.05$), few ASMs ($p = 0.05$), poor ASM adherence ($p = 0.03$), and fatigue or stimulant drinks such as coffee ($p < 0.001$) were common in patients suffering from seizure worsening after vaccination (Table 4). Logistic regression analysis found that poor ASM adherence (OR 15.06, 95% CI 1.75-129.87, $p = 0.01$) and fatigue/stimulant drinks such as coffee (OR 50.59, 95% CI 7.57-337.94, $p < 0.01$) were significantly associated seizure worsening in PWE after vaccination (Table 5).

Discussion

Our study reported on vaccination coverage, vaccination willingness, variables associated with being vaccinated, and seizure aggravation after vaccination during a short-term follow-up among adult people with epilepsy in eastern China.

We found that 42.51% of patients had been vaccinated against COVID-19, which was slightly higher than previous studies assessing adult PWE in China

in recent months[3, 11, 19], and dramatically lower than the general population[3]. Increased awareness about the importance and safety of the vaccine in China is responsible for increases in the vaccination rate. The herd immunity threshold to extinguish SARA-CoV-2 is estimated to be between 55% and 82%[20], and the vaccination rate among PWE is still far below this threshold. PWE are more hesitant than others to accept the COVID-19 vaccine mainly due to a fear of worsening seizures[13]. The occurrence of adverse events in the present study was lower than in some previous studies[5, 6, 12, 21]. First, different vaccine types could help explain this phenomenon. It has been reported that having a local adverse event after vaccination is significantly more frequent with mRNA vaccines than with inactivated vaccines[6]. In this study, all people received inactivated vaccines, except for one person who received recombinant novel Coronavirus vaccines. The majority of people in reported studies with PWE received mRNA vaccines[5, 6, 12, 21]. Clinical trials of vaccines have demonstrated that local adverse events occurred more frequently in patients with mRNA vaccines (83% after the first dose; 78% after the second dose) than in those with inactivated vaccines (overall 2.7%)[22, 23], and the rate was even lower than that of this study. Moreover, advances in vaccine technology are important for the low rate of adverse events while vaccinating a large number of people during the pandemic. Another reason could be racial differences between study populations.

We analyzed potential factors associated with receiving the vaccine and found that patients without jobs, patients with many ASMs, and patients with a high seizure frequency were less likely to receive the COVID-19 vaccination. It is unsurprising that unemployed patients were less likely to be vaccinated. First, there is speculation that jobless patients are less socially connected and have less access to information about current affairs than others. Therefore, they could have insufficient awareness about vaccine importance and safety. One study suggested that COVID-19 risk perception was found to be significantly associated with vaccine acceptance[24]. Second, people without jobs might

have more frequent seizures and a huge social stigma or concerns about occupational safety. This scenario could further result in increased unemployment and people without jobs also have great concerns regarding the safety of the vaccine. Third, if the classmates or colleagues of PWE are vaccinated, it could affect their willingness to obtain a vaccination. This emphasizes the importance of spreading vaccine awareness, particularly for those not associated with a school or place of work. The scientific community should also continue to stress the safety and efficacy of the COVID-19 vaccine. Vaccine hesitancy is a global issue, especially for PWE. Consistent with previous studies[10, 11], patients affected by poor-controlled epilepsy were unwilling to get vaccinated primarily because they were concerned about their epilepsy worsening, which is the key epilepsy-related factor in delayed vaccination. Another factor for vaccine hesitancy was concerns regarding non-epileptic adverse effects [3, 5]. False beliefs about infections stemming from a vaccine were also associated with vaccine hesitancy[13], which would gradually decrease due to public education campaigns.

The most common adverse reaction or concerns about the inactivated vaccine were febrile reactions and autoimmune disorders[25]. Only one person reported having a fever within a week after receiving the second dose and did not experience a seizure. Some studies have reported on the attitudes, coverage, and general side effects of COVID-19 vaccines in people with epilepsy[3, 10, 11, 13, 14], but few have focused on epilepsy-related adverse effects[4, 12, 15]. In some cases, obtaining a vaccinated cohort was difficult[4, 12], making the conclusions less robust. In the vaccinated group, 16 patients (7.50%) experienced seizure worsening, and all seizures in this study were habitual. No patients experienced status epilepticus. One multicenter study from Italy suggested that 7.65% (25/327) of people with epilepsy suffered from worsening seizures after vaccination, which was based on the mean monthly change in seizures[15]. A multicenter report out of China demonstrated that 9.31% (19/204) of patients experienced seizure worsening, with the seizure

frequency change assessed from the first injection until 1 week later[3]. One study of 82 vaccinated patients from Kuwait found that most patients (93.90%) did not report seizures worsening at least one week after vaccination[5]. Another study of 54 people with epilepsy from Germany reported that one person experienced increased seizure frequency one day after receiving the first COVID-19 vaccine and another one with the occurrence of a new seizure type[12]. In general, the COVID-19 vaccine has a low risk of epilepsy worsening and is well-tolerated among PWE in the short term. However, future investigations into long-term vaccine effects in a large cohort are still needed.

Our multivariate analysis demonstrated that patients with poor ASM adherence or fatigue/stimulant drinks were more likely to suffer from seizure exacerbation within one month of being vaccinated. In the current study, patients felt fatigued mainly due to high-intensity work and insomnia after vaccination, and “stimulant drinks” were considered drinks such as common coffee. Epilepsy worsening might not be a direct effect of the vaccine, even if the seizure frequency was more severe than before. As previous studies suggested, ASM adherence[26] and caffeine intake[27] are associated with seizure control in PWE. Vaccines could affect patients whose condition worsened due to unstable cortical excitability because of poor ASM adherence or fatigue/stimulant drinks. However, it remains unclear whether vaccines play a role in seizure worsening. Additionally, there was no control group of unvaccinated patients that was observed around the same time. It is unclear whether normal variability in seizure control can explain these results. Therefore, our findings must be confirmed in a case-control prospective study. One recent study reported that only pre-vaccine seizure frequency was associated with seizure worsening in vaccinated patients, which suggests that uncontrolled epilepsy could affect post-vaccine seizure frequency rather than be a direct effect of the vaccine[15]. Other studies failed to identify the potential risks of seizure worsening after vaccination due to small sample sizes[4, 5, 12].

This was a short-term study that estimated the safety and efficacy of the

COVID-19 vaccines; however, more extensive, and long-term studies are required in the future. Importantly, no control group was included, making it unclear how much normal variability in seizure control accounts for the seizure worsening. Future research with additional subgroups such as persons with mental comorbidities or children is needed to fully demonstrate vaccine safety in PWE.

Conclusion

This study demonstrates that almost two-fifths of people with epilepsy have received the COVID-19 vaccine. Education focusing on increasing the vaccination rate in PWE is needed, especially for individuals who do not work. The risk of seizure worsening after vaccination was minimal in the short term. Poor ASM adherence or fatigue due to insufficient rest periods or regularly taking stimulant drinks could be associated with seizure worsening after vaccination; however, these findings must be confirmed in a case-control prospective study.

Conflict of interest statement

The authors declare no conflicts of interest.

Acknowledgments

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Figure legends

Fig. 1 Age distribution in the entire cohort and vaccinated group.

Abbreviation: Y = Year

Fig. 2 Proportion of seizure-free rate among four groups. The asterisk represents the difference between the seizure-free rate between unvaccinated and vaccinated groups within 6 ($p < 0.001$) and 12 ($p < 0.001$) months.

Abbreviation: ASMs = anti-seizure medications; SF = seizure-free; n-SF = non-seizure-free; m = months

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Table 1. Comparison of clinical characteristics between patients with and without COVID-19 vaccines.

Demographic variables	Whole (N=501)	Vaccinated (N=213)	Not vaccinated (N=288)	P-value
Age, Y (IQR)	29.00 (23.00-39.50)	28.00 (23.00-38.00)	29.50 (24.00-41.00)	0.37[c]
Gender, male	251 (50.10%)	107 (50.23%)	144 (50.00%)	0.96[a]
Level of education, ≧ high school	340 (67.86%)	157 (73.71%)	183 (63.5%)	0.02[a]
Marital status				0.27[b]
Unmarried	257 (51.30%)	114 (53.52%)	143 (49.65%)	
Married	237 (47.31%)	98 (46.01%)	139 (48.26%)	
Divorced/widow	7 (1.40%)	1 (0.47%)	6 (2.08%)	
Procreated	217 (43.31%)	88 (41.31%)	129 (44.79%)	0.44[a]
Occupation				
Unemployed	127 (25.35%)	39 (18.31%)	88 (30.56%)	<0.01[a]
Employed	292 (58.3%)	133 (62.44%)	159 (55.21%)	0.11[a]
Student	82 (16.37%)	41 (19.25%)	41 (14.24%)	0.13[a]
Seizure onset, Y, median (IQR)	18.00 (14.00-27.00)	18.00 (13.00-27.00)	19.00 (14.00-28.00)	0.53[c]
Epilepsy duration, M, median (IQR)	96.00 (48.00-180.00)	96.00 (48.00-168.00)	96.00 (48.00-204.00)	0.30[c]
Seizure type				0.10[a]
Focal onset	453 (90.42%)	186 (87.32%)	267 (92.71%)	
Generalized onset	39 (7.78%)	23 (10.80%)	16 (5.56%)	
Unknown onset	9 (1.80%)	4 (1.88%)	5 (1.74%)	
Pharmacoresistant epilepsy	167 (33.33%)	35 (16.43%)	132 (45.83%)	<0.01[a]
Seizure frequency				<0.01[a]
At least once per week	75 (14.97%)	20 (9.39%)	55 (19.10%)	
At least one per month	120 (23.95%)	35 (16.43%)	85 (29.51%)	
At least one per year	140 (27.94%)	57 (26.76%)	83 (28.82%)	
Less than once every year	166 (33.13%)	101 (47.42%)	65 (22.57%)	
History of BTCS	327 (65.27%)	137 (64.32%)	190 (65.97%)	0.70[a]
History of BTCS within one year	161 (32.14%)	50 (23.47%)	111 (38.54%)	<0.01[a]
Number of seizure type, median (IQR)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	<0.01[c]
Number of ASMs, median (IQR)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	2.00 (1.00-2.00)	<0.01[c]
MRI finding				0.04[a]
Normal	233 (50.1%)	109 (51.17%)	124 (43.06%)	
Abnormal	232 (49.9%)	87 (40.85%)	145 (50.35%)	
EEG finding, presence of IEDs	225 (49.8%)	90 (42.25%)	135 (46.88%)	0.25[a]

a Pearson's chi-square test

b Fisher's exact test

c Nonparametric Mann-Whitney U test

Abbreviation: COVID = Coronavirus disease; IQR = interquartile range; M = month; BTCS = bilateral tonic-clonic seizure; ASMs = anti-seizure medications; MRI = Magnetic Resonance Imaging; EEG = Electroencephalography; IEDs = interictal epileptiform discharges.

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Table 2. Logistic analysis of predictors for taking the COVID-19 vaccine among adult people with epilepsy

Variables	95% CI	OR	P value
Level of education, ≧high school	0.83-2.03	1.30	0.25
Occupation			
Unemployed	0.37-0.95	0.59	0.03
Pharmacoresistant epilepsy	0.30-1.03	0.55	0.06
Seizure frequency			
Several times per week		1	
Several times per month	0.64-2.62	1.30	0.47
Several times per year	0.55-2.26	1.11	0.77
Less than once every year	1.06-4.59	2.21	0.03
History of BTCS within one year	0.44-1.21	0.73	0.22
Number of seizure types	0.50-1.04	0.72	0.08
Number of ASMs	0.55-0.95	0.72	0.02
MRI finding, abnormal	0.62-1.42	0.94	0.77

Abbreviations: COVID = Coronavirus disease; CI = confidence interval; OR = odds ratio; BTCS = bilateral tonic clonic seizure; ASMs = anti-seizure medications; MRI = Magnetic Resonance Imaging.

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Table 3. Factors associated with COVID-19 vaccine hesitancy or refusal in the future six months.

Variables	Hesitated or unwilling to receive vaccines (N=180)	Willing to receive vaccines (N=108)	P value
Co-exist other diseases	13 (7.22%)	8 (7.41%)	0.95[a]
Breast-feeding	0	1 (0.93%)	0.38[b]
Pregnancy	2 (1.11%)	2 (1.85%)	0.63[b]
Ready to be pregnant	1 (0.56%)	0	1.00[b]
Fear of vaccine safety	105 (58.33%)	73 (67.59%)	0.10[a]
Fear of seizure worsening	160 (88.89%)	84 (77.78%)	0.01[a]
History of severe allergies	3 (1.67%)	1 (0.93%)	1.00[b]

a Pearson's chi-square test

b Fisher's exact test

Abbreviation: COVID = Coronavirus disease.

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Table 4. Clinical characteristics and seizure worsening within one month after vaccination in people with epilepsy.

Variables	Whole cohort (N=213)	Non-seizure aggravation (N=197)	Seizure aggravation (N=16)	P-value
Age (IQR)	28.00 (23.00-38.00)	27.00 (23.00-38.00)	32.00 (25.00-40.00)	0.27[c]
Gender, male	107 (50.23%)	100 (50.76%)	7 (43.75%)	0.59[a]
Seizure onset, Y, median (IQR)	18.00 (13.00-27.00)	18.00 (13.00-26.50)	24.50 (15.75-37.75)	0.05[c]
Epilepsy duration, M, median (IQR)	96.00 (48.00-168.00)	96.00 (48.00-168.00)	69.00 (15.00-126.00)	0.08[c]
Pharmacoresistant epilepsy	35 (16.43%)	33 (16.75%)	2 (12.50%)	1.00[b]
Seizure type				0.77[b]
Focal onset	186 (87.32%)	172 (87.31%)	14 (87.50%)	
Generalized onset	23 (10.80%)	21 (10.66%)	2 (12.50%)	
Unknown onset	4 (1.88%)	4 (2.03%)	0	
Number of seizure type, median (IQR)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.0 (1.00-2.00)	0.41[c]
Seizure frequency				0.85[b]
Several times per week	20 (9.39%)	19 (9.64%)	1 (6.25%)	
Several times per month	35 (16.43%)	33 (16.75%)	2 (12.50%)	
Several times per year	57 (26.76%)	51 (25.89%)	6 (37.50%)	
Less than once every year	101 (47.42%)	94 (47.72%)	7 (43.75%)	
History of BTCS	137 (64.32%)	127 (64.47%)	10 (62.50%)	0.87[a]
History of BTCS within one year	50 (23.47%)	48 (24.37%)	2 (12.50%)	0.44[a]
Number of ASMs, median (IQR)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.00 (0-1.75)	0.05[c]
MRI finding, abnormal	87 (40.85%)	81 (41.12%)	6 (37.50%)	0.72[a]
EEG finding, presence of IEDs	90 (42.25%)	83 (42.13%)	7 (43.75%)	1.00[a]
Poor ASM adherence	4 (1.88%)	2 (1.02%)	2 (12.50%)	0.03[b]
Fatigue or stimulant drinks	6 (2.82%)	2 (1.02%)	4 (25.00%)	<0.01[b]
Seizure free within six months	121 (56.81%)	113 (57.36%)	8 (50.00%)	0.57[a]

a Pearson's chi-square test

b Fisher's exact test

c Nonparametric Mann-Whitney U test

Abbreviation: IQR = interquartile range; BTCS = bilateral tonic-clonic seizure; ASMs = anti-seizure medications.; MRI = Magnetic Resonance Imaging; EEG = Electroencephalography.

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Table 5 Logistic regression analysis of variables associated with seizure aggravation after vaccination.

Variables	95% CI	OR	P-value
Age onset	1.00-1.07	1.03	0.05
Number of ASMs, median (IQR)	0.31-1.27	0.62	0.20
Poor ASM adherence	1.75-129.87	15.06	0.01
Fatigue or stimulant drinks	7.57-337.94	50.59	<0.01

Abbreviations: CI = confidence interval; OR = odds ratio; ASMs = anti-seizure medications.

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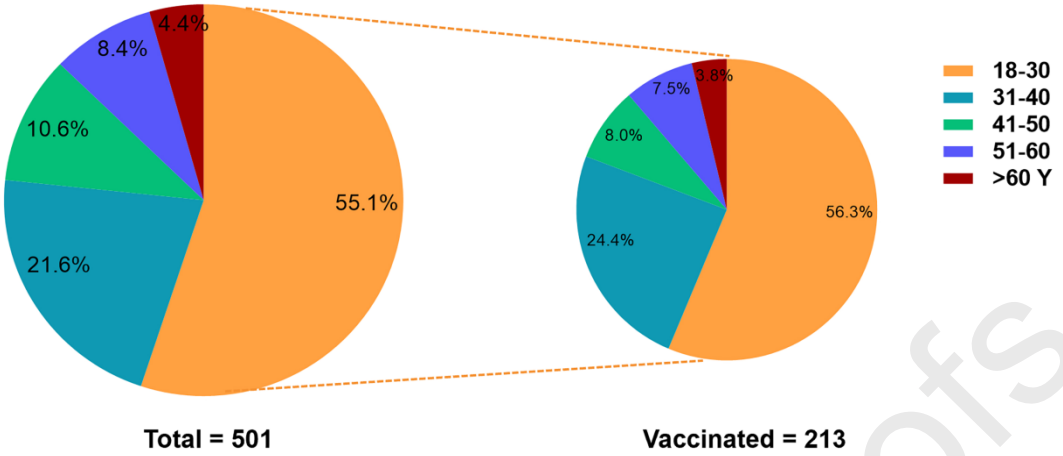

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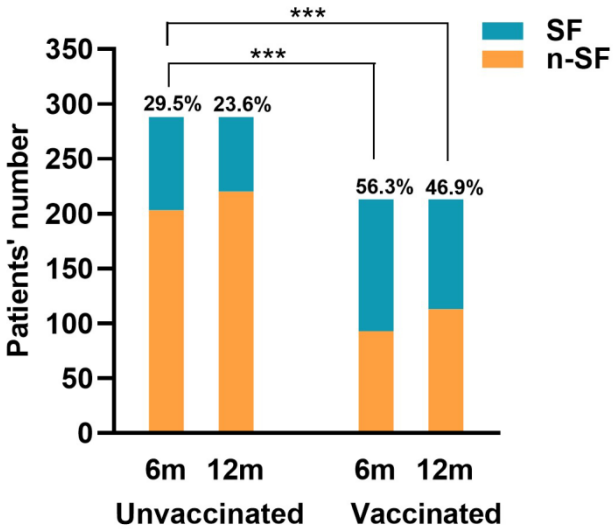

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1.Almost two-fifths of patients with adult PWE have received a COVID-19 vaccine.

2. Attention should be paid to educating epilepsy patients without jobs on the significance and safety of the vaccine.

3. There was a low risk of seizure worsening in the short term after vaccination in PWE.

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The authors declare that they have no competing interests.

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