Effect of COVID-19 Vaccination on Seizures in Patients With Epilepsy: a Multicenter, Retrospective Study

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Abstract

**Background:** Previous study have shown that seizures may occur as a result of vaccination. This study aimed to evaluate the risk and correlative factors of seizures in patients with epilepsy (PWE) after being vaccinated with COVID-19 and to provide reference opinions for PWE to receive COVID-19 vaccine.

**Methods:** We retrospectively enrolled PWE patients who were vaccinated against COVID-19 in the epilepsy centers of nine hospitals in China. The binary logistic regression analysis included variables with a P-value less than 0.1 in the univariate analysis.

**Results:** The study included 290 patients, of which 40 (13.8%) developed seizures within 14 days after vaccination, whereas 250 (86.2%) remained seizure-free. The binary logistic regression analysis revealed statistical significance in seizures within three months before vaccination (P<0.001, OR=10.121, 95% CI: 4.301-23.816) and withdrawal or reduction of anti-seizures medications (ASM) during the peri-vaccination period (P=0.027, OR=4.452, 95% CI: 1.182-16.768). In addition, 32 of 33 patients (97.0%) who were seizure-free within three months before vaccination and had normal EEG results before vaccination did not have any seizures within 14 days following vaccination.

**Conclusions:** SARS-CoV-2 may induce epilepsy through an inflammatory cascade. It is recommended to provide the COVID-19 vaccine to seizure-free patients for at least three months before vaccination, and the vaccination is safer if EEG result is normal. During peri-vaccination period, all PWE should be prohibited from reducing ASM dosage. PWE with well-controlled seizures who have discontinued ASM might consider resuming ASM during the peri-vaccination period if their EEG results are aberrant.

Background

COVID-19 emerged as a zoonotic virus at the end of 2019. Its pathogen is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection can lead to various clinical outcomes, ranging from asymptomatic infection to severe acute respiratory distress and death.\(^1\) According to relevant data, over 200 million patients were diagnosed worldwide as of the end of August 2021. The most effective solution to end this pandemic is by administering safe and effective vaccines. With the release of the viral genome in January 2020,\(^2\) developing various vaccines was started.

Patients with epilepsy (PWE) are a special group of people, and vaccination may have a certain impact on their condition. Existing studies indicated that diphtheria, tetanus, pertussis vaccines (DTP) and measles, mumps, rubella vaccines (MMR), the two long-lived vaccinations could significantly increase the risk of febrile convulsions and seizures.\(^3,4\) In addition, some COVID-19 vaccines currently approved on the market have been associated with many adverse reactions, including severe neurological adverse reactions such as transverse myelitis.\(^5\) This has prompted neurologists and PWE to consider whether PWE should be vaccinated against COVID-19. According to an investigation, most neurologists would recommend injections for PWE only when COVID-19 vaccine was safe and reliable.\(^6\) Another study

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\(^1\)WHO. 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019

\(^2\)WHO. 2020. https://www.who.int/mandela

\(^3\)WHO. 2021. https://www.who.int/health-topics/diseases/epilepsy

\(^4\)WHO. 2021. https://www.who.int/health-topics/vaccination

\(^5\)WHO. 2021. https://www.who.int/health-topics/epilepsy

\(^6\)WHO. 2021. https://www.who.int/health-topics/vaccination
revealed that approximately one-third of PWE were unwilling to receive COVID-19 vaccine for fear of worsening their seizures. On the one hand, neurologists and PWE are concerned that vaccination may increase the risk of seizures. On the other hand, they are concerned that PWE lacks vaccine protection, making them susceptible to SARS-CoV-2 spread. However, since studies have demonstrated that COVID-19 epidemic will worsen the physical and psychological conditions of PWE, ultimately resulting in seizure aggravation, COVID-19 vaccination seems to be imperative for PWE. Therefore, clinical evidence of the risk of seizures in PWE after COVID-19 vaccination is critical in guiding PWE to vaccinate. Therefore, we designed this multicenter, retrospective study to evaluate the impact of COVID-19 vaccination on seizures in PWE, aiming to provide reference opinions for neurologists and PWE.

**Methods**

**Patients and study design**

From May 1st 2021 to August 1st 2021, patients who were vaccinated with COVID-19 vaccine (regardless of the vaccine type) and diagnosed with epilepsy according to the criteria proposed by ILAE in 2017 were collected retrospectively from the epilepsy centers of nine hospitals in China (Qilu Hospital of Shandong University, Provincial Hospital Affiliated to Shandong First Medical University, Affiliated Hospital of Jining Medical College, Affiliated Hospital of Weifang Medical College, Linyi People's Hospital, Dezhou People's Hospital, Affiliated Hospital of Qingdao University, Liaocheng People's Hospital, and Zhucheng People's Hospital). Patients were divided into two groups based on whether they experienced seizures within 14 days of vaccination: patients with seizures were assigned to the SAV group, while the remaining patients were assigned to the SFAV group. The current major vaccines in China included Sinopharm COVID-19 vaccine (inactivated vaccine, two doses) and Sinovac COVID-19 vaccine (inactivated vaccine, two doses). The interval between the two vaccine doses was generally 14-28 days. We did not impose any restrictions on the type of COVID-19 vaccine that patients received.

**Exclusion criteria**

The patients are excluded from the study if the following conditions occur: 1. the patients or their guardians refused to sign the informed consent; 2. patients failed to inject COVID-19 vaccines as required or violated post-vaccination regulations; 3. patients cannot cooperate to complete the questionnaire or follow-up; 4. patients are unable to provide an accurate history of seizures (including before and after vaccination); and 5. patients were lost to follow-up, or withdraw from the study by themselves.

**Collection of patients’ data**

All patients included in the study will fill out a questionnaire. In addition to the basic information and related information about vaccination, the questionnaire also contained the status of epilepsy control before vaccination, the type of seizure, the cause of epilepsy, the anti-seizures medications (ASM) taken and their adverse reactions, the results of the last electroencephalogram (EEG) before vaccination, seizures within 14 days after vaccination, the medication after vaccination, as well as the adverse reactions.
reactions and their severity of vaccination. If the patients were vaccinated for less than 14 days, they would be followed up by telephone to obtain relevant data. Before vaccination, we divided patients into five levels based on their seizure-free duration: I. less than three months, II. three months to six months, III. six months to one year, IV. one year to two years, and V. more than two years. The types of seizures were classified according to ILAE 2017 standard.

**Primary observation indicator**

Seizures that occur within 14 days after vaccination are highly correlated with vaccination.\(^{10-14}\) Therefore, the primary observation indicator was whether patients experienced seizures within 14 days after vaccination (for a multi-dose vaccine, patients are classified into SAV group as long as they experienced seizures within 14 days after any dose). Based on this, we defined the peri-vaccination period as 14 days before and after any dose of vaccination.

**Secondary observation indicator**

The secondary observation indicators included frequency and severity of non-epileptic adverse events following vaccination.

**Statistical Analysis**

The Chi-square test or Fisher’s exact test was used to analyze the difference of categorical variables between two groups, while differences within a group were analyzed using Bonferroni correction. Kolmogorov-Smirnov test was employed to determine whether the continuous variable was conformed to normal distribution. The independent sample t-test was utilized for the continuous variable conforming to normal distribution, and the Mann-Whitney U test was deployed for the continuous variable that did not conform to normal distribution. A binary logistic regression analysis was performed for the factors with P-value less than 0.1 in the univariate analysis. If the P-value was less than 0.05, it was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics 26.

**Results**

**Demographics**

In our study, we collected 323 patients, of which 33 were excluded because due to the following reasons: (1) inability to complete the questionnaire or follow-up, (2) inability to fully answer the questions in the questionnaire, and (3) inability to provide accurate seizure information. As a result, this analysis included data from 290 patients. A total of 40 (13.8%) patients were assigned to the SAV group, while the remaining 250 (86.2%) patients were assigned to the SFAV group.

The age range of 290 patients was 14 to 80 years, including 158 (54.5%) males and 132 (45.5%) females. A total of 84 (29.0%) patients had a clear cause of epilepsy and 47 (16.2%) stopped taking ASM or reduced its dose during peri-vaccination period. There were 40 (13.8%), 44 (15.2%), 37 (12.8%), 57 (19.7%), and 112 (38.6%) patients had seizure-free duration grades of I, II, III, IV and V, respectively. The
most frequent type of seizures (214, 73.8%) was focal seizures (with or without impaired awareness). Frequent ASM included valproate (87, 30%), oxcarbazepine (76, 26.2%), levetiracetam (69, 23.8%), carbamazepine (59, 20.3%), lamotrigine (41, 14.1%), topiramate (15, 5.2%), lacosamide (16, 5.5%), and perampanel (12, 4.1%). There were 36 (12.4%), 150 (51.7%), 81 (27.9%), and 23 (7.9%) patients taking 0, 1, 2, and more than 2 types of ASM, respectively. Table 1 compares epilepsy-related indexes between SAV and SFAV groups.
Table 1
Demographics

| Variables                              | SAV\(n=40\) | SFAV\(n=250\) |
|----------------------------------------|-------------|---------------|
| Age, year \(\leq 18\)                 | 1\(\%\)    | 19\(\%\)     |
|                                        | 12\(\%\)   | 7\(\%\)      |
| > 18 and \(\leq 30\)                 | 18\(\%\)   | 112\(\%\)    |
|                                        | 45\(\%\)   | 44\(\%\)     |
| > 30 and \(\leq 40\)                 | 9\(\%\)    | 63\(\%\)     |
|                                        | 22.5\(\%\) | 25.2\(\%\)   |
| > 40 and \(\leq 50\)                 | 9\(\%\)    | 32\(\%\)     |
|                                        | 22.5\(\%\) | 12.8\(\%\)   |
| > 50 and \(\leq 60\)                 | 2\(\%\)    | 13\(\%\)     |
|                                        | 5\(\%\)    | 5.2\(\%\)    |
| > 60                                   | 1\(\%\)    | 11\(\%\)     |
|                                        | 2.5\(\%\)  | 4.4\(\%\)    |
| Male \(\leq 60\)                      | 24\(\%\)   | 134\(\%\)    |
|                                        | 60\(\%\)   | 53.6\(\%\)   |
| Epileptic etiology \(\leq 60\)        |            |               |
| Unknown                                | 28\(\%\)   | 178\(\%\)    |
|                                        | 70\(\%\)   | 71.2\(\%\)   |
| Trauma                                 | 5\(\%\)    | 32\(\%\)     |
|                                        | 12.5\(\%\)| 12.8\(\%\)  |
| Heredity                               | 3\(\%\)    | 15\(\%\)     |
|                                        | 7.5\(\%\)  | 6.0\(\%\)    |
| Inflammation                           | 1\(\%\)    | 7\(\%\)      |
|                                        | 2.5\(\%\)  | 2.8\(\%\)    |
| Tumor                                  | 1\(\%\)    | 5\(\%\)      |
|                                        | 2.5\(\%\)  | 2.0\(\%\)    |
| Vascular                               | 2\(\%\)    | 10\(\%\)     |
|                                        | 5\(\%\)    | 4.0\(\%\)    |
| Metabolism                             | 0\(\%\)    | 3\(\%\)      |
|                                        | 0\(\%\)    | 1.2\(\%\)    |
| Withdrawl or reduction of ASM \(\leq 60\) | 13\(\%\)  | 32\(\%\)     |
|                                        | 32.5\(\%\)| 13.6\(\%\)  |
| Duration of seizure free \(\leq 60\)  |            |               |
| Grade I                                | 20\(\%\)   | 20\(\%\)     |
|                                        | 50\(\%\)   | 8\(\%\)      |
| Grade II                               | 6\(\%\)    | 38\(\%\)     |
|                                        | 15\(\%\)   | 15.2\(\%\)   |
| Grade III                              | 3\(\%\)    | 34\(\%\)     |
|                                        | 7.5\(\%\)  | 13.6\(\%\)   |
| Grade IV                               | 3\(\%\)    | 54\(\%\)     |
|                                        | 7.5\(\%\)  | 21.6\(\%\)   |
| Grade V                                | 8\(\%\)    | 104\(\%\)    |
|                                        | 20.0\(\%\)| 41.6\(\%\)   |
| Seizure type                           |            |               |
| Focal (with or without impaired awareness) | 31 (77.5%) | 183 (73.2%) |
|------------------------------------------|------------|------------|
| Generalized                              | 4 (10%)    | 30 (12%)   |
| Unknown                                  | 5 (12.5%)  | 37 (14.8%) |

**Use of ASM (%)**

| Valproate                                 | 13% (32.5%) | 74% (29.6%) |
|-------------------------------------------|-------------|-------------|
| Carbamazepine                             | 9% (22.5%)  | 50% (77.5%) |
| Oxcarbazepine                             | 11% (27.5%) | 65% (26.0%) |
| Levetiracetam                             | 5% (12.5%)  | 64% (25.6%) |
| Lamotrigine                               | 1% (2.5%)   | 40% (16.0%) |
| Topiramate                                | 3% (7.5%)   | 12% (4.8%)  |
| Perampanel                                | 4% (10%)    | 8% (3.2%)   |
| Lacosamide                                | 5% (12.5%)  | 11% (4.4%)  |

**Number of ASM (%)**

| None                                      | 10% (25%)   | 26% (10.4%) |
|-------------------------------------------|-------------|-------------|
| 1                                         | 13% (32.5%) | 137% (54.8%)|
| 2                                         | 11% (27.5%) | 70% (28%)   |
| 3 or more than 3                          | 6% (15.0%)  | 17% (6.8%)  |

Abbreviation: ASM, anti-seizures medications.

**Univariate analysis**

Univariate analysis of the above factors revealed that duration of seizure-free (P < 0.001), or taking lacosamide (P=0.025), and number of ASM taken (P=0.007) differed significantly between the two groups (Table 2). In addition, we performed a within-group analysis on seizure-free duration and found that the proportion of patients with seizure-free grades II, III, IV, and V who experienced seizures following vaccination was significantly lower than that of patients with grade I (P < 0.05), but there was no significant difference between grades II, III, IV, and V (P > 0.05).
Table 2
Result of univariate analysis

| Variables                                    | P value |
|----------------------------------------------|---------|
| Age                                          | 0.622   |
| Sex                                          | 0.281   |
| Epileptic etiology                           | 0.981   |
| Withdrawal or reduction of ASM                | 0.005   |
| Duration of seizure free                     | <0.001  |
| Seizure type                                 | 0.886   |
| Use of ASM                                   |         |
| Valproate                                    | 0.713   |
| Carbamazepine                                | 0.677   |
| Oxcarbazepine                                | 0.848   |
| Levetiracetam                                 | 0.075   |
| Lamotrigine                                  | 0.025   |
| Topiramate                                   | 0.444   |
| Perampanel                                   | 0.068   |
| Lacosamide                                   | 0.053   |
| Number of ASM                                | 0.007   |

Abbreviation: ASM, anti-seizures medications.

**Binary logistic regression analysis**

In the univariate analysis, we performed a binary logistic regression analysis on the factors with P-value less than 0.1. For seizure-free duration, based on univariate analysis results (no significant difference existed between seizure-free grades II, III, IV, and V), we incorporated it as a binary variable with a three-month limit. The results revealed that seizures within three months before vaccination (P<0.001, OR=10.121, 95% CI: 4.301-23.816) and withdrawal or reduction of ASM during the peri-vaccination period (P=0.027, OR=4.452, 95% CI: 1.182-16.768) were found to be statistically significant correlation factors (Table 3). A total of 8% (20/250) patients who were seizure-free within three months before vaccination experienced seizures following vaccination, compared with 50% (20/40) patients with seizures within three months before vaccination (Figure 1). Seizures occurred in 27.7% (13/47) of patients who withdraw or reduced ASM compared with 11.1% (27/243) of those who did not withdraw or reduce ASM.
Table 3
Result of multivariate analysis

| Variables                                    | Odds ratio | 95% CI     | P value |
|----------------------------------------------|------------|------------|---------|
| Seizure within three months before vaccination | 10.121     | 4.301-23.816 | <0.001  |
| Withdrawal or reduce the dosage             | 4.452      | 1.182-16.768 | 0.027   |
| Lamotrigine                                  | 0.118      | 0.013-1.073  | 0.058   |
| Levetiracetam                                 | 0.327      | 0.093-1.147  | 0.081   |
| Number of ASM                                |            |            | 0.095   |
| 0                                            | 1          |            |         |
| 1                                            | 1.086      | 0.245-4.816 |         |
| 2                                            | 1.872      | 0.405-8.646 |         |
| 3 or more                                    | 8.221      | 1.051-64.285 |        |

Abbreviation: ASM, anti-seizures medications.

Results of the last EEG before vaccination of some patients

We obtained the results of the last EEG performed by 69 patients before vaccination (Figure 2). Among these 69 patients, 36 had normal EEG results, of which 3 were in the SAV group; 33 patients had abnormal EEG results, of which 6 were in the SAV group. The proportion of patients with normal EEG results having seizures after vaccination was lower than those with abnormal EEG results (8.3% vs. 18.2%), but the difference was not statistically significant (P=0.294). Notably, 32 of 33 patients (97.0%) who had no seizures within three months before vaccination and whose EEG results were normal before vaccination did not develop any seizure within 14 days after vaccination.

Non-epileptic side reactions

A total of 62 (21.4%) patients experienced non-epileptic side reactions after vaccination. A total of 46 (15.9%) patients experienced pain or itching at the injection site; 7 (2.4%) developed lumps or induration at the injection site; 3 (1.0%) experienced low-grade fever (37.1°C-38°C) after vaccination, although none of these three patients experienced seizures; 20 (7.0%) patients felt tired, 14 (4.8%) experienced dizziness or headache, 13 (4.5%) had muscle soreness, 4 (1.7%) had nausea or vomit, and 1 (0.4%) experienced stomachache or diarrhea. Patients with these adverse reactions can tolerate and did not require medical intervention. Only two patients (0.7%) experienced different serious adverse reactions: syncope and generalized rash (Figure 3). However, these adverse reactions were not significantly different between SAV and SFAV groups (P>0.05).

Discussion
This study provided important data about the impact of COVID-19 vaccine on seizures in PWE. Our results indicated that seizure (within 14 days after vaccination) was a frequent side reaction (13.8%) in PWE after vaccination. The binary logistic regression analysis revealed that seizures within three months before vaccination and withdrawal or reduction of ASM during the peri-vaccination period were correlative factors. In addition, vaccination may be safer for patients with normal EEG results. As far as we know, no studies have been conducted to evaluate the risk of seizures in PWE after COVID-19 vaccination. As the first study to assess the risk of seizures after COVID-19 vaccination, our findings provide critical guidance to PWE regarding vaccination.

This study chose seizures within 14 days after vaccination as the primary observation index rather than seizure frequency. This was because PWE with frequent seizures were not allowed to be vaccinated against COVID-19 in China. Therefore, for PWE with infrequent seizures, no appropriate comparison target for seizure frequency existed. Although taking perampanel or lacosamide was statistically significant in univariate analysis, we excluded them from the binary logistic regression analysis. This was because we believed that demographic characteristics of patients who took these two drugs were significantly different from those taking other ASM. We analyzed the distribution of seizure-free duration grades in patients treated with these two drugs and found statistically significant differences. These two medications were only recently approved in China, and few patients used them for more than two years, let alone seizure-free for more than two years (in fact, none of patients taking perampanel or lacosamide in our study was seizure-free for more than two years).

At present, a large-scale injection of COVID-19 vaccine in China has just started, and many people, including PWE, are skeptical about the vaccine's safety. Our results revealed that the safety of COVID-19 vaccine was worthy of recognition. Among 290 patients, 62 (21.4%) experienced mild non-epileptic side reactions, while only 2 (0.7%) had serious side reactions. However, for the special population of PWE, whether to vaccinate against COVID-19 still needs to be considered. In our study, 13.8% of PWE experienced seizures within 14 days after vaccination, which is much higher than previous studies of other vaccines; by contrast, even in patients with Dravet syndrome, the rate of seizures after MMR vaccination was only 2.3%. Karina et al. found that the risk of seizures following vaccination with various vaccines did not even increase. In our study, the high seizure rate after COVID-19 vaccination may be due to the following reasons: 1. first, most patients in the SAV group have a seizure-free duration of less than three months. For these patients whose epilepsy control status was not ideal, the seizures after vaccination may be derived from the characteristics of epilepsy itself, but not vaccination. 2. Verbeek et al. found that the longer the use of ASM, the higher the risk of post-vaccination seizures in children with epilepsy. In our study, the minimum age of patients was 14, implying that our patients used ASM for a longer time than childhood epilepsy patients; demographic characteristics may lead to such results. 3. Mental disorders can promote the onset of epilepsy. Unlike vaccines such as DTP and MMR, COVID-19 vaccination has not started too long. PWE continues to have concerns about the vaccine's safety and effectiveness, resulting in mental health problems in PWE following vaccination and then increasing seizures.
Unsurprisingly, injecting COVID-19 vaccine can induce seizures. Aladdin et al. once reported a case of refractory status epilepticus after ChAdOx1 nCoV-19 vaccine injection. Although DTP and MMR can promote seizures by inducing additional fever, in our study, the three patients who developed a fever after vaccination did not experience seizures. Therefore, the mechanism by which COVID-19 vaccine promotes seizures may not be correlated with fever induction. Existing studies have proved that coronaviruses, particularly β-coronavirus to which SARS-CoV-2 belongs, were not limited to infecting the respiratory tract but often invaded the central nervous system (CNS). SARS-CoV-2 virus can enter CNS through a variety of ways: spreads through blood and crosses blood-brain barrier (BBB); spreads across synapses; and enters through blood-cerebrospinal fluid or structures around ventricles. After entering CNS, the virus mainly binds to various nerve cells through angiotensin-converting enzyme 2 (ACE2). Coronavirus mainly infected neurons in the brainstem associated with cardiopulmonary control; damage to these areas may aggravate respiratory depression and even lead to respiratory failure, and can also increase the risk of sudden epileptic death. In addition, SARS-CoV-2 infection can induce a systemic inflammatory storm and release many pro-inflammatory factors, resulting in BBB destruction, damage of glia limitans, activation of Toll-like receptors in microglia, and astrocytes, and ultimately promoted neuroinflammation, which may severely disrupt brain homeostasis and cause neuronal death. On the one hand, many studies have revealed that activating Toll-like receptors can cause epilepsy; On the other hand, BBB disruption can cause entry of immune cells and serum proteins from peripheral blood into the brain, promoting the occurrence of epilepsy. Finally, SARS-CoV-2 transcriptome had molecular similarities with the epitopes of human CNS protein, producing various autoantibodies and may eventually trigger autoimmunity to aggravate inflammatory storms. Overall, we imply that SARS-CoV-2 induces epilepsy mainly through an inflammatory cascade. Given the potential epileptogenic capacity of SARS-CoV-2, we do not propose injecting attenuated vaccines in PWE.

In the binary logistic regression analysis, seizures within three months before vaccination were a correlative factor with statistical significance. The results revealed that, in the three months before vaccination, the risk of seizures in patients with seizures was 10.121 times that of those who were seizure-free (P<0.001, 95% CI: 4.301-23.816). Therefore, PWE who are seizure-free for at least three months can be considered for vaccination. In China, "uncontrolled epilepsy" was a contraindication to COVID-19 vaccination, but no accurate definition for "uncontrolled epilepsy" existed. A study defined it as having a seizure within 12 months. However, in univariate analysis, we found that for patients with a seizure-free duration of more than three months, as duration was further extended, the seizure rate after vaccination would not change significantly. Therefore, we considered "uncontrolled epilepsy" as having any seizure within three months. However, it should be noted that 7.8% of patients who were seizure-free for more than three months experienced seizures after vaccination. Another correlative factor with statistical significance was withdrawal of reduction of ASM during peri-vaccination period (P=0.027, OR=4.452, 95% CI: 1.182-16.768). According to this, we suggest that ASM reduction should be forbidden during peri-vaccination period. For patients with well-controlled seizures who have withdrawn, whether
they need to retake ASM should be based on EEG results. Finally, regardless of EEG results, patients who withdraw by themselves must retake ASM.

Our study included a factor that was not statistically significant but worthy of attention. Although EEG results of 69 patients were not significantly different between the two groups, 32 of 33 patients (97.0%) who had no seizures within three months before vaccination and had normal EEG results did not experience any seizure following vaccination. According to a meta-analysis by Lamberink et al., abnormal EEG before drug withdrawal was a risk factor for epilepsy recurrence in PWE after drug withdrawal. This means that compared with PWE who have abnormal EEG, PWE with normal EEG have a better seizure control status and are therefore less likely to develop seizures induced by various factors. Therefore, for PWE who are seizure-free for at least three months and whose EEG results are normal before vaccination, it will be safer to vaccinate against COVID-19.

Additionally, our study had some limitations. First, this was a retrospective study, with small sample size and lack of control. Second, the patients’ seizure information was mainly obtained from patients themselves or their relatives, ignoring seizures in some PWE. Third, we only divided seizure-free duration into five levels, and too large intervals may affect the accuracy of our results. Finally, because patients were received inactivated vaccinations, our conclusions may not be generalizable to other types of vaccines. In the future, prospective randomized controlled studies with a large sample may be required to further evaluate the impact of COVID-19 vaccination on seizures in PWE.

**Conclusions**

In summary, our findings indicate that although seizure is a common adverse event in PWE vaccinated with COVID-19, the benefits of COVID-19 vaccination far outweigh the risks for PWE who are seizure-free for more than three months before vaccination. In addition, vaccination is safer if EEG result is normal. Finally, PWE who withdraw or reduce their ASM during the peri-vaccination period are at higher risk of vaccination, demonstrating that ASM regimen should be appropriately adjusted in this population.

**Abbreviations**

| Abbreviation | Description                      |
|--------------|----------------------------------|
| ASM          | Anti-seizures medications        |
| PWE          | Patients with epilepsy           |
| DTP          | Diphtheria, tetanus, pertussis vaccines |
| MMR          | Measles, mumps, rubella vaccines |
| CNS          | Central nervous system           |
| BBB          | Blood-brain barrier              |
| ACE2         | Angiotensin-converting enzyme 2  |
Declarations

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Author's contributions

XF, SQ and XL designed the study. XF, SQ, RZ, TY, ZW, QK, MS, JG, CF, YC, YL, YS, DZ, LQ, WS, JW and XL provided or collected the data. XF and XL analysed the data. XF and XL wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The experiment was approved by the Medical Ethics Committee of Qilu Hospital of Shandong University (2021035). All patients or their guardians who agreed to participate in this study signed an informed consent form.

Consent for publication

All patients or their guardians agreed to publish their information related to the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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**Figures**
Figure 1

The distribution of different seizure-free grades of patients in the two groups
Figure 2

Result of electroencephalogram
Figure 3

Non-epileptic adverse reactions