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Medium-term changes in patients with epilepsy during the COVID-19 pandemic

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Abstract

Objectives: The novel coronavirus disease (COVID-19) pandemic has led to social distancing measures and impaired medical care of chronic neurological diseases, including epilepsy, which may have adversely affected well-being and quality of life of patients with epilepsy (PWE). The objective of this study is to evaluate the impact of the COVID-19 pandemic in the levels of anxiety, depression, somnolence, and quality of life using validated scales in PWE in real-life clinical practice.

Materials & Methods: Self-administered scales of anxiety disorders (GAD-7), depression (NDDI-E), somnolence (Epworth Sleepiness Scale; ESS), and quality of life (QOLIE-31-P) in PWE treated in a Refractory Epilepsy Unit were longitudinally analyzed. Data were collected before the beginning (December 2019 – March 2020) and during the COVID-19 pandemic (September 2020–January 2021).

Results: 158 patients (85 from the first round and 73 from the second round) 45.0 ± 17.3 years of age, 43.2% women, epilepsy duration 23.0 ± 14.9 years, number of antiepileptic drugs 2.1 ± 1.4, completed the survey. Significant longitudinal reduction of QOLIE-31-P (from 58.9 ± 19.7 to 56.2 ± 16.2, $p = .035$) and GAD-7 scores (from 8.8 ± 6.2 to 8.3 ± 5.9, corrected $p = .024$) was identified. No statistically significant longitudinal changes in the number of seizures (from 0.9 ± 1.9 to 2.5 ± 6.2, $p = .125$) or NDDI-E scores (from 12.3 ± 4.3 to 13.4 ± 4.4, $p = .065$) were found. Significant longitudinal increase of ESS (from 4.9 ± 3.7 to 7.4 ± 4.9, $p = .001$) was found.

Conclusions: During the COVID-19 pandemic, quality of life and anxiety levels were lower in PWE, and sleepiness levels were raised, without seizure change.

KEYWORDS
anxiety, COVID-19, epilepsy, pandemic, quality of life, sleep

1 | INTRODUCTION

The novel coronavirus disease (COVID-19) pandemic has been a worldwide urgent public health threat which has led to strict public health measures in order to control SARS-CoV-2 transmission.[1] Lockdown measures related to COVID-19 include severe economic damage, legal/ethical issues, and psychological effects on the confined population.[2]

Recent studies have shown that the COVID-19 lockdown has caused a psychological impact on the general population in which higher levels of stress, anxiety, and symptoms of post-traumatic stress have been observed.[3,4] Moreover, a temporal increase of anxiety, depression, and stress scores during the COVID-19 lockdown

has been found.[5] It is well known that psychiatric comorbidities, including mood and anxiety, are common in patients with epilepsy (PWE), often occurring at rates twofold to threefold or higher than in the general population without epilepsy.[6]

Besides that, the pandemic and the consequent situation of lockdown have also caused changes in the lifestyle habits[7,8] such as sleep disorders.[9] Important efforts have been made in order to provide adequate care for neurological conditions,[10] such as the rapid development of telemedicine.[11] Nevertheless, support networks have become less accessible[12,13] or have been cancelled,[14] which may have also negatively affected the QoL of PWE, considering the possible effects of social isolation.

Finally, neurological chronic disorders are not associated with a significant risk for COVID-19 infection.[15] However, the COVID-19 viral infection itself can induce a febrile status, which in turn can reduce seizure threshold.[16] To date, a few studies evaluating seizure control during the COVID-19 lockdown have shown that nearly 20% of subjects reported worsened seizure control.[17] However, longitudinal effects on quality of life (QoL), psychiatric comorbidities, sleep and seizure control are still unknown.

Therefore, the purpose of this study was to examine the medium-term effects of the COVID-19 pandemic in the QoL, anxiety, depression, changes in sleep and seizure frequency in PWE using standardized tools.

2 | MATERIALS AND METHODS

2.1 | Participants

The sample was composed of patients with epilepsy recruited from the Refractory Epilepsy Unit from a tertiary hospital in Spain. This institution is a Reference Center for epilepsy surgery. Patients follow an epilepsy diary as part of the standard of care. There were two rounds of recruitment. In the first round, the patients were recruited consecutively before the beginning of the restrictions related to the COVID-19 pandemic in Spain, between December 2019 and March 2020. In the second round, between September 2020 and January 2021, the patients who accepted to participate in the study in the first round and additional patients were invited to take part in the study. All the patients who participated in at least one of the recruitment roads were considered to be included in the study. During the second round of recruitment, in our environment, there was no restrictive lockdown except in some basic small health areas with a high number of COVID-19 diagnosed cases. In this context, lockdown is equivalent to staying home with restricted activities involving public contact. Leisure activities outside home and going to work were allowed in subjects without COVID-19 positive diagnosis or close contact to someone with a positive diagnosis.

It must be clarified that, for the first round of recruitment, the objective of the study was to assess quality of life and symptoms of insomnia, anxiety, and depression in PWE, without consideration of the pandemic.

Inclusion criteria were diagnosis of epilepsy for at least one year with current or past use of antiepileptic drugs (AED). Exclusion criteria were age under 18 and cognitive impairment that avoided to properly understand the questions included in the survey.

In the first recruitment round, the patients were invited to participate in the study during the in-person visit to the Epilepsy Unit. Moreover, a written informed consent was signed by the patients who agreed to answer the survey. In the second round, the patients who did not take part in the first round were invited following the same procedure, while the patients who answered the first survey were invited during the in-person consultation or via phone call. To take part in the second round, the participants gave their verbal consent and accepted to participate in the first question of the survey.

The first survey was conducted during in-person visits and the second survey was conducted online following the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines.[18] The study was approved by the Ethics Committee of the Hospital.

2.2 | Variables of study

In the two rounds of surveys, the main demographic and clinical variables were age, gender, duration of epilepsy (years), seizure frequency in the last month or 30 days, occurrence of nonepileptic paroxysmal events, and number of AED. Furthermore, drug-resistant epilepsy was considered as failures to adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom, following the International League Against Epilepsy guidelines.[19] In the second survey, additional variables associated with the COVID-19 pandemic were collected: change and problems to acquire AED, positive diagnosis of COVID-19 via real-time polymerase chain reaction, and subjective worsening of epilepsy. The subjective worsening of epilepsy refers to the global perception of feeling worse in association with epilepsy during the COVID-19 lockdown.

The symptoms of depression were analyzed with the Spanish version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).[20,21] The NDDI-E includes six self-reported items with a Likert rating scale from 1 to 4 (1="never"; 4="always or often"). This questionnaire refers to the life experiences from the last two weeks. Scores higher than 13 were considered to represent symptoms of major depression.

The Spanish version of the 7-item Generalized Anxiety Disorder (GAD-7) scale was used to assess the levels of anxiety.[22] The seven self-reported items are scored with a Likert rating scale from 0 to 3 (0="not at all"; 3="nearly every day"). This questionnaire refers to the life experiences from the last 15 days. A cut-off value of 10 was used as reference to consider major anxiety disorder.

The levels of somnolence were measured with the Spanish version of the Epworth sleepiness scale (ESS), which is related to the daytime sleepiness.[23] The ESS contains eight self-reported items with a Likert rating scale from 0 to 3 (0="would never doze"; 3="high chance of dozing"). Scores higher than 10 were considered to

represent sleepiness. Furthermore, variables including information about any sleep disturbance, waking up during the night, number of sleeping hours, and problems to fall asleep were used, together with the diagnosis of sleep apnea-hypopnea syndrome (SAHS) were gathered.

The Spanish version of the Patient-Weighted Quality of Life in Epilepsy inventory (QOLIE-31-P) questionnaire was employed to evaluate the QoL.[24] This questionnaire includes 38 self-reported items and eight subscales. The eight subscales assess energy, mood, daily activities, cognition, medication effects, seizure worry, overall QoL, and health state. All the subscales except the health state subscale are used to determine the global score. The first item is scored using a 0–10 scale, and the last item using a 0–100 scale, being 0 the worst situation and 10 or 100 the best situation. For the items 2 to 37, a Likert rating scale from 1 to 3, 4, 5, or 6 is employed, where 1 could be the best or the worst situation depending on the item. The global and subscale scores are computed and rescaled to obtain a score from 0 (worst score) to 100 (best score).

It is worth noting that the NDDI-E and QOLIE-31-P scales were specifically designed for patients with epilepsy, considering that some questions include aspects related to epileptic seizures or AED effects. Therefore, we did not recruit healthy controls because the aforementioned scales are not appropriate to evaluate subjects without epilepsy. Moreover, the objective of our study was to evaluate changes among PWE before and during the COVID-19 pandemic.

2.3 | Statistical analysis

The mean and standard deviation were used to report the continuous data. For the categorical variables, group proportions were employed.

Generalized linear mixed models (GLMM) were used to carry out the longitudinal analysis of the NDDI-E, GAD-7, ESS, and QOLIE-31-P (including its subscales) scores, considering each subject as random factor. The longitudinal variable was the round (categorical variable) when the survey was answered. The first round was used as reference and interactions with the other covariates were introduced to assess their possible time dependence.

Firstly, univariate models were employed to assess whether there were longitudinal changes in the four main scales. The same model was employed to analyze longitudinal changes in the seizure frequency. In a separate analysis with the answers from the second round, generalized linear models (GLM) with a Gaussian distribution were used to study the effect of the four variables particularly related to COVID-19.

The final analysis of the four scales and the QOLIE-31-P subscales was implemented with a backwards strategy to obtain the definite multivariate model, including all the variables and the longitudinal interactions in the first iteration. The objective was building an explanatory model to determine the relationship between the independent variables. The Benjamini-Hochberg false-discovery rate (FDR) method was used to correct the results for multiple comparisons.[25] The regression coefficients were obtained with the 95% confidence interval (CI).

The longitudinal analysis with multiple covariates was performed with the subjects who completed both rounds of surveys. All the subjects from both rounds were assessed in the analysis of the global associations of the symptoms of anxiety, depression, sleepiness, and quality of life with the remaining covariates, adjusting by longitudinal variables when necessary.

p-values below 0.05 were considered statistically significant. The whole analysis was performed with R statistical software, version 3.5.2. For the missing values associated with the QOLIE-31-P scores, the imputation was carried out following the original reference.[24] Complete case analysis was the procedure otherwise.

3 | RESULTS

A total of 158 answers were included, 85 from the first and 73 from the second round. Thirty-seven patients answered both surveys, 48 subjects only the first and 36 subjects only the second survey. Table 1 shows the most important values. Regarding the patients with diagnosed COVID-19, two subjects presented only suspected and were discarded in the assessments related to the COVID-19 diagnosis variable. The sample from both surveys presented similar demographic features. We included 41 (48.2%) and 34 (46.6%) women in the first and second survey, respectively; aged 44.3 ± 17.4 (first survey) and 42.1 ± 15.6 (second survey) years. Some of the most remarkable features of the patients who answered both surveys were focal epilepsy (23/37 = 62.2%), impaired awareness seizures (10/37 = 27.0%), tonic-clonic seizures (9/37 = 24.3%), and temporal lobe epilepsy (5/37 = 13.5%). Other locations or features were marginal. See Table 1 for demographic and clinical details.

3.1 | Univariate analysis

Regarding the variables related to COVID-19, no significant associations were found between the scales and changes of AED or problems to acquire AED. A positive diagnosis of COVID-19 presented a statistically significant association with NDDI-E (β = 4.03 [0.81,7.25], p = .017) and GAD-7 (β = 4.82 [0.72,8.93], p = .024). Moreover, it was associated with lower QOLIE-31-P scores (β = −18.82 [−29.08,−8.56], p < .001), including the mood (β = −19.74 [−36.58,−2.90], p = .025), cognition (β = −23.68 [−44.17,−3.18], p = .027), medication effects (β = −28.08 [−53.39,−2.76], p = .033), and seizure worry (β = −25.14 [−44.57,−5.70], p = .014) subscales.

With regard to the subjective self-reported worsening of epilepsy, it was significantly associated with the NDDI-E (β = 6.25 [2.41,10.10], p = .002) and GAD-7 (β = 8.08 [3.20,12.95], p = .002) scores. Statistically significant associations were also found between the subjective worsening and lower scores of QOLIE-31-P scores (β = −20.84 [−33.64,−8.04], p = .002), including the energy (β = −31.63 [−48.19,−15.08], p < .001), mood (β = −36.27

TABLE 1 Characteristics of the patients with epilepsy

Characteristics	First Round *N* = 85	Second Round *N* = 73
Age (years)	44.3 (17.4)	42.1 (15.6)
Gender, *N* [%]		
Male	44 [51.8]	39 [53.4]
Female	41 [48.2]	34 [46.6]
Duration of epilepsy (years)	21.5 (15.9)	20.6 (14.9)
Seizure frequency (attacks/month)	1.7 (4.9), *N* = 84	2.5 (6.1)
Nonepileptic paroxysmal events, *N* [%]	6 [7.1]	12 [16.4]
Number of antiepileptic drugs	1.9 (1.2)	2.1 (1.3)
Number of AED ≥2, *N* [%]	48 [56.5]	43 [58.9]
Change of AED, *N* [%]	N/A	12 [16.4]
Problems to acquire AED during COVID−19 pandemics, *N* [%]	N/A	4 [5.5]
Positive diagnosis of COVID−19, *N* [%]	N/A	8 [11.0]
Subjective worsening of epilepsy during COVID−19 pandemics, *N* [%]	N/A	5 [6.8]
Number of sleeping hours	7.5 (1.8), *N* = 73	7.1 (1.3)
Sleep disturbance, *N* [%]	32 [38.1], *N* = 84	37 [50.7]
Waking up during the night, *N* [%]	28 [33.3], *N* = 84	50 [68.5]
Problems to fall asleep, *N* [%]	24 [28.6], *N* = 84	37 [50.7]
GAD−7	7.6 (5.4), *N* = 84	7.9 (5.7)
GAD−7 > 9, *N* [%]	22 [28.5]	23 [31.5]
NDDI-E	12.4 (4.4), *N* = 84	12.6 (4.5)
NDDI-E > 13, *N* [%]	28 [33.3]	28 [38.4]
ESS	5.4 (3.9), *N* = 77	7.7 (4.6)
ESS >10, *N* [%]	11 [14.3]	17 [23.3]
QOLIE−31-P	62.0 (19.2), *N* = 48	59.6 (15.0), *N* = 72
Energy	54.0 (25.9), *N* = 48	47.5 (19.8)
Mood	60.6 (25.2), *N* = 47	61.0 (23.4)
Daily activities	66.4 (30.7), *N* = 47	61.2 (12.0), *N* = 70
Cognition	59.2 (25.1), *N* = 48	58.6 (28.5)
Medication effects	40.5 (30.4), *N* = 48	52.8 (33.0), *N* = 67
Seizure worry	51.8 (27.7), *N* = 47	49.9 (27.3), *N* = 71
Overall quality of life	64.0 (18.7), *N* = 46	61.3 (20.6), *N* = 69

Note: N/A: not applicable. In this context, number of AED ≥2 was considered equivalent to drug-resistant epilepsy and/or a diagnosis of drug-resistant epilepsy on patient medical records.

[−55.95,−16.60], $p < .001$), cognition ($\beta = -32.84$ [−57.74,−7.93], $p = .012$), and overall QoL ($\beta = -20.27$ [−38.56,−1.99], $p = .033$) subscales.

Concerning the longitudinal analysis, no significant longitudinal changes were identified for either the NDDI-E and GAD-7 scores or the seizure frequency (univariate analysis). ESS scores increased significantly during the COVID-19 crisis ($\beta = 2.30$ [1.23,3.38], $p<0.001$). Statistically significant lower QOLIE-31-P scores were found in the second round ($\beta = -4.17$ [−7.76,−0.48], $p = .028$). The same statistically significant associations were found for the subjects who completed both rounds of surveys.

3.2 | Analysis with multiple covariates

The results for each of the four scales are detailed in diverse subsections.

3.2.1 | NDDI-E

Seizure frequency ($\beta = 0.22$, adjusted-$p = .001$) and sleep disturbance ($\beta = 2.21$, adjusted-$p = .005$) were significantly associated with higher NDDI-E scores. These results show that higher levels of depression are linked to higher seizure frequency and sleep disturbance. The detailed results of the GLMM regarding these variables are shown in Table 2.

Considering exclusively the analysis of the subjects from both surveys, no statistically significant longitudinal changes were found during the pandemic.

3.2.2 | GAD-7

Three variables which were significantly linked to higher GAD-7 scores: drug-resistant epilepsy ($\beta = 2.13$, adjusted-$p = .023$), problems to fall asleep ($\beta = 2.14$, adjusted-$p = .023$), and waking up during the night ($\beta = 1.63$, adjusted-$p = .043$). These results reflect higher levels of anxiety in patients with drug-resistant epilepsy and the mentioned sleep problems.

Regarding the longitudinal analysis of the subjects who answered both surveys, statistically significant lower GAD-7 values were found during the COVID-19 pandemic ($\beta = -1.28$, adjusted-$p = .043$). This result shows lower anxiety levels during the pandemic. The complete results, including the previous three variables and the longitudinal results, are shown in Table 3.

It is worth noting that, in Table 1, higher GAD-7 values in the second survey were found. This increase was produced because of the higher percentage of patients with drug-resistant epilepsy and sleep disorders in the second survey, rather than the longitudinal effect itself. In Figure 1, the longitudinal effect can be observed in the patients with drug-resistant epilepsy and sleep disorders.

TABLE 2 NDDI-E model with multiple covariates

Characteristics	Coefficient [95% CI]	*p*-value	Adjusted *p*-value (FDR)
Independent term	10.93 [6.91, 15.02]	<.001	<.001
Seizure frequency	0.22 [0.10, 0.34]	<.001	.001
Number of sleeping hours	0.01 [−0.50, 0.51]	.976	.976
Sleep disturbance	2.21 [0.82, 3.58]	.002	.005

Note: The model was adjusted by time and time*number of sleeping hours. No longitudinal variables presented statistically significant differences in the analysis that included exclusively the subjects who answered both surveys.

TABLE 3 GAD-7 model with multiple covariates

Characteristics	Coefficient [95% CI]	*p*-value	Adjusted *p*-value (FDR)
Independent term	5.28 [3.85, 6.73]	<.001	<.001
Drug-resistant epilepsy	2.13 [0.47, 3.80]	.014	.023
Problems to fall asleep	2.14 [0.39, 3.86]	.012	.023
Waking up during the night	1.63 [0.09, 3.17]	.043	.043
Longitudinal variables			
Time (2 vs. 1)	−1.65 [−3.02, −0.43]	.023	.038

Note: The model with the non-longitudinal variables was adjusted by time.

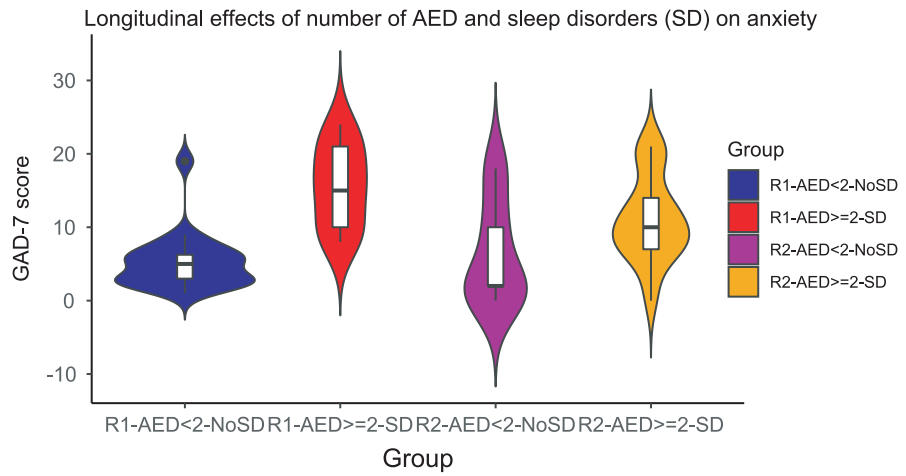

FIGURE 1 Distribution of the GAD-7 scores depending on the sleep disorders (problems to fall asleep and waking up during the night) and the round. In the patients with two or more AED and sleep disorders, the center of the distribution was placed on lower GAD-7 values during the COVID-19 pandemic (orange; R2) compared to the distribution in the previous period (red; R1). In the patients with less than two AED and no sleep disorders, the GAD-7 scores presented a higher variability in the second survey (purple), due to the low number of subjects (five), compared to the first survey (blue)

3.2.3 | ESS

TABLE 4 ESS model with multiple covariates

Characteristics	Coefficient [95% CI]	*p*-value	Adjusted *p*-value (FDR)
Longitudinal model			
Independent term	5.02 [3.59, 6.46]	<.001	<.001
Time (2 vs. 1)	2.39 [1.05, 3.74]	.001	.001

Statistically significant results were found exclusively in the longitudinal model with the subjects from both surveys. Significantly higher ESS values (β = 2.66, adjusted-p < .001) were observed during the COVID-19 pandemic. These results reflect higher somnolence during the pandemic. The complete model is shown in Table 4. The distribution of ESS values before and during the COVID-19 pandemics is shown in Figure S1.

TABLE 5 QOLIE-31-P model with multiple covariates

Characteristics	Coefficient [95% CI]	*p*-value	Adjusted *p*-value (FDR)
Independent term	95.96 [89.19, 102.74]	<.001	<.001
Gender (Male vs. Female)	3.83 [0.43, 7.19]	.033	.043
Drug-resistant epilepsy	−6.19 [−9.58, −2.81]	<.001	.002
NDDI-E	−1.58 [−2.10, −1.06]	<.001	<.001
GAD−7	−1.36 [−1.90, −0.84]	<.001	<.001
Positive diagnosis of COVID−19	−7.45 [−14.16, −0.71]	.038	.043
Problems to fall asleep	−3.89 [−7.53, −0.22]	.045	.045

Note: The model was adjusted by time and time*GAD-7. No longitudinal variables presented statistically significant differences in the analysis that included exclusively the subjects who answered both surveys.

3.2.4 | QOLIE-31-P

Men presented significantly higher QOLIE-31-P scores (β = 3.83, adjusted-p = .043). Statistically significant lower QOLIE-31-P scores were related to higher scores of GAD-7 (β = −1.36, adjusted-p < .001) and NDDI-E (β = −1.36, adjusted-p < .001), drug-resistant epilepsy (β = −6.19, adjusted-p = .002), positive diagnosis of COVID-19 (β = −7.45, adjusted-p = .043), and problems to fall asleep (β = −3.89, adjusted-p = .045). These results reflect that higher levels of anxiety, depression, drug-resistant epilepsy, COVID-19 positive diagnosis, and problems to fall asleep are related to lower QoL. The detailed results of the GLMM regarding these variables are shown in Table 5. Regarding the subjects who completed both surveys, no longitudinal significant differences were appreciated.

Concerning the longitudinal analysis with the subjects from both surveys, statistically significant lower scores were found for the daily activities (β = −76.92, adjusted-p < .001) subscale. Higher scores (better situation) were detected for the medication effects subscale (β = 13.61, unadjusted- p = .031), but this result was non-significant after correction for multiple comparisons.

In the same analysis, the significant negative effects of the sleep disturbance were counterbalanced during the COVID-19 pandemic, but it was non-significant after the correction for multiple comparisons (β = −16.06 + 15.71 = −0.35, unadjusted-p = .044) in the energy subscale scores. The negative effects of sleep disturbance in the mood scores (β = −16.17 + 26.42 = 10.25, adjusted-p = .015) were counterbalanced during the COVID-19 pandemic. The time-dependent variable of the daily activities model with statistically significant effect was NDDI-E, whose negative effects were counterbalanced during the pandemic (β = −3.74 + 5.44 = 1.70, adjusted-p < .001). For the overall QoL subscale scores, the negative effects of NDDI-E were worsened during the COVID-19 pandemic (β = −1.01–2.02 = −3.03, adjusted-p = .030). In Figures S2–5, the distribution of the subscale scores and their relationship with some of the variables mentioned in this paragraph is shown. The complete results of the QOLIE-31-P subscale models can be found in Tables S1–7.

4 | DISCUSSION

Our study presents a medium-term evaluation of the impact of the COVID-19 pandemic in PWE regarding seizure frequency, depression, anxiety, somnolence, and QoL. According to our results, seizure frequency remained stable during the COVID-19 pandemic, confirming previous reports[26-28]. PWE presented no problems acquiring their medication, what has been reported in few patients due to expired prescription or unavailability.[27] Interestingly, no concerns about access to medication prescriptions have been found in remote interviews.[29]

Regarding the potential relationship between seizures and SARS-CoV-2 infection, seizure exacerbation has been associated with exposure history to COVID-19,[26] although it remains controversial.[27]

Moreover, little is known about the influence of COVID-19 in psychiatric comorbidities or perceived well-being of this group of patients. In our study, PWE and confirmed COVID-19 experienced higher levels of depression and lower QoL, but not seizure worsening, similar to previous reports.[28] Regarding the longitudinal effects of the COVID-19 pandemic, we found lower QoL, particularly related to daily activities, and higher somnolence. Furthermore, anxiety levels were lower during the COVID-19 pandemic, especially in patients with neither sleep disorders nor drug-resistant epilepsy. With regard to depression levels, these were higher in patients with higher seizure frequency and bad quality of sleep, without particular effect of the COVID-19 pandemic.

4.1 | Depression during the COVID-19 pandemic

Higher NDDI-E scores in PWE (whole sample) were associated with higher seizure frequency. Higher levels of depression were found in PWE at early stages of the confinement,[27] but without standardized measurement tools. Our results show that higher medium-term NDDI-E scores are associated with seizure frequency. These results could be related to the well-known association between psychiatric comorbidities and seizure recurrence or drug-resistant epilepsy.[30]

Moreover, higher NDDI-E scores were also associated with sleep disturbance. Depression negatively affects sleep in PWE[31] and sleep deprivation is a known precipitating factor for seizures.[32] Therefore, higher levels of depression, in association with sleep disturbances, could explain worsening seizure frequency in some PWE during the confinement.[26]

Compared to the Spanish general population, PWE from our sample presented a higher prevalence of depression before and during the COVID-19 pandemic (33.3 and 38.4%, respectively, according to NDDI-E scores, against 6.7% before the pandemic in the general population according to the Spanish Ministry of Health).[33] Our results suggest that depression depends more on epilepsy itself than on the effects of the COVID-19 pandemic or the diagnosis of COVID-19, although a higher incidence of psychiatric disorders has been reported in COVID-19 patients.[34]

4.2 | Anxiety during the COVID-19 pandemic

Our results showed lower GAD-7 values during the pandemic. Although it has been found that anxiety longitudinally increases in the general population,[5] similar levels of anxiety in PWE have been found compared with the general population in a cross-sectional study.[35] The longitudinal reduction of GAD-7 scores could be related to the reduced possibility of having seizures at work or walking across the street among other reasons. Nonetheless, higher GAD-7 scores were associated with drug-resistant epilepsy and sleep disturbances. Previous studies have reported higher levels of anxiety in PWE,[36] and these levels have increased in the general population[4] and PWE[16] during the pandemic. However, despite the fact that the predetermined severity of epilepsy is an important factor in defining the risk of anxiety,[30] according to our results, it has not been a key factor in COVID-19 associated increased anxiety in PWE. Perhaps, the COVID-19 pandemic situation after the strict lockdown might not be associated with more severe anxiety compared to epilepsy itself. Anyway, some patients may have developed new sleep disorders related to problems falling asleep or waking up during the night during the pandemic, which would contribute to raising the levels of anxiety. Therefore, sleep disturbances, such as insomnia reported during the pandemic,[26] might be related to anxiety worsening during the COVID-19 pandemic in PWE.

Compared to the Spanish general population, PWE from our sample presented a higher prevalence of anxiety before and during the COVID-19 pandemic (28.5% and 31.5%, respectively, against 6.7% before the pandemic in the Spanish general population).[33] The increase of the prevalence of anxiety in our sample was more related to the unstable situation of epilepsy than to the effects of the pandemic. In the general population and patients with COVID-19, the levels of anxiety have increased during the pandemic.[5,35] Therefore, the levels of anxiety, as discussed with depression, seem more associated with epilepsy compared to the effects of the pandemic. Finally, although we did not evaluate stress levels in PWE, higher levels of stress have been found in the general population[5] and in PWE[37] during the COVID-19 pandemic, which could have triggered seizures in patients with stress-sensitive epilepsy.[38] Thus, the influence of anxiety on seizure control might also vary depending on stress sensitivity in PWE.

4.3 | Somnolence during the COVID-19 pandemic

Interestingly, our results show that PWE had higher somnolence during the pandemic. This result might be related to change in lifestyle habits, in PWE during the pandemic.[39] Changes in sleep habits, such as earlier bedtime and increased sleep duration, have been found in a longitudinal study in the general population during the pandemic.[40] However, sleep quality during COVID-19 outbreak was not associated with higher ESS scores.[41] Our results exhibit that PWE presented higher ESS scores during the pandemic, which could reflect lifestyle changes during the pandemic such as increased usage of digital media near bedtime,[42] less physical activity,[43,44] being more time at home, and reduced exposure to light.[45]

Additionally, a relationship between better quality of sleep and improvement in seizure frequency in PWE has been found.[16] It is well known that sleep disorders (sleep and sleep deprivation) may influence seizure control.[46] Therefore, our results suggest that better management of sleep during the pandemic leading to higher sleep quality might improve seizure frequency and the global situation of PWE.

4.4 | QoL during COVID-19 pandemic

Reduced QoL was associated with depression, drug-resistant epilepsy, SARS-CoV-2 infection, and sleep disturbances. The levels of anxiety also contributed to lower QoL, although their impact was lower during the pandemic after the strict lockdown, perhaps in relation to the lower levels of anxiety following our GAD-7 results.

Previous studies have shown that QoL is influenced not only by seizure frequency, but also by psychiatric comorbidities.[45] Moreover, in patients with drug-resistant epilepsy, psychiatric comorbidities have been associated with a poorer QoL.[47] Thus, the adequate management of depression in PWE during COVID-19 pandemic could help to improve QoL in these patients.

Besides, drug-resistant epilepsy, which has been linked to worse QoL,[48] remains to be an important factor related to impairment in QoL during the pandemic.

On the other hand, we found that QoL during SARS-CoV-2 infection in PWE was reduced, as observed in patients without epilepsy.[49] Sleep disturbances found during COVID-19 pandemic were related to lower QoL in our study, which has been previously reported to be important in PWE.[50]

Regarding subscales, we found that PWE presented reduced daily activity scores during the pandemic, possibly related to the psychological effects of the confinement and reduced outdoors

activities. These results could be explained by changes in daily activities in PWE due to the pandemic.

4.5 | Limitations of the study

There are some limitations in our study which should be remarked. Firstly, our sample is not completely representative of all PWE since it was collected from the Refractory Epilepsy Unit; however, these patients are closely followed up on a regular basis increasing certainty about diagnosis and follow-up variables included in the study, such as seizure frequency. The use of an online survey in the second round instead of an in-person or paper survey might have limited the evaluation of older PWE. Furthermore, the sample size, especially in the first survey, was slightly low, but the recruitment was interrupted due to the beginning of the COVID-19 pandemic and the corresponding restrictions. Anyway, we could find significant longitudinal changes with the present sample size. Finally, to avoid an excessively long survey, we did not ask for specific changes in employment status or lifestyle habits that may be related to the evaluation of psychiatric comorbidities.

5 | CONCLUSION

There is scarce evidence on how the COVID-19 pandemic affects patients with chronic neurological disorders, such as epilepsy. Our results provide an overview of the consequences of the confinement measures and restructuring of the healthcare system in QoL, anxiety, depression, sleep, and seizure frequency in PWE. It is, to our knowledge, the first longitudinal study evaluating the QoL of PWE with a standardized tool during the pandemic and baseline scores gathered before the beginning of the pandemic. We found a longitudinal reduction in QoL related to daily activities and increased sleepiness during COVID-19 pandemic, with no changes in seizure frequency. Moreover, anxiety levels are reduced in patients with a stable situation compared to before the pandemic. These results might reflect the importance of adequate management of QoL-associated factors in PWE in the upcoming phases of the COVID-19 pandemic.

6 | AVAILABILITY OF DATA AND MATERIAL

The data used in this study are available upon reasonable request to the corresponding author.

7 | CODE AVAILABILITY

The R code used for the statistical analysis is available upon reasonable request to the corresponding author.

8 | CONSENT TO PARTICIPATE

For the first round of recruitment, a written informed consent was signed by the patients who agreed to answer the survey (in-person visit). For the second round of recruitment, the participants gave their verbal consent and accepted to participate in the first question of the survey (online survey).

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CONFLICT OF INTEREST

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

ETHICS APPROVAL

The study was approved by the Ethics Committee of the Hospital Universitario de la Princesa (Madrid, Spain).

DATA AVAILABILITY STATEMENT

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

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