Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Long-term analysis of the effects of COVID-19 in people with epilepsy: Results from a multicenter on-line survey across the pandemic waves

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ABSTRACT

Purpose: The worldwide pandemic caused by SARS-CoV-2 virus posed many challenges to the scientific and medical communities, including the protection and management of fragile populations. People with epilepsy (PWE) are a heterogenous group of subjects, with different treatment regimens and severity of symptoms. During the National lockdown, in Italy many patients with chronic conditions lost their regular follow-up program. The aim of this study was to investigate the impact of COVID-19 on their health status, from the start of the pandemic (March 2020) to July 2021 and one year later.
Methods: We proposed an online questionnaire to subjects followed up at different epilepsy centers located in Milano, Monza & Lodi, three of Lombardy, Northern Italy, the most affected areas by the pandemic. Survey evaluated age, sex, characteristics of patients, type of epilepsy and therapies, COVID-19 diagnosis, vaccines, sleep quality, and anxiety status.
Results: Among 178 analyzed surveys, 37 individuals reported symptoms of COVID-19 in closed contacts, including 9 with molecular diagnosis and 16 PWE performing the nasopharyngeal swab with 3 positive cases. One year later, 35 individuals reported at least one symptom overlapping with those typical of COVID-19, 8 received COVID-19 diagnosis, among which 6 were positive for SARS-CoV-2 infection. According to the sleep quality scale assessment, most PWE (52.3%) had poor sleep quality. Assessing anxiety status, 32 (38.1%) had a pathological score.
Conclusion: In this multicenter study, we observed that PWE do not appear to be at a higher risk of severe COVID-19. It will be fundamental monitoring this group to assess possible differences in long-COVID-19 and/or neuro-COVID-19 prevalence. On the other hand, our survey confirmed the impact of the pandemic on anxiety and quality of sleep in PWE. Thus, it is important to promptly recognize and treat psychological distress in PWE, because it could be a risk factor in seizure aggravation and quality-of-life deterioration. Telemedicine appears to be a useful tool to support patients with chronic diseases, such as epilepsy.

1. Introduction

In December 2019, an outbreak of pneumonia of unknown cause occurred in Wuhan, in the Hubei province of China posing a new and serious threat to public health [1]. This condition was soon described as coronavirus disease 2019 (COVID-19) [2,3] and it is caused by SARS-CoV-2 virus. From China, SARS-CoV-2 has rapidly expanded to the rest of the world and, in a few months, many countries have been hit by the consequences of this pandemic.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, Intensive Care Unit; PWE, people with epilepsy; VPA, Valproic acid; ASM, antiseizures medication; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; 3CLpro, SARS-CoV-2-3-chymotrypsin-like protease.

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On March 11, 2020, the World Health Organization defined the global situation due to COVID-19 as a pandemic. To date (May 2021), there are nearly 170 million confirmed cases of COVID-19 worldwide, including 3.5 million deaths. In Italy, confirmed cases are about 4.2 million and 126,000 deaths [4].

Among European countries, Italy was the first to be involved in the pandemic wave and Lombardy region was the epicenter. In February 2020, the first patient diagnosed with COVID-19 in Italy was hospitalized in one of the Lombardy Intensive Care Unit (ICUs) for respiratory failure, after that an exponential increase in registered cases was recorded in Lombardy. Within a month, Italy became the second most affected country in the world by SARS-CoV-2 [5].

Severe COVID-19 is caused by the production of an inflammatory state, characterized by the release of several cytokines that lead to a condition defined as a "cytokine storm"[6,7]. A spectrum of neurological manifestations has been reported in the literature associated with SARS-CoV-2 [8,9], and epilepsy is infrequently reported [10,11].

Seizures are neurological complications that can be produced by SARS-CoV-2; however, they do not seem to be frequent, happening in about 0.5 % or even less number of patients with COVID-19 [12]. On the other hand, it is unclear whether or not people with epilepsy (PWE), characterized by a chronic condition, are at a higher risk of a severe COVID-19 [13].

The social impact of COVID-19 also involved access to health facilities which was significantly limited. The reason was the possible patient-to-patient or healthcare provider-to-patient transmission of SARS-CoV-2. Additionally, in hospitals with COVID-19 inpatients or in areas with widespread SARS-CoV-2 infection, hospitalizations for other conditions have been severely limited [14].

Typically, PWEs are regularly followed up with outpatient visits, at least yearly, based on clinical conditions. In particular, a high number of seizures and poor tolerance to antiseizure medications (ASMs) are the most frequent causes of requests for assistance [15]. During COVID-19 pandemic, telemedicine has been an alternative for allowing patients to maintain contact with their physician [16,17].

Moreover, studies report that PWE are more vulnerable to the psychological effects of the COVID-19 pandemic than those without epilepsy [18–20]. Although the extent of impact is uncertain, the pandemic has certainly had an impact on the mental health of the general population including patients with epilepsy. Should the effects be understood, psychological comorbidities could be minimized [11].

Hence, the aim of this study – through a protocol consisting of an online questionnaire directed to patients with epilepsy treated with ASMs followed up at different tertiary care units in Lombardy – was to investigate if during the first wave peak of SARS-CoV-2 spreading there was a different response in a specific fragile population – PWE – compared to the general population. Specifically, we investigated whether PWE would manifest different symptoms – more severe or milder – in response to the infection caused by SARS-CoV-2 and a possible correlation with the type of concomitant antiseizure therapy, the possible variation of the frequency and of intensity of the seizures. Moreover, we conducted a second survey with the PWE who answered our first questionnaire one year later, in order to verify whether they have been infected by SARS-CoV-2 in the meantime.

We also evaluated their adherence to the anti-COVID vaccination campaign and whether patients with epilepsy experienced sleep disorders or increased amount of anxiety and whether there is a correlation between the two problems. The intent was to assess also anxiety status and sleep quality in PWE after a year of pandemic that has imposed a long period of stress on people around the world.

2. Materials and methods

2.1. Study population and survey

An online survey was created using the free open-access GoogleTM Forms (https://www.google.com/forms/about/) application. The survey included an informed consent verification. No sensitive data were collected, data were assembled and analyzed anonymously and were treated according to the European regulation GDPR n. 2016/679. The survey was sent by e-mail to patients followed up at outpatient epilepsy centers ASST Santi Paolo Carlo Milano, Monza & Lodi. The referring doctor sent the survey individually by email. The study was approved by the local ethics committee (Comitato Etico Interaziendale Milano Area A, protocol approval numbers N. 0001649). Enrolled subjects/caregivers gave informed consent in accordance with the Declaration of Helsinki.

The study involved the enrollment of adult patients (over 18y. o.) with epilepsy resident in the Lombardy Region, through the involvement of neurologists belonging to the Italian League against Epilepsy – Lombardy Section, who are in charge of medical follow-up (no deaths were recorded in the selected period). For the second phase of the study, participants who had given consent to be re-contacted were contacted. Patients independently completed a questionnaire relating to the presence or absence of symptoms typical of COVID-19, concomitant antiseizure therapy, any variation in the frequency, and intensity of the seizures. Patients were grouped according to the type of therapy and the severity of the COVID-19 symptoms (in terms of type and intensity of the symptoms in relation to different degrees of medical interventions, e.g. home-based treatment, hospitalization or intensive care unit), also in relation to the severity of family members/cohabitants. The first questionnaire was sent at the end of the first wave of COVID-19 (May–July 2020) when many of the effects of this virus were not yet known, especially in our population of interest.

With the Decree of March 12, 2021, our Country adopted the new national strategic plan for the prevention of SARS-CoV-2 infections for the execution of the national vaccination campaign (prepared by the Ministry of Health, Extraordinary Commissioner for emergency, Istituto Superiore di Sanità, AGENAS and AIFA). Age and the presence of pathologies represented the main correlation variables with mortality from COVID-19. The order of priority of the categories of people to be vaccinated in the campaign was: category 1 were highly frail people; category 2 were people between 70 and 79 years of age; category 3 were people between 60 and 69 years of age; category 4 were people under the age of 60 with comorbidities but without the connotation of severity reported for category 1; category 5 represented the rest of the population under the age of 60. In addition, some categories have also been identified as priorities, regardless of age and pathological conditions: school and university staff, armed police and public aid forces, penitentiary services, and other residential communities.

The first vaccines available in Italy were mRNA BNT162b2 (Comirnaty) produced by Pfizer and BioNTech and Spikevax (mRNA-1273), the vaccine developed by Moderna. This was followed by the introduction of the ChAdOx1-S vaccine, developed by the University of Oxford and AstraZeneca and the vaccine developed by the pharmaceutical company Janssen (of the Johnson & Johnson group) – the last two suspended in May 2021.

In the second questionnaire, we added questions related to quality of life, sleep, anxiety, and adherence to the anti-COVID vaccination campaign. The second questionnaire was sent exactly one year after the first (June–July 2021) which corresponded to the end of the third wave of the pandemic in Italy.

We administered the Pittsburgh Sleep Quality Index (PSQI) scale to assess sleep quality. PSQI [21] is a 19-item self-

administered questionnaire used to evaluate sleep disturbances and sleep quality over a period of a month. Each item is rated on a four-point Likert-like scale. The combination of the different items generates seven scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the 7 scores produces a global score. A global score of 5 or higher provides a sensitive and specific measure of poor sleep quality.

We assess the State-Trait Anxiety Inventory (STAI) scale to assess traits and anxiety status. STAI S-Anxiety Scale [22] is a 20-item, self-report questionnaire used to evaluate state anxiety; each item is rated on a four-point Likert scale. STAI S-Anxiety scale is one of the two parts of STAI questionnaire (Spielberg et al. 1970), which is composed of 40 items, 20 for trait anxiety (T-Anxiety) evaluation, and 20 for state anxiety (S-Anxiety) evaluation. Range of scores for each subtest is 20–80, the higher score indicating greater anxiety. A cutoff of 39–40 has been suggested to detect clinically significant symptoms for the S-Anxiety scale. In this survey, we asked PWE how they accessed medical care and whether they used telemedicine. The surveys are available in the supplementary information (Supplementary Table 1 and 2).

2.2. Statistical analysis

For data analysis, chi-square testing was performed to test the difference between the outcomes in our study group and the general population. The analysis of variance test – ANOVA – was used to analyze a possible correlation between the antiseizure therapy and the appearance of symptoms attributable to COVID-19. P-value ≤ 0.05 was considered significant.

3. Results

3.1. First phase of survey

About 280 surveys were sent by e-mail in the period from May 5th to July 30th, 2020. In the study, we enrolled all patients answering the questions upon informed consent of data use. A total of 187 subjects (66.7 %) accessed the online survey, and 178 of them (63.5 %) gave their consent to proceed with the questionnaire and processing of personal data. Among the subjects who gave their consent, the age range went from those born in 1946 to those born in 2000 (age mean 42 years old, SD = 14.8, median 41 years of age) – 108 are females (60.7 %) and 70 males (39.3 %) (Table 1). The age of diagnosis of epilepsy was in a range from 0 to 76 years, mean 21.7 ± 1.2, and median 17 ± 0.6 years of age.

Our study population mainly concerns Lombardy and is distributed as follows: 86 Milan (48.3 %), 17 Monza Brianza (9.5 %), 14 Lodi (7.8 %), 7 Bergamo (3.9 %), 5 Brescia (2.8 %), 5 Varese (2.8 %), 3 Como (1.7 %), 3 Cremona (1.7 %), 3 Pavia (1.7 %), 2 Novara (1.1 %), 1 Lecco (0.5 %), 1 Mantova (0.5 %), 1 Sondrio (0.5 %) and 23 other municipalities in other regions of Italy (12.9 %) (Fig. 1) – 7 participants did not give information on this matter.

The type of epilepsy appears to be generalized epilepsy in 85 individuals (47.7 %), 74 focal epilepsy (41.6 %) and the other cases unspecified epilepsy. During the survey period, only 17 subjects (9.5 %) changed antiepileptic therapy, but 8 of them (47 %) had uncontrolled seizures for at least a year – in 133 PWE (75 %) seizures were under control.

In the study population a total of 48 (27 %) patients were receiving treatment with valproic acid-VPA (Table 1): 16 patients were treated with VPA alone (9 %), or in combination (32 patients, 18 %). Among the other most commonly taken treatments were Levetiracetam (24, 13.4 %), Carbamazepine (16, 9 %), and Lamotrigine (11, 6.2 %). Forty-three patients (24 %) received flu vaccination during the months preceding pandemic.

Table 1
Characteristics and antiseizures therapy in the PWE.

Characteristics of patient therapies	Total n = 178 (%)
Females	108 (60.7)
Males	70 (39.3)
Age (years)	
Average	42
Age groups	
80–60	28 (15.8)
59–40	61 (34.5)
39–20	86 (48.6)
<19	2 (1.1)
Age of diagnosis of epilepsy	21.7 ± 1.25
Antiseizure medication	
Carbamazepine	16 (9)
Lacosamide	4 (2.2)
Lamotrigine	11 (6.2)
Levetiracetam	24 (13.5)
Oxcarbazepine	4 (2.2)
Perampanel	1 (0.6)
Phenobarbital	1 (0.6)
Phenytoin	1 (0.6)
Primidone	3 (1.7)
Topiramate	2 (1.1)
Valproic acid	16 (9)
Zonisamide	1 (0.6)
Therapies in combinations	94 (52.8)
Risk factors for SARS-CoV-2	n = 77 (43.3 %)
Comorbidities of patients	
Allergies	5 (2.8)
Asthma	2 (1.1)
Cardiovascular diseases	5 (2.8)
Chronic respiratory diseases	9 (5.1)
Diabetes	5 (2.8)
Hypercholesterolemia	2 (1.1)
Hypertension	15 (8.4)
Obesity	12 (6.7)
Thyroid diseases	18 (10.1)
Tumors	4 (2.2)
Smokers	30 (16.9)
> 5 cigarettes per day	23 (12.3)

Among all participants, 92 individuals (51.7 %) reported at least one symptom overlapping with COVID-19 from January 2020, 65 individuals (36.5 %) declared they had at least two symptoms possibly caused by COVID-19 – based on self-report. We show that 25 PWE reported fever (14 %), 10 anosmia, ageusia (absence of smell and taste) (5.6 %), 25 cough (14 %), 35 cold (19.6 %), 23 diarrheas, nausea or vomiting (13 %), 37 asthenia/fatigue (20.8 %), and 13 conjunctivitis (7.3 %); 24 PWE (13.5 %) underwent a nasopharyngeal swab test for SARS-CoV2, 12 % were positive.

Among PWE who reported at least two symptoms, 16 performed the nasopharyngeal swab and among these we found the 3 positive cases plus one negative but with positive serological SARS-CoV2 IgG test in our entire population. Six subjects (3.4 %) were hospitalized and, among them, 4 had nasopharyngeal swabs for SARS-CoV2, but only 2 were positive. No correlation was found between treatment and the presence of symptoms (>2) related to COVID-19. In our study population, we observed a significant difference (p-value = 0.01, $\leq$0.05) between subjects who reported onset of symptoms (>2) related to COVID-19 (42, 23.6 %) and subjects who did not report (88, 49.4 %), regardless of medication taken. Out of the total population, the percentage of subjects tested

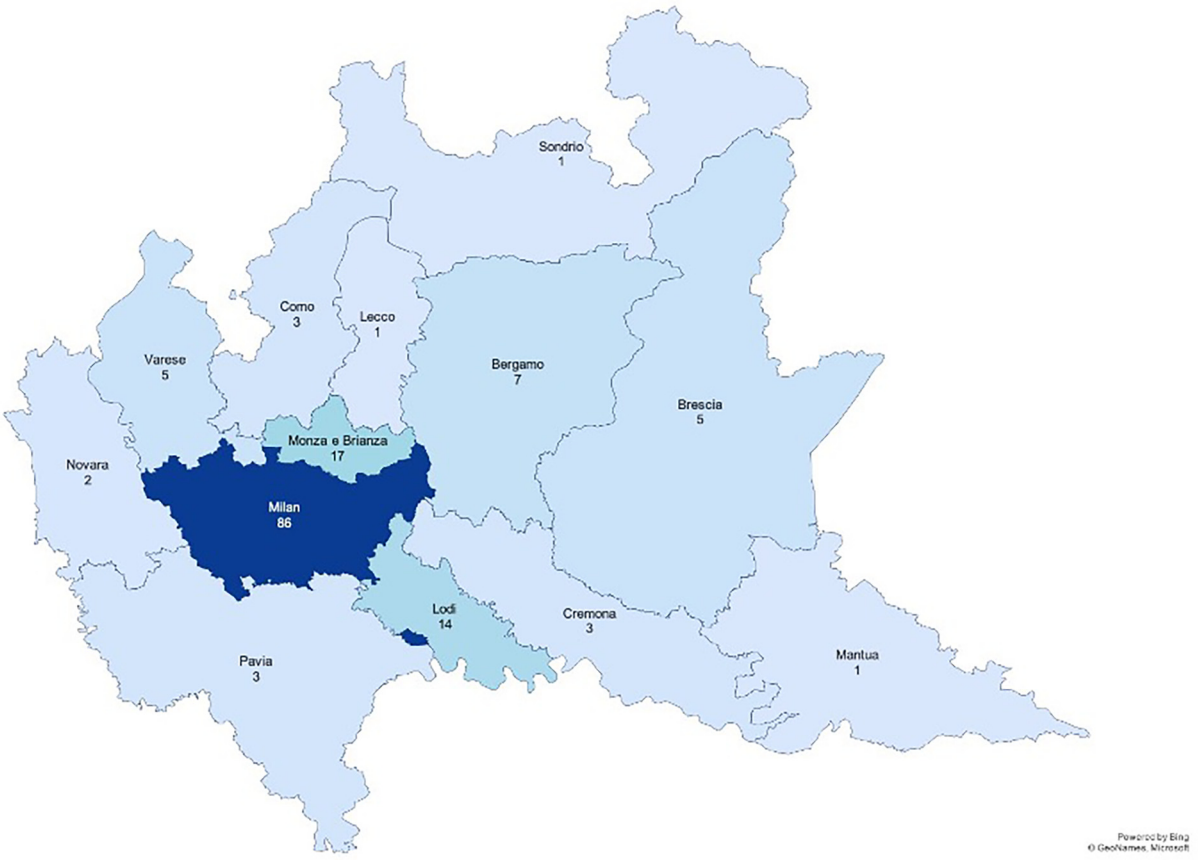

Fig. 1. Geographic distribution of the study population. The map represents the distribution of PWE in the different provinces in Lombardy; the color is darker where there is a greater number of patients who participated in the study.

positive for SARS-CoV-2 is 1.7 %. Furthermore, 37 PWE family members reported symptoms of COVID-19, including 9 with molecular diagnosis.

In Italy, the general population as per January 2021 presents a positive/cases tested ratio that stands at 29.5 % and shows a considerable regional variability – Lombardy stands at 31.5 % (Data from Italian National Health Institute, publicly available). Updated reports of the general population show that the number of total positive cases corresponds to 4.2 % (2.560.957) in Italy and 5.3 % (539.147) in Lombardy. Among hospitalized patients –3.489 in Lombardy – the percentage of access in ICUs corresponds to 10.6 % (371). A chi-square test was performed to examine the relation between hospitalized patients in our study population and Lombardy population – the difference between these outcomes was significant (p-value = 0.00001, $\leq$0.05).

No significance difference was found among ICU admission in our study population (none) and those recorded in Lombardy (7.2 % of SARS-CoV-2 positive tested).

3.2. Second phase of survey

In the second phase of the study, 155 surveys were sent by e-mail in the period from June 25th to July 30th, 2021. We enrolled all patients answering the questions upon informed consent of data use. A total of 86 subjects (55.5 %) accessed the online survey, and 84 of them (54.2 %) gave their consent to proceed with the questionnaire and processing of personal data. Among the subjects who gave their consent, the age range went from those born in 1937 to those born in 2002 (age mean 43 years old, SD = 13.6, median 41 years of age) – 61 are females (73.5 %) and 23 males (27.5 %). The age of diagnosis of epilepsy was in a range from 0 to 64 years, mean 20.4 and median 17 years of age.

In our second study group, the type of epilepsy appears to be generalized epilepsy in 48 individuals (57.1 %), 32 focal epilepsy (38.1 %), and the other cases with unspecified epilepsy. From October 2020, only 18 of them (21.4 %) had uncontrolled seizures for at least a year – in 66 PWE (78.6 %) seizures were under control. In this second survey, our population had a total of 15 (1.9 %) patients receiving treatment with VPA: 6 patients were treated with valproic acid (VPA) alone (7.1 %), or in combination (9 patients, 10.7 %). Three patients (3.5 %) received flu vaccination during this period.

Within the study group, 72 subjects (85.7 %) received vaccination for SARS-CoV-2 and, among them, 25 (34.7 %) received both flu and SARS-CoV-2 vaccination. Among PWE who received SARS-CoV-2 vaccination: 51 Comirnaty (70.8 %, Pfizer/BioNTech), 10 Moderna (13.8 %, Biotech), 7 Vaxzevria (9.7 %, Astrazeneca), 3 heterologous vaccine covid Comirnaty and Vaxzevria (4.2 %), and only 1 Johnson & Johnson (1.4 %, Janssen). During the first phase there were no vaccines against COVID-19 and limited diagnostics; hence comparison is not possible.

Among all participants, 35 of them (41.6 %) reported at least one symptom overlapping with COVID-19 from October 2020, 24 individuals (28.5 %) declared they had at least two symptoms possibly caused by COVID-19 – based on self-report. We found that, among 35 PWE reported at least one symptom, 27 PWE (32.1 %) underwent a nasopharyngeal swab test for SARS-CoV2. Among PWE who reported at least one symptom, 8 (9.5 %) received COVID-19 diagnosis (7 females and 1 male). Among 3 PWE not vaccinated, 2 reported several symptoms overlapping with COVID-19 and

received flu vaccination. 2 individuals presented other pathologies and only one had seizures not controlled by medications. No subject who received COVID-19 diagnosis were treated with VPA.

Among those subjects who completed the second survey, 6 (7.1 %) tested positive to SARS-CoV-2 infection: 1 had controlled seizures, 1 had an improvement on seizures, and 1 changed antiseizure therapy during the last period. 4 of them were treated for COVID-19 and 3 performed antibody testing for COVID-19 and resulted positive. All of them had family members who reported symptoms of COVID-19, including 5 with molecular diagnosis. No individuals were hospitalized.

3.3. Access to medical care and psychological side effects

Out of the total population, from October 2020 to July 2021, 82 (97.6 %) had access to medical care and most of them (72, 85.7 %) had the opportunity to contact the physician epileptologist: 7 by email, 16 by phone, 8 in telemedicine, and 41 in presence. The remaining subjects reported no contact with the physician, as some did not have the need for it and others were waiting for their annual visit.

According to the PQSI scale assessment, 29 PWE (34.5 %) were found to have good sleep quality while most (44, 52.3 %) had poor sleep quality. Among the latter, 10 (22.7 %) had a severe score of poor sleep quality in terms of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (PSQI score > 10)(Fig. 2).

Assessing anxiety status using the STAI scale, 11 subjects (13.1 %) presented a borderline score, while 32 (38.1 %) had a pathological score (Fig. 2). We compared the results of PSQI and STAI questionnaires among them and evaluated the possible presence of correlations with these variables: sex, age, controlled seizures, presence of other pathologies, and Covid diagnosis. We analyzed the results of PSQI and STAI to assess if there was a correlation between pathological states and or versus normal results. None of the correlations were statistically significant (p = 0.4354).

Although not reaching statistical significance, 52.3 % of patients reported Poor SQ and 38.1 % of patients a pathological anxiety status.

4. Discussion

Since Northern Italy, and specifically Lombardy, has been reached by Coronavirus disease 2019 (COVID-19) pandemic among the first regions worldwide, people with chronic diseases, such as epilepsy, were concerned about the management of their seizures and both about the possible effects of this new infection in PWE. Thus, we delineated an observational survey directly fulfilled by patients or their caregivers, living in Lombardy at the time of the first pandemic spread and a follow-up after one year, in order to capture the impact of COVID-19 on this population of frail subjects. Responder anonymity represents a limitation of the study but, considering the demographic and clinical data, our cohort mirrors PWE who are followed up in our centers.

However, online survey research has multiple advantages as it allows saving time and fundings [23]. Further, because of the mitigation measures during COVID-19 pandemic, chronic patients reported issues in access both to drugs and medical care [24]. To this end, it has been suggested that different types of e-health applications should be used simultaneously – as complementary resources – to improve the outcomes of chronic patients including PWE [25,26]. This fundamental aspect should be considered for SARS-CoV-2 future pandemic waves and/or other emerging pathogens, as modern technologies represent an invaluable tool for guarantying medical support to those in need.

We perceived a good response to the survey, as the responder rate reached 63 % in the first phase; indeed, the responders were spread between 20 and 74 years demonstrating a more difficult use of technological resources by eldest individuals. In the second phase, the response rate was 54.2 %. We also observed unbalance for sex, with a clear predominance of females. However, our percentage of female respondents was quite similar to the proportion of female users on the Facebook social network in Italy [27,28]. The regional distribution of the answers to the survey could be explained by both population density and possibly a more habit to research interviews given that in Milan there are 4 Medical Research Universities.

Regarding the characteristics of epilepsy, both generalized and focal epilepsies are represented in the study cohort, and a high percentage of PWE have their seizures controlled, in line with other similar studies [29]; however, some studies report an increase in seizure frequency in patients with change in sleep, increase in stress and reduced compliance to ASMs [30,31]. This scenario reflects the overall prevalence of drug-resistance in PWE [32], and allows considering our sample representative of population with epilepsy.

We collected information about ASM and found that the most used were Valproic acid, Carbamazepine, Clobazam, Levetiracetam, Lamotrigine, and Perampanel in monotherapy or in combination.

It is interesting to note that VPA is an histone deacetylase (HDAC) inhibitor and Gordon and colleagues [33] listed HDAC2 among the interactors of the major viral protease SARS-CoV-2-3-chymotrypsin-like protease (3CLpro). Whether this interaction has positive or negative consequences on viral replication is still

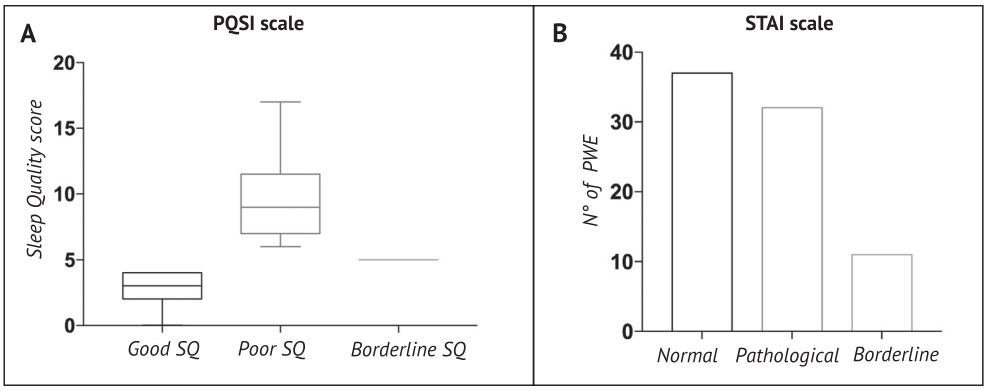

Fig. 2. (A) Sleep Quality (SQ) scale. Good SQ (in blue) score < 5; Poor SQ (in red) score > 5; Borderline SQ = 5. (B) Anxiety status STAI scale. Normal STAI (in blue) score < 40; Pathological STAI (in red) score ≥ 45; Bordeline STAI (in yellow) score 40–44.

to be elucidated, but other authors [34] suggested HDACi ability to prevent SARS-CoV-2 entry into target cells. VPA would seem to be a possible candidate for further use in patients at risk of COVID-19 [35].

The first aim of our study was to verify if PWE were at major risk of COVID-19. We confirmed that only 3 individuals (1.7 %) in the first phase in our population had a confirmed coronavirus infection, and an additional 11 % reported some suggestive symptoms albeit not confirmed by specific testing. Our data are in line with other surveys conducted in the Spanish PWE [36,37]. Our study reflects the effect of the first wave of COVID-19 pandemic, when the tracking of asymptomatic cases was not performed. For this reason, the incidence of SARS-CoV-2 in our sample was not specifically investigated.

Two out of the three patients with COVID-19 were hospitalized, all of them recovered completely. They had a diagnosis of generalized epilepsy, in two of them seizures were not controlled by medications. Intriguingly, none of them was on VPA treatment. The three patients who experienced COVID-19 were also affected by comorbidities known to increase the risk of hospitalization such as diabetes, hypertension, obesity, and chronic respiratory disease. When analyzing hospital admission in respect to the available data for Lombardy, PWE appeared at a significant lower risk compared to the general population, even if it is accepted that data on COVID-19 is underestimated, especially in the first wave, for lack of testing. The possible role of epilepsy as risk factor associated with poor outcome for SARS-CoV-2 infection is much debated. An early study in Spain reported epilepsy as an independent risk factor for COVID-related death [38]. Other studies found no association of epilepsy and COVID-19 death rate [39–41]. Further analysis on a wider population would be of great importance.

In the second phase, 7.1 % individuals in our population tested positive for SARS-CoV-2 infection. An additional 2.3 % received diagnosis of SARS-CoV-2 based on clinical symptoms albeit not confirmed by specific test. These numbers are in line with pandemic situation at the time in the Lombardy. This observation appears to support that the PWE population does not present an increased risk of severe COVID-19 compared with the general population.

Although, it is now recognized that PWE do not exhibit an increased risk of SARS-CoV-2, nevertheless specific guidelines for treating PWE with COVID-19 have been developed by National and International scientific societies [42–44].

To the best of our knowledge, no survey has been proposed to the same group of PWE from the first peak of pandemic to the third, including the 2021 summer when PWE had the opportunity to receive the anti-SARS-CoV2 vaccination. The long-term results of our study indicate that the chance of being infected by SARS-CoV-2 for PWE is comparable to the general population as reported also by the *Center of Disease Control and Prevention* (CDC)[45], while QoL of PWE worsened, and anxiety level increased.

Regarding the adherence of PWE to the vaccination campaign, we do know that PWE were concerned about the safety of the COVID-19 vaccines [46], probably due to concern of possible side effects, but PWE usually have a good safety profile and a low risk of epilepsy worsening. We observed a high adherence to the vaccination campaign (85.7 %) from patients responses, in line with the national population response.

A number of studies described the consequences of the lockdown measures on daily life of PWE [17,47], we confirmed that COVID-19 pandemic had an impact on sleep quality and anxiety level in our sample. Psychological distress in PWE should be promptly captured and adequately treated because it could also result in seizure aggravation and quality-of-life deterioration [48]. Indeed, telemedicine implementation can support patients with chronic diseases, such as epilepsy, and thus reducing the distance between PWE and their treating physicians [49,50]. The use of telemedicine has grown significantly over the past decade because of the clear advantages: the ability to provide care for people with mobility limitations, people living in rural areas, and costs savings. This tool became essential during the recent pandemic. Unfortunately, this methodology presents obvious limitations: for example, blood tests and the most common diagnostic tests require an in-person approach. Further digital data require a secure plan for data management and storage [51,52]. Our data regard only one region, and it is difficult to compare with others given the specific age/socioeconomic status. The impact of ethnicities and socio-economic status may have an additional effect on severe SARS-CoV-2 disease, considering that our study population has a high social economic status. Indeed, socioeconomic determinants were strongly associated with COVID-19 outcomes in racial and ethnic minority populations [53]. Moreover, additional environmental risk factors (e.g., air pollution, high mobility, and high population density) may be determinant in the spread of SARS-CoV-2 infection in an industrialized region such as Lombardy, but are difficult to rule out [54].

Clearly, using a self-completing questionnaire, this study has limitations – also due to obvious reasons, especially during the first phase of the study – concerning the lack of a control group, the uncertainty about the temporal relationship in vaccinated patients between vaccination and COVID-19 symptoms. Moreover, it should be taken into account that different variants of Sars-Cov2 may have different characteristics, for example in contagiousness and severity of symptomatology, so that the current situation may be different from previous waves.

5. Conclusions

During the first wave peak of COVID-19, scarce information was available about fragile population including PWE. Despite the lockdown measures forcing us to use a self-filled survey method – in order to reach a wider group of people in a shorter period of time – we observed that PWE in our study population do not demonstrate an increased risk of severe COVID-19.

Despite some recent literature, it is still unclear whether epilepsy is an independent risk factor for both incidence and mortality of COVID-19 [55]. Overall, our data suggest excluding epilepsy from risk factors for developing severe COVID-19, accordingly with other studies conducted in different populations [56,57]. However, it is important to continue monitoring this fragile population and patients who have recovered from COVID-19. This is to understand if they will develop long-COVID-19 and/or neuro-COVID-19 with different characteristics or prevalence from the general population (difference in age, clinical expression, severity and length of symptoms, etc.).

In conclusion, this study provides further information that will be useful in the management of this fragile population in the context of the global pandemic caused by SARS-CoV-2.

6. Data availability statement

Raw data are available upon appropriate request.

7. Compliance with ethical standards

The study is in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent of patients or caregivers were collected. The study was approved by the local ethics committee (Protocol approval numbers N. 0001649).

8. Consent to Participate

Online informed consent of patients or caregivers were collected.

9. Consent for publication

Patients signed informed consent regarding publishing their data in anonymized form.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108900.

References

[1] Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. novel coronavirus outbreak in Wuhan. China Int J Infect Dis 2020;91:264–6.
[2] World Health Organization. Novel Coronavirus(2019-nCoV) Situation Report, 22. 2020.
[3] Zhu Na, Zhang D, Wang W, Li X, Yang Bo, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382 (8):727–33.
[4] WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data n.d. https://covid19.who.int/ (accessed May 30, 2021).
[5] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region. Italy JAMA 2020;323 (16):1574.
[6] Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021;93:250–6. https://doi.org/10.1002/jmv.26232.
[7] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm'' in COVID-19'. J Infect 2020;80:607–13. https://doi.org/10.1016/j.jinf.2020.03.037.
[8] Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care 2021;34(3):1062–71.
[9] Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. J Clin Neurosci 2020;77:8–12. https://doi.org/10.1016/j.jocn.2020.05.017.
[10] Vohora D, Jain S, Tripathi M, Potschka H. COVID-19 and seizures: Is there a link? Epilepsia 2020;61:1840–53. https://doi.org/10.1111/epi.16656.
[11] Kuroda N. Epilepsy and COVID-19: Associations and important considerations. Epilepsy Behav 2020;108:107122.
[12] Asadi-Pooya AA. Seizures associated with coronavirus infections 2020. doi: 10.1016/j.seizure.2020.05.005.
[13] Sanchez-Larsen A, Gonzalez-Villar E, Díaz-Maroto I, Layos-Romero A, Martínez-Martín Á, Alcahut-Rodriguez C, et al. Influence of the COVID-19 outbreak in people with epilepsy: analysis of a Spanish population (EPICOVID registry). Epilepsy Behav 2020;112:107396.
[14] Blecker S, Jones SA, Petrilli CM, Admon AJ, Weerahandi H, Francois F, et al. Hospitalizations for chronic disease and acute conditions in the time of COVID-19. JAMA Intern Med 2021;181(2):269.
[15] Fesler JR, Stanton S, Merner K, Ross L, McGinley MP, Bena J, et al. Bridging the gap in epilepsy care: a single-center experience of 3700 outpatient tele-epilepsy visits. Epilepsia 2020;61(8). https://doi.org/10.1111/EPI.16619.
[16] Datta P, Barrett W, Bentzinger M, Jasinski T, Jayagopal LA, Mahoney A, et al. Ambulatory care for epilepsy via telemedicine during the COVID-19 pandemic. Epilepsy Behav 2021;116:107740.
[17] Fonseca E, Quintana M, Lallana S, Luis Restrepo J, Abraira L, Santamarina E, et al. Epilepsy in time of COVID-19: a survey-based study. Acta Neurol Scand 2020;142(6):545–54.
[18] Hao X, Zhou D, Li Z, Zeng G, Hao N, Li E, et al. Severe psychological distress among patients with epilepsy during the COVID-19 outbreak in southwest China. Epilepsia 2020;61(6):1166–73.
[19] Kuroda N, Kubota T. Psychological impact of the COVID-19 pandemic for patients with epilepsy: a systematic review and meta-analysis. Epilepsy Behav 2021;124:108340.
[20] Tashakori-Miyanroudi M, Souresrafil A, Hashemi P, Jafar Ehsanzadeh S, Farrahizadeh M, Behroozi Z. Prevalence of depression, anxiety, and psychological distress in patients with epilepsy during COVID-19: a systematic review. Epilepsy Behav 2021;125:108410.
[21] Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
[22] Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Polo Alto, CA: Consulting Psychologists Press; 1970.
[23] Wright KB. Researching internet-based populations: advantages and disadvantages of online survey research, online questionnaire authoring software packages, and web survey services. J Comput Commun 2005;10(3).
[24] Casassa C, Moss R, Goldenholz DM. Epilepsy during the COVID-19 pandemic lockdown: a US population survey. Epileptic Disord 2021;23:257–67. https://doi.org/10.1684/epd.2021.1259.
[25] Reiners F, Sturm J, Bouw LJW, Wouters EJM. Sociodemographic factors influencing the use of eHealth in people with chronic diseases. Int J Environ Res Public Health 2019;16(4):645.
[26] Bitar H, Alismail S. The role of eHealth, telehealth, and telemedicine for chronic disease patients during COVID-19 pandemic: a rapid systematic review. Digital Health 2021;7.
[27] Digital 2020 Italia – We Are Social Italia n.d. https://wearesocial.com/it/digital-2020-italia.
[28] Lanzone J, Cenci C, Tombini M, Ricci L, Tufo T, Piccioli M, et al. Glimpsing the impact of COVID19 lock-down on people with epilepsy: a text mining approach. Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.00870.
[29] Trivisano M, Specchio N, Pietrafusa N, Calabrese C, Ferretti A, Ricci R, et al. Impact of COVID-19 pandemic on pediatric patients with epilepsy – the caregiver perspective. Epilepsy Behav 2020;113:107527.
[30] Alkhotani A, Siddiqui MI, Almuntashri F, Baothman R. The effect of COVID-19 pandemic on seizure control and self-reported stress on patient with epilepsy. Epilepsy Behav 2020;112:107323. https://doi.org/10.1016/j.YEBEH.2020.107323.
[31] Zeng C, Meng H, Zhu Y, Yao L, Lian Y, Zhu Y, et al. Correlation of seizure increase and COVID-19 outbreak in adult patients with epilepsy: findings and suggestions from a nationwide multi-centre survey in China. Seizure 2021;88:102–8.
[32] Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: a systematic review and meta-analysis. Epilepsia 2018;59:2179–93. https://doi.org/10.1111/epi.14596.
[33] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;583(7816):459–68.
[34] Liu Ke, Zou R, Cui W, Li M, Wang X, Dong J, et al. Clinical HDAC inhibitors are effective drugs to prevent the entry of SARS-CoV2. ACS Pharmacol Transl Sci 2020;3(6):1361–70.
[35] Pitt B, Sutton NR, Wang Z, Goonewardena SN, Holinstat M. Potential repurposing of the HDAC inhibitor valproic acid for patients with COVID-19. Eur J Pharmacol 2021;898:173988. https://doi.org/10.1016/j.ejphar.2021.173988.
[36] Conde Blanco E, Manzanares I, Centeno M, Khawaja M, Betrán O, Donaire A, et al. Epilepsy and lockdown: a survey of patients normally attending a Spanish centre. Acta Neurol Scand 2021;143(2):206–9.
[37] Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology 2020;95(8).
[38] Cabezudo-García P, Ciano-Petersen NL, Mena-Vázquez N, Pons-Pons G, Castro-Sánchez MV, Serrano-Castro PJ. Incidence and case fatality rate of COVID-19 in patients with active epilepsy. Neurology 2020;95:e1417–25. https://doi.org/10.1212/WNL.0000000000010033.
[39] Balestrini S, Koepp MJ, Gandhi S, Rickman HM, Shin GY, Houlihan CF, et al. Clinical outcomes of COVID-19 in long-term care facilities for people with epilepsy. Epilepsy Behav 2021;115. https://doi.org/10.1016/j.YEBEH.2020.107602.
[40] Granata T, Bisulli F, Arzimanoglou A, Rocamora R. Did the COVID-19 pandemic silence the needs of people with epilepsy? Epileptic Disord 2020;22:439. https://doi.org/10.1684/EPD.2020.1175.
[41] Asadi-Pooya AA, Emami A, Akbari A, Javanmardi F. COVID-19 presentations and outcome in patients with epilepsy. Acta Neurol Scand 2021;143:624–8. https://doi.org/10.1111/ANE.13404.
[42] Ekstein D, Noyman I, Fahoum F, Herskovitz M, Linder I, Ben Zeev B, et al. Treating epilepsy patients with investigational anti-COVID-19 drugs: recommendations by the Israeli chapter of the ILAE. Isr Med Assoc J 2020;11:665–72.
[43] Alotaibi F, Althani Z, Aljaafari D, Tayeb HO, Baarmah D, Aljalal N, et al. Saudi epilepsy society consensus on epilepsy management during the covid-19 pandemic. Neurosciences 2020;25(3):222–5.

[44] von Oertzen TJ, Macerollo A, Leone MA, Beghi E, Crean M, Oztuk S, et al. EAN consensus statement for management of patients with neurological diseases during the COVID-19 pandemic. Eur J Neurol 2021;28(1):7–14.
[45] CDC. People with Certain Medical Conditions | CDC n.d. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html (accessed December 11, 2021).
[46] Massoud F, Ahmad SF, Hassan AM, Alexander KJ, Al–Hashel J, Arabi M. coronavirus disease (COVID-19) vaccines among people with epilepsy (PwE): a cross-sectional study. Seizure 2021;92:2–9.
[47] Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.00737.
[48] Cross JH, Kwon CS, Asadi-Pooya AA, Balagura G, Gómez-Iglesias P, Guekht A, et al. Epilepsy care during the COVID-19 pandemic. Epilepsia 2021;62:2322–32. https://doi.org/10.1111/EPI.17045/FORMAT/PDF.
[49] Members of the Digital Technologies, Web and Social Media Study, Group of the Italian Society of Neurology. Letter to the Editor 2020. doi: 10.1016/j.yebeh.2020.107164.
[50] von Wrede R, Moskau-Hartmann S, Baumgartner T, Helmstaedter C, Surges R. Counseling of people with epilepsy via telemedicine: experiences at a German tertiary epilepsy center during the COVID-19 pandemic. Epilepsy Behav 2020;112:107298.
[51] Kuroda N. Decision making on telemedicine for patients with epilepsy during the Coronavirus Disease 2019 (COVID-19) crisis. Front Neurol 2020;11:722. https://doi.org/10.3389/FNEUR.2020.00722/BIBTEX.
[52] Bloem BR, Dorsey ER, Okun MS. The Coronavirus Disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. JAMA Neurol 2020;77:927–8. https://doi.org/10.1001/JAMANEUROL.2020.1452.
[53] Magesh S, John D, Li WT, Li Y, Mattingly-app A, Jain S, et al. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status: a systematic-review and meta-analysis. JAMA Netw Open 2021;4(11):e2134147.
[54] Xu R, Rahmandad H, Gupta M, Digennaro C, Ghaffarzadegan N, Amini H, et al. Weather, air pollution, and SARS-CoV-2 transmission: a global analysis. Lancet Planet Heal 2021;5:e671–80. https://doi.org/10.1016/S2542-5196(21)00202-3.
[55] Kuroda N. Epilepsy and COVID-19: Updated evidence and narrative review. Epilepsy Behav 2021;116:107785. https://doi.org/10.1016/J.YEBEH.2021.107785.
[56] Rathore C, Baheti N, Bansal AR, Jabeen SA, Gopinath S, Jagtap S, et al. Impact of COVID-19 pandemic on epilepsy practice in India: a tripartite survey. Seizure 2021;86:60–7.
[57] Bosak M, Mazurkiewicz I, Wężyk K, Słowik A, Turaj W. COVID-19 among patients with epilepsy: Risk factors and course of the disease. Epilepsy Behav 2021;120:107996. https://doi.org/10.1016/J.YEBEH.2021.107996.