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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The impact of one-year COVID-19 containment measures in patients with mesial temporal lobe epilepsy: A longitudinal survey-based study

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ABSTRACT

Background: We assessed levels of depression, anxiety, stress, anhedonia, somatization, psychological distress, sleep, and life quality in patients with mesial temporal lobe epilepsy (MTLE) after one year of containment measures started in Italy to stem the COVID-19 pandemic.
Methods: We consecutively enrolled 51 patients with MTLE, administering an online survey that compared the year before and after the COVID-19 propagation. We analyzed clinical data (e.g., seizure frequency, life quality) and neuropsychological assessment through Somatic Symptom Scale–8 (SSS-8), Beck Depression Inventory (BDI-2), State-Trait Anxiety Inventory (STAI-Y), Depression, Anxiety and Stress Scale (DASS-21), Pittsburgh Sleep Quality Index (PSQI), Snaith-Hamilton Pleasure Scale (SHAPS), Impact of Event Scale-Revised (IES-R). The BDI-2 and STAI-Y scores were compared to those acquired in the same patients before the COVID-19 outbreak.
Results: Comparing our population with MTLE before and after COVID-19 outbreak, we found a significant worsening in life quality ($p = 0.03$), SSS-8 ($p = 0.001$), BDI-2 ($p = 0.032$), and STAI-Y scores ($p < 0.001$). After one year of pandemic, 88.2% of patients obtained pathological scores at PSQI, 19.6% at SHAPS, 29.4% at IES-R. Reduction of life quality correlated with anxiety, depression, stress, and somatization. Higher levels of anhedonia correlated with stress, depression, and anxiety. Somatization correlated with depression, anxiety, and sleep quality. Distress levels correlated with anxiety, somatization, and depression.
Conclusions: We demonstrated a significant worsening of depression, anxiety, life quality, and somatization in patients with MTLE after one year of COVID-19 beginning. Concomitantly, results suggest that the pandemic had a negative impact on sleep quality, psychological distress, and anhedonia, but not on epilepsy itself.

1. Introduction

In early December 2019, pneumonia of unknown origin evolving in respiratory failure, septic shock, and death suddenly emerged in the Chinese city of Wuhan. On 7 January, the World Health Organization (WHO) announced to have identified a new coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its illness coronavirus disease 2019 (COVID-19). Meanwhile, the disease started to spread outside of China, and on 11 March, the WHO declared the outbreak to be pandemic. Italy was the first Western country affected by COVID-19 and forced strict quarantine measures to limit diffusion [1]. In the general population, the social lockdown, physical distancing, and other containment strategies contributed to increasing symptoms of depression, anxiety, anger, stress, as well as higher alcohol assumption and domestic violence [2]. Furthermore, during the first months of pandemic diffusion, the COVID-19 emergency did not allow access to the healthcare system for all non-urgent conditions, such as chronic neurological diseases. Consequently, changes in healthcare contributed to higher levels of distress in patients with epilepsy compared to healthy controls [3], and recent studies found associations between increased seizure frequency during the lockdown and higher depression and anxiety levels [3,4].

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Mesial temporal lobe epilepsy (MTLE) is the most common type of focal epilepsy in adulthood. In TLE, psychiatric symptoms can be comorbidities, found in 20–40% of patients (up to 70% when associated with hippocampal sclerosis). Mood disorders, such as depression, are the main psychiatric symptoms, followed by anxiety, psychotic, and personality disorders [5,6]. Previous published works in people with epilepsy showed the negative effect of the COVID-19 pandemic on life [7] and sleep [8] quality, the higher rates of depression, anxiety, and psychological distress [3,4]. In these studies, major limits were the lack of homogeneous samples (i.e., cohorts included people with generalized and focal epilepsy not matched for type) [3,4,7,8] and the lack of longitudinal data (most studies being cross-sectional) [3,8].

In a homogeneous cohort of consecutive patients with MTLE, our aims were to: (1) test differences between levels of anxiety and depression measured one year after COVID-19 containment and those previously acquired in the same cohort one year before the COVID-19 outbreak; (2) compare clinical features before and after the pandemic began, through ad-hoc questionnaires assessing seizures frequency, anti-seizure medication (ASM) assumption, psychotropic drugs use, life quality, somatization, alcohol assumption, smoke habit, modified work condition; (3) assess correlations among scores of depression (Beck Depression Inventory-BDI-2) [9], anxiety (State-Trait Anxiety Inventory-STAI-Y) [10,11], stress (Depression, Anxiety and Stress Scale-DASS-21) [12,13], sleep quality (Pittsburgh Sleep Quality Index-PSQI) [14], somatization (Somatic Symptom Scale-8-SSS-8) [15], anhedonia (Snaith-Hamilton Pleasure Scale-SHAPS) [16,17], and psychological distress related to COVID-19 pandemic (Impact of Event Scale-Revised - IES-R) [18,19]; and (4) find a relationship among all the above mentioned clinical data and the neuropsychological scores.

2. Material and methods

2.1. Subjects

Fifty-three subjects were consecutively contacted to complete the survey, but two of them refused to participate. Therefore, 51 patients with MTLE (29 female, mean age = 40.96 ± 14.2) were enrolled from March 2021 to May 2021, one year after the Italian government started COVID-19 containment measures. All clinical data are summarized in Table 1. The diagnosis of MTLE was determined by evaluating clinical seizures semiology, typical temporal auras, and interictal electroencephalography (EEG), recording epileptiform discharges with a maximum over the temporal regions [20,21]. Forty-eight patients (94.1%) were taking one or more ASMs at the survey time. All subjects had an unremarkable neurological examination and were older than 18 years. None of the participants had mental retardation. Eleven out of 51 patients (21.6%) had radiological (MRI) evidence of hippocampal sclerosis, and 45 (88.2%) were MRI-negative [22]. All subjects included in the study had a previous assessment for depression and anxiety through BDI-2 and STAI-Y scores, tested yearly in our tertiary epileptic center [23]. Local research ethics committee approval was obtained.

Table 1
Demographical and clinical features of patients with Mesial Temporal Lobe Epilepsy (MTLE).

	Patients with MTLE ($n°$= 51)
Age (years)	40.96 ± 14.20
Gender (% female)	29/51 (56.9%)
Mean age at epilepsy onset (years)	24.47 ± 11.81
Duration (years)	16.55 ± 13.72
Family history of FS†/epilepsy, $n°$ (%)	17/51 (33.3%)
Personal history of FS†, $n°$ (%)	7/51 (13.7%)
Educational status, $n°$ (%)	
Elementary school	3/51 (5.9%)
Secondary school	14/51 (27.5%)
High school	26/51 (51%)
Graduation	8/51 (15.7%)
Marriage status, $n°$ (%)	
Unmarried	17/51 (33.3%)
Married	30/51 (58.8%)
Divorced	3/51 (5.9%)
Widow/Widower	1/51 (2%)
Home sharing, $n°$ (%)	
Yes	45/51 (88.2%)
No	6/51 (11.8%)
Employment status before March 2020, $n°$ (%)	
Self-employed	2/ 51 (3.9%)
Public employees	7/51 (13.7%)
Private employees	11/51 (21.6%)
Unemployed	31/51 (60.8%)
Interictal EEG‡, $n°$ (%)	
Unilateral left	22/51 (43.1%)
Unilateral right	12/51 (23.5%)
Bilateral	6/51 (11.8%)
Normal	9/51 (17.6%)
Hippocampal sclerosis side, $n°$ (%)	
Left	5/51 (9.8%)
Right	6/51 (11.8%)
Bilateral	0/51 (0%)
None	40/51 (78.4%)
Mean ASM§ taken, $n°$	1.39 ± 0.70

† FS: Febrile Seizures; ‡ EEG: Electroencephalogram; § ASM: Anti-seizure medication.

2.2. Survey-based questionnaire

The online survey was created through the free open-access GoogleTM Forms (https://www.google.com/forms/about/) application. An informed consent verification was added, stopping the survey without further questions for those who disagreed with its use terms. Data were treated according to the European regulation GDPR n. 2016/679. The questionnaire contained four sections:

1) Introduction, which explained the aim of the study, and the mandatory informed consent.
2) Demographic and social data: age, gender, marriage status, education level, type of work, and home-sharing.
3) Period before COVID-19 spread: seizures frequency, difficulties in contacting the physician and/or booking a visit, problems during sleep (specifying their duration and the possible hypno-inducers assumed), anxiety (and the eventual anxiolytic treatment), depressive symptoms (and the psychotherapy or antidepressant therapy), alcohol assumption, smoke habits, life quality (evaluated through ad hoc scale of 10-points, where zero is the worst possible quality of life and 10 the best one), and SSS-8.
4) Pandemic time (comprehending period from March 2020 until March 2021) is divided into two subsections. In the first one, there were questions about SARS-CoV-2 disease, anti-COVID-19 vaccination, seizures frequency, difficulties contacting the physician and/or prenoting a visit, modification of ASM therapy, problems during sleep (specifying their duration and the possible hypno-inducers assumed), anxiety (and the eventual anxiolytic therapy), depression (and the psychotherapy or antidepressant treatment), alcohol assumption, smoke habits, changes in food intake, weight and work condition, and SSS-8. An ad hoc scale of 10 points, where zero is the worst possible condition and 10 the best one, evaluated the life quality. Through the same scale, the patients had to judge how much the COVID-19 pandemic impacted their life quality and interpersonal relationships. The second subsection included the self-administered ques-

tionnaires assessing BDI-2, STAI-Y, DASS-21, PSQI, SHAPS, and IES-R. Each neuropsychological test we used is extensively described as follows.

2.3. Neuropsychological assessment

The BDI-2 consists of 21 items validated to detect depression in the general population by 13- to 80-year old. Each item receives a rating from zero to three summed to obtain a global score range 0–63, estimating the severity of depressive symptoms. Scores of 0–13 points indicate depression as absent, 14–19 as mild, 20–28 as moderate, and 29–63 as severe. The internal consistency was around 0.92, and the test–retest reliability was 0.93 [9].

The STAI-Y [10] form is a measure of state and trait anxiety based on a four-point Likert scale. The state anxiety scale (STAI Form Y-1) has 20 items evaluating current feelings of tension, activation/arousal of the autonomic nervous system, anxiety, and nervousness. The trait anxiety scale (STAI Form Y-2) consists of 20 items that assess stable aspects of "anxiety proneness," including states of calmness, confidence, and security. Scores for both scales ranged from a minimum of 20 to a maximum of 80 points. Scores of 20–40 points indicate anxiety as mild, 41–60 as moderate, and 61–80 as severe. Internal consistency coefficients for the scale varied from 0.86 to 0.95; test–retest reliability ranged from 0.65 to 0.75 over a 2-month interval [11].

The DASS-21 comprises 21 items divided into three subscales that measure depression, anxiety, and stress [12]. Every item could be scored on a scale from 0 ("did not apply to me at all") to 3 ("applied to me very much or most of the time"). Per each subscale, the points on the items are added and then multiplied by a factor of 2. The scores for each of the subscales may range between zero and 42. A score of 0–9 points indicates depression as absent, 10–13 as mild, 14–20 as moderate, 21–27 as severe, and over 28 as extremely severe. A score of 0–7 points defines anxiety as absent, 8–9 as mild, 10–14 as moderate, 15–19 as severe, and over 20 as extremely severe. Cutoff scores rank stress as absent (0–14 points), mild (15–18 points), moderate (19–25 points), severe (26–33 points), and extremely severe (over 34 points). The test–retest reliability was αdass_T1 = 0.95 (αdass_T1 = 0.91 for depression subscale) and αdass_T2 = 0.92 (αdass_T2 = 0.86 for depression subscale) [13].

The PSQI assesses sleep quality and disturbances over a 1-month time interval through seven "components": subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each item is rated from 0 ("no difficulty") to 3 ("severe difficulty"). The sum of scores for all components yields one global score, ranging from 0 to 21. A global score higher than five indicates a significant sleep disturbance [14].

The SSS-8, an abbreviated 8-item version of the Patient Health Questionnaire-15 questionnaire, assesses the common somatic symptoms and their severity, evaluating a 7-day time frame. A 5-point option is available for each item, and the total score ranges from 0 to 32. Cutoff points rank somatic symptom burden as absent or minimal (0–3 points), low (4–7 points), medium (8–11 points), high (12–15 points), and very high (16–32 points). The test had good reliability (Cronbach $\alpha = 0.81$), and all corrected item-total correlations exceeded 0.4 [15].

The SHAPS comprehends 14 items that measure hedonic experience or positive valence in the domains of social interaction, food and drink, sensory experiences, achievement, and pastimes. Each of these items has a set of four response categories: Strongly Agree, Agree, Disagree, and Strongly Disagree. Either of Agree responses has a score of zero, and either of the Disagree responses receives a score of one. Total score ranges from 0 to 14, with higher scores indicating a lower level of hedonic experience or a higher level of Anhedonia. Cutoff score ≥ 3 points indicates a significant reduction of hedonic tone [16]. The Italian validation demonstrated an intraclass coefficient for test–retest reliability of 0.65 for the total score [17].

IES-R is a 22-item scale that evaluates subjective psychological distress related to a traumatic event using three subscales divided into eight items of intrusion (e.g., repeated thoughts about the event), eight items of avoidance (e.g., effortful avoidance of situations that remind the trauma), and six items of hyperarousal (e.g., anger, irritability, hypervigilance, difficulty concentrating). All items are rated on a 5-point scale extending from 0 ("not at all") to 4 ("extremely"), and the total score ranges from 0 to 88. Although not diagnostic, an IES-R cutoff score of 33 demonstrated the best accuracy for correlation to the post-traumatic disorder, providing a sensitivity of 0.91, a specificity of 0.82, positive predictive power of 0.90, and negative predictive power of 0.84 [18,19]. The three subscales showed a high degree of intercorrelation (rs = 0.52 to 0.87). High levels of internal consistency have been reported, with Cronbach's alpha of 0.57–0.94 for Intrusion, of 0.84–0.85 for Avoidance, of 0.79–0.90 for Hyperarousal. Test–retest correlation coefficient ranged from 0.57 to 0.94 for intrusion, 0.51 to 0.89 for avoidance, and 0.59 to 0.92 for hyperarousal [19]. We indicated the COVID-19 pandemic outbreak as a trauma event for the participants.

2.4. Statistical analysis

The Shapiro–Wilk test and a visual inspection of histograms, Q-Q plots, and box plots were used to assess the normal distribution of each variable. Data were assumed to be normally distributed for *p*-values above 0.05. Association between variables was quantified through Pearson's correlation coefficient for normally distributed data, whereas if one or both tested variables presented a non-normal distribution, Spearman's rho non-parametric rank correlation coefficient was used. A scatter plot with a regression line was drawn to evaluate the data distribution pattern, and the relationship strength between two variables was calculated through the squared correlation coefficient (R^2). For normally distributed data, a paired sample t-test was performed to compare the means of the same variable measured in the pre-pandemic and COVID-19 pandemic periods. The non-parametric Wilcoxon Signed-Ranks test was used to compare the data with the non-normal distribution measured both in the pre-pandemic and COVID-19 pandemic periods. Categorical variables distribution was compared using Fisher's exact test. *P*-values <0.05 were considered significant after correction for multiple comparisons using the Bonferroni method. Statistical analysis was performed using IBM Statistical Package for Social Science software (SPSS, version 26.0, Chicago, IL, USA) for Windows.

3. Results

3.1. Demographic and clinical data

The demographic data, including marital status, home-sharing, employment status before March 2020, and educational level, are summarized in Table 1. From March 2020 until March 2021, 28/51 (54.9%) patients with MTLE needed to modify the antiepileptic treatment.

3.2. COVID-19 infection and vaccine

Forty-nine out of 51 (96.1%) patients with MTLE did not get SARS-CoV-2 infection. Of the two patients who got infected, only one patient had severe interstitial pneumonia needed for hospital

recovery, while the other manifested mild, long-lasting symptoms, like fever, cough, hyposmia, and a prolonged SARS-CoV-2 polymerase chain reaction positive test for two months. During the period from pandemic start to May 2021, 9/51 (17.6%) patients with MTLE received the COVID-19 vaccine.

3.3. Self-reported clinical data

All clinical data describing patient status before and after the COVID-19 pandemic are reported in detail in supplementary Table 2. The Wilcoxon Signed-Ranks test found no significant differences in seizures frequency, difficulties to contact a physician, sleep-related problems, self-reported anxiety and depression and eventual medications, alcohol intake, and smoking habits before and after one year of COVID-19 pandemic. The Fisher's exact test calculated no significant differences in the number of patients employed and unemployed before and after virus propagation.

3.4. Quality of life

Before the pandemic, patients with MTLE reported an average quality of life equal to 6.8 ± 2.1. After one year of the COVID-19 outbreak, the mean value of quality of life was 6.1 ± 2.3. Patients judged the impact of the pandemic on quality of life as 6.5 ± 2.8 (with 10 being the worst possible impact degree) and its impact on interpersonal relationships as 6.7 ± 2. The Wilcoxon Signed-Ranks test found significant differences in overall quality of life before and after the COVID-19 propagation ($p = 0.03$).

3.5. Neuropsychological assessment

All neuropsychological data are reported in supplementary table 3. Before and after one year of COVID-19 diffusion, the mean SSS-8 total score was 8.4 ± 6.7 and 10.6 ± 7.9, respectively. The Wilcoxon Signed-Ranks test found significant differences in SSS-8 total scores before and after the virus propagation ($p = 0.001$). After one year of the COVID-19 pandemic, 45/51 patients (88.2%) obtained a pathological global score at PSQI (mean value: 7.5 ± 3.1). The most disturbing component was the habitual sleep efficiency (mean value: 2.5 ± 1.1), followed in decreasing order by sleep efficiency (mean value: 1.2 ± 0.6), sleep latency (mean value: 1 ± 0.8), sleep duration (mean value: 1 ± 1), subjective sleep quality (mean value: 1 ± 0.7), daytime dysfunction (mean value: 0.8 ± 0.7), use of sleep medication (mean value: 0.2 ± 0.6).

Before and after one year of virus propagation, the mean BDI-2 total score was 10.8 ± 9.6 and 12.8 ± 12.5, respectively. The Wilcoxon Signed-Ranks test found a significant difference before and after the COVID-19 pandemic in BDI-2 scores ($p = 0.032$).

Before the COVID-19 outbreak, the mean score was 47.2 ± 11.4 for the STAI state and 47.2 ± 12.6 for the STAI trait. After one year of the virus propagation, the mean total score was 52.1 ± 13.4 for the STAI state and 48.9 ± 12.8 for the STAI trait. The Wilcoxon Signed-Ranks test found significant differences in STAI-Y state scores before and after the COVID-19 beginning ($p < 0.001$). The paired t-test did not demonstrate significant differences between pre-pandemic and pandemic STAI trait scores.

After one year of the COVID-19 propagation, the mean DASS-21 score in patients with MTLE was 15.6 ± 12.1 for depression subscale, 11.1 ± 9.4 for anxiety subscale, and 10.2 ± 12.1 for stress subscale.

Concomitantly, 10/51 (19.6%) and 15/51 patients (29.4%) obtained pathological scores at SHAPS and IES-R, respectively. The mean score was 1.32 ± 0.94 for the Avoidance subscale, 1.06 ± 0.84 for the Intrusion subscale, and 1.22 ± 0.95 for the Hyperarousal subscale.

3.6. Correlations

The IES-R total score correlated with female gender (valuated as zero in the dataset, $p < 0.001$, rho = −0.439, $R^2 = 0.253$), with DASS-21 subscales of depression ($p = 0.001$, rho = 0.441, $R^2 = 0.254$) and anxiety ($p < 0.001$, rho = 0.488, $R^2 = 0.270$), with BDI-2 ($p < 0.001$, rho = 0.479, $R^2 = 0.281$), with SSS-8 ($p < 0.001$, rho = 0.579, $R^2 = 0.418$), STAI trait ($p < 0.001$, rho = 0.559, $R^2 = 0.372$) and state ($p < 0.001$, rho = 0.530, $R^2 = 0.318$) scales measured during COVID-19 pandemic. Then we evaluated which IES-R subscale mostly influences these results, as shown in Fig. 1. Intrusion ($p = 0.001$, rho = −0.468, $R^2 = 0.195$) and Hyperarousal ($p = 0.008$, rho = −0.371, $R^2 = 0.130$) correlated with female gender. Intrusion ($p < 0.001$, rho = 0.513, $R^2 = 0.268$), Hyperarousal ($p < 0.001$, rho = 0.515, $R^2 = 0.316$) and, less, Avoidance ($p = 0.001$, rho = 0.446, $R^2 = 0.194$) correlated with the DASS-21 subscale of depression. Intrusion ($p < 0.001$, rho = 0.517, $R^2 = 0.277$), Hyperarousal ($p < 0.001$, rho = 0.522, $R^2 = 0.273$) and, less, Avoidance ($p = 0.002$, rho = 0.426, $R^2 = 0.202$) correlated with the DASS-21 subscale of anxiety. Intrusion ($p < 0.001$, rho = 0.552, $R^2 = 0.313$), Hyperarousal ($p < 0.001$, rho = 0.634, $R^2 = 0.429$) and, less, Avoidance ($p = 0.001$, rho = 0.454, $R^2 = 0.187$) correlated with the STAI state. Intrusion ($p < 0.001$, rho = 0.556, $R^2 = 0.358$), Hyperarousal ($p < 0.001$, rho = 0.646, $R^2 = 0.477$) and, less, Avoidance ($p = 0.001$, rho = 0.482, $R^2 = 0.237$) correlated with the STAI trait. Intrusion ($p < 0.001$, rho = 0.495, $R^2 = 0.262$), and Hyperarousal ($p < 0.001$, rho = 0.572, $R^2 = 0.358$) correlated with the BDI-2 score. Intrusion ($p < 0.001$, rho = 0.606, $R^2 = 0.456$), Hyperarousal ($p < 0.001$, rho = 0.625, $R^2 = 0.459$) and, less, Avoidance ($p = 0.001$, rho = 0.462, $R^2 = 0.270$) correlated with the SSS-8 scale. The life quality during pandemic correlated with DASS-21 subscales of depression ($p < 0.001$, rho= −0.723, $R^2 = 0.335$), anxiety ($p < 0.001$, rho= −0.654, $R^2 = 0.506$) and stress ($p < 0.001$, rho = −0.583, $R^2 = 0.291$), with SSS-8 score ($p < 0.001$, rho = −0.587, $R^2 = 0.357$), with STAI trait ($p < 0.001$, rho = −0.583, $R^2 = 0.250$) and state ($p < 0.001$, rho = −0.640, $R^2 = 0.292$) scales, as shown in Fig. 2. The SSS-8 total score correlated with DASS-21 subscales of depression ($p = 0.001$, rho = 0.664, $R^2 = 0.458$), anxiety ($p < 0.001$, rho = 0.758, $R^2 = 0.571$), and stress ($p < 0.001$, rho = 0.704, $R^2 = 0.522$), with PSQI global score ($p < 0.001$, rho = 0.539, $R^2 = 0.342$), with BDI-2 ($p < 0.001$, rho = 0.704, $R^2 = 0.562$), STAI trait ($p < 0.001$, rho = 0.724, $R^2 = 0.510$) and state ($p < 0.001$, rho = 0.685, $R^2 = 0.445$) scales measured during COVID-19 pandemic, as represented in Fig. 3. The SHAPS scale correlated with DASS-21 subscales of depression ($p < 0.001$, rho = 0.479, $R^2 = 0.196$), anxiety ($p < 0.001$, rho = 0.472, $R^2 = 0.172$) and stress ($p < 0.001$, rho = 0.565, $R^2 = 0.298$), with STAI trait ($p < 0.001$, rho = 0.513, $R^2 = 0.146$) and state ($p = 0.002$, rho = 0.420, $R^2 = 0.106$) scales, as displayed in Fig. 4.

4. Discussion

During last year, many studies extensively investigated anxiety, depression, seizure frequency, sleep changes, and life quality in patients with epilepsy, but most of them did not classify the type of epilepsy, thus not evaluating whether an epileptic syndrome was particularly vulnerable to such a dramatic change in the manner of living to steam virus diffusion. Moreover, two studies conducted a longitudinal analysis of changes in life quality and in seizures' frequency [3,7], lacking the comparison between the psychopathological data obtained during the pandemic and those collected before the COVID-19 began [8,24]. To the best of our knowledge, this is the first study aiming to assess longitudinally the neuropsychological impact of the COVID-19 pandemic on patients with MTLE specifically. Having data on depression and anxiety levels

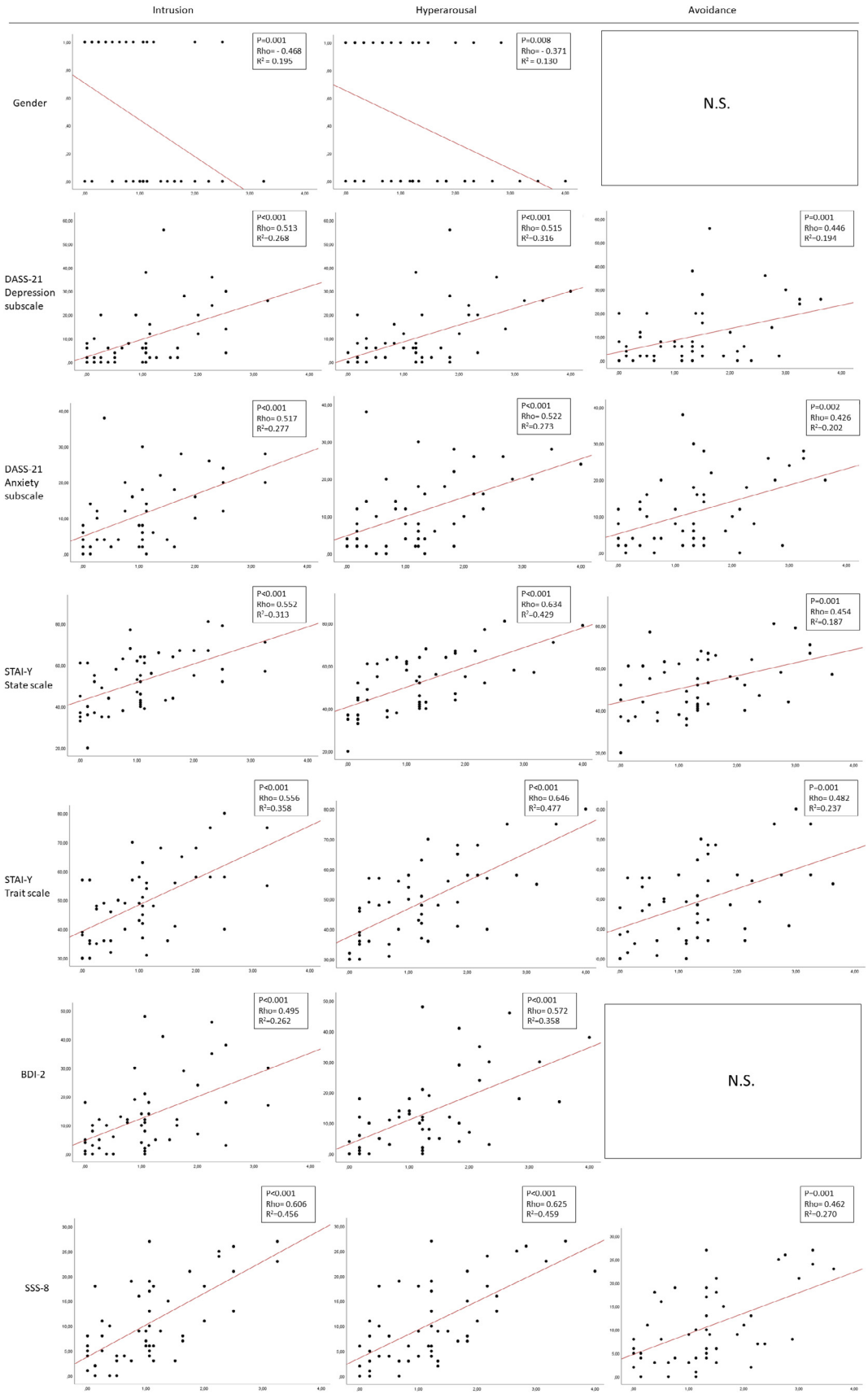

Fig. 1. Significant correlations of Impact of Event Scale-Revised subscales during the year after COVID-19 beginning. Scatter plots with the regression line showing the data distribution pattern of each Impact of Event Scale-Revised (IES-R) subscales (Intrusion, Hyperarousal and Avoidance) and the correlated variables on the *x* and *y* axis, respectively (bottom up: female gender, Depression, Anxiety and Stress Scale-21 (DASS-21) depression subscale, DASS-21 anxiety subscale, State-Trait Anxiety Inventory (STAI-Y) state scale and STAI-Y trait scale). The *p*-value, Spearman's rho non-parametric rank correlation and squared correlation coefficients (R^2) were also reported for each correlation indicated.

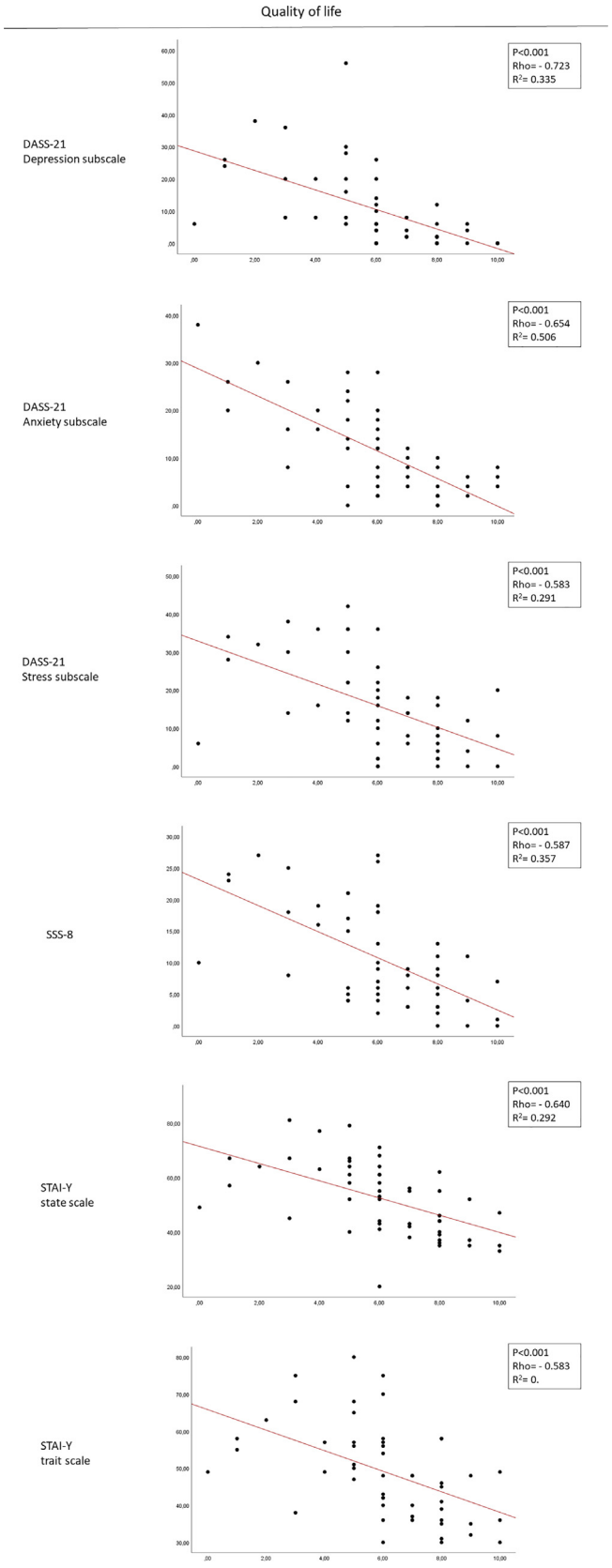

Fig. 2. Significant correlations of life quality measurement during the year after COVID-19 beginning. Scatter plots with the regression line showing the data distribution pattern of life quality and the correlated variables on the *x* and *y* axis, respectively (bottom up: DASS-21 depression subscale, DASS-21 anxiety subscale, DASS-21 stress subscale, Somatic Symptom Scale-8 (SSS–8), STAI-Y state scale and STAI-Y trait scale). The *p*-value, Spearman's rho non-parametric rank correlation and squared correlation coefficients (R^2) were also reported for each correlation indicated.

acquired one year before the virus diffusion, we could conduct a longitudinal analysis. In this population, we demonstrated a significant worsening of depression, anxiety, life quality, and somatization after one year of COVID-19 beginning regardless of seizure frequency. Interestingly, results suggest that this peerless event negatively affected sleep quality, psychological distress, and anhedonia without affecting epilepsy itself.

Our study started exactly one year after the pandemic began and before vaccines against SARS-CoV-2 were massively administered, allowing us to observe the impact of a longer period of containment measures on seizures frequency, life quality, sleep, mood disorders, and psychological distress. Although several studies reported a worsening in seizures frequency [3,4], a recent literature review highlighted that these frequency changes regarded < 10% of patients with epilepsy, reducing further after some months of COVID-19 propagation [8]. In line with this, we did not find any pandemic-related significant increase in seizure frequency in our sample, probably because our study started after a more prolonged period since the contagion massively began.

Some studies speculated that difficulties to healthcare access are a possible factor involved in higher levels of depression and distress in patients with epilepsy [3]. Thanks to numerous telehealth instruments, like emails, WhatsApp messenger, and calls, our patients with MTLE did not report a significant change in clinical care between the year before and after COVID-19 diffusion.

Among patients with epilepsy, sleep disturbances seem to be diffused similarly to the general population [24,8]. Although our population did not self-report statistically significant sleep changes after COVID-19, 88% of patients with MTLE had a pathological score at PSQI. After the COVID-19 propagation, higher alcohol consumption was described in the general population, especially in younger males [25]. Several surveys recorded an increase in smoking cigarettes associated with higher levels of distress [26,27]. Our patients did not indicate a rise in alcohol intake and smoking during the examined period, probably because these habits were already discouraged in people affected by a chronic disease and undergoing antiepileptic therapy.

In the general population, a reduction of physical activity [26], poorer diet quality, and weight gain were associated with social distancing, telework, fear of contagion, cutoff of social relationships [28]. In our study, about 20% and 30% of patients with MTLE reported a reduction and a mild increase in food intake, respectively. At the same time, about 20% of patients lost weight, and 40% put on up to 10 Kg.

Previous studies measured a worsening of life quality in all types of patients with epilepsy, correlating with higher seizure frequency, depression, and anxiety levels [29,7]. We found a significant reduction in life quality in our population with MTLE. At the time of the study, only nine out of 51 patients received a vaccine against SARS-CoV-2. Then, after a year, physical distancing, face masks, fear of getting the infection were needed, contributing to a different perception of life quality. Our patients with MTLE judged that COVID-19 spread impact on their life and relationships from a moderate to a high degree (6.5 ± 2.8 and 6.7 ± 2, respectively). In our sample, the reduction of life quality reported at one-year after pandemic beginning negatively correlated with anxiety, and, less, with depression, stress, and somatic symptoms. Our study did not show a correlation between life quality and clinical factors, as seizures frequency, number of ASMs taken by patients, epilepsy duration.

At the time we conducted the study, hence after one year of living with containment measures, about 30% of patients with MTLE showed depression, and all of them had some degree of anxiety. In addition, about 50% of our patients presented a certain stress level.

Psychiatric disorders are frequent comorbidities in MTLE, manifesting in about 75% of these patients, compared to lower rated reported in extratemporal and generalized epilepsies [30]. More than half of patients with MTLE suffer from depression, and about 40% of them from anxiety, including post-traumatic stress disorder and generalized anxiety disorder. Among all epileptic syndromes, TLE carried the higher suicide risk with a 6.57 standardized mortal ratio [31]. Previous works highlighted higher levels of depression in patients with epilepsy compared to the control group during the COVID-19 pandemic [24,8]. In detail, less than 10% had a severe score at BDI-2 and started to take a psychotropic drug [8]. Another study correlated the higher levels of depression in this population with difficult access to healthcare [3]. In the light of the above-mentioned reasons, it is crucial to monitor psychiatric comorbidities in TLE [30]: we compared the levels of depression and anxiety during COVID-19 diffusion to those recorded before the pandemic beginning. Compared to the period antecedent virus propagation, we found a significant increase in depression scores measured after one year of containment measures. No patient started a new antidepressant therapy, but two patients reported inefficacy of the ongoing treatment. In addition, a significant increase was recorded in the current anxiety state compared to that measured before the COVID-19 spread, while trait scores were – as expected – unchanged. Our population presented a significant increase in the presence and severity of somatization, tested before and after the COVID-19 outbreak. The somatic symptoms reported by our patients as more significantly different were the stomach or bowel problems. The severity of somatization correlated greatly with depression and anxiety levels and, less, with sleep quality. Furthermore, about 20% and 30% of patients with MTLE had pathological levels of anhedonia and psychological distress, respectively. Higher levels of anhedonia correlated, above all, with the presence of stress and with depression, and anxiety too.

Previous works used the Kessler Psychological Distress Scale [32] and the IES-R [4] to measure the psychological distress in patients with epilepsy, reporting a correlation with seizure frequency and anxiety [4]. We found that distress levels significantly correlated with anxiety and somatic symptoms and, less, with depression. Moreover, the female gender presented high levels of distress compared to the male one. The Intrusion (repetitive thought about the pandemic) and the Hyperarousal (hypervigilance with difficulty concentrating) subscales influenced, above all, the anxiety levels and somatization, also contributing to depression. Our study did not show a correlation between neuropsychological tests and clinical factors, as seizures frequency, number of ASMs taken by patients, epilepsy duration. Anxiety, depression, and somatization are highly related comorbidities, partially overlapping and constituting a well-characterized association. Each of these features demonstrated an independent, additive, and differential effect on several domains of life quality [23]. After one year of continuous pandemic containment measures, our patients experienced pathological levels in each component of the somatization-anxiety-depression triad, influencing their life quality and sleep.

Our study is not without limitations. Firstly, the self-assessment questionnaire was a limit of our survey, as patients' reports could be not objective nor quantitative; however, it was the only instrument practicable remotely and performing a longitudinal compar-

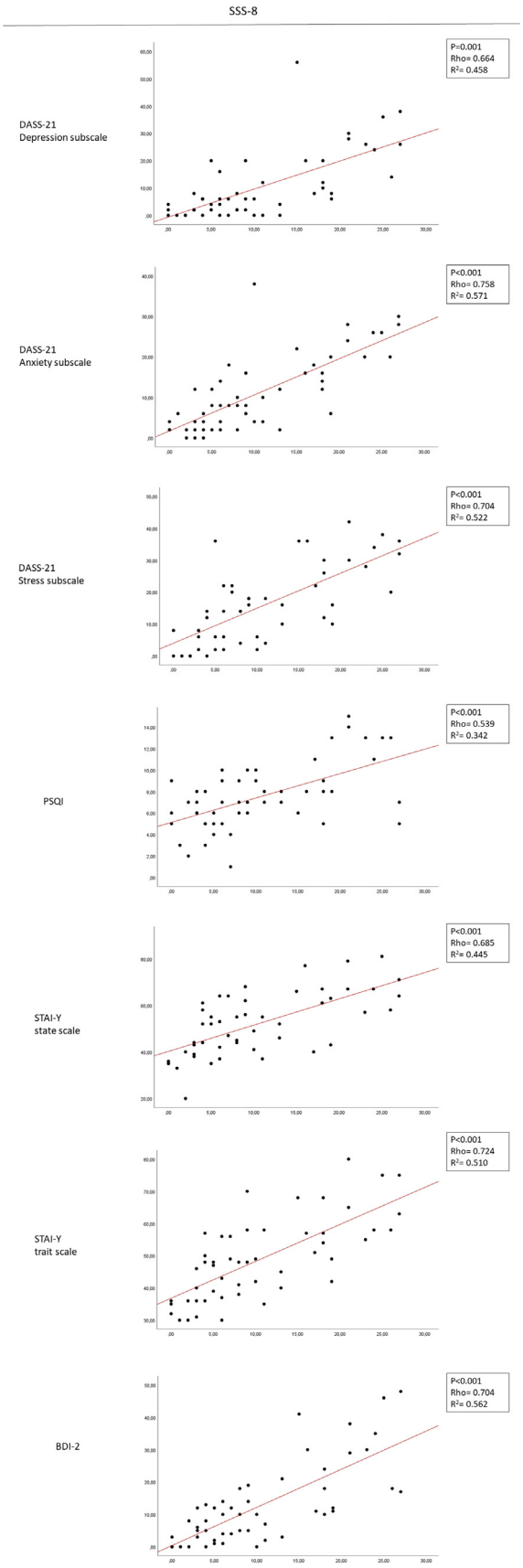

Fig. 3. Significant correlations of somatization scale during the year after COVID-19 beginning. Scatter plots with the regression line showing the data distribution pattern of SSS-8 and the correlated variables on the *x* and *y* axis, respectively [bottom up: DASS-21 depression subscale, DASS-21 anxiety subscale, DASS-21 stress subscale, Pittsburgh Sleep Quality Index (PSQI), STAI-Y state scale, STAI-Y trait scale and Beck Depression Inventory – 2 (BDI-2)]. The *p*-value, Spearman's rho non-parametric rank correlation and squared correlation coefficients (R^2) were also reported for each correlation indicated.

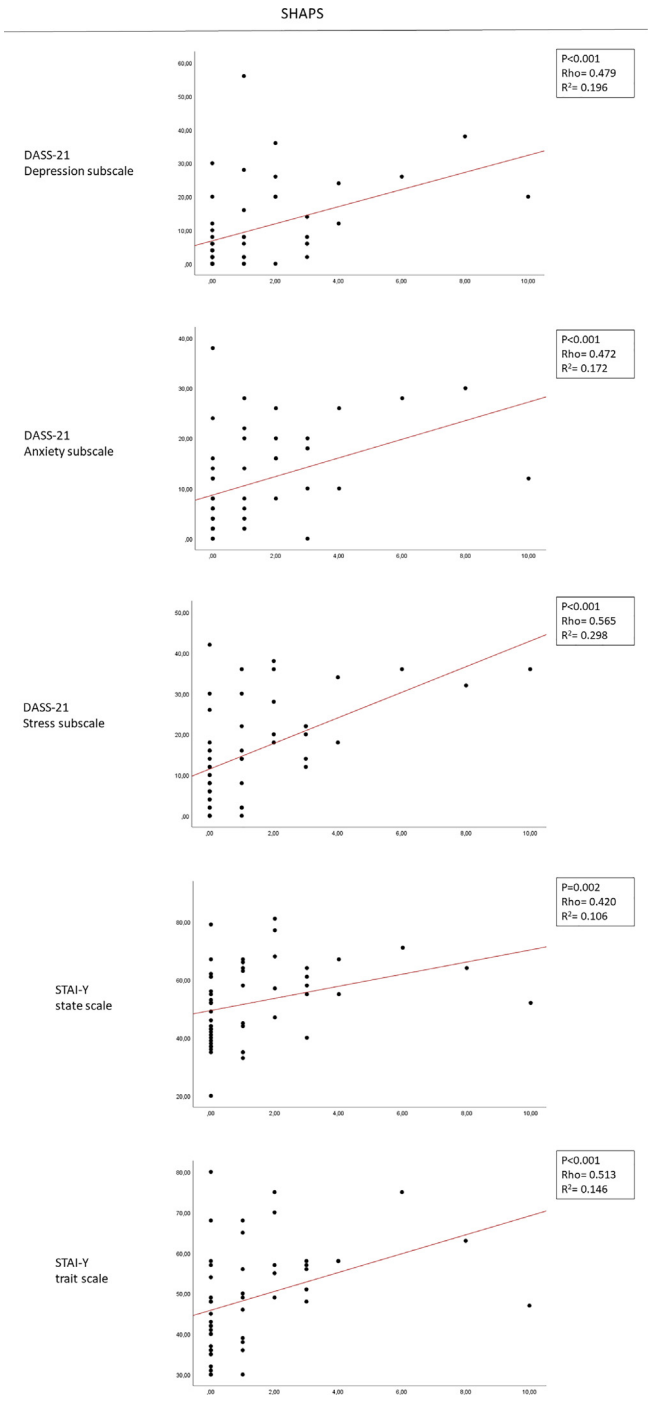

Fig. 4. Significant correlation of anhedonia scale during the year after COVID-19 beginning. Scatter plots with the regression line showing the data distribution pattern of SHAPS and the correlated variables on the *x* and *y* axis, respectively (bottom up: DASS-21 depression subscale, DASS-21 anxiety subscale, DASS-21 stress subscale, STAI-Y state scale and STAI-Y trait scale). The *p*-value, Spearman's rho non-parametric rank correlation and squared correlation coefficients (R^2) were also reported for each correlation indicated.

ison for all those assessments not previously acquired. Secondly, our study did not show a difference between seizure frequency before and after COVID-19 beginning, as well as the influence of epileptic clinical factors (i.e., number of ASMs taken) on neurophysiological features. These results might be due to our small sample; however, we decided to include a highly selective population with epilepsy with prevalent mild cases.

5. Conclusions

Our study was specifically designed to explore the effect of the COVID-19 pandemic on patients with MTLE. Having data on depression and anxiety levels acquired one year before the virus spread, we could conduct a longitudinal study on psychiatric comorbidities in patients with MTLE during the pandemic time. We demonstrated a significant worsening of depression and anxiety levels in these subjects after one year of containment measures. At various degrees, pathological levels of sleep quality, psychological distress, and anhedonia were observed at the same time. In addition, patients with MTLE showed a worsening in life quality and somatization. All these findings suggested that, in patients with MTLE, the COVID-19 pandemic had a more substantial neuropsychological impact rather than a clinical effect. Future follow-up studies might evaluate how, in this population, depression, anxiety, psychological distress, life, and sleep quality could continue to change, especially if the COVID-19 pandemic will not arrest.

Disclosures

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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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None.

Ethical standards

This survey has been approved by our Institution's Ethics Committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We obtained patients' informed consent and data were treated according to the European regulation GDPR n. 2016/679.

Data availability statement

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108600.

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