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Seizure control during the COVID-19 pandemic: Correlating Responsive Neurostimulation System data with patient reports

Cemal Karakas, Ryan Ward, Mohamed Hegazy, Henry Skreho, Zulfi Haneef

Division of Pediatric Neurology, Department of Neurology, University of Louisville, Louisville, KY 40202, USA
Norton Children’s Medical Group, Louisville, KY 40202, USA
Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA
Neurology Care Line, VA Medical Center, Houston, TX 77030, USA

Objective: To understand the impact of the Coronavirus Disease-2019 (COVID-19) pandemic on seizure frequency in persons with epilepsy with a Responsive Neurostimulation (RNS) system implanted.

Methods: Weekly long episode counts (LEC) were used as a proxy for seizures for six months pre-COVID-19 and during the COVID-19 period. Telephone surveys and chart reviews were conducted to assess patient mental health during the pandemic. The change in LEC between the two time periods was correlated to reported stressors.

Results: Twenty patients were included. Comparing the pre-COVID-19 period to the COVID-19 period, we found that only 5 (25%) patients had increased seizures, which was positively correlated with change in anti-seizure medications (ASM, p = 0.03) and bitemporal seizures (p = 0.03). Increased seizures were not correlated to anxiety (p = 1.00), depression (p = 0.58), and sleep disturbances (p = 1.00). The correlation between RNS-detected and patient-reported seizures was poor (p = 0.32).

Conclusions: Most of our patients did not have an increase in seizures following the COVID-19 pandemic. Changes in ASM and bitemporal seizures were positively correlated to increased LEC. There was no correlation between pandemic-related stress and seizures in those found to have increased seizures.

Significance: This is the first study correlating RNS-derived objective LECs with patient self-reports and potential seizure risk factors during the COVID-19 pandemic.

1. Introduction

In December 2019, a novel coronavirus was discovered in Wuhan, China, and was later identified and named the Coronavirus Disease-2019 (COVID-19) (Guan et al., 2020). The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 (WHO). The COVID-19 pandemic has had a tremendous impact on the worldwide medical care (Guan et al., 2020). This unique virus also had an exceptional impact on delivering care to persons with epilepsy (PWE) (Albert et al., 2020). While there is little evidence that PWE are not more likely to be infected with the...
COVID-19 virus or develop the more severe form of COVID-19, PWE can be impacted in several ways (Albert et al., 2020, Cross et al., 2021, Hogan et al., 2020, Rosengard et al., 2021). It is well known that systemic infections can trigger seizures in PWE, and as such, COVID-19 can cause increased seizure frequency in PWE (French et al., 2020, Zarocostas, 2020). In addition, the indirect infodemic impact, including socio-economic and psychological distress, can be more severe in PWE, particularly in patients with drug-resistant epilepsy (DRE), which can also lead to increased seizure frequency (Alkhotani et al., 2020, d’Orsi et al., 2004, Dos Santos Lunardi et al., 2021, Hao et al., 2020, Neshige et al., 2021, Zarocostas, 2020). However, for some patients, the pandemic may have brought about a decrease in daily demands and stressors, eliminating the stress of the daily commute and other social obligations leading to decreased seizure frequency (Neshige et al., 2021, Reilly et al., 2021, Rosengard et al., 2021, Tedrus et al., 2021). Some studies have shown that a considerable proportion of PWE (8 to 31%) had an increase of seizure frequency during the pandemic related to an increase in stressors (Sanchez-Larsen et al., 2021). Conversely, other studies reported a decrease in the seizure frequency in around 3.5 to 13.5% of PWE (Neshige et al., 2021, Reilly et al., 2021, Rosengard et al., 2021, Tedrus et al., 2021). Additionally, the pandemic also affects patients’ ability to access care, including clinic appointments and medication refills (Abokalawa et al., 2021). This has led to more utilization of telemedicine to provide care for PWE (Aleboyeh et al., 2021, Datta et al., 2021).

The Responsive Neurostimulation (RNS) System is a US Food and Drug Administration (FDA)-approved neuromodulation system used as an adjunctive treatment in patients with focal DRE that utilizes continuous monitoring of intracranial electrocorticography (ECoG) through leads implanted in the brain to detect seizures and deliver a brief electrical impulse in response (Skarpaas et al., 2019). The data recorded by the device is stored and uploaded to an online portal which the patient’s epileptologist can access and help guide management (Skarpaas et al., 2019). This enables an unprecedented opportunity to observe long-term ambulatory ECoG responses to changes in the management of epilepsy (Quigg et al., 2020). During the COVID-19 pandemic, this represents an opportunity to provide remote care for PWE (Mirro and Halpern, 2020), and enable an objective analysis of their state of seizures (Mirro and Halpern, 2020, Quaishi et al., 2020).

While there have been studies for COVID-19 impact in epilepsy care (Neshige et al., 2021, Reilly et al., 2021, Rosengard et al., 2021, Sanchez-Larsen et al., 2021, Tedrus et al., 2021), there have been no studies using RNS data to understand the impact of COVID-19 pandemic on seizure frequency of PWE. While surveys and record reviews provide some indication of the effect of the pandemic on seizures, RNS can potentially provide more accurate counts and an excellent way to objectively study this (Albert et al., 2020, Young et al., 2018).

The objectives of this study are 1) to better understand the impact of the COVID-19 pandemic on seizure frequency in a population of patients with an RNS system implanted, 2) to assess patient mental health during the pandemic, including the emergence of anxiety/depression symptoms, sleep disturbances, infection, job changes, and other stressors, 3) to assess the correlation between changes in RNS long episode counts (LECs) as an objective proxy for seizure counts and reported stressors between the PWE with and without increased seizure frequency.

2. Methods

2.1. Participants and data collection

The study was approved by the institutional review board of the Baylor College of Medicine. All adult patients (age > 21-year-old) with RNS System implantation at the Baylor College of Medicine Comprehensive Epilepsy Center before the COVID-19 pandemic declaration by WHO (March 11, 2020) were eligible to participate in this study. There were three sources for the data used in the study. Due to the relatively small eligible patient population, no sampling methods were used, and all eligible patients were included in the study.

2.1.1. RNS device data

Information collected included RNS implant date and detection/stimulation settings at different dates during the period of interest from the Patient Data Management System (PDMS), an FDA-approved online portal for reviewing RNS data. Additional data were obtained from the manufacturer (Neuropace Inc, Mountain View, CA) after institutional approval and a data share agreement. Data analyzed included long episodes (LEs) - a longer periods of abnormal activity where the ECoG pattern of concern persists for a preset duration, typically 10-60 seconds, and represents electrographic seizures or prolonged epileptiform activity (Quigg et al., 2015, Spencer et al., 2016).

LEs were counted in each patient for the half-year period (26 weeks) before and after the WHO pandemic declaration on March 11, 2020, to allow adequate data to compare the longer-term effects of the pandemic on seizure frequency. The first epoch from September 2019 (or if implanted after this date, from the date of implantation) to March 2020 was termed the “pre-COVID-19 period”, and the second epoch from March 2020 to September 2020 was termed the “COVID-19 period”.

2.1.2. Questionnaire-based telephone survey

A telephone survey questionnaire was designed to evaluate the following stressors - depression, anxiety, sleep disturbance, loss of job, infections, any new illness. The questionnaire was pre-tested with five medical students to assess question clarity. This questionnaire also assessed seizure frequency, COVID-19 symptoms or diagnosis, psychiatrist/psychologist visits, medication compliance, access to antiseizure medication (ASM), changes in ASM or RNS settings, access to epilepsy care, new illness, and whether the patient stayed home during the pandemic. Data were abstracted from the medical records where the survey data was not available. Missing variables were coded as unknown. Telephone surveys were conducted throughout August and September 2021. The study was reported according to the Checklist for Reporting of Survey Studies (CROSS) (Sharma et al., 2021).

2.1.3. Chart review

Additional data obtained through chart review included age, sex, marital status, occupation, and race, co-morbidities, seizure characteristics including the type of seizure, etiology, duration of epilepsy, number of ASM, and prior surgical intervention including vagal nerve stimulation (VNS) therapy or resection.

2.2. Data preparation

LEC was used as a proxy for the seizure counts (Quaishi et al., 2020). The RNS data includes a continuous record of the hourly rates of LE. We analyzed weekly LECs instead of hourly or daily counts so that an adequate variance for statistical analyses was available. To preserve data validity, weeks with less than 100 hours of data (out of the possible 168 hours in a week) were removed from the analysis. Data could be missing related to several reasons, including patient-related (e.g., not uploaded) or device-related (e.g., low battery) factors. Variables were not otherwise modified or imputed prior to analysis. Additionally, no sensitivity analysis or methods to adjust for the non-representativeness of the sample were used. All data were de-identified and stored using serial
identification (ID) numbers, and after data collection, there were no identifiers in the data being analyzed.

2.3. Data analysis

Outliers from weekly LECs were removed using interquartile range (IQR) - data points falling outside the range of the first quartile minus 1.5*IQR and the third quartile plus 1.5*IQR were removed (Tukey, 1977). We divided patients into two groups based on RNS-detected LEC: patients with increased or decreased/no change seizure frequency. The telephone survey data were analyzed to identify relationships between patient stress/mental health status during the pandemic and changes in clinical seizure frequency. Independent sample t-tests were then used to find which patients had increases, decreases, or no change in LECs. PWE with and without seizure increase were compared with respect to demographics, epilepsy-related conditions (change in ASM or RNS settings, access to epilepsy care and ASM, epilepsy duration, type of seizures, number of ASMs, non-ASM treatment modalities, and ASM compliance), psychosocial situation, and mental health. The Benjamini-Hochberg method was used to control false discovery rates from multiple comparisons. Fisher’s exact test was used to find significant associations among categorical variables. For categorical variables with a larger than 2x2 contingency table (ethnicity, marital status), a chi-square test of independence was used. For continuous variables (age, epilepsy duration, ASM number), independent sample t-tests were used. We then chose relevant variables to perform logistic regression and ordinary least squares linear regression. Significance was set at p = 0.05. Correlation between percent change in RNS-detected LECs and patient-reported change in seizures was found by using Spearman’s ρ. Patient-reported change in seizures were given numerical values (no change = 0, mild increase = 1, moderate increase = 2, severe increase = 3, mild decrease = −1, moderate decrease = −2, and severe decrease = −3) to calculate the correlation coefficient. The basis for this categorization was to enable patients to easily and quickly describe how their clinical seizures had subjectively changed over time. All statistical analyses were performed using Python (version 3.8.8) and its libraries including pandas (v1.2.4), SciPy (v1.6.2), NumPy (v1.20.1), and statsmodels (v0.12.2) (Van Rossum and Drake, 2009).

3. Results

3.1. Patient selection

We identified 55 adult patients with RNS implants – 25 had implantation before the COVID-19 pandemic, 20 of whom were included in the study (see Fig. 1 for patient selection). Out of 20 patients included in the analysis, 13 (65%) patients responded to the survey.

3.2. Demographic information and social factors

The average age was 41.2 years (SD = 11.9). All patients reported to stay home during the COVID-19 pandemic.

3.3. COVID-19 exposure and other comorbidities during the pandemic

Two patients had COVID-19 symptoms, however only one had a confirmed diagnosis of COVID-19 and that patient did not have any change in seizure frequency based on both RNS-detected LEC and patient report. Subjects had a range of other pre-existing comorbidities, which included hypertension (n = 7), hyperlipidemia (n = 3), hypothyroidism (n = 2), sleep apnea (n = 2), diabetes (n = 1), obesity (n = 1), deep venous thrombosis (n = 1), deafness (n = 1), vitamin-B12 deficiency (n = 1), anemia (n = 1), prior stroke (n = 1), chronic lymphocytic thyroiditis (n = 1), and benign prostate hyperplasia (n = 1).

3.4. Mental health/stressors during COVID-19 pandemic

Data were available regarding anxiety, depression, or sleep disturbance for 17 patients and included mild (n = 3), moderate (n = 4), or no (n = 10) anxiety, mild (n = 3), moderate (n-2) or no (n = 12) depression. Three (15%) patients reported sleep disturbance (1 with excessive sleep vs. 2 with lack of sleep). Data regarding visits to mental healthcare providers were available for 15 patients (12 did not visit, 3 visited).

3.5. Seizure characteristics and impact of confinement during the COVID-19 on epilepsy care

Table 1 summarizes the seizure characteristics and access to epilepsy care during the COVID-19 pandemic. The average duration of seizures was 17.3 years (SD: 12) before the pandemic. Three (15%) patients self-reported increased seizure frequency, and 17 (85%) reported no increase in seizure frequency during the pandemic. Table 2 shows an average number of LECs per week during the pre-COVID-19 period (mean: 32.4 LE, range 0–238.3) and...
We found that five (25%) patients had a statistically significant increase in LEC during the COVID-19 period, while 15 (75%) patients did not have a statistically significant increase in LEC (see Fig. 2). Among the 15 patients with no increase, four had a significant decrease, and 11 had no significant change in seizure frequency. Change in ASM, and bitemporal seizures were independently related to seizure increase. Additionally, we did not find a correlation between pandemic-related stress and seizures in those found to have increased seizures.

4. Discussion

In this study, we correlate RNS-derived objective LECs with seizure self-reports and potential seizure risk factors during the COVID-19 pandemic. We did not find a significant increase in seizure frequency during the pandemic in most patients. We observed that changes in ASM and bitemporal seizures were independently related to seizure increase. Additionally, we did not find a correlation between pandemic-related stress and seizures in those found to have increased seizures.

4.1. Seizure outcomes during COVID-19

The impact of the COVID-19 outbreak on medical care is beyond question. This is also true for PWE, particularly patients with DRE who need frequent ambulatory clinic visits, ancillary testing, and inpatient monitoring. Despite the scientific community’s effort to study COVID-19’s effect on seizure frequency in PWE and to identify associated risk factors, there are contradictory results. In our study, 75% of patients had no significant increase in seizure frequency. We feel that some patients had better seizure control due to improvement in stressors (less work/life-related stresses), while others had worsened control due to fewer clinic visits, fewer medication adjustments, stress related to job loss, sickness in family, stress about the pandemic in general or other factors (Sanchez-Larsen et al., 2021, Sun et al., 2021, Thorpe et al., 2021). The current study is unique by virtue of objective long-term RNS data before and during the COVID-19 pandemic period, eliminating recall bias and providing objective seizure counts. As such, our study may be more reliable than prior literature and could explain some of the conflicting reports (Neshige et al., 2021, Reilly et al., 2021, Rosengard et al., 2021, Sanchez-Larsen et al., 2021, Tedrus et al., 2021). The contradictory results in previous reports may be due to several factors including the absence of baseline seizure data before the pandemic and self-reported seizure frequency with attendant recall and information biases. Additionally, we found that bitemporal seizures were associated with increased seizure frequency during the COVID-19 pandemic. We speculate that this may be related to better efficacy of RNS in unilateral compared to bilateral seizures (Nair et al., 2020).

4.2. Impact of psychosocial factors

The pandemic brought significant changes to daily life, increasing deaths, and causing sudden city lockdowns, resulting in dramatic fear and distress, the effects of which may be augmented
in PWE. This gave clinical researchers a unique opportunity to objectively assess the stressors as risk factors for seizures in PWE. PWE who reported worsened seizure control during the COVID-19 pandemic were significantly more likely to report stressors such as anxiety, depression, and sleep disturbance (Hao et al., 2020, Pierce et al., 2020, Rosengard et al., 2021). We surveyed the effect of these stressors on seizure control during the COVID-19 pandemic and found that most patients showed varying degrees of stressors. Interestingly, as reported in some previous studies (Millevert et al., 2021), despite the high prevalence of stressors in PWE, most of our patients did not seek mental health counseling, although all reported adequate access to medical care. The fear of getting infected with COVID-19 and the assumption that healthcare providers are occupied may have played a role in the reluctance to seek mental healthcare (Millevert et al., 2021). We also found no correlation between increases in LEC and demographics, most epilepsy-related conditions (except change in ASM and bitemporal seizure type), and stressors including psychosocial situation, anxiety, depression, or sleep disturbances. This lack of correlation may be partly related to our questionnaire-based survey

Table 2
The impact of the COVID-19 pandemic on long episode counts and patient-reported change in seizure frequency.

| Patient | Long-episode count pre-COVID-19 | Long-episode count during COVID-19 | P value | Patient reported change in seizure frequency |
|---------|---------------------------------|-----------------------------------|---------|---------------------------------------------|
| 1       | 22.3 ± 8.9                      | 20.3 ± 9.1                        | 0.53    | Increase (moderate)                         |
| 2       | 0.5 ± 0.8                       | 0.3 ± 0.5                         | 0.69    | Decrease (mild)                             |
| 3       | 56.1 ± 58.5                     | 89.3 ± 47.1                       | 0.01*   | Increase (mild)                             |
| 4       | 17.0 ± 22.4                     | 17.1 ± 19.1                       | 0.61    | Decrease (mild)                             |
| 5       | 1.8 ± 1.7                       | 1.1 ± 1.8                         | 0.02*   | Decrease (moderate)                         |
| 6       | 40.6 ± 9.5                      | 30.5 ± 9.3                        | <0.01*  | No change                                   |
| 7       | 25.8 ± 13.4                     | 20.2 ± 10.5                       | 0.03*   | Decrease (moderate)                         |
| 8       | 72.7 ± 37.1                     | 43.4 ± 18.7                       | <0.01*  | Decrease (mild)                             |
| 9       | 4.2 ± 2.0                       | 4.4 ± 1.6                         | 0.76    | No change                                   |
| 10      | 4.8 ± 3.7                       | 6.2 ± 2.3                         | <0.01*  | No change                                   |
| 11      | 6.5 ± 7.2                       | 12.7 ± 8.5                        | <0.01*  | No change                                   |
| 12      | 78.0 ± 39.8                     | 49.0 ± 43.8                       | 0.01*   | No change                                   |
| 13      | 3.1 ± 2.2                       | 5.5 ± 4.3                         | <0.01*  | Decrease (mild)                             |
| 14      | 14.3 ± 17.8                     | 4.5 ± 2.3                         | <0.01*  | None                                        |
| 15      | 0.0 ± 0.0                       | 0.0 ± 0.0                         | N/A     | Decrease (severe)                           |
| 16      | 4.8 ± 2.9                       | 58.4 ± 54.9                       | <0.01*  | Decrease (severe)                           |
| 17      | 17.2 ± 25.3                     | 17.1 ± 22.9                       | 0.53    | Increase (moderate)                         |
| 18      | 238.3 ± 184.4                   | 66.7 ± 59.7                       | <0.01*  | No change                                   |
| 19      | 30.0 ± 15.5                     | 36.1 ± 18.8                       | 0.26    | No change                                   |
| 20      | 9.2 ± 13.3                      | 4.3 ± 1.3                         | 0.76    | Decrease (mild)                             |

Abbreviations- COVID-19: Coronavirus Disease-2019.
* Indicates significance (p ≤ 0.05).
methodology. A full battery stress/depression/sleep inventory (BDI, GAD-7, PHQ-9, PSQI) may have elicited more data points to reveal latent correlations. The number of participants was also low as this was a single-center study on patients with RNS implants. Although the survey included a relatively small number of patients due to the retrospective nature and inherent limitations of retrospective studies and included a single-center study with the inherent limitations of retrospective studies.

Indeed, an international study that evaluated the impact of COVID-19 on patients and their psychosocial well-being of respondents might significantly differ (Millevert et al., 2021). The comparison between studies is problematic because the characteristics of patients varied significantly between the studies. Although the study was a single-center study with the inherent limitations of retrospective studies, it was a considerably higher rate than in previous studies (Millevert et al., 2021, Rosengard et al., 2021). In a study assessing seizure control, stress, and access to care during the COVID-19 pandemic, among subjects who reported worsening seizure control, nearly one-half (48.4%, 15/31) did not contact their neurologist or otherwise seek medical care, although the reasons for this were not investigated (Rosengard et al., 2021). These patients were also more likely to report trouble obtaining their medications during COVID-19 (4/0 vs. 11/0, p = 0.19).

4.3. Access to care and medications

All patients reported adequate access to epilepsy care and ASM during the pandemic. This was a considerably higher rate than in previous studies (Millevert et al., 2021, Rosengard et al., 2021). In a study assessing seizure control, stress, and access to care during the COVID-19 pandemic, among subjects who reported worsening seizure control, nearly one-half (48.4%, 15/31) did not contact their neurologist or otherwise seek medical care, although the reasons for this were not investigated (Rosengard et al., 2021). These patients were also more likely to report trouble obtaining their medications during COVID-19 (4/0 vs. 11/0, p = 0.19).

4.4. Self-reports vs. RNS data

Literature suggests that subjective patient seizure reports (seizures diaries) report only about 45% of all seizures, and nocturnal seizures may even be around 14% (Hoppe et al., 2007). Inaccurate seizure counts due to recall bias may be a challenge for clinicians to understand how to evaluate the efficacy of current treatment and make necessary adjustments. RNS may be a better proxy for seizures than less reliable patient self-reports (Chen and Koubeissi, 2020, Quigg et al., 2020, Quigg et al., 2015, Young et al., 2018). Quigg et al. showed that RNS LECs correlated with seizures with an overall interrater agreement of 79% (Quigg et al., 2015). This motivated us to use LEC as a proxy for seizures to investigate the COVID-19 pandemic's effect on seizures in PWE, eliminating recall bias (Quraishi et al., 2020). We found that RNS reports did not correlate to patient self-reports of increased/worsened seizures. The trend in LEC or interictal epileptiform activity (detections) may be used as valuable metrics to determine improvement in seizure control and may prompt the clinician to contact a patient to assess their overall well-being (Quraishi et al., 2020). RNS data can be used to rule out seizures in case of seizure mimickers such as panic attacks, psychogenic events, somatic symptom disorder, or acute postictal psychosis (Issa Roach et al., 2020). This is particularly of value during the COVID-19 pandemic, as elective admissions to characterize neuropsychological features (Gursky et al., 2021, Kharkar et al., 2014). A study in Wuhan reported that exposure to COVID-19 and a change of ASM regimen during the pandemic increased the risk for seizures (Huang et al., 2020). We found that increased seizures were not more likely to report COVID-19.

4.5. Limitations

This study has several limitations. This study was a single-center study with the inherent limitations of retrospective studies and included a relatively small number of patients due to the relatively small number of PWE with RNS implants. Although the sur-
very response rate was only 65%, it was comparable to similar survey-based studies with response rates between 65–79% (Koh et al., 2021, Valente et al., 2021). Some information regarding psychosocial stressors was missing, which may have affected the statistical analysis. We did not assess the psychosocial stressors before the pandemic for baseline. It is possible that some patients may not remember certain information accurately as the survey was done almost a year after the COVID-19 pandemic declaration. Many patients do not keep seizure diaries or record ASM compliance. Our choice of March 11, 2020, as the start of the COVID-19 pandemic period, was somewhat arbitrary. This choice was based on several factors including increasing public health awareness and COVID-19 surges following the WHO declaration of the global pandemic on March 11, 2020. Our decision to group patients into those with increased seizure frequency and those with no change/decrease is another limitation as this may affect the analysis results. Another way to analyze the data was to compare patients with decreased seizure frequency vs. no change/increase. We chose our grouping strategy (increased vs. no change/decrease) following the typical pattern seen in the literature (Alkhotani et al., 2020, Huang et al., 2020, Rosengard et al., 2021). The categorization of the seizures as mild, moderate, and severe has a subjective nature. While validated seizure intensity questionnaires are more rigorous than simple descriptors, we felt that it would be unreasonable to expect patients to be able to accurately respond to tools such as the Epilepsy Self-Efficacy Scale for several months retrospectively. Although there were no racial differences in seizure control, most of our patients were White, and it is unclear whether our results will be generalizable to other demographics. Finally, seizure control has natural fluctuations irrespective of the pandemic, and the changes in seizure control our patients experienced may not all be related to the COVID-19 pandemic.

5. Conclusions

This is the first study correlating RNS-derived objective LECs with patient self-reports and potential seizure risk factors during the COVID-19 pandemic. Most of our patients did not have an increase in seizures. In those with increased seizures, we did not find a correlation with pandemic-related stress. We did find that ASM changes and bitemporal seizures were independently associated with seizure increases. This study highlights the value of RNS as it can potentially provide more accurate counts and an excellent way to objectively study the impact of seizure risk factors on epilepsy care.

CRediT authorship contribution statement

Ryan Ward: Data curation, Writing - review & editing.

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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Availability of data and materials

Access to de-identified data can be granted upon request to any qualified researcher upon request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/jclinph.2022.05.003.

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