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COVID-19 presentations and outcome in patients with epilepsy

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Objective: To determine whether patients with epilepsy (PWE) are particularly over-represented in a very large cohort of patients with COVID-19. We also investigated whether COVID-19 is associated with a different clinical picture or a more severe course of illness in PWE (compared with others).

Methods: All consecutive patients who referred to and admitted at healthcare facilities anywhere in Fars province (located in the south of Iran with a population of 4,851,000 people) from February 19, 2020 until November 20, 2020 were included.

Results: A total of 37,968 patients were studied. Eighty-two patients (0.2%) had pre-existing epilepsy. Seizures were significantly more frequent among PWE as a presenting manifestation of COVID-19 compared with that in people without epilepsy (Odds Ratio = 27; $p = 0.0001$). Furthermore, PWE less often reported cough (significantly) and more often had gastrointestinal symptoms (vomiting and anorexia; as trends) compared with those in people without epilepsy. Patients with epilepsy were not differently likely to be intubated or admitted at ICUs. Case fatality rates were not different between the two groups [9.8% in PWE and 8.5% in people without epilepsy; $p = 0.690$].

Conclusion: Patients with epilepsy are not susceptible to contracting COVID-19 more than other individuals. Furthermore, COVID-19 in PWE is not associated with a more severe illness or a poorer prognosis. However, PWE and COVID-19 may present somewhat differently than others with such an illness. Why PWE less often present with cough and more often present with gastrointestinal symptoms is not clear yet and should be investigated and clarified in the future studies.

KEYWORDS
coronavirus, COVID, epilepsy, mortality, seizure

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) has caused a devastating and fatal pandemic since late 2019 (COVID-19).[1] Patients with COVID-19 may experience a severe illness characterized by acute respiratory distress syndrome, neurological involvement, multi-organ failure, and death.[1] Main risk factors for a more severe illness among patients with COVID-19 have been identified as older age, diabetes mellitus, chronic respiratory problems, hypertension, and cardiovascular disorders, among others.[1,2] One study suggested that the cumulative incidence of COVID-19 in patients with epilepsy (PWE) was higher compared with that in people without epilepsy. The total case fatality rate was also higher in PWE compared to that in those without epilepsy.[3] However, another study refuted these observations.[4] Therefore, the evidence on the susceptibility of PWE to contracting COVID-19 and its severity, should it happen, is scarce and contradictory.

On the other hand, epilepsy is a common worldwide problem.[5] A recent systematic review estimated that the prevalence of epilepsy in Iran is 1%.[6] Hence, it is both helpful and important for PWE, their

caregivers, and the scientific community to know whether they are at increased risk of contracting COVID-19, and also whether this viral infection might cause a more severe illness, should it happen in PWE.

The first confirmed cases of COVID-19 were reported in Iran on February 19, 2020. As of January 2, 2021 there has been 55,337 COVID-19-related deaths with 1,231,429 confirmed infections in Iran.[7] The aim of the current study was to determine whether PWE are particularly over-represented (significantly more than 1% rate, which is the prevalence rate of epilepsy in Iran) in a very large cohort of patients with COVID-19; this might help us conclude on their susceptibility to contracting this viral infection. We also investigated whether COVID-19 is associated with a different clinical picture or a more severe course of illness in PWE (compared with others).

2 | METHODS

2.1 | Patients

In this study, all consecutive patients who referred to and admitted at healthcare facilities anywhere in Fars province (located in the south of Iran with a population of 4,850,000 people) from February 19, 2020 until November 20, 2020 were included. The patients had a confirmed COVID-19 diagnosis by a positive result on real-time polymerase chain reaction testing of nasopharyngeal and oropharyngeal samples, or a probable COVID-19 diagnosis by a positive chest computerized scan (CT) characteristic for COVID-19, or a possible COVID-19 diagnosis by clinical manifestations (i.e., history and physical examination) compatible with COVID-19.

2.2 | Data collection

For all patients, who were admitted with a diagnosis of COVID-19, the following data were collected at the emergency room by the admitting physician and entered into a database (on admission): age, sex, presence of fever, cough, respiratory distress, muscle pain, dizziness, headache, loss of smell, seizure, abdominal pain, nausea, vomiting, and anorexia. Other collected data included: real-time polymerase chain reaction test results, chest CT scan results, the need for intubation, and admission to a hospital ward (i.e., COVID-specific ward, intensive care unit [ICU], or others). Underlying chronic health problems were also collected (self-declared) (e.g., renal, liver, cardiac, neurological disorders [including epilepsy]). No data were available about the hospital course of the patients (e.g., laboratory test results, complications). However, the outcome was also recorded in the database, as dead or discharged.

2.3 | Statistical analyses

This was a nested case-control study. All the statistical analyses were performed by SPSS software version 22. Values were presented as mean ± standard deviation (SD) for continuous variables and as number (percent) of subjects for categorical variables. Fisher's exact test (FE), Pearson's chi-square (PCS), and *t*-test were used for univariate comparisons. The associations between pre-existing epilepsy with other variables were determined using the logistic regression analysis; the variables with $p < 0.1$ from the univariate analyses were entered into the logistic regression analysis model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A *p* value less than 0.05 (2-sided) was considered as significant.

2.4 | Standard protocol approvals, registrations, and patient consents

Shiraz University of Medical Sciences Review Board approved this study as a minimal-risk research using the data that were collected for routine clinical practice and waived the requirement for informed consent. The data were collected and entered into the electronic registry of Shiraz University of Medical Sciences (Ethics code: IR.SUMS.REC.1399.022).

3 | RESULTS

3.1 | General characteristics of the patients

During the study period, 37,968 patients (20,189 [53.2%] men and 17,779 [46.8%] women) were hospitalized with a diagnosis of COVID-19 (13,165 patients [34.7%] with confirmed diagnoses, 9400 patients [24.8%] with probable diagnoses, and 15,403 patients [40.6%] with possible diagnoses). The mean age (± standard deviation) of the patients was 52 (± 23) years (range: 0 to 129 years). In total, 3229 patients died (case fatality rate = 8.5%).

3.2 | Representation of PWE among patients with COVID-19

Eighty-two patients (0.2%) had pre-existing epilepsy, 1004 patients (2.6%) had other CNS problems (e.g., pre-existing cerebrovascular accident [CVA] [*N* = 208], Alzheimer's disease [AD] [*N* = 62], Parkinson's disease [PD] [*N* = 41], multiple sclerosis [MS] [*N* = 26], unspecified [*N* = 570]) and 15,069 patients (39.7%) had other chronic medical problems. Even if speculatively, we considered half of those with unspecified CNS problems as if they had epilepsy, the total number of patients with epilepsy would be about 370 people (0.9%).

3.3 | Presenting clinical manifestations of COVID-19 in PWE

Table 1 shows the clinical manifestations of COVID-19 (on admission) in PWE compared with those in people without epilepsy.

We included all the variables with a p value <0.1 in a regression analysis model. The results of the binary logistic regression analysis are shown in Table 2 (only the significant associations or trends). The model that was generated by this test was significant (p = 0.0001) and could predict the underlying epilepsy in 99.5% of the patients.

Seizures (breakthrough/exacerbation) were significantly more frequent among PWE as a presenting manifestation of COVID-19 compared with (de novo) seizures in people without epilepsy (OR = 27; p = 0.0001). Furthermore, PWE less often reported cough (p = 0.01) and more often had gastrointestinal symptoms (vomiting [p = 0.07] and anorexia [p = 0.09]; as trends) compared with those in people without epilepsy. While age was significantly different between the groups, it was not a clinically helpful differentiating variable (OR = 0.989). When we included only patients with a confirmed or a probable COVID-19 diagnosis (N = 22,565), similar results were obtained (as in Table 2).

3.4 | Clinical course and outcome of COVID-19 in PWE

Patients with epilepsy were not differently likely to be intubated (9 patients [11%]) compared with those without epilepsy (3322 [8.7%]); p = 0.435. They were neither differently likely to be admitted at ICUs (9 patients [11%]) compared with those without epilepsy (3847 [10%]); p = 0.957. Finally, case fatality rates were not different between the two groups (9.8% in PWE [8 people] and 8.5% in people without epilepsy [3221 people]; p = 0.690). When we included only patients with a confirmed or a probable COVID-19 diagnosis (N = 22,565), similar results were obtained.

In a subanalysis, we selected PWE with no other underlying chronic medical disorders (N = 63) and compared them with people without epilepsy and any other underlying chronic medical disorders (N = 21,960). Similar results were obtained, and these two groups were not significantly different with respect to receiving intubation (7 vs. 1525 patients; p = 0.197), ICU admission (5 vs. 1863 persons; p = 0.655), or fatality (4 vs. 1081 people; p = 0.998).

4 | DISCUSSION

4.1 | Patients with epilepsy are not over-represented among patients with COVID-19

In this study, we observed that PWE are not over-represented (significantly more than 1% rate) in a very large cohort of patients with COVID-19. In one previous study, among 5700 PWE, who were managed at the studied centers, only 14 patients (0.2%) tested positive for SARS-CoV2.[4] Their rate is similar to our observation, and their study corroborates our finding. While another study suggested that the cumulative incidence of COVID-19 in PWE was higher compared with that in the population without epilepsy (1.2% vs. 0.5%),[3] their results were based on a small number of PWE (21 patients compared with 82 PWE in our study), and their conclusion should be interpreted with caution. In addition, the potential population differences may explain the observed difference between our study and this latter report by

TABLE 1 Clinical presentations of patients with COVID-19 with or without epilepsy in univariate analyses

Variable (statistical test)	Patients with epilepsy, N = 82 (%)	Patients without epilepsy, N = 37,886 (%)	p Value
Age (mean ± standard deviation), years (t)	42 ± 24 (range: 0 to 93 years; median: 41; interquartile range: 29)	53 ± 23 (range: 0 to 129 years; median: 55; interquartile range: 32)	0.0001
Sex (Male: Female) (FE)	44: 38	20,145: 17,741	0.999
Fever (FE)	29 (35%)	14125 (37%)	0.730
Cough (FE)	20 (24%)	15303 (40%)	0.004
Muscle pain (FE)	21 (26%)	10275 (27%)	0.798
Respiratory distress (FE)	44 (54%)	18385 (49%)	0.377
Loss of smell (PCS)	3 (4%)	554 (1%)	0.038
Headache (PCS)	11 (13%)	3227 (9%)	0.001
Dizziness (PCS)	0 (0)	1149 (3%)	0.0001
Seizure (PCS)	14 (17%)	208 (0.5%)	0.0001
Abdominal pain (PCS)	1 (1%)	1204 (3%)	0.002
Nausea (PCS)	5 (6.1%)	2443 (6.4%)	0.005
Vomiting (PCS)	8 (10%)	1971 (5%)	0.001
Anorexia (PCS)	10 (12%)	2702 (7%)	0.002
Diarrhea (PCS)	3 (3.7%)	1652 (4.4%)	0.004

Note: Pearson's chi-square (PCS), Fisher's exact test (FE), and t-test (t).

TABLE 2 Significant associations (or trends) between COVID-19 clinical characteristics and pre-existing epilepsy

	Odds ratio	95% confidence Interval	*p* Value
Age	0.989	0.980–0.998	0.019
Cough	0.529	0.316–0.886	0.016
Seizure	27.259	13.913–53.406	0.0001
Vomiting	2.249	0.936–5.403	0.070
Anorexia	1.816	0.912–3.616	0.090

Cabezudo-García et al.[3] However, we can conclude that based on the available evidence, PWE are not at a higher risk of contracting symptomatic COVID-19 (requiring hospitalization). Furthermore, there is no plausible biological reasons to suppose that PWE are at an increased risk of contracting viral infections, including COVID-19; such evidence does not exist for influenza or other viral infections, to the best of our knowledge. However, some special populations of PWE may be at a higher risk of contracting (severe) COVID-19 and other infections; being on immunosuppressive therapy (e.g., for autoimmune epilepsy) or adrenocorticotropic hormone (ACTH) (for West syndrome) are examples of such circumstances.[8,9]

4.2 | Patients with epilepsy may have different clinical manifestations of COVID-19

We observed that PWE and COVID-19 may present differently compared with people without pre-existing epilepsy. Breakthrough/exacerbation of seizures were particularly common among PWE. This observation has significant clinical implications. First, a breakthrough seizure or exacerbation of seizure in a person with epilepsy should not be exclusively attributed to the underlying epilepsy and the treating physician should not dismiss other possible etiologies. It is warranted to consider and investigate the possibility of COVID-19 in all PWE, who refer with breakthrough seizure(s) or exacerbation of seizures, during this pandemic. Second, both patients and their caregivers should be aware of the risk of seizure exacerbation in PWE who contract COVID-19. A previous systematic review suggested that patients with pre-existing neurological disorders and COVID-19 may develop exacerbation of their neurological symptoms; however, only one patient with epilepsy was included in that study.[10] In a previous study, 18% of PWE reported seizure worsening, which was best explained by the number of anti-seizure medications (ASMs) and the severity of sleep disorder.[11] Exacerbation or breakthrough seizures in PWE and COVID-19 may be a multifactorial phenomenon. SARS-CoV2 may have neurotropism, and COVID-19 has been associated with seizures (even in people without pre-existing epilepsy) in many previous studies.[12] Furthermore, this pandemic has caused significant disruption in the quality and availability of care to PWE, as well as increased stress and social isolation rates; these may contribute to exacerbation or breakthrough seizures in PWE.[11,13] Finally, some patients with COVID-19 may develop a seizure as a consequence of hypoxemia, organ failure, metabolic derangements, or drug-drug interactions.[14] Healthcare professionals, who are taking care of patients with COVID-19, should investigate and promptly manage seizures in these patients (both in PWE or otherwise).

We also observed that PWE less often presented with cough and more often presented with gastrointestinal symptoms (vomiting and anorexia) compared with people without epilepsy. Non-respiratory manifestations of COVID-19 are increasingly being recognized in the more recent literature. Gastrointestinal (GI) symptoms, while less common compared to respiratory symptoms, have gained increased attention lately; these may coexist with respiratory symptoms or they may be the only presentations of the disease.[15] Early identification and prompt attention to GI symptoms of COVID-19 are important because hospitalized COVID-19 patients with concomitant GI symptoms may develop a more severe disease.[15] While we cannot provide any plausible explanation for this observation, ASMs may hypothetically represent a possible cause for the higher prevalence of gastrointestinal symptoms in PWE. This should be explored in future studies.

4.3 | Patients with epilepsy do not have a more severe course of COVID-19 illness

While we did not have access to the hospital records of the patients, the authors can address some variables that may reflect on the clinical course and outcome of PWE and COVID-19. In the current study, the rates of receiving intubation, ICU admission, and mortality were not different between PWE and other people with COVID-19 who were hospitalized. This is in line with the results from a previous study.[4] While another study suggested that the total case fatality rate was higher in PWE compared to patients without active epilepsy (23.8% vs. 3.6%; $p < 0.001$),[3] their results were based on a small number of PWE and their conclusion should be interpreted with caution. It seems that PWE do not have a more severe or a more complicated course of COVID-19 illness. However, this statement should be further investigated in the future.

5 | LIMITATIONS

The pre-existing medical conditions were based on self-declaration, and no validation was done. Furthermore, we did not have access to the whole medical records of the patients to clarify the complete clinical picture and also the course of illness in these patients. In addition, among 13,165 patients with confirmed diagnoses of COVID-19 (with positive real-time polymerase chain reaction test results), only 25 patients (0.18%) had pre-existing epilepsy; statistical analyses were not possible due to small numbers. Finally, we do not know the rate of pre-existing epilepsy among patients with mild COVID-19 or those who had asymptomatic infections (The observed 0.2% percentage is much lower than the prevalence of epilepsy in

Iran (1%), and the sample of the present study may not be a representative of Iran population).

6 | CONCLUSION

Based on the current study, we can suggest that PWE are not susceptible to contracting COVID-19 more than that in other individuals. Similarly, we may conclude that COVID-19 in PWE is not associated with a more severe illness or a poorer prognosis. However, PWE and COVID-19 may clinically present somewhat differently than others with such an illness. Why PWE less often present with cough and more often present with gastrointestinal symptoms is not clear yet and should be investigated and clarified in the future studies.

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CONFLICT OF INTEREST

Ali A. Asadi-Pooya, M. D.: Honoraria from Cobel Daruo, RaymandRad, Sanofi, and Tekaje; Royalty: Oxford University Press (Book publication). Others: None.

AUTHOR CONTRIBUTIONS

Ali A. Asadi-Pooya, M. D.: Designed and conceptualized the study; analyzed the data; drafted and revised the manuscript. Others: Collected the data and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data are confidential and will not be shared as per the regulations of Shiraz University of Medical Sciences.

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REFERENCES

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;*109*:e102433.
2. Javanmardi F, Keshavarzi A, Akbari A, Emami A, Pirbonyeh N. Prevalence of underlying diseases in died cases of COVID-19: a systematic review and meta-analysis. *PLoS One*. 2020;*15*:e0241265.
3. 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-e1425.
4. Granata T, Bisulli F, Arzimanoglou A, Rocamora R. Did the COVID-19 pandemic silence the needs of people with epilepsy? *Epileptic Disord*. 2020;*22*:439-442.
5. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017;*88*:296-303.
6. Asadi-Pooya AA, Simani L. Epilepsy syndromes in Iran: a systematic review. *Acta Neurol Scand*. 2021;*143*(5):475-480.
7. https://www.worldometers.info/coronavirus/country/iran. Accessed on January 2, 2021.
8. Zaidan M, Legendre C. Solid organ transplantation in the era of COVID-19: lessons from the past six months. *Transplantation*. 2020;*105*:61-66. https://doi.org/10.1097/TP.0000000000003536
9. Shumiloff NA, Lam WM, Manasco KB. Adrenocorticotropic hormone for the treatment of West Syndrome in children. *Ann Pharmacother*. 2013;*47*:744-754.
10. Kubota T, Kuroda N. Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: a systematic review. *Clin Neurol Neurosurg*. 2020;*200*:e106349.
11. Assenza G, Lanzone J, Brigo F, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol*. 2020;*11*:737.
12. Asadi-Pooya AA, Simani L, Shahisavandi M, Barzegar Z. COVID-19, de novo seizures, and epilepsy: a systematic review. *Neurol Sci*. 2020;*42*(2):415-431.
13. Asadi-Pooya AA, Farazdaghi M, Bazrafshan M. Impacts of the COVID-19 pandemic on Iranian patients with epilepsy. *Acta Neurol Scand*. 2020;*142*(4):392-395. https://doi.org/10.1111/ane.13310
14. Asadi-Pooya AA. Seizures associated with coronavirus infections. *Seizure*. 2020;*79*:49-52.
15. Perisetti A, Goyal H, Gajendran M, Boregowda U, Mann R, Sharma N. Prevalence, mechanisms, and implications of gastrointestinal symptoms in COVID-19. *Front Med (Lausanne)*. 2020;*7*:e588711.

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