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Clinical characteristics of 30 COVID-19 patients with epilepsy: A retrospective study in Wuhan

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ABSTRACT

Objective: This study aims to present the clinical characteristics of 30 hospitalized cases with epileptic seizures and coronavirus disease 2019(COVID-19).

Methods: This is a retrospective observational research study. Clinical data were extracted from electronic medical records in 1550 patients with a laboratory-confirmed diagnosis of COVID-19, who were hospitalized in Wuhan Central Hospital, China, from 1 January to 31 April 2020. 30 COVID-19 patients with the diagnosis of epilepsy were enrolled. The clinical characteristics, complications, treatments, and clinical outcomes of 30 cases were collected and analyzed.

Result: Of 30 patients with a diagnosis of epilepsy and COVID-19, 13 patients (43.4%) had new-onset epileptic seizures without an epilepsy history(new-onset seizure group, NS group), ten patients(33.3%) had an epilepsy history with a recurrent epileptic seizure (recurrent seizure group, RS group) and seven patients(23.3%) had an epilepsy history but no seizure during the course of COVID-19 (epilepsy history group, EH group). Patients in the RS group had a larger number of other-neurological-disease histories than those in the NS and EH groups (7/10[70%] VS 1/13 [7.7%] VS 1/7[14.3%]); the difference between the RS group and NS group is significant (P < 0.05). Patients in the NE and RS groups suffered more severe/critical COVID-19 infection than patients in the EH group (10/13[76.9%] VS 6/10[60%] VS 1/7[14.3%]); the difference between the NS group and EH group is significant (P < 0.05). 36.7% of patients had one to five neurological complications, and 46.4% of patients had 6–10 neurological complications. The complications in patients with seizures (in the RS and NS groups) seem to be more than those without seizures (in the EH group), but it did not reach statistical significance. The proportion of antiepileptic drugs (AEDs) treatment before admission was higher in the EH group than in the RE group(7/7 [100%] VS 2/10 [20%], P < 0.05). The mortality of 30 patients with epilepsy and COVID-19 was 36.67%. The mortality of the NS group(38.5%) and the RS group(50%) were a little higher than in the EH group(14.3%). None of the convalescent patients had a recurrent seizure, and there were no more deaths in the 3-month follow-up after discharge.

Conclusions: COVID-19 patients with recurrent epileptic seizures had more underlying neurological diseases than patients who had an epilepsy history but without a seizure. Patients with new-onset and recurrent epileptic seizures suffered more severe/critical COVID-19, which may lead to a worse prognosis. If patients with epilepsy history continue using AEDs during COVID-19 pandemics, the risk of recurrent seizure may be reduced, and a good prognosis for patients with epilepsy history could be expected.

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Introduction

Since the end of December 2019, COVID-19, a new type of coronavirus pneumonia began to spread rapidly in many countries and regions and has become a global public health emergency.

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Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), the pathogen of COVID-19, mainly involves the human respiratory system and causes fever, cough, shortness of breath, myalgia, or fatigue (Huang et al., 2020). However, it is worth noting that about 25%–36.4% of hospitalized patients with COVID-19 may exhibit neurological manifestations (Mao et al., 2020). A few patients may have more specific neurological symptoms, such as seizures (about 0.5%) (Mao et al., 2020). A seizure is defined as a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbance, or a combination of these symptoms. Epilepsy is a group of related disorders in the brain's electrical systems characterized by a tendency to cause recurrent seizures. Epilepsy is considered a systemic component with a high prevalence of comorbidity, not just a neurological condition (Yuen et al., 2018). About 2%–3% of patients who have new-onset seizures will go on to develop epilepsy (Gavvala and Schuele, 2016). Up to now, over 70 million people are diagnosed with epilepsy worldwide (Thijs et al., 2019); they deserve more attention when suffering from COVID-19.

What's more, new-onset or recurrent seizures in COVID-19 patients may pose even more severe and costly problems, which may lead to higher mortality. However, since the onset of the COVID-19 pandemic, in large retrospective, multicenter studies, only one or two cases with COVID-19 who suffered seizures (Mao et al., 2020) have been reported6, and only a few studies described seizures in COVID-19 patients in detail (Moriguchi et al., 2020; Sohal and Mansur, 2020). What is unclear is the incidence, characteristics, and pathogenesis of COVID-19 patients with seizures or epilepsy. We are interested in learning which factors cause seizures in COVID-19 patients and whether the occurrence of seizures affects the prognosis of COVID-19 patients. In this retrospective study, we report the clinical characteristics of 30 COVID-19 patients with epileptic seizures who were hospitalized in a fever ward from January to April 2020.

Methods

Study design and participants

Clinical data of patients diagnosed with epilepsy at discharge were extracted from electronic medical records in 1550 hospitalized patients in Wuhan Central Hospital with a laboratory-confirmed diagnosis of COVID-19 from 1 January to 31 April 2020. COVID-19 was confirmed by one of the following etiological or serological evidence: a positive result from pharyngeal swab of novel coronavirus nucleic acid by real-time reverse transcriptase PCR; a positive result serum novel coronavirus specific IgM and IgG; or novel coronavirus specific IgG in the serum was changed from negative to positive or increased by more than four times in the recovery period compared with the acute phase. The severity of the disease was classified as mild/moderate or severe/critical. Patients diagnosed with epilepsy at discharge were confirmed by two neurological experts according to the diagnosis and classification of the International League Against Epilepsy (Scheffer et al., 2017). Patients who had epileptic seizures with and without an epileptic seizure history were retrospectively enrolled in the new-onset seizure group (NS group) or the recurrent seizure group (RS group).

In contrast, patients who had no seizures but with an epilepsy history were enrolled in the epilepsy history group (EH group). This study was approved by the Ethics Commission of the Central Hospital of Wuhan. Written informed consent was waived by the Ethics Commission of the designated hospital under the criteria of emerging infectious diseases.

Table 1
Demographics, past medical history, classification of disease severity status and nosocomial infection in patients with epilepsy and COVID-19.

	Total	NS group	RS group	EH group	P
	N = 30	N = 13 (43.3%)	n = 10 (33.3%)	n = 7 (23.3%)	
Age, median (IQR), y	57.5 (50.75,66.75)	56 (51.5,61.5)	59 (50.75,71.0)	62 (30.0,69.0)	0.821
Distribution					
<40	2 (6.7%)	0 (0%)	0 (0%)	2 (28.6%)	0.151
40–60	12 (40.0%)	7 (53.8%)	4 (40.0%)	1 (14.3%)	
>60	16 (53.3%)	6 (46.2%)	6 (60.0%)	4 (57.1%)	
Gender					
Male	15 (50%)	6 (46.2%)	5 (50%)	4 (57.1%)	1
Femal	15 (50%)	7 (53.8%)	5 (50%)	3 (42.9%)	
Past medical history					
Epilepsy	17 (56.7%)	0 (0%)	10 (100%)	7 (100%)	0
Neurological disease except for epilepsy	9 (30.0%)	1 (7.7%)*	7 (70%)	1 (14.3%)	0.005
Cerebral hemorrhage	5 (16.7%)	1 (7.7%)	4 (40%)	0 (0%)	0.094
Cerebral infarction	2 (6.7%)	0 (0%)	1 (10%)	1 (14.3%)	0.313
Brain truama	3 (10%)	0 (0%)	3 (30%)	0 (0%)	0.038
Brain tumor	1 (3.3%)	0 (0%)	1 (10%)	0 (0%)	0.567
Brain operation	2 (6.7%)	0 (0%)	2 (20%)	0 (0%)	0.152
Hypertension	13 (43.3%)	7 (53.8%)	5 (50%)	1 (14.3%)	0.237
Cardiovascular disease	2 (6.7%)	1 (7.7%)	1 (10%)	0 (0%)	1
Chronic kidney disease	3 (10%)	2 (15.4%)	1 (10%)	0 (0%)	0.776
Diabetes	4 (13.3%)	1 (7.7%)	2 (20%)	1 (14.3%)	0.801
Malignant tumor	2 (6.7%)	1 (7.7%)	0 (0%)	1 (14.3%)	0.701
No medical history	3 (10%)	3 (23.1%)	0 (0%)	0 (0%)	0.228
Disease severity status					
Mild/moderate	13 (43.3%)	3 (23.1%)**	4 (40%)	6 (85.7%)	0.038
Severe/critical	17 (56.7%)	10 (76.9%)**	6 (60%)	1 (14.3%)	
COVID-19 infection					
Nosocomial acquired,%	12 (40%)	6 (46.2%)	4 (40%)	2 (28.6%)	0.891
Community acquired,%	18 (60%)	7 (53.8%)	6 (60%)	5 (71.4%)	

NS group: New-onset seizure group without epilepsy history; RS group: recurrent seizure with epilepsy history; EH group: epilepsy history group.
P less than 0.05 was considered statistcally significant.
*Differences between NS and RS group, P < 0.05; **Differences between NS and EH group, P < 0.05.

Data collection

30 hospitalized COVID-19 patients with epilepsy were enrolled. Data were extracted, including demographic characteristics, past medical history, symptoms on admission, laboratory tests, complications, and treatments. Patients' complications besides COVID-19 and epilepsy were recorded according to the diagnosis at discharge. The clinical outcome at discharge was either rehabilitation or death. All participants were laboratory-confirmed COVID-19. All specimens were examined in the laboratory department.

Statistical analysis

All data were analyzed using SPSS 20.0. Continuous variables were expressed as median (IQR) and tested by the non-parametric Mann-Whitney *U* test Categorical variables were expressed as a percentages (%) and tested by Fisher's exact test or X^2 test. P less than 0.05 was considered statistically significant.

Results

In this retrospective study, we included 30 hospitalized patients diagnosed with epilepsy from 1550 hospitalized COVID-19 patients. Of 30 patients with a diagnosis of epilepsy and COVID-19, thirteen patients (43.4%) had new-onset epileptic seizures without an epilepsy history (NS group), ten patients(33.3%) with an epilepsy history had a recurrent epileptic seizure (RS group), and seven patients(23.3%) with an epilepsy history had no seizure during the course of COVID-19 (EH group). Patients' demographics, past medical history, classification of disease severity status, and nosocomial infection with COVID-19 are summarized in Table 1.

The median age of all patients was 57.5 years, 16(53.3%) of the patients were >60 years of age, twelve (40.0%) of them were between 40 and 60 years, and two (6.7%) of those in the EH group were <40 years of age. There were 15 (50%) males and 15 (50%) females. Three patients in the NS group had no medical history. 17 cases(56.7%) in the RS group and EH group had an epilepsy history. Nine cases (30%) had other-neurological-disease histories except for epilepsy; there is a statistical difference among the three groups(RS group:7/10,[70%], NS group: 1/13, [7.7%], EH group 1/7,[14.3%], P < 0.05). Patients in the RS group more often had other-neurological-disease histories (especially brain trauma) than those in the NS group(P < 0.05). Seven out of ten patients in the RS group had at least one other neurological disease, including cerebral hemorrhage(four cases), brain trauma(three cases), brain operation(two cases), cerebral infarction(one case), and brain tumor(one case). In addition to neurological diseases, other medical histories were hypertension (43.3%), diabetes(13.3%), chronic kidney disease(10%), cardiovascular disease(6.7%), and malignant tumor(6.7%). As to the disease severity status, 17 cases (56.7%) were severe/critical. The proportion of severe/critical patients in the NS group and RE group were higher than EH group (10/13[76.9%] VS 6/10[60%] VS 1/7[14.3%], P < 0.05), and the difference between the NS group and EH group is significant (P < 0.05). Twelve (40%) patients were considered to have COVID-19 by nosocomially acquired infection, because they were admitted for diseases other than COVID-19. The other eighteen (60%) patients, who contracted COVID-19 by community infection, were admitted due to typical symptoms of COVID-19.

Table 2
Onset symptoms to hospital admission and laboratory data of patients with epilepsy and COVID-19.

	Total	NS group	RS group	EH group	P
	N = 30	N = 13 (43.3%)	n = 10 (33.3%)	n = 7 (23.3%)	
Onset symptoms to hospital admission					
Typical symptoms					
Fever	18 (60%)	9 (69.2%)	5 (50%)	4 (57.1%)	0.641
Cough	8 (26.7%)	3 (23.1%)	2 (20%)	3 (42.9%)	0.659
Expectoration	4 (13.3%)	3 (23.1%)	1 (10%)	0 (0%)	0.523
Dyspnea	5 (16.7%)	3 (23.1%)	2 (20%)	0 (0%)	0.572
Chest distress	5 (16.7%)	1 (7.7%)	3 (30%)	1 (14.3%)	0.396
Chest pain	3 (10%)	1 (7.7%)	2 (20%)	0 (0%)	0.584
Fatigue	13 (43.3%)	8 (61.5%)	4 (40%)	1 (14.3%)	0.134
Vomiting	11 (36.7%)	7 (53.8%)	4 (40%)	0 (0%)	0.054
Neurological symptoms					
Seizure	3 (10%)	1 (7.7%)	2 (20%)	0 (0%)	0.584
Headache	8 (26.7%)	4 (30.8%)	4 (40%)	0 (0%)	0.211
Dizziness	4 (13.3%)	3 (23.1%)	1 (10%)	0 (0%)	0.523
Impaired consciousness	11 (36.7%)	5 (38.5%)	5 (50%)	1 (14.3%)	0.356
Language disorder or aphasia	10 (33.3%)	6 (46.15%)	3 (30%)	1 (14.3%)	0.761
Activity obstacle or paralysis	9 (30%)	4 (30.8%)	4 (40%)	1 (14.3%)	0.463
Numness of the limbs	3 (10%)	2 (15.4%)	1 (10%)	0 (0%)	0.776
Gatism	3 (10%)	1 (7.7%)	2 (20%)	0 (0%)	0.584
No above neurological symptoms	13 (43.3%)	4 (30.8%)	3 (30%)	6 (85.7%)	0.052
Laboratory data					
White blood cell, $(3.5–9.5)\times10^9$/L	6.97 (5.11,12.44)	6.97 (5.05,14.6)	7.23 (5.07,12.45)	6.97 (4.41,7.95)	0.748
Neutrophil count1, $(1.8–6.3)\times10^9$/L	4.9 (3.45,9.73)	5.56 (3.88,12.9)	4.82 (3.33,10.16)	4.58 (3.0,5.86)	0.462
Lymphocyte count, $(1.1–3.2)\times10^9$/L	1.26 (0.83,1.72)	0.96 (0.62,1.34)	1.47 (0.86,1.92)	1.5 (1.26,1.63)	0.149
Hemoglobin, (115–150)g/L	132.0 (113.5,140.5)	127 (95,147)	134.5 (120.75,137.5)	141 (113,154)	0.471
D-dimer, (0–1)ug/mL	0.88 (0.26,2.39)	1.24 (0.65,2.39)	1.64 (0.18,5.11)	0.28 (0.11,1.19)	0.114
Albumin, (40–55)g/L	39.3 (33.8,43.75)	36.85 (29.15,43.78)	40.95 (33.88,44.73)	40.8 (36.9,43.1)	0.441
Alanine aminotransferase, (9–50)U/L	23.3 (12.1,33.3)	27.25 (10.85,32.28)	18.3 (12.48,31.25)	26.6 (11.9,57.0)	0.886
Aspartate aminotransferase, (15–40)U/L	26.4 (17.1,45.0)	26.55 (21.33,36.15)	32.95 (16.95,58.57)	21.2 (16.7,35.1)	0.758
Serum creatinine, (57–111)umol/L	71.3 (52.6,92.5)	72.6 (65.0,144.48)	68.4 (59.3,73.08)	72.6 (65.0,85.0)	0.856
Creatine kinase, (38–174)U/L	125.0 (69.45,182.5)	147.7 (72.9,225.0)	107.0 (60.75,152.88)	88.5 (67.58,692.75)	0.761
Lactate dehydrogenase, (82–285)U/L	237 (161.0 , 325.0)	336.0 (186.0,420.0)	232.0 (161.25,317.0)	150.5 (132.75,406.25)	0.094
Blood glucose, (3.9–6.1)mmol/L	5.81 (4.99,7.92)	6.19 (5.1,8.33)	7.15 (4.9,8.83)	5.09 (4.67,5.81)	0.249
Brain natriuretic peptide, (<100)pg/ml	120.9 (27.73,924.88)	372.0 (84.12,13710.0)	73.76 (16.53 , 229.15)	96.0 (17.5 , 1030.4)	0.095

NS group: New-onset seizure group without epilepsy history; RS group: recurrent seizure with epilepsy history; EH group: epilepsy history group.
P less than 0.05 was considered statistcally significant.

The onset symptoms and laboratory data of patients with epilepsy and COVID-19 on hospital admission are summarized in Table 2. The most common symptoms were fever(60%), fatigue (43.3%), and vomiting(36.7%). Special neurological symptoms include impaired consciousness(36.7%), language disorder or aphasia(33.3%), activity obstacle or paralysis(30%), and headache (26.7%). Three patients (10%) had a seizure before hospital admission, one was in the NS group, and the other two were in the RS group. Thirteen patients (43.3%) had no neurological symptoms on admission to the hospital, including six patients (85.7%) in the EH group, four patients(30.8%) in the NS group, and three(30.0%) in the RS group. One patient in the EH group had neurological symptoms (confusion and unable to speak) on admission to the hospital, whose MRI indicated cerebral infarction in the left frontotemporal lobe, and lung CT indicated ground-glass infection in both lungs. The laboratory results of patients with epilepsy and COVID-19 showed no significant difference between the three groups.

The complications of patients with epilepsy and COVID-19 are reported in Table 3. Twenty-six out of thirty (86.7%) patients had more than one compilation, while four patients(13.3%) had no other complications besides COVID-19 and epilepsy. One of them was in the RS group, and the other three were in the EH group. 36.7% of patients had one to five other complications, and 46.4% of patients had 6–10 other complications. The median number of complications in this study was 5.5(3–9). The complications in patients with seizures (the median number was seven in the NS group and five in the RS group) were more than those without

seizures(the median number was four in the EH group), but the difference was not statistically significant. The most common complications in this cohort were hypertension(18, 60%), the others were respiratory distress or failure (14, 46.6%), cerebral hemorrhage(13,43.3%), gastrointestinal ulcer(13,43.3%),hepatic injury(ten, 33.3%),cerebral infarction (six, 20%), hypoproteinemia (six, 20%), kidney failure (six, 20%), brain trauma (five, 16.7%), cerebrovascular malformation (five, 16.7%), and coronary heart disease (five, 16.7%), and diabetes (five, 16.7%) in sequence. In 13 patients with cerebral hemorrhage, ten patients had hypertension, two patients had brain trauma and cerebrovascular malformation. Two patients had brain trauma, while three patients had cerebrovascular malformations (cerebral aneurysm, or Moyamoya disease).

Treatments, outcomes, and a 3-month follow-up of all patients are summarized in Table 4. All patients had oxygen support, 50% of them just used a nasal cannula, and 36.7% needed further invasive mechanical ventilation. The proportion of AEDs treatment before admission was higher in the EH group than the RS group (7/7, [100%] VS 2/10 [20%], P < 0.05). 46.2% of patients in the NS group received AEDs during hospitalization, while 100% of patients in the EH group and 60% of patients in the RS group were treated with AEDs.

Eleven (36.8%) patients died; ten of them had seizures, including five with new-onset seizures and five with recurrent seizures. Patients in the NS group and RS group seem to have a higher mortality rate than patients in the EH group, but it did not reach statistical significance. The cause of seizure in six deceased

Table 3
Complictaions in patients with epilepsy and COVID-19.

	Total	NS group	RS group	EH group	P
	N = 30	N = 13 (43.3%)	n = 10 (33.3%)	n = 7 (23.3%)	
Numbers of complications	5.5 (3–9)	7 (3.5–9)	5 (3.25–9.25)	4 (0–7)	0.642
0	4 (13.3%)	0 (0%)	1 (10%)	3 (42.9%)	0.082
1–5	11 (36.7%)	5 (38.5%)	5 (50%)	1 (14.3%)	
6–10	14 (46.7%)	8 (61.5%)	3 (30%)	3 (42.9%)	
>10	1 (3.3%)	0 (0%)	1 (10%)	0 (0%)	
Complications					
Hypertension	18 (60%)	10 (76.9%)	5 (50%)	3 (42.9%)	0.261
Respiratory distress or failure	14 (46.7%)	6 (46.2%)	6 (60%)	2 (28.6%)	0.517
Cerebral hemorrhage	13 (43.3%)	8 (61.5%)	4 (40%)	1 (14.3%)	0.134
Gastrointestinal ulcer	13 (43.3%)	6 (46.2%)	5 (50%)	2 (28.6%)	0.721
Bacterial pneumonia	13 (43.3%)	7 (53.8%)	4 (40%)	2 (28.6%)	0.645
Hepatic injury	10 (33.3%)	5 (38.5%)	4 (40%)	1 (14.3%)	0.55
Cerebral infarction	6 (20%)	3 (23.1%)	2 (20%)	1 (14.3%)	1
Hypoproteinemia	6 (20%)	2 (15.4%)	3 (30%)	1 (14.3%)	0.724
Kidney failure	6 (20%)	4 (30.8%)	0 (0%)	2 (28.6%)	0.121
Brain truauma	5 (16.7%)	3 (23.1%)	2 (20%)	0	0.572
Cerebrovascular malformation	5 (16.7%)	3 (23.1%)	2 (20%)	0 (0%)	0.572
Coronary heart disease	5 (16.7%)	4 (30.8%)	0 (0%)	1 (14.3%)	0.161
Diabetes	5 (16.7%)	3 (23.1%)	1 (10%)	1 (14.3%)	0.828
Circulatory failure	4 (13.3%)	3 (23.1%)	1 (10%)	0 (0%)	0.523
Pneumonectasis	3 (10%)	1 (7.7%)	1 (10%)	1 (14.3%)	1
Electrolyte disturbance	3 (10%)	3 (23.1%)	0 (0%)	0 (0%)	0.228
Anemia	3 (10%)	2 (15.4%)	1 (10%)	0 (0%)	0.776
Atrial fibrillation	2 (6.7%)	1 (7.7%)	0 (0%)	1 (14.3%)	0.701
Sepsis	2 (6.7%)	1 (7.7%)	1 (10%)	0 (0%)	1
Anxiety	2 (6.7%)	1 (7.7%)	0 (0%)	1 (14.3%)	0.701
Hypoglycemia	1 (3.3%)	1 (7.7%)	0 (0%)	0 (0%)	1
Pituitary adenoma	1 (3.3%)	0 (0%)	1 (10%)	0 (0%)	0.567
Hypothyroidism	1 (3.3%)	0 (0%)	1 (10%)	0 (0%)	0.567
Acute pancreatitis	1 (3.3%)	1 (7.7%)	0 (0%)	0 (0%)	1
Tumor of breast	1 (3.3%)	1 (7.7%)	0 (0%)	0 (0%)	1
Lung cancer	1 (3.3%)	0 (0%)	0 (0%)	1 (14.3%)	0.233
Thrombus of lower extremity veins	2 (6.7%)	1 (7.7%)	0 (0%)	1 (14.3%)	0.701
Pulmonary embolism	1 (3.3%)	1 (7.7%)	0 (0%)	0 (0%)	1
Lupus nephritis	1 (3.3%)	1 (7.7%)	0 (0%)	0 (0%)	1

NS group: New-onset seizure group without epilepsy history; RS group: recurrent seizure with epilepsy history; EH group: epilepsy history group.
P less than 0.05 was considered statistcally significant.

Table 4
Treatments, outcomes and 3 month follow-up in patients with epilepsy and COVID-19.

	Total	NS group	RS group	EH group	P
	N = 30	N = 13 (43.3%)	n = 10 (33.3%)	n = 7 (23.3%)	
Treatment stragies, %					
Oxygen support					
Nasal cannula	15 (50%)	6 (46.2%)	4 (40%)	5 (71.4%)	0.52
Non-invasive ventilation or hig flow nasal cannula	3 (10%)	1 (7.7%)	1 (10%)	1 (14.3%)	1
Invasive mechanical ventilation	11 (36.7%)	5 (38.5%)	5 (50%)	1 (14.3%)	0.356
Antiviral therapy	27 (90%)	13 (100%)	8 (80%)	6 (85.71%)	0.305
Antibiotics	25 (83.3%)	12 (92.3%)	8 (80%)	5 (71.4%)	0.482
Corticosteroid	11 (37.9%)	4 (33.3%)	5 (50%)	2 (28.6%)	0.698
Continuous renal replacement therapy	4 (13.3%)	2 (15.4%)	2 (20%)	0 (0%)	0.651
Use of AEDs					
Before admission	9 (30%)	0 (0%)**	2 (20%)*	7 (100%)	0
During hospitalization	19 (63.33%)	6 (46.2%)	6 (60%)	7 (100%)	0.054
Clinical outcomes, %					
Rehabilitation	19 (63.3%)	8 (61.5%)	5 (50%)	6 (85.71%)	0.356
Death	11 (36.8%)	5 (38.5%)	5 (50%)	1 (14.3%)	
3 months follow-up in 3 months					
Use of AEDs after discharge (% in Rehabilitation)	11 (11/19 , 36.67%)	0 (0/8,0%)	5 (5/5,100%)	6 (6/6,100%)	0
Recurrent seizure recurrent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA

NS group: New-onset seizure group without epilepsy history; RS group: recurrent seizure with epilepsy history; EH group: epilepsy history group; AEDs:antiepileptic drugs.
P less than 0.05 was considered statistcally significant.
*Differences between RS and EH group, P < 0.05; **Differences between NS and EH group, P < 0.05.

patients was thought to be cerebral hemorrhage, and the inducement of cerebral hemorrhage was cerebral vascular malformation (three cases) and cerebral trauma (two cases). They all had different degrees of dizziness, headache, and disturbance of consciousness before admission. Another four deceased patients had high fever and fatigue before admission and the occurrence of new-onset seizures during hospitalization; one of them was diagnosed with subarachnoid hemorrhage by cerebral CT.

At 3-month follow-up, none of the rehabilitation patients in the NS group received AEDs, while all rehabilitation patients in the EH group continued using AEDs after discharge. None of the rehabilitation patients had a recurrent seizure, and there were no more deaths in the 3-month follow-up after discharge.

Discussion

To our knowledge, this is the first report on the detailed characteristics of hospitalized patients with COVID-19 and epileptic seizures, including COVID-19 patients with a new-onset epileptic seizure, recurrent epileptic seizures, and with an epilepsy history. Among 1550 hospitalized patients with COVID-19, the incidence of epileptic seizures was 1.49% (new-onset epileptic seizures and recurrent seizures were 0.84% and 0.65%, respectively), as low as in previous studies (Mao et al., 2020; Lu et al., 2020). The incidence of COVID-19 patients with an epilepsy history is also very low. Patients with an epilepsy history have not been shown to be more susceptible to COVID-19. Epilepsy is a chronic disorder affecting all ages and has a bimodal distribution according to age, with peaks in the youngest and in the elderly (Beghi and Giussani, 2018). In our study, all COVID-19 patients with new-onset or recurrent seizures were >40 years old.

When clinical doctors diagnose epilepsy, it's an important process to determine the predisposing factors or etiology, because some seizures are provoked, and others are unprovoked. According to the classification of ILAE in 2017, the etiologies of epilepsy include hereditary, structural, metabolic, immunological, infectious, and unknown reasons (Scheffer et al., 2017). All patients with seizures in this cohort were infected with COVID-19. However, it is impossible to confirm the diagnosis of viral encephalitis or meningitis in these patients by cerebrospinal fluid (CSF)

examination, as lumbar puncture is a high-risk operation in an epidemic of COVID-19. We still need to look for viral encephalitis in patients with fever, nausea, vomiting, headache, disturbance of consciousness, seizure, neck stiffness, and other symptoms of increased intracranial pressure. Central nervous system infection is one of the most important risk factors in epilepsy. The risk of seizure in patients with encephalitis or meningitis in patients is much higher than the general population, and viral encephalitis is more likely to induce seizures than bacterial meningitis. The formation of cerebral cortical vascular thrombosis, aggregation of metabolites, and cerebral edema caused by viruses and inflammation may also affect nerve cell membranes' stability and may lead to CNS manifestations and cause epileptic seizures. In a recent case report, the specific SARS-CoV-2 RNA was detected in the CSF of a 24-year-old man brought in by ambulance due to a convulsion accompanied by unconsciousness (Moriguchi et al., 2020). So far, there is little literature about COVID-19 induced encephalopathies. However, a previous report in the pandemic of Severe Acute Respiratory Syndrome(SARS) showed that the SARS-CoV genome sequence was detected in the brain of all SARS autopsies using real-time TR-PCR (Gu et al., 2005). The genomic sequence of SARS-CoV-2 is similar to SARS-CoV; therefore, they may share the ACE2 receptor and invade the same place in human brains (Yu et al., 2020). Growing evidence shows SARS-CoV-2 having the potential to invade the nervous system. Researchers have recently observed a virus in neural and capillary endothelial cells in frontal lobe tissue obtained at postmortem examination from a patient infected with SARS-CoV-2 (Paniz-Mondolfi et al., 2020). More clinical and laboratory evidence is needed to confirm this hypothesis.

In this cohort, the proportion of severe/critical patients in the new-onset seizure group (76.9%) and the recurrent seizure group (60%) were higher than the epilepsy history group(14.3%). In the early period of COVID-19 pandemics in Wuhan, the general mortality of the hospitalized COVID-19 population was about 13.47%–28.3% (Liu et al., 2020; Zhou et al., 2020a). Another previous report from Wuhan estimated that the mortality was 1.1% in non-severe patients and 32.5% in severe cases (Li et al., 2020). By contrast, the mortality of new-onset and recurrent seizure patients with COVID-19 was a little higher, 38.5%, and 50%, respectively. To explore the reason for high mortality in these COVID-19 patients

with epileptic seizures, we analyzed their past medical history, onset symptoms, and complications.

Past medical history

We found that patients with recurrent seizures had a larger number of other-neurological-disease histories than those with new-onset seizures and those with epilepsy history(P < 0.05). Underlying neurological disease may lead them to be more vulnerable to direct or indirect damage from COVID-19. A pooled analysis shows that there is an approximately 2.5-fold increase in the odds of a severe COVID-19 illness with a history of cerebrovascular disease (Aggarwal et al., 2020). A history of CNS injury (including stroke and traumatic brain injury), duration of epilepsy, frequency of seizures before control, history of previously failed tapering, and history of smoking/alcoholic/tobacco intake may also increase the possibility of further recurrent seizures (Haut and Shinnar, 2008; Kumar et al., 2020).

Onset symptoms on admission

About 70% of patients in the new-onset seizure and recurrent seizure groups had neurological symptoms on admission to the hospital. The remaining 30% of patients in these two groups developed seizures and other neurological symptoms during hospitalization. A previous report suggested that more severely affected COVID-19 patients were more likely to have neurological involvement than less severe ones(45.5% VS 30.2%) (Mao et al., 2020). Therefore, most patients were severe on admission to the hospital. On the other hand, our study showed that 40% of COVID-19 patients with epileptic seizures were nosocomial infections, which is much higher than other studies in a similar period (about 12.3%–12.5%) (Wang et al., 2020; Carter et al., 2020). Most nosocomial infection patients were admitted for some emergency or severe disease, and they had to stay in hospital to continue receiving treatments.

Complications

COVID-19 infection may be one of the provoking factors for seizure. What's more, it is possible that some COVID-19 patients developed seizures as a consequence of other complications: viral infection, hypoxia, metabolic derangement, head injuries, neurological surgeries, altered homeostasis due to organ failure and toxin exposure (Asadi-Pooya, 2020), and so on. Patients with COVID-19 and epilepsy are often accompanied by a variety of complications. 86.7% of patients (26/30) with COVID-19 and epilepsy had at least one complication, and 50% of them(15/30) had more than five complications. This was higher than the proportion of complications in general inpatients with COVID-19 from other research (Zhou et al., 2020b). Some complications may occur in the recent course of COVID-19, others may have already existed as a recorded past history or even be undetected and ignored. We found hypertension was another common complication. The proportion of patients with hypertension increased to 60% during hospitalization, while only 43.3% in general have a history of hypertension. Current evidence suggests that hypertension may be a cause of seizures and epilepsy. The Renin-angiotensin system might play a central role in the direct interaction between hypertension and epilepsy. On the other hand, hypertension-related small vessel disease, large-artery stroke, and posterior reversible leukoencephalopathy syndrome can lead to epilepsy by indirect mechanisms (Gasparini et al., 2019). Other diseases, including heart disease, peptic ulcers, depression, anxiety, dementia, migraine, and arthritis, are up to several times in people with epilepsy than in the general population (Keezer et al., 2016).

In this study, ten patients (58.8%) out of 17 with an epilepsy history had a recurrence of seizures. What factors may cause the recurrence of epilepsy? Besides a more complicated past history and more complications during hospitalization, we noticed that individuals with recurrent seizures in the RS group had an obviously lower proportion of AEDs treatment before admission than those in the EH group (P < 0.05). According to guidelines for the management of seizure, adults with an unprovoked first seizure should be informed that their risk of seizure recurrence is greatest within the first two years (Huff et al., 2014), and this risk appears to be lower for patients treated with AEDs. Although AEDs treatments of patients with new-onset seizures were stopped after discharge by an evaluating neurologist, patients were not found to have recurrent epilepsy in this study's short-term follow-up. Long-term follow-up is still needed, to observe whether patients will have recurrent epilepsy and assess the risk factors for the recurrence of epilepsy.

There were some limitations in our study. Firstly, this is a retrospective study; the sample size may not be large enough, and some bias may have occurred. Secondly, no routine or long-term electroencephalogram or cerebrospinal fluid examination was performed because of the risk of viral exposure to staff. Therefore, we cannot find evidence to confirm the correlation between COVID-19 and seizure.

Conclusion

This study provides an incidence of seizures in hospitalized patients with COVID-19 in China. COVID-19 patients with recurrent seizures had more neurological disease history than those without seizures. New-onset and recurrent seizure patients were accompanied by more severe and critical COVID-19 than patients who had an epilepsy history but without seizures, which may lead to a worse prognosis for COVID-19. The recurrent-seizure patients had a clearly lower proportion of AEDs treatment [AU] after before admission, a more complicated past history, and more complications during hospitalization. If patients with an epilepsy history continue using AEDs during COVID-19 pandemics, the risk rate of recurrent seizure may reduce, and a good prognosis for patients with epilepsy history may be expected.

Author contributions

H Zhang had full access to all data in the study and took responsibility for the integrity of the data and the data analysis accuracy. H Zhang and M Sun conceived and designed the experiments.

M Sun, X Ruan, Y Li, P Wang, S Zheng, G Shui, and L Li performed the data collection. M Sun, X Ruan, Y Li, P Wang, S Zheng analyzed the data. M Sun, X Ruan, Y Huang, and P Wang wrote the paper. M Sun, X Ruan, and P Wang contributed equally.

Financial & competing interests disclosure

Ethical conduct of research

This study was approved by the Ethics Commission of the Central Hospital of Wuhan. Written informed consent was waived

for this retrospective study. The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations., for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data availability

The data used to support the findings of this study are included in the article.

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