Original Article

Characteristics of febrile seizures with SARS-CoV-2 infection in the Omicron era

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Background: While the pandemic of coronavirus disease 2019 (COVID-19) is ongoing, the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been dominant recently. The Omicron variant causes more seizures in pediatric patients compared with previously circulated variants. This study aimed to investigate the incidence and clinical features of febrile seizure (FS) in pediatric patients with COVID-19 during the Omicron era.

Methods: The medical records of pediatric patients (≤18 years of age) diagnosed with COVID-19, who presented with FS between February 2020 and June 2022, were reviewed retrospectively to analyze clinical characteristics of FS in seven university-affiliated hospitals of Korea.

Results: Of 664 pediatric patients with COVID-19 during the study period, 46 during the pre-Omicron period and 589 during the Omicron period were included in the study analysis; 29 patients during the transition period were excluded. Among the included patients, 81 (12.8%) had concomitant FS, and most (76.5%) experienced simple FS. All FS episodes occurred during the Omicron period and none of them during pre-Omicron period (P=0.016). Sixty-five (80.2%) and 16 (19.8%) patients were categorized as FS (patient age ≤60 months) and late-onset FS (patient age >60 months), respectively. Underlying neurologic disease (P=0.013) and focal onset seizure (P=0.012) were more common in the late-onset FS group than in the FS group; however, overall clinical manifestations and outcomes including seizures consistent with characteristics of complex FS and subsequent epilepsy were similar between the two groups.

Conclusions: As the COVID-19 pandemic persists, the incidence of FS has increased with the emergence of the Omicron variant. About one-fifth of the patients experiencing FS due to infection by the Omicron variant of SARS-CoV-2 were aged >60 months; however, clinical characteristics and outcomes were favorable. More information and long-term prognoses in patients with FS due to COVID-19 should be acquired.

Keywords: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Omicron; febrile seizure (FS); late-onset febrile seizure

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Introduction

Since the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020, the pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection remains ongoing. SARS-CoV-2 is an RNA virus with multiple variants (1). Among the SARS-CoV-2 variants, the World Health Organization defined variants of concern (VOCs) when changes in virus characteristics such as transmissibility, epidemiology, and clinical manifestations; severity, and immune, diagnostic, or therapeutic escape were accompanied by a significant global public health effect (1). Following the previous four VOCs (Alpha, Beta, Gamma, and Delta), the fifth, the Omicron variant, has been circulating across the world recently (1). The Omicron variant was first identified in November 2021, in Botswana and spread rapidly worldwide, including East Asia (1,2). The Omicron variant, having about 50 amino acid changes compared with the original strain, is most transmissible among the defined VOCs, with weaker effects of monoclonal antibodies and vaccines (2). In the Omicron era, the proportion of pediatric patients, both outpatient and inpatient, increased (2,3). Although the proportion of asymptomatic infection increased and clinical severity decreased in patients infected by the Omicron variant compared with those infected by previously circulated variants (2), some reports described an increase in seizures accompanied by fever, which was uncommon in the previous variants (3-6).

Febrile seizure (FS) is a seizure or convulsion that occurs in young children aged 6 to 60 months with fever but no evidence of central nervous system (CNS) infection such as meningitis or encephalitis or history of previous unprovoked seizure (7). The incidence for Caucasian children is 2–5%, while that for Asian children is 8–10% (7). FS is commonly caused by respiratory viral infection, such as rhinovirus, influenza, adenovirus, and enterovirus, and most episodes exhibit favorable outcomes (7,8). Seizures accompanied by fever also occur in pediatric patients beyond the age range of FS, and usually show a benign nature (9). Despite the ongoing pandemic of COVID-19, characteristics of pediatric patients with FS or seizures accompanied by fever were infrequently reported, especially during the Omicron era (4-6). This study aimed to investigate the clinical characteristics of seizures accompanied by fever in pediatric patients with COVID-19 during the surge of the Omicron variant. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-579/rc).

Highlight box

Key findings

- The incidence of febrile seizure has increased with the emergence of the Omicron variant compared with previous variants of SARS-CoV-2.

What is known and what is new?

- Clinical characteristics and overall outcomes of febrile seizure in the Omicron era are favorable and similar to those of other respiratory viruses.
- However, the Omicron variant showed increased rate of late-onset febrile seizures in children older than 60 months.

What is the implication, and what should change now?

- Children infected by the Omicron variant tended to experience seizures accompanied by fever at an older age compared with those infected by other respiratory viruses, without significant differences in clinical prognosis.

Methods

We conducted a retrospective review of electronic medical records of pediatric patients (≤18 years of age) who visited one of the seven Catholic University-affiliated hospitals in Korea to identify patients diagnosed with COVID-19 between February 2020 and June 2022. The seven hospitals comprised two in Seoul (the capital of Korea), three in the Seoul metropolitan area, one in Incheon Metropolitan city (adjacent to Seoul), and one in Daejeon Metropolitan city (located 140 km from Seoul). COVID-19 was diagnosed when polymerase chain reaction testing for SARS-CoV-2 using nasopharyngeal samples showed a positive result. Among the patients with COVID-19, those experiencing seizures accompanied by fever were included in this study. Seizure episodes occurring in patients with a previous history of epilepsy were regarded as breakthrough seizures and were excluded.

For the included patients, we collected demographic data for age at presentation and sex, clinical data of underlying disease, previous history of FS, family histories of FS and epilepsy, presenting symptoms, clinical diagnosis of fever, acute complications [oxygen therapy and admission to the intensive care unit (ICU)], seizure characteristics and outcomes, and electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) findings. The included patients were divided into an FS group and a late-onset FS group based on age, and the investigated data were

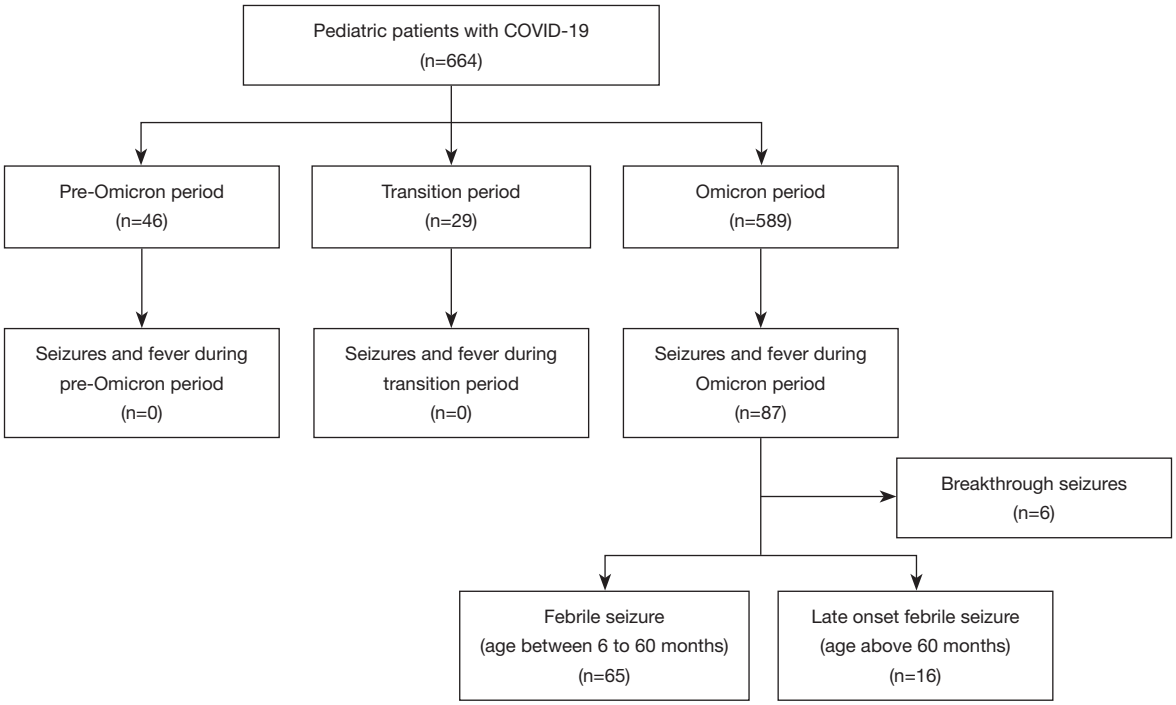

Figure 1 Flowchart of the inclusion process. COVID-19, coronavirus disease 2019.

compared between the two patient groups. The FS group included patients aged between 6 and 60 months without evidence of CNS infection or previous history of epilepsy. Patients aged >60 months without a history of epilepsy and presenting with seizures accompanied by fever were categorized into the late-onset FS group. Complex FS was defined as presence of any of the following seizure characteristics: focal type, recurrence within 24 hours, or lasting for >15 minutes. The study was divided into three periods according to the dominantly circulated SARS-CoV-2 variant in Korea based on the surveillance genetic study results by the Korea Disease Control and Prevention Agency (KDCA) (10): pre-Omicron period (February 2020 to December 2021), transition period (January 2022), and Omicron period (February 2022 to June 2022). In Korea, the first patient with COVID-19 was diagnosed on January 20, 2020, and the first patient infected by the Omicron variant of SARS-CoV-2 was identified on November 25, 2021 (10). The Omicron variant comprised <10% of identified SARS-CoV-2 strains during the pre-Omicron period, 10–90% during the transition period, and >90% during the Omicron period (10). The frequency of FS was compared between the pre-Omicron and Omicron periods, and the transition period was excluded due to inconsistent composition of variants. The study was conducted in accordance with the Helsinki Declaration (as revised in 2013), and was approved by the Institutional Review Board of The Catholic Medical Center, with a waiver for the requirement to obtain informed consent due to the retrospective nature of this study (approval No. DC22WISI0038).

Statistical analysis

In comparisons between groups, the Mann-Whitney test and chi-square test were used for continuous and categorical variables, respectively. We used the SPSS 29 software program (IBM Corp., Armonk, NY, USA) to perform statistical analysis, and statistical significance was set with P value less than 0.05.

Results

From February 2020 to June 2022, a total of 664 pediatric patients were diagnosed with COVID-19 in the seven study hospitals (*Figure 1*). During the pre-Omicron and Omicron

periods, 46 patients and 589 patients with COVID-19 were identified, respectively. Twenty-nine patients diagnosed with COVID-19 during the transition period were excluded. Between pre-Omicron and Omicron periods, sex (P=0.483) and age (P=0.058) distributions were comparable, and no COVID-19 vaccinations were administered. The number of nationwide pediatric patients with COVID-19 was reported by the KDCA as 112,194 during the pre-Omicron period and 4,426,115 during the Omicron period (11), of which respective 0.04% and 0.01% were included here (P<0.001). Among the included patients, 87 (13.1%) experienced seizures, and all seizure episodes were accompanied by fever. Six (6.9%) patients with breakthrough seizures were excluded, the remaining 81 (93.1%) were included in the study analysis: 58 (71.6%) patients were discharged from the emergency room, 19 (23.5%) were admitted to a general ward, 1 (1.2%) was admitted to the ICU, and 3 (3.7%) were transferred to other hospitals. In the pre-Omicron period, no patient presented with seizures accompanied by fever; all included patients were in the Omicron period (0.0% *vs.* 13.8%, P=0.016).

Demographic and clinical characteristics of patients with seizure accompanied by fever

The included patients had a median age of 3 years (range, 1–14 years), and 43 (53.1%) patients were males. The FS and late-onset FS groups included 65 (80.2%) and 16 (19.8%) patients, respectively (*Table 1*). Underlying neurologic diseases were identified in 6 (7.4%) patients, with a significantly higher frequency in the late-onset FS group than in the FS group (25.0% *vs.* 3.1%, P=0.013; *Table 1*). Two patients with underlying neurologic disease in the FS group had developmental delay and attention deficit hyperactive disorder (ADHD), respectively. Among the four neurologically affected patients in the late-onset FS group, two had developmental delay, another had intellectual disability and ADHD, and the fourth had sensorineural hearing loss. For underlying non-neurologic diseases, 1 (1.5%) patient in the FS group had asthma, and 1 (6.3%) patient in the late-onset FS group had hyperlipidemia. Previous history of FS, family history of FS, and family history of epilepsy were identified in 40.7%, 19.8%, and 4.9% of the included patients, respectively, with comparable frequencies between the FS and late-onset FS groups (*Table 1*). Among clinical symptoms, rhinorrhea (22.2%) was most common, followed by cough (19.8%) and sputum (11.1%). Subjective symptoms such as sore throat, abdominal pain, and headache were more common in the late-onset FS group than in the FS group (*Table 1*). The difference in prevalence of subjective symptoms may be due to age. Most patients were diagnosed with fever without localizing signs (54.3%) or upper respiratory tract infection (39.5%). One (6.3%) patient in the late-onset FS group was diagnosed with encephalopathy. This 11-year-old boy with underlying hyperlipidemia presented with confusion after a generalized tonic-clonic seizure that lasted for 5 minutes and was treated in the ICU for 5 days. His CSF analysis results were normal, and he was discharged from the hospital on the ninth day with complete recovery, prescribed valproic acid until his EEG findings normalized.

Seizure semiology in patients with seizures and fever

Most episodes of seizures were generalized (93.8%), occurred within 24 hours of fever onset (92.6%), and were consistent with characteristics of simple FS (76.5%, *Table 1*). Significantly more patients in the late-onset FS group experienced focal seizures than those in the FS group (P=0.012), while frequencies of seizures consistent with characteristics of complex FS were comparable (*Table 1*). EEG was performed in 7 (10.8%) and 11 (68.8%) patients in the FS and late-onset FS groups, respectively, and comparable frequencies of abnormality were identified between the two patient groups (*Table 1*). Brain MRI was performed in 7 (10.8%) and 9 (56.3%) patients in the FS and late-onset FS groups, respectively, and none of them showed abnormal findings. One (6.3%) 5-year-old girl in the late-onset FS group, who experienced her first seizure during the study period, presented with multiple unprovoked seizures two months later and eventually was diagnosed with epilepsy. A neurologic complication of unknown causal relationship was found in a 21-month-old girl who complained of left facial nerve palsy ten days after FS. The palsy resolved three weeks later. *Figure 2* shows the numbers of patients with FS and late-onset FS during the Omicron period.

Discussion

In this study, clinical characteristics of pediatric patients experiencing seizures accompanied by fever due to SARS-CoV-2 infection during the Omicron era were analyzed and compared between FS and late-onset FS groups. About one-fifth of the patients experiencing seizures accompanied by fever were aged >60 months; however, neurologic

Table 1 Comparison of characteristics between febrile seizure and of late-onset febrile seizure groups

Factor	FS group (n=65)	Late-onset FS group (n=16)	P value
Male sex	34 (52.3)	9 (56.3)	0.777
Age (years), median [range]	2 [1–5]	7 [5–14]	<0.001
Underlying disease			
Neurologic disease	2 (3.1)	4 (25.0)	0.013
Others	1 (1.5)	1 (6.3)	0.358
Previous history of FS	24 (36.9)	9 (56.3)	0.159
Family history			
FS	12 (18.5)	4 (25.0)	0.726
Epilepsy	2 (3.1)	2 (12.5)	0.173
Presenting symptoms			
Fever	65 (100.0)	16 (100.0)	NA
Rhinorrhea	15 (23.1)	3 (18.8)	1.000
Cough	12 (18.5)	4 (25.0)	0.726
Sputum	6 (9.2)	3 (18.8)	0.370
Sore throat	3 (4.6)	5 (31.3)	0.006
Dyspnea	1 (1.5)	0 (0.0)	1.000
Abdominal pain	4 (6.2)	4 (25.0)	0.045
Vomiting	4 (6.2)	0 (0.0)	0.580
Diarrhea	3 (4.6)	1 (6.3)	1.000
Headache	1 (1.5)	3 (18.8)	0.023
Dizziness	0 (0.0)	1 (6.3)	0.198
Myalgia	0 (0.0)	0 (0.0)	NA
Altered smell/taste	0 (0.0)	0 (0.0)	NA
Clinical diagnosis			
Fever without localizing signs	40 (61.5)	4 (25.0)	0.009
Upper respiratory infection	24 (36.9)	8 (50.0)	0.338
Lower respiratory infection	1 (1.5)	0 (0.0)	1.000
Acute gastroenteritis	0 (0.0)	3 (18.8)	0.007
Encephalopathy	0 (0.0)	1 (6.3)	0.198
Seizure type			0.012
Generalized seizures	63 (96.9)	13 (81.3)	
Focal seizures	0 (0.0)	2 (12.5)	
Others	2 (3.1)	1 (6.3)	
Seizures consistent with complex FS	13 (20.0)	6 (37.5)	0.187
>15 minutes of duration	4 (6.2)	1 (6.3)	
Recurrence within 24 hours	10 (15.4)	5 (31.3)	
Focal seizures	0 (0.0)	2 (12.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Factor	FS group (n=65)	Late-onset FS group (n=16)	P value
Time from fever onset to seizure			0.088
<24 hours	62 (95.4)	13 (81.3)	
≥24 hours	3 (4.6)	3 (18.8)	
Abnormal test results			
Electroencephalography	1/7 (14.3)	3/11 (27.3)	1.000
Brain MRI	0/7 (0.0)	0/9 (0.0)	NA
Acute complications			
Oxygen therapy	0 (0.0)	1 (6.3)	0.198
ICU	0 (0.0)	1 (6.3)	0.198
Neurologic complications			
Facial nerve palsy	1 (1.5)	0 (0.0)	1.000
Subsequent epilepsy	0 (0.0)	1 (6.3)	0.198

Data are presented as number (%) unless otherwise stated. FS, febrile seizure; MRI, magnetic resonance imaging; ICU, intensive care unit; NA, not available.

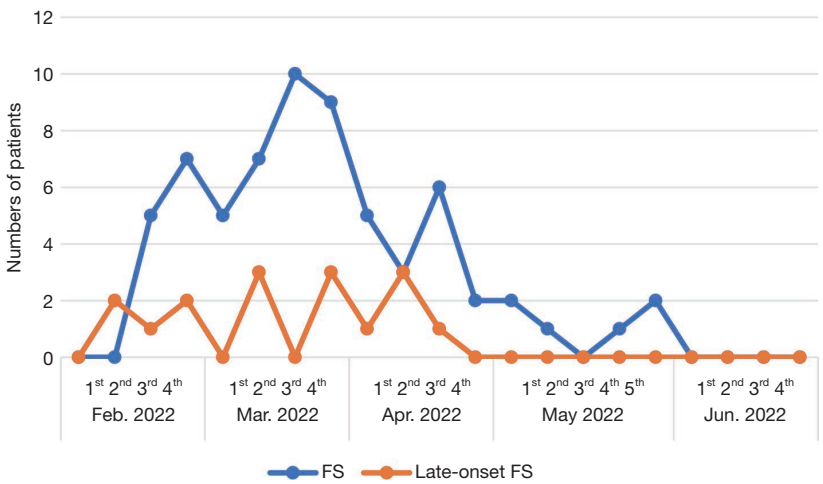

Figure 2 Numbers of patients with FS and late-onset FS during Omicron period. FS, febrile seizure.

complications and grave outcomes were uncommon in these patients. Clinical characteristics and outcomes of patients with FS were similar to those previously reported in children with FS (8,9,12).

In pediatric patients with COVID-19, headache and dizziness were the most common neurologic manifestations, and seizures accompanied by fever occurred infrequently (0.5–3.4%) during the pre-Omicron era (13-15). With emergence of the Omicron variant, seizures accompanied by fever were increasingly reported among pediatric patients with COVID-19 (3-6). The higher number of pediatric patients diagnosed with COVID-19 in the Omicron era than in previous VOC eras might have impacted the increase in number of patients with seizures accompanied by fever. However, the proportion of patients with seizures accompanied by fever including FS also significantly increased in the Omicron era than in the previous VOC eras (4,6,16,17). The incidence of seizures accompanied by fever increased from 1.7% in the pre-Omicron era to 14.6% in the Omicron era in Japanese pediatric patients (4),

and it increased from 0.0% in the pre-Omicron period to 13.8% in the omicron period in our study. These incidence rates were higher than that of FS, 6.9–9.9%, in community-acquired respiratory coronavirus infections (18).

Several mechanisms were suggested to explain neurologic manifestations associated with COVID-19: direct CNS involvement via the olfactory nerve, production of cytokines causing blood-brain barrier (BBB) disruptions, and coagulopathies with endothelial dysfunction (19). Considering that cases of infection or inflammation of the CNS should be excluded from diagnosis of FS, mechanisms related to viral CNS invasion or neurotropism are not applicable for FS development. Most cerebrospinal fluid samples from pediatric patients with FS did not contain SARS-CoV-2 (20-22). This suggests indirect effects of systemic inflammatory responses to FS in patients with COVID-19, similar to those with other respiratory viral infections (23). Most cases of FS develop in the early phase of an infection, within 24 hours of fever onset, and therefore, seem the result of activated innate immune reactions rather than adaptive immune reactions. The Omicron variant did not exhibit increased capability to escape T cell immunity compared with other VOCs (24,25). However, it did show higher viral replication despite higher concentrations of secreted antiviral interferons, the principal components of an innate immune response, compared with other VOCs in the early phase of infection (26,27). This suggests development of more intense innate immune reactions in the Omicron variant infection than in other VOC infections and may induce a larger number of episodes of FS in the Omicron period compared with the pre-Omicron period.

Previous studies including small numbers of patients at the beginning of the Omicron era reported that >50% of patients with seizures accompanied by fever experienced complex FS (5,6). However, our study and a recent Japanese study reported similar proportions of seizures consistent with characteristics of complex FS (about one-quarter) to that reported in FS associated with other respiratory virus infections (8,12,28). Risk factors for FS and seizure outcomes were comparable with those previously reported in FS associated with other respiratory virus infections (8,12). Therefore, additional neurologic evaluations and interventions may not be considered for most patients with seizures accompanied by fever during the COVID-19 pandemic.

Exceptionally, the proportion of patients experiencing late-onset FS in this study was higher than in pediatric patients infected by other respiratory viruses; the incidence of seizures accompanied by fever was reported as 4–6% before the age of 6 months and 6% after 5 years of age (9,23). Other studies on pediatric patients with COVID-19 during the Omicron era reported that about one-third of those with seizures accompanied by fever were aged >60 months (4-6). Underlying neurologic diseases were more frequent in the late-onset FS group than in the FS group; however, 16.0% of patients, excluding those with underlying neurologic disease, were aged >60 months. Encephalopathy and subsequent epilepsy were each diagnosed in two patients in the late-onset FS group; however, their occurrence rates were not significantly higher than those of the FS group. We previously reported that 22.7% of patients with seizures accompanied by fever were aged >5 years, and their clinical characteristics and outcomes were similar to those of younger children with FS among patients with influenza (9). Considering that influenza virus and SARS-CoV-2 have higher mutation rates compared with other respiratory viruses, pathophysiologic similarity for late-onset FS between these two viruses should be studied further.

This study had some limitations, including those related to its retrospective nature. The type of VOC was expected based on the surveillance data of the KDCA, instead of being defined in each patient using genetic analysis. To exclude confounding effects of the Delta variant, we defined a transition period and included an Omicron-only period when the Omicron variant accounted for >90% of circulating SARS-CoV-2 strains in the community. Among the sublineages of Omicron variant, BA.1.1 and BA.2 were dominant during the study period, while BA.5 is the dominant variant most recently circulating in Korea (10). Clinical differences between sublineages of Omicron variant should be further evaluated. Diagnostic testing for other respiratory viruses was performed in only 6.2% of the included patients, and confounding effects of other viruses might be a concern. During the Omicron period, rhinovirus and respiratory syncytial virus were most prevalent in Korea (29). Rhinovirus showed a similar prevalence throughout the pre-Omicron and Omicron periods. Respiratory syncytial virus was dominant during the first few weeks of the Omicron period but is not considered a common cause of FS. Thus, the increase of FS caused by co-infections with other respiratory viruses during the Omicron period was thought to be minimal. Moreover, a recent meta-analysis has shown a low, 5.4% co-infection rate of respiratory viruses and SARS-CoV-2 in pediatric

patients (30). With the increase in pediatric patients with COVID-19 after the emergence of the Omicron variant, the Korean government required that local clinics to treat pediatric patients with COVID-19 in February, 2022. This change in government policy should result in an underestimation rather than an overestimation of the incidence of FS during the Omicron period in this study. This underestimation can be attributed to all the study hospitals having cared for patients with COVID-19 before the Omicron period, and the proportion of patients visiting the study hospitals relative to nationwide patients decreased significantly during the Omicron period compared with the pre-Omicron period. At the completion our study, a median of 96 days (range, 26–133 days) had passed since the seizure event in our patients. In order to evaluate the occurrence of epilepsy or neurologic diseases, long-term follow up is necessary for further studies.

Conclusions

As the COVID-19 pandemic persists, an increased risk of FS related with the Omicron variant has been observed compared with previous VOCs. In particular, late-onset FS occurs more frequently compared with other respiratory virus infections. Fortunately, overall characteristics and outcomes of seizures accompanied by fever in patients with COVID-19 during the Omicron era were similar to those in patients infected by other respiratory viruses. However, more information on long-term outcomes and clinical changes in COVID-19 patients experiencing seizures accompanied by fever should be collected as new variants of SARS-CoV-2 continue to emerge.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-579/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-579/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-579/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Helsinki Declaration (as revised in 2013), and was approved by the Institutional Review Board of The Catholic Medical Center, with a waiver for the requirement to obtain informed consent due to the retrospective nature of this study (approval No. DC22WISI0038).

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