

# Comparison of severe pediatric complicated influenza patients with and without neurological involvement

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## Abstract

Although influenza is generally an acute, self-limited, and uncomplicated disease in healthy children, it can result in severe morbidity and mortality. The objectives of this study were to analyze and compare the clinical features and outcome of severe pediatric influenza with and without central nervous system (CNS) involvement.

We conducted a retrospective observational study of children admitted to the pediatric intensive care unit (PICU) of China Medical University Children's Hospital in Taiwan with a confirmed diagnosis of influenza. The demographic data, clinical and laboratory presentations, therapeutic strategies, and neurodevelopmental outcomes for these patients were analyzed. Furthermore, comparison of patients with and without CNS involvement was conducted.

A total of 32 children with severe influenza were admitted during the study periods. Sixteen children were categorized as the non-CNS (nCNS) group and 16 children were categorized as the CNS group. Nine of them had underlying disease. The most common complication in the nCNS group was acute respiratory distress syndrome, (n=8/16), followed by pneumonia (n=7/16, 44%). In the CNS group, the most lethal complication was acute necrotizing encephalopathy (n=3/16) which led to 3 deaths. The overall mortality rate was higher in the CNS group (n=6) than in the nCNS group (n=1) (37.5% vs 6.25%,  $P=.03$ ).

The mortality rate of severe complicated influenza was significantly higher with CNS involvement. Children with primary cardiopulmonary abnormalities were at high risk of developing severe complicated influenza, while previously healthy children exhibited risk for influenza-associated encephalitis/encephalopathy.

**Abbreviations:** ADEM = acute disseminated encephalomyelitis, ADRS = acute respiratory distress syndrome, CNS = central nervous system, CT = computed tomography, DMD = Duchenne muscular dystrophy, IAE = influenza associated encephalitis/encephalopathy, MRI = magnetic resonance imaging, PICU = pediatric intensive care unit, PIM2 = Pediatric Index of Mortality 2, rRT-PCR = reverse transcription polymerase chain reaction.

**Keywords:** central nerve system, children, severe complicated influenza infection

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets generated during and/or analyzed during the current study are publicly available.

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## 1. Introduction

Influenza is a major global cause of illness and death, resulting in an estimated 3 to 5 million cases of severe influenza illness and 250,000 to 500,000 deaths annually.<sup>[1]</sup> Severe complicated influenza infections, which consists of infections with evidence of pneumonia, neurologic symptoms, myocarditis, pericarditis, or invasive bacterial infection, have previously been reported.<sup>[2,3]</sup> A modeling analysis of population-based surveillance data for the influenza seasons following the 2009 pandemic (i.e., for the 2010–2011 and 2012–2013 seasons) estimated that influenza was associated with 114,018 to 633,001 hospitalizations, 18,476 to 96,667 pediatric intensive care unit (PICU) admissions, and 4866 to 27,810 deaths per year in the United States.<sup>[4]</sup> In Taiwan, among all cases of influenza, about 0.5% require hospitalization, with approximately 7% of the hospitalized children experiencing serious complications requiring intensive care, and around 20% of those cases requiring intensive care resulting in mortality.<sup>[5]</sup> Nonetheless, while seasonal flu outbreaks infect millions of children around the world every year, the detailed risk and prognostic factors for severe complicated influenza in children remain unclear.

Cases of influenza associated encephalitis/encephalopathy (IAE) are relatively rare and have high rates of morbidity and mortality, the specific causes of which have been reported to

include the following: seizures, encephalopathy, acute disseminated encephalomyelitis (ADEM), myelitis, Guillain-Barre syndrome, and acute necrotizing encephalopathy (ANE).<sup>[6–8]</sup> Central nervous system (CNS) complications of influenza are rare in children; if present, the manifestations are heterogeneous, ranging from simple febrile seizure to severe ANE.<sup>[9,10]</sup>

IAE is more prevalent in East Asia, and ANE, first reported first in 1979 in Japan, is most prevalent in Japan, Taiwan, and South Korea.<sup>[11–13]</sup> There have been a few studies that addressed the topic of emerging influenza infections with CNS complications in recent years, but no studies have conducted direct comparisons between severe influenza infection with CNS complications and severe influenza infections without CNS complications.<sup>[13,14]</sup> In this study, therefore, we collected and evaluated data for critical influenza cases treated at China Medical University Children's Hospital between January 2012 and September 2019 in order to analyze and compare the clinical characteristics of severe complicated influenza with and without CNS involvement.

## 2. Material and methods

### 2.1. Study subjects

This study was approved by the Institutional Review Board of our hospital (CMUH106-REC1–117 (FR)). China Medical University Children's Hospital is a tertiary referral hospital in Taiwan with 14 beds in its PICU. First, in the preliminary inclusion phase, we screened 40,002 children ( $\leq 18$  years of age) who were diagnosed with seasonal influenza at this hospital (both in inpatient and outpatient clinical settings, and whether the patients previously had normal health or had comorbidities) between January 1, 2012, and December 31, 2019. Second, any patients who did not meet the criteria for severe complicated influenza infection or who were infected with influenza infection during their hospitalization were excluded. Third, we manually reviewed the remaining children's medical records to extract those

who were admitted mainly for the treatment of severe complicated influenza infection. Finally, we included those patients who were candidates for severe complicated influenza infection.

Influenza virus infection was suspected based on the following: classic symptoms, which included abrupt onset of fever, headache, myalgia, malaise, and accompanied by manifestations of respiratory-tract illness. Contact history with an infected person. The diagnosis for a given patient was confirmed by either isolation of the virus in tissue-cell culture or a real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for respiratory specimens during the patient's illness, with these tests being conducted at the National Health Ministry Laboratories of Taiwan's Center for Disease Control. Furthermore, the influenza A virus was also subtyped there. The children ultimately included in this study were divided into 2 groups, a non-CNS group (nCNS), which include those who had complications without CNS involvement, and CNS group, which included those who had complications with CNS involvement.

The following data were collected and recorded for each patient: demographics characteristics, clinical presentation, laboratory findings, neuroimaging studies, PICU admission day, intubation duration, and neurologic sequelae. All of the children were admitted to the pediatric PICU for influenza and the associated complications. Since we wanted to analyze the direct and straightforward impacts of influenza on individual patients, any children who were infected with influenza during their hospitalization for some other reason were excluded from this study (Fig. 1).

### 2.2. Definitions

Children with severe complicated influenza infection were defined as those who needed to be treated in a PICU or who died within 2 weeks after the onset of flu-like symptoms due to influenza-associated complications (such as pulmonary compli-

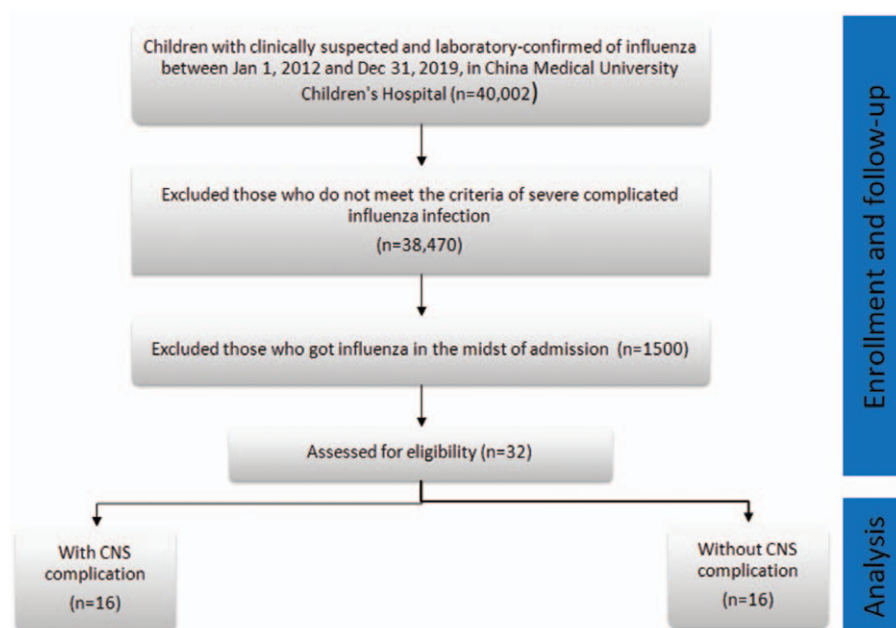


Figure 1. Diagnostic algorithm of the study.

cations, neurological complications, invasive bacterial infections, myocarditis, or pericarditis). The nCNS group included children who developed influenza associated complications such as pulmonary complications, invasive bacterial infections, myocarditis, or pericarditis. The CNS group, as the name implies, consisted of patients with neurological complications, including aseptic meningitis, acute encephalitis, acute disseminated encephalomyelitis (ADEM), and acute necrotizing encephalopathy (ANE).

Of those, encephalitis was defined as alteration of consciousness due to inflammation presented either in cerebrospinal fluid (CSF) or brain imaging lasting at least 24 hours but not related to acute stroke or hypoxic brain injury or any neuromuscular disorders.<sup>[15]</sup> ANE was proved by magnetic resonance imaging (MRI) with evidence of symmetric, multifocal brain lesions which involved the bilateral thalami, cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellar medulla, and the diagnosis was based on diagnostic criteria proposed by Mizuguchi.<sup>[11]</sup> For each patient, the Pediatric Index of Mortality 2 (PIM2) score on admission was recorded.<sup>[16]</sup> In children with bacteremia, data were collected from blood cultures taken at presentation or within 24 hours of admission and during the course of their hospital stay. Septic shock was defined as sepsis with acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.<sup>[17]</sup> Acute respiratory distress syndrome (ARDS) was defined according to the 1994 American European Consensus Conference before 2012, and using the Berlin definition after 2012.<sup>[18,19]</sup>

### 2.3. Analysis

Continuous variables are presented as medians and interquartile ranges (IQR) and were analyzed using the Wilcoxon rank-sum test. Categorical variables are presented as frequency and proportions (%) and were analyzed using the chi-squared test or Fisher exact test. All analyses were 2-sided, and the significance level was set to 0.05. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## 3. Results

### 3.1. Data analysis

The investigation of 40,002 children with influenza infections treated between January 1, 2012 and December 31, 2019, revealed a total of 32 pediatric children (0.25–16 years old, 18 men, and 14 women) who developed severe complicated influenza infections and were eligible for this study (22 had type A influenza, 10 had type B). The participants' mean age was 5.3 years (standard deviation, 2.4 years). The proportion of boys was higher than that of girls (64.3% vs 35.6%). The participants' demographic characteristics are presented in Table 1.

### 3.2. Underlying disease/comorbidities among CNS group and nCNS group

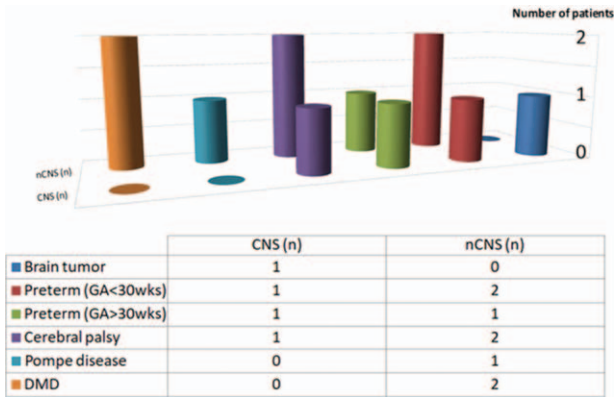
Nine of the total of 32 patients had underlying disease/comorbidities, including 3 with neuromuscular disorders, 5 with neurodevelopmental disorders, and 1 with medulloblastoma

**Table 1**

**Demographic data of children with severe complicated influenza infection.**

Demographic data	Children with severe complicated influenza infection (n=32)		P
	CNS (n=16), %	nCNS (n=16), %	
Sex			.99
Male	9 (56.2)	9 (56.2)	–
Female	7 (43.8)	7 (43.8)	–
Influenza type			.66
A	10 (62.5)	12 (75%)	–
B	6 (37.5)	4 (25%)	–
Mean age of onset, yrs (SD)	6 (14.5)	4.5 (13.9)	.82
Received seasonal influenza vaccine	0 (0)	0 (0)	.99
Clinical presentation (%)			.01
Fever	16 (100)	16 (100)	–
Cough and dyspnea	1 (6.2)	16 (100)	–
Seizure	14 (87.5)	0 (0)	–
Lethargy/Impaired consciousness	12 (75)	0 (0)	–
Personality changes	4 (25)	0 (0)	–
PIM2	0.43	0.12	.05
Lab data			
WBC ( $10^3/\mu\text{L}$ ) (SD)	8.7 (4.2)	7.4 (3.8)	.96
Neutrophils (%) (SD)	64.2 (21.2)	69.8 (15.6)	.36
Platelet ( $10^3/\mu\text{L}$ ) (SD)	190.0 (52.0)	183.5 (42.0)	.82
CRP, mg/dL (SD)	0.66 (0.39)	6.77 (3.5)	.002
Major underlying disease before influenza episode (%)			.82
Yes	3 (18.8)	6 (37.5)	–
No	13 (81.2)	10 (62.5)	–
Length of stay (days) (SD)	<b>6 (2.2)</b>	<b>16.5 (3.4)</b>	<b>.003</b>
Length of ICU stay (days) (SD)	<b>3 (1.3)</b>	<b>12 (3.2)</b>	<b>.002</b>
Intubation, (days) (SD)	<b>4 (2.5)</b>	<b>10 (3.2)</b>	<b>.03</b>
Death	6 (37.5)	1 (6.2)	.03

CRP=C reactive protein, ICU=Intensive Care Unit, PIM2=pediatric index of mortality2, SD=standard derivation, WBC=white blood cell, yrs=years.



**Figure 2.** Underlying disease/comorbidities among CNS group and nCNS group. CNS=central nervous system, DMD=Duchenne muscular dystrophy, nCNS=non-central nervous system.

being treated with chemotherapy (Fig. 2). All the children received neuraminidase inhibitor for 5 to 10 days immediately after diagnosis. Sixteen of the children had complications without CNS involvement (the nCNS group) and 16 children had complications with CNS involvement (the CNS group). One patient in the nCNS group died, while 6 children in the CNS group died ( $P=.03$ , odds ratio=11.66). The overall mortality rate was 21.88% in this study. All of the patients had not received an influenza vaccination within the previous year before admission. (Table 1)

**3.3. Complications, treatment, and prognosis among CNS group and nCNS group**

Table 2 shows the associated complications and treatment strategies of the CNS group and the nCNS group. The most common and serious complication in the nCNS group was ARDS ( $n=8/16$ ), followed by pneumonia ( $n=7/16$ ), septic shock ( $n=2/$

16, 12.5%), and myocarditis ( $n=1/16$ ). Eleven ( $n=11/16$ ) patients developed respiratory failure and required mechanical ventilation. All the survivors ( $n=15$ ) in the nCNS group fully recovered after treatment, with no obvious sequelae after discharge. In the CNS group, the most lethal complication was ANE ( $n=3/16$ ), which lead to 3 deaths, accounting for 50% of the deaths recorded in the CNS group. The most common complication was encephalitis ( $n=11/16$ ), which resulted in 3 deaths. The remaining 2 children had ADEM, which caused no mortality. The 2 patients who received antibiotics were those who developed septic shock. The clinical information regarding mortality is summarized in Table 3. All of the children who survived received high-dose neuraminidase inhibitor for 10 days immediately after diagnosis. The 2 children with influenza-associated ADEM were administered steroid pulse therapy, and both survived. Among the 10 survivors in the CNS group, 8 of them recovered without any lasting overt neurologic sequelae, while 2 of them ( $n=2/10$ , 20%) long-term neurologic sequelae and required long-term anticonvulsants and rehabilitation. Among both groups, a total of 13 children received antibiotic therapy to treat or prevent the progression to septic shock ( $n=13/32$ , 40%). The mortality rate was higher in the CNS group than in the nCNS group ( $P=.03$ , odds ratio=11.66). Moreover, the children who died were likely to have higher severity of illness at initial presentation, with their PIM2 scores being significantly higher than those of the patients who survived ( $P=.0025$ ).

**3.4. Significance of laboratory studies among CNS group and nCNS group**

CSF analysis was performed for 14 patients in the CNS group, and half of them presented pleocytosis. All of the bacterial cultures of CSF were negative. On the other hand, the mean CRP level was significantly higher in the nCNS group than in the CNS group ( $P=.002$ ). Eleven children in the nCNS group were intubated, while 6 in the CNS group were intubated. The intubation duration was significantly longer in the nCNS group

**Table 2**  
**Associated complications and treatment strategy among CNS group and nCNS group.**

	Children with severe complicated influenza infection (n=32) (%)		P
	CNS (n=16), %	nCNS (n=16), %	
Associated complications			.01
ARDS	0 (0)	8 (50)	–
Pneumonia only	0 (0)	7 (43.7)	–
Septic shock	2 (12.5)	2 (12.5)	–
Myocarditis	0 (0)	1 (6.25)	–
ANE	3 (18.7)	0 (0)	–
Encephalitis	11 (68.7)	0 (0)	–
ADEM	2 (12.5)	0 (0)	–
Treatment with neuraminidase inhibitor	16 (100)	16 (100)	.99
Treatment with antibiotics	2 (12.5)	9 (56.3)	.03
Immunomodulatory therapy			<.01
IVIG (2 g/kg)	10 (62.5)	0 (0)	–
High-dose methylprednisolone*	2 (12.5)	0 (0)	–
Patients who intubated during admission	8 (50)	11 (68.7)	.28
ECMO	0 (0)	1 (6.25)	.66
Brain MRI			–
Positive findings	8 (50)	N/A	N/A

ADEM=acute disseminated encephalomyelitis, ANE=acute necrotizing encephalopathy, ARDS=acute respiratory distress syndrome, ECMO=extracorporeal membrane oxygenation, IVIG=intravenous immunoglobulin, MRI=magnetic resonance imaging, N/A=not available.

\* High-dose methylprednisolone refers to 20–30mg/kg/d of methylprednisolone (maximum dose of 1g/d) for 3–5 days.

**Table 3****Clinical information of 7 mortalities in this study.**

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	M	M	M	F	F	M	F
Age, yrs	16	7	2	3	12	2	1
Classification of Group	nCNS	CNS	CNS	CNS	CNS	CNS	CNS
Influenza type	A (H1N1)	B	A (H3N2)	A (H3N2)	A (H1N1)	A (H1N1)	A (H1N1)
Seasonal influenza vaccination	No	No	No	No	No	No	No
Underlying disease	No	No	No	No	No	No	No
Primary disease related to death	ARDS and shock	Encephalitis	Encephalitis	Encephalitis and shock	ANE	ANE	ANE
Immunomodulatory therapy	No	No	IVIg	IVIg	Methylprednisolone	No	No
Direct cause of death	Cardiopulmonary failure	Brain swelling	Brain swelling	Brain swelling	Brain swelling	Brain herniation	Brain herniation
Days from admission to death	18	8	2	4	2	2	5

ANE = acute necrotizing encephalopathy, ARDS = acute respiratory distress syndrome, CNS = central nervous system, F = female, IVIg = intravenous immunoglobulin, m = male.

than in the CNS group ( $P = .03$ ), and the lengths of hospital stay and PICU stay were both significantly longer in the nCNS group than in the CNS group ( $P = .003$  and  $P = .002$ , respectively). (Table 1)

#### 4. Discussion

This study reports our experiences with children hospitalized in a PICU for critical influenza infections with nCNS and CNS complications from 2012 to 2019. The overall mortality in the study was 21.88%, and the mortality rate was higher in the CNS group than in the nCNS group ( $P = .03$ , odds ratio = 11.66). To our knowledge, this is the first study to compare children with CNS and nCNS complications associated with influenza infections.

Furthermore, a thorough analysis of each case revealed a higher incidence of intrinsic lung diseases or structural pulmonary and cardiac abnormalities among the nCNS group. It is noteworthy that, among the 16 nCNS children, 2 of the children had Duchenne muscular dystrophy (DMD), 1 had Pompe disease, 4 were early preterm infants with chronic lung disease, none had received an influenza vaccination before their flu events, and all suffered from disease exacerbating to respiratory failure. A possible mechanism in terms of DMD and influenza was proposed in a study using a Zebrafish model,<sup>[20]</sup> and we believe that a similar principle could probably be applied to the child with Pompe disease. As a result, all children with DMD or a disease related to pulmonary compromise of varying degrees are at higher risk of developing severe complicated influenza, and so it is suggested that such children be vaccinated against influenza.

Our results showed that the children with CNS involvement who died within a few days of admission or experienced grave neurological sequelae (such as spastic diplegia) were healthy children before the influenza event, although the fulminant course brought forth lethal or otherwise severe consequences. We did not identify a specific risk factor among these children except that not all had received a vaccine against influenza. Meanwhile, even though half of them were younger in age, this phenomenon still make us wonder whether there is a subtle link between infections and genetics.<sup>[21]</sup> Related studies regarding the pathogenesis of fulminant hepatitis have been conducted.<sup>[22–24]</sup>

To date, a few risk factors have been reported to be associated with severe influenza infection, such as age older than 65 years, pregnancy, underlying chronic medical conditions, obesity, hypertension, a history of smoking, and diabetes.<sup>[25]</sup> In children, studies have proposed a number of possible independent risk

factors for influenza-related mortality: age younger than 5 years old, chronic neurologic condition, immune compromise, acute myocarditis, encephalitis, and bacterial co-infection.<sup>[25,26]</sup> Our results once again echo the findings of those previous studies. Furthermore, we found that being a preterm infant (gestational age <37 weeks) is a mutual risk factor for both CNS and nCNS complications. Also, although our patients with chronic neurologic conditions (2 were early preterm with periventricular leukomalacia and 1 had a brain tumor and underwent surgery) had developed severe complicated influenza, they were able to return to their baseline status without significant long-term sequelae after intensive care and treatment. Hence, data regarding factors predisposing individuals to the development of severe influenza and even to death in the pediatric age group remain difficult to interpret.<sup>[27]</sup> Take ANE (which led to the highest mortality among the CNS group) as an example: it is a fatal neurological disorder with an ominous outcome whose etiology and pathogenesis are incompletely understood at present. Although a few microorganisms, including influenza A virus, have been reported as causative agents, it is believed that this disease is most likely immune-mediated.<sup>[6]</sup> Moreover, ANE is clearly more common among people of Asian ethnicities (being especially common in Japan, Taiwan, and Korea).<sup>[6,7]</sup> It is thus possible that genetic and environmental factors could affect the risk of developing ANE and mortality related to IAE. Further studies are needed to substantiate this suspicion.<sup>[6]</sup>

All of the children in this study had not received the seasonal vaccine against influenza, and we could not establish a comparison group of patients with severe complicated influenza who had received the vaccine. As a result, the significant findings, stress the importance of vaccination, as it could protect against not only mild influenza illness but also severe complicated influenza.<sup>[28,29]</sup>

On the other hand, Chaves et al.<sup>[30]</sup> reported that patients with H1N1 influenza A infections had higher odds of severe disease than patients with either H3N2 influenza A or influenza B virus infections. The most important risk factors related to mortality among critically children in our study were IAE and ANE. In our study, 6 children died of influenza A (4 H1N1 and 2 H3N2) infections, and only 1 died of an influenza B infection. Therefore, the mortality of influenza A was higher than that of influenza B in our study, which is consistent with the report from Chaves et al.<sup>[30]</sup> Notably, we found that no one in the nCNS group progressed to encephalopathy, whereas intubation was required in 9 children in the CNS group who required respiratory control (56.25%). The pathogenesis of development into influenza-

associated neurological complications remains unclear,<sup>[11,31,32]</sup> but is thought to be related to increased cytokine and macrophage activation. Another study revealed that transcription of the interleukin (IL)-6, IL-10, and tumor necrosis factor- $\alpha$  genes was up-regulated to a greater extent in patients with encephalopathy than in those without neurologic complications, even as the influenza virus load was similar among patients with encephalopathy or febrile convulsions or without neurologic complications. This phenomenon might imply that fatal cytokine storm is more serious in IAE (i.e., in those with CNS complications) than in those with nCNS complications.<sup>[33–35]</sup> Additionally, the antiviral therapy neuraminidase inhibitor is routinely used for patients with critical influenza infection, while immunomodulatory therapy with steroids, immunoglobulin G, and hypothermia are alternative therapeutical strategies.<sup>[31,36]</sup> All of the children in the present study were treated with Oseltamivir/Zanamivir/Peramivir as soon as possible, and the 2 survivors with ADEM received steroid pulses therapy. Among the non-survivors in the CNS group, 2 had received intravenous immunoglobulin (IVIG) (2 g/kg) and 1 had received steroid pulses therapy. As a result, one can conclude that IAE is a progressive and devastating disease, regardless of treatment. However, future studies are necessary for tailoring effective therapies to target mediators of both inflammation and repair, particularly in IAE.<sup>[34]</sup>

There are no biochemical markers that can help to predict the clinical course and prognosis of critical influenza infection or neurological complications. Increased CSF vascular endothelial growth factor and platelet derived growth factor have previously been found in IAE, and serum neutrophil elastase and neopterin levels were previously found to be significantly elevated in children with neurological complications compared with uncomplicated influenza.<sup>[37,38]</sup> However, in our study, we found that the mean CRP level was significantly higher in the nCNS group than in the CNS group, and the percentage of neutrophil was significantly lower in the children who did not survive than in those who did. The finding of high CRP levels in the nCNS group could be explained by the fact that there was more pulmonary involvement in the nCNS group, and the microbiome in the respiratory tract is influenced by viral infection, which could easily combine with bacterial infection to result in high CRP levels. However, the reason for decreased neutrophil in the non-survivors remains unclear.

There were some limitations in our study. First, this was a retrospective, single-center study, and the sample size was not large enough to be representative of the entire population, although it was still significant and might be representative of children. In any case, more in-depth studies with larger sample sizes are encouraged to explore this issue further in the future. Secondly, the lack of a consistent treatment protocol in the study owing to varied individual clinical course was an inevitable drawback. Thirdly, this was an observational study that sought to explore the different characteristics of severe influenza infections in children, so children with severe influenza infections during the observational period were regarded as the optimal subjects for this study, regardless of whether they were previously healthy or not. However, the results could be biased because the inclusion of children with different underlying diseases/comorbidities might have influenced the outcomes of the severe influenza infections. Therefore, future studies enrolling only previously healthy children are essential for understanding the natural outcomes of severe influenza infections with or without CNS complications. Nonetheless, this study is still informative

because it demonstrated a higher mortality rate for severe complicated influenza in children with CNS involvement, especially those who were previously healthy children.

## 5. Conclusion

In summary, we categorized severe complicated influenza infections into those with CNS involvement and those with nCNS involvement among a pediatric population and found that mortality was significantly higher with CNS involvement than without it. In addition, we found that the children with primary or structural pulmonary and cardiac abnormalities were at high risk of developing severe complicated influenza and that previously healthy children had a relatively high risk of IAE. Although the laboratory results from this study are still insufficient to provide a clear conclusion regarding the predicted outcomes of children with severe pediatric complicated influenza, it is suggested that all children receive the seasonal influenza vaccine to reduce the risks of severe complicated influenza infection. Further studies are necessary to tailor effective therapies for severe complicated influenza in children.

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