Observational Study

Medicine®

OPEN

Mortality risk factors in children with severe influenza virus infection admitted to the pediatric intensive care unit

Tingting Shi, MD[a,b], Zhiqiang Nie, MD[c], Li Huang, MD[b], Huifeng Fan, MD[a], Gen Lu, MD, PhD[a,*], Diyuan Yang, MD[a], Dongwei Zhang, MS[b]

Abstract

Some children hospitalized for severe influenza virus infection require intensive care or die because of disease progression, which may be combined with other complications. The objective of this study was to identify the mortality risk factors in the patients with severe influenza virus infection admitted to the pediatric intensive care unit (PICU).

Seventy-seven pediatric patients with severe influenza virus infection who were admitted in the PICU at Guangzhou Women and Children's Medical Center between 2013 and 2017 were evaluated. Data were transcribed and analyzed.

The patients' median age was 3.0 years (interquartile range, 1.0–4.0 years), with 59.7% of the patients aged <3 years. The mortality was 16.9%, and patients aged >3 years accounted for 69.2% of the cases. Influenza A virus infection was found in 83.1% of the patients. Coinfection was detected in 58.7% of the patients. *Haemophilus influenzae* (11.7%) and adenovirus (9.1%) were the predominant bacterial and viral pathogens isolated, respectively. Older age, oxygen saturation level of <90% at admission, acute respiratory distress syndrome, pneumorrhagia, influenza-associated encephalopathy (IEA), septic shock, low ratio of partial pressure of oxygen in arterial blood (PaO_2, <60 mm Hg) to the fraction concentration of oxygen in inspired air (FiO_2; *P/F*), higher oxygenation index, increased alanine aminotransferase level (>100 IU/L), increased aspartate aminotransferase level (>100 IU/L), increased lactate dehydrogenase level (>500 IU/L), high fraction concentration of oxygen in inspired air (FiO_2 > 60%), and positive end-expiratory pressure (>8 cmH_2O) were associated with poor outcome. The deceased patients were more likely to have oxygen saturation levels of <90% at admission and IEA than those who survived. Higher *P/F* ratio was a protective factor against death in patients.

The children with severe influenza virus infection who were admitted in the PICU were mainly aged <3 years. The presence of an oxygen saturation level of <90% at admission and IEA were the prognostic variables independently associated with mortality. Higher *P/F* ratio was a protective factor against death in patients.

Abbreviations: ARDS = acute respiratory distress syndrome, BAL = bronchoalveolar lavage, FiO_2 = fraction concentration of oxygen in inspired air, HRCT = high-resolution computed tomography, IEA = influenza-associated encephalopathy, IQR = interquartile range, MV = mechanical ventilation, OI = oxygenation index, *P/F* = the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the fraction concentration of oxygen in inspired air (FiO_2), PaO_2 = partial pressure of oxygen in arterial blood, PEEP = median positive end-expiratory pressure, PICU = pediatric intensive care unit, RT-PCR = real-time reverse transcriptase-polymerase chain reaction.

Keywords: children, influenza virus, pediatric intensive care unit, risk factor

1. Introduction

Influenza virus infection is common in children. Rates of influenza virus infection are consistently highest in children in different countries,[1,2] and a systematic review published in the Lancet in 2011 estimated that 90 million cases of influenza occur each year in children aged <5 years worldwide.[3] Approximately 870,000 preschool children are hospitalized around the world due to influenza virus infection each year.[4] While influenza virus infection may often be self-limited, it can also lead to severe clinical outcomes or even death because of its complications. In a meta-analysis, Nair et al estimated that in 2008, >100,000 deaths in children aged <5 years were due to influenza-related causes, 99% of which occurred in developing countries.[3] Some previous studies[5–7] found a few of risk factors for severe influenza virus infection in children such as ages under 2 years old, premature, presence of chronic, severe underlying medical conditions, and immaturity of the immune system.

In this study, we analyzed 77 pediatric patients with severe influenza infection who were admitted to the pediatric intensive

Editor: Babak Abdinia.

TS and ZN contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Respiratory, [b] Pediatric Intensive Care Unit, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, [c] Department of Epidemiology, Guangdong General Hospital, Guangdong Academy of Medical Science, Guangzhou, China.

[*] Correspondence: Gen Lu, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, No 9, Jinsui Road, Zhujiang New City, Tianhe District, Guangzhou, Guangdong 510120, China (e-mail: lugen5663330@sina.com).

Medicine (2019) 98:35(e16861)

Received: 21 February 2019 / Received in final form: 9 July 2019 / Accepted: 24 July 2019

http://dx.doi.org/10.1097/MD.0000000000016861

care unit (PICU). The purpose of this study was to identify the mortality risk factors in children with severe influenza virus infections who were admitted to the PICU. This information may be useful in the optimal utilization of scarce resources for the most effective preventive and early management strategies.

2. Methods

2.1. Setting

This study included 77 patients with severe influenza virus infections who were admitted to the PICU at Guangzhou Women and Children's Medical Center between January 2013 and December 2017 and had a respiratory specimen positive for seasonal influenza virus A or B. A list of patients was generated by identifying respiratory samples positive for influenza in real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The respiratory specimens consisted primarily of nasopharyngeal secretions. The patients with incomplete data (discharged against medical advice) were excluded. Chest radiography was performed in all the patients. Thirty patients underwent high-resolution computed tomography (HRCT) according to the wide range of lesions found on chest radiography. All the patients underwent indirect immunofluorescence viral testing of nasopharyngeal secretions during the acute phase of the disease to identify other viral infections. Blood and/or bronchoalveolar lavage (BAL) cultures were obtained for suspected bacterial infection with *Mycoplasma pneumoniae* or fungal infection. Flexible bronchoscopy was performed in the 28 patients who exhibited consolidation on chest radiography or HRCT. This study was approved by the ethics committee of Guangzhou Women and Children's Medical Center, Guangzhou Medical University.

2.2. Data collection

For each patient, data on demographics, clinical presentation, laboratory findings, microbiologic and radiologic findings, treatment, response to therapy, and outcome were collected. We also collected mechanical ventilation (MV) data. Oxygenation index (OI [fraction of inspired oxygen × mean airway pressure]/partial pressure of arterial oxygen) and the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the fraction concentration of oxygen in inspired air (FiO_2; *P/F*) were calculated on the 1st day of PICU admission. Acute respiratory distress syndrome (ARDS) was defined on the basis of the Pediatric Acute Lung Injury Consensus Conference criteria.[8] Septic shock was defined on the basis of the International Pediatric Sepsis Consensus Conference criteria.[9] Influenza-associated encephalopathy (IEA: neurologic complications including seizures, encephalitis, encephalopathy, Reye syndrome, and other neurologic disorders associated with influenza virus infection) was defined on the basis of the Center of Disease Control and Prevention criteria.[10]

2.3. Data analyses

All statistical analyses were performed using the SPSS 24.0 software. Categorical data were presented as frequency with the corresponding percentage, and continuous data were presented as median with the interquartile range (IQR). The Chi-squared or Fisher exact test was used to compare categorical variables between the survivors and nonsurvivors. Univariate analyses were performed to determine the risk factors significantly associated with seasonal influenza-associated pediatric deaths of children admitted in the PICU. To determine the independent contribution of each factor to the case outcomes, multiple logistic regression analysis was performed. Two-tailed *P*-values of $<.05$ were considered statistically significant.

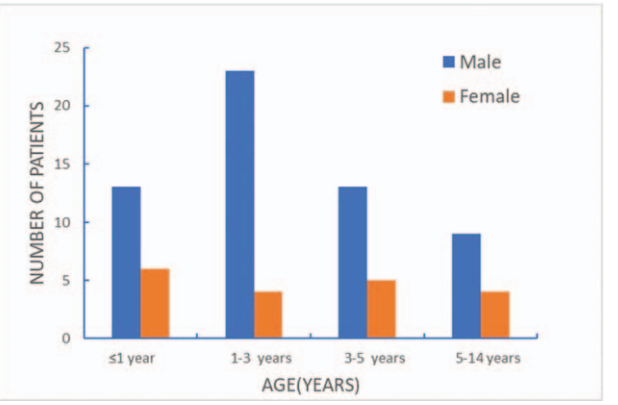

Figure 1. Age distribution of the children with severe influenza virus infection.

3. Results

3.1. Demographics and comorbid conditions

Over the 5-year period, 1770 hospitalized patients had a respiratory specimen positive for seasonal influenza A or B, of whom 80 were admitted to the PICU and 13 died. Of those who were admitted to the PICU, 3 were not enrolled in this study because of discharge against medical advice. Of the 77 PICU patients enrolled, 75.3% (58/77) were boys and 24.7% (19/77) were girls, with ages ranging from 1 month to 12 years. The median age was 3.0 years (IQR, 1.0–4.0 years), with 83.1% (64/77) of the patients aged <5 years and 59.7% (46/77) aged <3 years as shown in Figure 1. The most common period with the largest number of severe influenza infection cases in our study was April to June in the recent 5 years as shown in Figure 2. Of the 77 patients, 28 (36.4%, 28/77) had comorbid conditions. Renal and cardiovascular diseases were most common (10.4%, 8/77), followed by asthma (9.1%, 7/77) and prematurity (7.8%, 6/77; Table 1).

3.2. Clinical characteristics and laboratory findings

Cough (96.1%,74/77) and fever (90.9%,70/77) were the most common symptoms in our study, followed by shortness of breath or increased work of breathing (88.3%, 68/77) and altered sensorium (58.4%, 45/88). The median duration of cough was 4.0 days (IQR, 2.0–6.0 days), and that of fever was 4.0 days (2.0–5.0 days). Complications occurred in all 77 the patients, with pneumonia occurring in all the patients (100%, 77/77), followed by respiratory failure (96.1%, 74/77), ARDS (22.1%, 17/77), septic shock (15.6%, 12/77), and IEA (13.0%, 10/77). The abnormal clinical symptoms, physical examination findings, complications, laboratory findings are presented in Table 2.

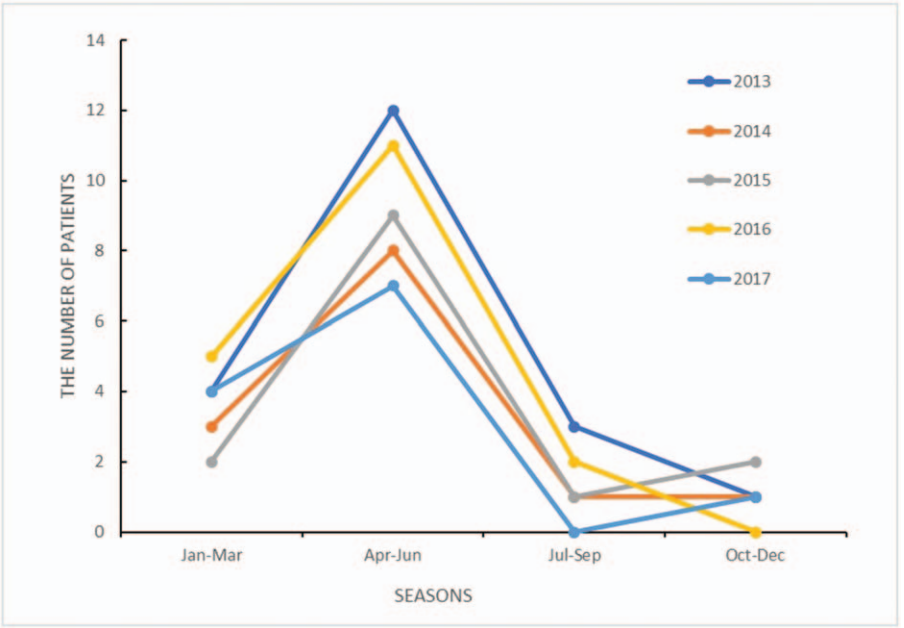

Figure 2. Seasonal distribution of the children with severe influenza virus infection.

3.3. Radiologic and microbiologic findings

Chest radiographic examination results mostly exhibited diffuse infiltration of both lungs (Fig. 3). Segmental or lobar infection distribution which predominantly involved the lower and middle lobes. The patients who died tended to present more severe infection on radiography. The most common finding on HRCT was consolidation (Fig. 4). The other main chest imaging findings were pleural effusion (28.6%, 22/77) and pneumothorax (6.5%, 5/77). Among the 77 patients, 83.1% (64/77) and 16.9% (13/77) had influenza A and B virus infections, respectively, with an influenza A to B ratio of 4.9:1.0. Besides influenza A/B, another causative agent (defined as coinfection) was detected in 58.7% (46/77) of the cases, with bacterial coinfections accounting for 36.4% (28/77), *M pneumoniae* coinfections for 11.7% (9/77), and viral coinfection for 11.7% (9/77). Of the bacterial coinfection cases, *Haemophilus influenzae* (11.7%, 9/77) and *Streptococcus pneumoniae* (7.8%, 6/77) were the predominant typical bacteria isolated in children with severe influenza virus infection. The most common viral pathogen isolated was adenovirus (9.1%, 7/77). The abnormal radiologic and microbiologic findings are shown in Table 3.

Table 1

Demographics and underlying medical conditions of the children with severe influenza infection who were admitted in the pediatric intensive care unit.

Characteristics	Total N = 77 Number (%)	Survivors N=64 Number (%)	Nonsurvivors N=13 Number (%)	*P*-value*
Demographics				
Male	58	49	9	.725
Female	19	15	4	
Age distribution, yr				.045
≤1	19	16	3	
1–3	27	26	1	
3–5	18	14	4	
5–14	13	8	5	
Underlying comorbid conditions				
Asthma	7	6	1	>.999
Chronic lung disease	1	1	0	>.999
Cardiovascular disease	8	6	2	.616
Renal disease	8	6	2	.616
Prematurity	6	5	1	>.999
Immunocompromized	1	0	1	.169
Malnutrition	4	3	1	.530
Abnormality in airway	3	2	1	.430
Neurologic disorder	5	3	2	.196

* Pearson Chi-squared test or Fisher exact test when appropriate.

Table 2

Clinical characteristics and laboratory findings of the children with severe influenza infection who were admitted in the pediatric intensive care unit.

Characteristics	Total N = 77 Number (%)	Survivors N = 64 Number (%)	Nonsurvivors N = 13 Number (%)	*P*-value*
Clinical symptoms				
Fever	70	59	11	.336
Axillary temperature >39.0°C	44	35	9	.334
Fever ≥5 d	27	24	3	.525
Cough	74	62	12	.130
Cough ≥5 d	32	27	5	.804
Vomiting/diarrhea	25	18	7	.104
Shortness of breath/increased work of breathing	68	56	12	>.999
Cyanosis	34	28	6	.874
Seizures	8	5	3	.128
Altered sensorium	45	36	9	.387
Physical examination findings				
Respiratory rate >70/min (≤1 yr) or >60/min (>1 yr)	11	9	2	>.999
Heart rate >180/min (≤1 yr) or >160/min (>1 yr)	41	33	8	.511
Oxygen saturation <90%	35	25	10	.012
Crackles	66	56	10	.384
Wheezing	33	28	5	.725
Decreased breath sounds	31	27	4	.444
Complications				
Respiratory failure	72	59	13	.582
Pneumonia	77	64	13	NA
ARDS	17	11	6	.032
Pneumorrhagia	8	3	5	.003
Heart failure	5	3	2	.196
Hydropericardium	10	8	2	.674
Gastrointestinal hemorrhage	12	10	2	.059
Influenza associated encephalopathy	10	6	4	.036
Septic shock	12	5	7	<.001
Acute renal failure	3	1	2	.072
Laboratory index				
PO_2 < 60 mm Hg	20	12	8	.003
PCO_2 > 50 mm Hg	43	33	10	.093
P/F				<.001
200 < *P/F* < 300	16	16	0	
100 < *P/F* < 200	46	42	4	
P/F < 100	15	6	9	
OI				<.001
OI < 4	3	3	0	
4 ≤ OI ≤ 8	25	25	0	
8< OI < 16	30	25	5	
OI ≥ 16	19	11	8	
Abnormal WBC < 5.0×10^9/L or >12.0×10^9/L	67	56	11	>.999
Hemoglobin <80 g/L	18	13	5	.169
Abnormal platelet <100×10^9/L or >500×10^9/L	50	42	8	>.999
Alanine aminotransferase >100 IU/L	10	5	5	.003
Aspartate aminotransferase >100 IU/L	10	5	5	.003
Creatine kinase-MB fraction >100 IU/L	6	4	2	.266
Lactate dehydrogenase >500 IU/L	31	22	9	.019
Serum albumin <35 g/L	47	40	7	.560
Creatinine >62 mg/dL	6	4	2	.266
C-reactive protein >10 mg/L	49	39	10	.354

NA = not available, WBC = white blood cell.

* Pearson Chi-squared test or Fisher exact test when appropriate.

3.4. Treatment and outcome

Of the 77 patients with severe influenza infection, 13 died (16.9%), with the patients aged >3 years accounting for 69.2% (9/13) of them. All 77 patients needed assisted ventilation, including MV in 93.5% (72/77) and noninvasive ventilation in 6.5% (5/77), of whom 46.8% (36/77) needed assisted ventilation for >7 days. The median length of hospitalization was 15.0 days (IQR, 10.0–20.0 days). The median length of PICU stay was 8.0 days (IQR, 7.0–12.3 days). On the 77 patients, 71.4% (55/77) stayed in the PICU for >7 days. Table 4 shows the patients' treatments as follows: all

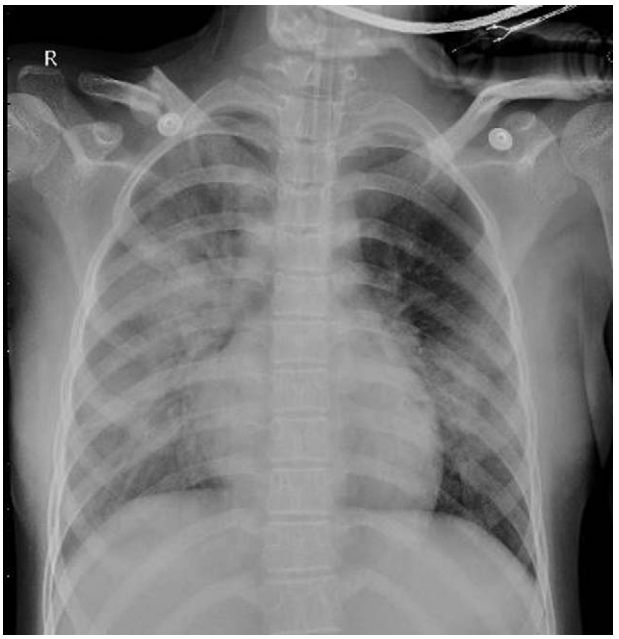

Figure 3. Chest radiograph showing bilateral diffuse infiltration indicative of acute respiratory distress syndrome.

the patients received oseltamivir antiviral drug treatment before hospitalization in 13 patients and after hospitalization in 64. The median time from onset of symptoms to initiation of antiviral therapy was 5.0 days (IQR, 3.0–6.0 days). Only 11.7% (9/77) and 77.9% (60/77) of the patients received antiviral therapy in 48 and >72 hours from the onset of symptoms, respectively. Of the patients, 84.4% (65/77) received antibiotics therapy and 72.7% (56/77) received corticosteroid therapy. On the 1st day of PICU MV therapy, the median FiO_2 was 55.5% (45–76.3%); median peak inspiratory pressure, 29.5 cmH_2O (26.0–32.0 cmH_2O); and median positive end-expiratory pressure (PEEP), 5.5 cmH_2O (5.0–7.75 cmH_2O).

3.5. Mortality risk factors in children with severe influenza virus infection

Older age, oxygen saturation level of <90% at admission, ARDS, pneumorrhagia, IEA, and septic shock were associated with mortality risk (all $P < .05$). The laboratory findings associated with death were lower PaO_2 (<60 mm Hg) and *P/F*, higher OI, and increased alanine aminotransferase (>100 IU/L), aspartate aminotransferase (>100 IU/L), and lactate dehydrogenase levels (>500 IU/L; all $P < .05$). The treatment associated with death was MV therapy, with higher FiO_2 (>60%) and PEEP (>8 cmH_2O), and length of PICU stay of >7 days (all $P < .05$). In the multivariate analysis, the independent risk factors of mortality were oxygen saturation level of <90% at admission (odds ratio [OR], 7.80; 95% confidence interval [CI], 1.02–50.54; $P = .048$), IEA (OR, 20.35; 95% CI, 1.62–256.13; $P = .020$). Higher *P/F* ratio ($P = .011$) was a protective factor against mortality in patients with severe influenza virus infection (Table 5). No relationship was found between death and comorbid conditions, specific pathogens, or radiological findings in the univariate and multivariate analyses.

4. Discussion

The outbreaks of influenza occur in winter in temperate zones and in rainy season in the tropic and subtropics.[11] The incidence peaked from April to July in Singapore,[12] but from June to September in India.[11] The most common months with the largest number of severe influenza virus infection cases in our study were April to June. The case fatality rate of severe influenza virus infection in the PICU ranges from 10.5% to 47% in other reports.[13–15] The mortality of severe influenza virus infections in patients in the PICU was 16.9% in our study, in line with previous reports. In the present study, severe influenza virus infection in the PICU mainly occurred in children aged <5 years, especially those aged <3 years. According to the surveillance data of the United States, patients with influenza virus infection aged <6 months and 6 to 23 months were >6 and >3 times more likely to die, respectively, than those aged 13 to 17 years.[16] Younger children and those with Advisory Committee on Immunization Practices-defined high-risk comorbid conditions such as asthma, neurologic disorders, cardiovascular disease, and renal disease may be at increased risk of influenza-related death.[16–18] However, it is an unexpected finding that the patients aged >3 years accounted for 69.2% of deaths and were significantly more likely to die than the younger patients ($P = .045$). In addition, the comorbid conditions were not associated with death in our study. The reason may be that the parents of these younger children with high-risk comorbid conditions paid more attention to them and took them to the hospital earlier. In the hospital, those children

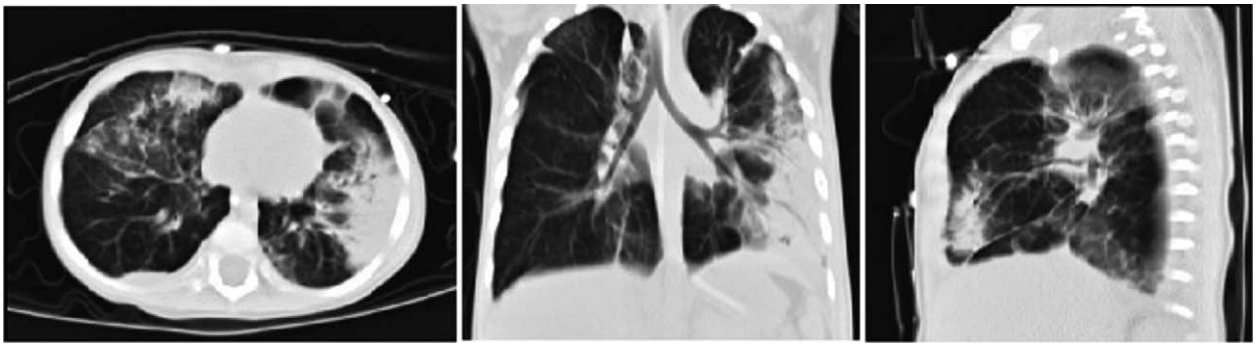

Figure 4. High-resolution computed tomography scan of the chest, showing areas of airspace consolidation in the left lower lobes and increased bilateral transparency in a 2-year-old child with severe influenza virus infection.

Table 3

Radiologic and microbiologic findings of the children with severe influenza infection who were admitted in the in pediatric intensive care unit.

Characteristics	Total N = 77 Number (%)	Survivors N = 64 Number (%)	Nonsurvivors N = 13 Number (%)	*P*-value*
Radiologic findings				
X-ray	77	64	13	.354
Infiltration (mild)	11	11	0	.194
Infiltration (moderate)	35	30	5	.260
Infiltration (severe)	31	23	8	.122
Pleural effusion	23	18	5	.523
Pneumothorax	5	3	2	.196
Fibro-bronchoscopy	45	39	6	.324
Plastic bronchitis	21	17	4	.742
Microbiologic findings				
Influenza A	64	52	12	.322
Influenza B	13	12	1	.449
Coinfection				
Influenza A/B-virus	9	8	1	>.999
Adenovirus	7	6	1	>.999
Respiratory syncytial virus	1	1	0	>.999
Rhinovirus	1	1	0	>.999
influenza A/B-bacteria	28	26	2	.117
Haemophilus influenzae	9	9	0	.343
Streptococcus pneumoniae	6	5	1	>.999
Klebsiella pneumoniae	4	3	1	.530
Staphylococcus aureus	3	3	0	>.999
Acinetobacter baumannii	3	3	0	>.999
Pseudomonas aeruginosa	1	1	0	>.999
Moraxella catarrhalis	1	1	0	>.999
Escherichia coli	1	1	0	>.999
Influenza A/B-*Mycoplasma pneumonia*	9	9	1	>.999

* Pearson Chi-squared test or Fisher exact test when appropriate.

were thought to be at higher risk of death and targeted for more-aggressive treatments as early as possible, which may have altered the course of their illness.

According to data from Taiwan, among patients admitted to the ICU, more had influenza A virus infection, with an influenza A-to-influenza B ratio of 2.6.[15]In Australia, influenza A was the predominant type (69%) in hospitalized children with influenza virus infection.[19] In the United States, 65% of pediatric influenza-related deaths are associated with influenza A infection.[16] In our study, 83.1% of the patients had influenza A

Table 4

Treatments of the children with severe influenza infection who were admitted in the in pediatric intensive care unit.

Characteristics	Total N = 77 Number (%)	Survivors N = 64 Number (%)	Nonsurvivors N = 13 Number (%)	*P*-value*
Treatments				
Oseltamivir treatment	77	64	13	>.999
<48 h from the onset of symptoms	9	7	2	.643
>48 and <72 h from the onset of symptoms	8	7	1	>.999
>72 h after the onset of symptoms	60	50	10	>.999
Antibiotics	65	54	11	>.999
Corticosteroid therapy	56	48	8	.325
Immunoglobulin	52	45	7	.331
Treatments admitted to PICU				
Noninvasive ventilation	4	4	0	>.999
Need for mechanical ventilation	73	60	13	.355
FiO_2 > 60%	38	27	11	.005
PIP > 30 cmH_2O	23	17	6	.191
PEEP > 8 cmH_2O	20	13	7	.032
The length of Mechanical ventilation >7 ds	29	24	5	>.999

PEEP = median positive end-expiratory pressure, PICU = pediatric intensive care unit.
* Pearson Chi-squared test or Fisher exact test when appropriate.

Table 5

Results of the multivariate analysis of the mortality risk factors in children with severe influenza infection who were admitted in the pediatric intensive care unit.

Variables	β	*P*	OR	OR 95% CI	
				Lower	Upper
Oxygen saturation <90%	2.05	.048	7.80	1.02	50.54
IEA	3.01	.020	20.35	1.62	256.13
P/F		.011			
$200 < P/F < 300$	−22.46	.998	0.00	0.00	>999.999
$100 < P/F < 200$	−2.88	.003	0.05	0.05	0.37
$P/F < 100$				Reference = 1	

CI = confidence interval, IEA = influenza-associated encephalopathy, OR = odds ratio.

infection, with a mortality of 84.6%. This result is consistent with previous reports. The incidence of bacterial coinfections caused by influenza viruses ranged from 7% to 43% in other reports,[16,18] and the incidence of viral coinfection ranges from 15.1% to 21.6%.[19] In our study, bacterial and viral coinfections accounted for 36.4% and 11.7%, respectively. The reason for the high incidence rate of bacterial coinfections in our study may be the long clinical courses of our patients and length of PICU stay, which could increase the risk of secondary bacterial infections. On the contrary, more than half (58.4%) of our patients underwent fibro-bronchoscopy, and BAL cultures were obtained for suspected bacterial infection; thereby, more bacterial coinfections may have been detected. According to another report,[20] bacterial coinfection can result in disease progression and severe disease in children. *Streptococcus* and *Staphylococcus aureus*, which were mainly responsible for secondary severe bacterial pneumonia, were the most commonly reported bacterial coinfections.[11,21] However, *H influenzae* was the predominant organism isolated in children with severe influenza virus infection in our patients. The reason may be that *H influenzae* vaccine was not free for children. In our study, most patients (84.4%) had received antibiotic therapy, including 48% (37/77) with bacterial coinfections and 66.2% (49/77) with a higher C-reactive protein level. This may be the reason we did not find any association between bacterial coinfection and mortality. Viral coinfections were infrequent in our study. The low incidence of other respiratory viruses may be explained by the fact that the incidence of the illness peaked in April to June before the winter respiratory viral season. Respiratory syncytial virus was the most frequently identified coinfection.[16] However, adenovirus was the most common viral pathogen in this study. Our data may suggest an increased prevalence of adenovirus in severe influenza virus infection cases or may even lead to fatal ones.

Severe influenza virus infections that resulted in death were accompanied by a wide range of complications, with pneumonia, septic shock, and ARDS being the most commonly reported.[17,21] In our study, the presence of septic shock, ARDS, and IEA were associated with death. Meanwhile, an oxygen saturation level of <90% at admission was associated with death from severe influenza virus infection in our univariable and multivariable analyses, similarly to previous studies in Taiwan and the United States in which shortness of breath or dyspnea were indicators of poor outcome.[15,20] Pneumonia is a common complication, and the influenza virus itself increases susceptibility to pneumonia. All our severe cases were diagnosed as pneumonia by chest radiography, and the patients who died tended to present with a more severe pneumonia patch or effusion, which coincided with prior evidence.[14,15] Severe pneumonia with more patch or effusion on radiography were more likely to develop into ARDS or even pneumorrhagia. In the present study, 46.2% of the patients who died had ARDS and 38.5% had pneumorrhagia. All of them needed higher FiO_2 and PEEP in MV therapy. ARDS and pneumorrhagia were associated with death from severe influenza virus infection in the univariable analysis. Similarly, lower PO_2 and *P/F*, and higher OI were also significantly associated with death (both $P < .05$). Higher *P/F* ($P = .011$) was identified as a protective factor against mortality in patients with severe influenza virus infection in the multivariate analysis. Neurologic complications such as IEA were present in a few patients, but it was a strong predictor of ICU admission or even death.[19] In the United State, IEA was only reported in 6% of influenza-associated deaths among children during one influenza season, while it was reported in 31.8% of influenza-associated deaths in Japan.[17,22] In our study, 30.8% of the patients who died had IEA with the presence of fever, coma, seizure, or even brain failure, higher than that in the United States but similar to that in Japan. In addition, IEA was associated with death and was an independent risk factor of death in our study. This may support the speculation of an East-Asian ethnic susceptibility to IEA.[23] Future prospective studies and more samples are needed to evaluate its contribution to mortality in severe influenza virus infections.

Previous studies showed that early oseltamivir treatment can decrease the risks of ICU admission and mortality.[24] Oseltamivir treatment should be started within 48 hours of illness onset, and patients with good outcome can benefit from the early use of oseltamivir treatment.[20] Although all the children in our study received oseltamivir treatment, only 11.7% received oseltamivir treatment within 48 hours from illness onset. The reason may be that the clinical signs and symptoms of influenza virus infection in children were nonspecific and influenza is difficult to differentiate from other respiratory infections. In addition, the primary care physicians in our country did not pay enough attention to these patients and realize the importance of early treatment. Therefore, pediatrician should be more likely to initiate antiviral medication earlier for patients suspected with influenza virus infection or use influenza rapid tests to confirm the infection during the influenza season. This may help to reduce the risk of PICU admission and mortality from severe influenza virus infection.

5. Conclusion

Our results showed that severe influenza virus infection occurred mainly in children aged <5 years, especially those aged <3 years, among those admitted in the PICU. The mortality from severe influenza virus infections was 16.9%; most of the patients who

died were aged >3 years. In the patients with coinfections, *H influenzae* and adenovirus were the most common bacterial and viral pathogen isolated, respectively. The presence of an oxygen saturation level of <90% at admission and IEA were the prognostic variables independently associated with death. Higher *P/F* ratio was a protective factor against mortality in the patients with severe influenza infection. Early recognition and intervention of severe cases can help to decrease PICU admission and mortality.

Author contributions

Data curation: Huifeng Fan.
Formal analysis: Diyuan Yang.
Investigation: Li Huang.
Project administration: Huifeng Fan.
Resources: Gen Lu, Li Huang.
Software: Diyuan Yang.
Supervision: Gen Lu.
Validation: Dongwei Zhang.
Visualization: Dongwei Zhang.
Writing – original draft: Tingting Shi, Zhiqiang Nie.
Writing – review & editing: Tingting Shi, Zhiqiang Nie, Gen Lu.

References

[1] Ruf BR, Knuf M. The burden of seasonal and pandemic influenza in infants and children. Eur J Pediatr 2014;173:265–76.
[2] Fraaij PL, Heikkinen T. Seasonal influenza: the burden of disease in children. Vaccine 2011;29:7524–8.
[3] Lafond KE, Nair H, Rasooly MH, et al. Global role and burden of influenza in pediatric respiratory hospitalizations, 1982-2012: a systematic analysis. PLoS Med 2016;13:e1001977.
[4] Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet 2011;378:1917–30.
[5] Garcia MN, Philpott DC, Murray KO, et al. Clinical predictors of disease severity during the 2009-2010 A(HIN1) influenza virus pandemic in a paediatric population. Epidemiol Infect 2015;143:2939–49.
[6] Centers for Disease C, PreventionUpdate: influenza-associated deaths reported among children aged <18 years–United States, 2003-04 influenza season. MMWR Morb Mortal Wkly Rep 2004;52:1286–8.
[7] Principi N, Esposito S. Severe influenza in children: incidence and risk factors. Expert Rev Anti Infect Ther 2016;14:961–8.
[8] Pediatric Acute Lung Injury Consensus Conference . Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatric Crit Care Med 2015;16:428–39.
[9] Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric Crit Care Med 2005;6:2–8.
[10] Centers for Disease C, PreventionNeurologic complications associated with novel influenza A (H1N1) virus infection in children - Dallas, Texas, May 2009. MMWR Morb Mortal Wkly Rep 2009;58:773–8.
[11] Kumar V. Influenza in children. Indian J Pediatrics 2017;84:139–43.
[12] Doraisingham S, Goh KT, Ling AE, et al. Influenza surveillance in Singapore: 1972–86. Bull World Health Organ 1988;66:57–63.
[13] Torres SF, Iolster T, Schnitzler EJ, et al. High mortality in patients with influenza A pH1N1 2009 admitted to a pediatric intensive care unit: a predictive model of mortality. Pediatric Crit Care Med 2012;13:e78–83.
[14] Chen WH, Lu CY, Shao PL, et al. Risk factors of severe novel influenza A (H1N1) infections in hospitalized children. J Formosan Med Assoc 2012;111:421–6.
[15] Ma HY, Wu JL, Lu CY, et al. Risk factors associated with severe influenza virus infections in hospitalized children during the 2013 to 2014 season. J Microbiol Immunol Infect 2016;49:387–93.
[16] Shang M, Blanton L, Brammer L, et al. Influenza-associated pediatric deaths in the United States, 2010-2016. Pediatrics 2018;141:
[17] Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003-2004. New Engl J Med 2005;353:2559–67.
[18] Chong CY, Tan NW, Menon A, et al. Risk factors for complicated influenza A (H1N1) 2009 disease in children. Ann Acad Med Singapore 2013;42:232–6.
[19] Li-Kim-Moy J, Yin JK, Blyth CC, et al. Influenza hospitalizations in Australian children. Epidemiol Infect 2017;145:1451–60.
[20] Centers for Disease C, PreventionSurveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection - United States, April-August 2009. MMWR Morb Mortal Wkly Rep 2009;58:941–7.
[21] Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004–2012. Pediatrics 2013;132:796–804.
[22] Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002;35:512–7.
[23] Britton PN, Dale RC, Blyth CC, et al. Influenza-associated encephalitis/encephalopathy identified by the Australian childhood encephalitis study 2013-2015. Pediatric Infect Dis J 2017;36:1021–6.
[24] Eriksson CO, Graham DA, Uyeki TM, et al. Risk factors for mechanical ventilation in U.S. children hospitalized with seasonal influenza and 2009 pandemic influenza A*. Pediatric Crit Care Med 2012;13:625–31.