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ORIGINAL ARTICLE

Risk factors associated with severe influenza virus infections in hospitalized children during the 2013 to 2014 season

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Abstract *Background:* An outbreak of influenza virus infection occurred in Taiwan from October 2013 to May 2014. We conducted a clinical study to identify risk factors associated with severe influenza virus infections in children.
Methods: During the outbreak period, data from 110 hospitalized children with influenza virus infection were collected. We analyzed the data, the need for intensive care, and patient outcome to identify clinical features and risk factors of severe infections, defined as the need of intensive care.
Results: Of the 110 inpatients, there were 57 male and 53 female patients; the median age was 2.6 (interquartile range, 1.0–6.3) years. Nineteen patients required intensive care and two patients died. Children who were underweight ($p = 0.01$) or those with neuromuscular disease ($p = 0.007$) and digestive tract disease ($p = 0.03$) were prone to severe infection. Occurrence of seizure ($p = 0.004$), conscious disturbance ($p = 0.02$), or low oxygen saturation at admission ($p = 0.04$) predicted the need for intensive care. Higher initial absolute neutrophil count ($p = 0.02$) and patch or pleural effusion on chest X-ray examination ($p = 0.02$) were associated with severe infection. In the multivariable analysis, digestive tract disease [$p = 0.03$; adjusted odds ratio (OR), 12.37; 95% confidence interval (CI), 1.28–119.43], seizure ($p = 0.001$; adjusted OR, 49.54; 95% CI, 4.61–532.76) and conscious disturbance ($p = 0.006$; adjusted OR, 131.61; 95% CI, 4.18–4141.64) were most significantly associated with severe influenza virus infection.

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Conclusion: Close monitoring of the important risk factors including underlying digestive tract diseases, seizure attack and conscious disturbance were recommended during the influenza season.

Introduction

Influenza virus can be subdivided by the surface antigen into three groups, designated types A, B, and C.[1] Influenza virus types A and B commonly cause human diseases but influenza C rarely does. There was an outbreak of influenza infection in Taiwan from October 2013 to May 2014. According to the statistical data from the Center for Disease Control, R.O.C. (Taiwan; Taiwan CDC),[2] there were 1671 cases of severe influenza infection during the 2013–2014 winter season. The United States Advisory Committee on Immunization Practices (ACIP) and many previous studies identified children with the following medical conditions to be at risk for complicated influenza disease: children aged 6–59 months; children who have chronic pulmonary (including asthma), cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus); children under immunosuppression; children who are receiving long term aspirin therapy; and children who are morbidly obese [body mass index (BMI) $\geq$ 40].[3–11]

According to our previous report of 61 hospitalized children during the 2009 novel H1N1 pandemic in a tertiary hospital in Taiwan, 21% of the patients required intensive care and 5% eventually died.[6] Complications of influenza infection, such as pneumonia, encephalitis, respiratory failure or shock, may subject children to intensive care.[6] As it was previously reported, respiratory distress, elevated C-reactive protein (CRP) level, chest radiography abnormality compatible with pneumonia, and delayed antiviral therapy were predictors for severe complications requiring intensive care.[4,12–14]

During the influenza outbreak in Taiwan from October 2013 to May 2014, there were differences in the presentation and clinical course compared with the previous report during the 2009 H1N1 pandemic. Therefore, we conducted a clinical study to identify clinical features and risk factors associated with severe influenza virus infections of children in Taiwan during the 2013–2014 influenza season.

Methods

Identification of influenza patients

This study was approved by the Ethics Committee of the National Taiwan University Hospital, Taipei, Taiwan. At the National Taiwan University Hospital, we included patients in the study who were hospitalized for laboratory confirmed influenza virus infections. Laboratory confirmed influenza viral infection was defined as either a positive culture of influenza virus from throat swab specimens, a positive result of real time reverse transcription-polymerase chain reaction (RT-PCR) for influenza virus from throat swab specimens, or a positive rapid influenza test (QuickVueA+B test; Quidel, San Diego, CA, USA) from nasopharyngeal swab specimens. Virus culture and identification in the Madin-Darby canine kidney (MDCK) cell line (ATCC, Manassas, VA, USA) were performed using standardized protocol in the virology laboratory of this tertiary medical center. The real-time RT-PCR with primers and probes (influenza A primer, forward: 5′ GAC CRA TCC TGT CAC CTC TGA C, reverse: 5′ AGG GCA TTY TGG ACA AAK CGT CTA, probe: 5′ TGC AGT CCT CGC TCA CTG GGC ACG (R is for A or G, Y for C or T, and K for G or T); influenza B primer, forward 5′ AAATACGGTGGATTAAATAAAAGCAA, reverse: 5′ CCAGCAATAGCTCCGAAGAAA, probe: 5′ CACCCATATTGGGCAATTTCCTATGGC) was performed according to the standard protocol of the virology laboratory. If the rapid influenza test proved positive for both influenza types A and B, the patients having this influenza infection were still included and the influenza viral type was described as undetermined.

Data collection and study design

From October 1, 2013 to May 31, 2014, the patients were identified through a weekly review of hospitalized pediatric patients and their virological results at the National Taiwan University Hospital. We systemically reviewed the chart of each patient, collected their demographics, underlying medical conditions, clinical signs and symptoms, laboratory and radiological data, prescription of antiviral and antimicrobial therapy, course of intensive care unit (ICU) care, severity score, discharge diagnosis, and final outcome.

Identified underlying medical conditions were classified according to organ systems, such as cardiovascular disease, neuromuscular disease, digestive tract disease or immunosuppressive status, etc. Each patient requiring intensive care was assigned a severity score according to the Therapeutic Intervention Scoring System (TISS), which divided ICU patients into four classes according to the total score.[15,16] For timing calculations, the day of admission was regarded to be hospital Day 0. The BMI was calculated by the formula: weight in kilograms divided by the square of the height in meters. Obesity and underweight were defined according to the age-corrected normal range of BMI released by the Taiwan Health Promotion Administration.[17]

We divided the patients into two groups, one group consisted of patients who did not need intensive care (non-ICU group) while the other group consisted of patients who required intensive care (ICU group), also defined as the severe influenza virus infection group. We then compared these two groups to identify risk factors for severe influenza virus infection in children.

Statistical analysis

Statistical comparisons of selected parameters were performed with Fisher's exact test for categorical variables and with the Mann-Whitney *U* test for continuous variables. We included the demographic data and underlying comorbidities that had a significance level < 0.1 for multivariable analysis. We also included the clinical features, laboratory data, and radiographic data with a significance level < 0.1 for multivariable analysis. All statistical analyses were performed with PASW version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows. A p value < 0.05 was considered statistically significant.

Results

Demographics and comorbidities

From October 1, 2013 to May 31, 2014, 110 children with influenza virus infection were hospitalized in the National Taiwan University Hospital. Nineteen children required intensive care (ICU group), while the other 91 children required only general care on the ward (non-ICU group). Three patients were admitted to a general ward initially, but transferred to ICU within 3 days of admission due to a deteriorated condition. We assigned these three patients to the ICU group. Table 1 shows patient demographics and comorbidities. The median age of all hospitalized patients was 2.6 years (interquartile range; IQR, 1.0—6.3) and the male to female ratio was 1.08 (57—53). The age distribution and male-to-female ratio did not have significant differences between the ICU group and the non-ICU group ($p = 0.64$ and $p = 0.13$, respectively).

Of the 110 patients, 53 (48%) had underlying medical conditions. Among 19 children of the ICU group, 13 (68%) had underlying disease and 40 (44%) of the 91 children in the non-ICU group had underlying disease ($p = 0.08$). There was a significantly higher prevalence of neuromuscular disease ($p = 0.007$) and digestive tract disease ($p = 0.03$) in the ICU group than in the non-ICU group. Although there was no significant difference in the distribution of BMI between the two groups ($p = 0.95$), the prevalence of underweight was significantly higher in the ICU group than the non-ICU group ($p = 0.02$). All of the five underweight children admitted to ICU had underlying diseases. One child had gastroesophageal reflux disease and bilateral Grade 4 intraventricular hemorrhage with ventriculoperitoneal shunt placement; one had epilepsy disorder with developmental delay and scoliosis complicated with respiratory tract anomaly; another had severe gastroesophageal reflux disease with fundoplication and previous history of intraventricular hemorrhage with sequelae of cerebral palsy and epilepsy. One child had developmental delay, failure to thrive and laryngomalacia with laryngoplasty. The last child had congenital emphysema with left lung lobectomy and asthma.

Clinical manifestations and laboratory findings

Symptoms and physical findings at presentation are listed in Table 2. Mean duration of fever before admission was 2.9 [standard deviation (SD), 2.7] days, with 1.7 (SD, 1.7) days of the ICU group and 3.1 (SD, 2.8) days of the non-ICU group ($p = 0.05$). Cough and rhinorrhea were the most common reported symptoms in all hospitalized patients. However, the occurrence of seizure and conscious disturbance was higher among the children admitted to the intensive care unit than those who were not ($p = 0.004$ and $p = 0.02$, respectively). Injected throat was the most common observed sign, followed by rales and wheezing during chest auscultation. A higher percentage of children in the ICU group had abnormal breathing sounds (rales, wheezing, rhonchi, and decreased breathing sound), retraction and

Table 1 Demographics and comorbidities

Variables	All ($n = 110$)	ICU group ($n = 19$)	Non-ICU group ($n = 91$)	p
Male/female	57/53	13/6	44/47	0.13
Age (y), median (IQR)	2.6 (1.0—6.3)	2.3 (1.4—10.4)	2.7 (1.0—5.9)	0.64
< 59mo	75 (68)	12 (63)	63 (69)	0.60
BMI,[a] mean (SD)	17.1 (3.0)	17.1 (2.7)	17.1 (3.1)	0.95
Obesity[b]	15 (14)	0 (0)	15 (16)	0.07
Underweight[b]	11 (10)	5 (26)	6 (7)	0.02
Comorbidities				
Any	53 (48)	13 (68)	40 (44)	0.08
CV disease	13 (12)	2 (11)	11 (12)	1.00
Pulmonary disease	25 (23)	5 (26)	20 (22)	0.76
Neuromuscular disease	20 (18)	8 (42)	12 (13)	0.007
Digestive tract disease	8 (7)	4 (21)	4 (4)	0.03
Genetic/metabolic disease	4 (4)	1 (5)	3 (3)	0.54
Hemato-oncology disease	5 (5)	1 (5)	4 (4)	1.00
Prematurity	25 (23)	5 (26)	20 (22)	0.76

[a] BMI data are missing for one patient.
[b] Obesity and underweight: Age-corrected normal range of BMI released by Taiwan Health Promotion Administration.
Data are presented as *n* (%).
BMI = body mass index; CV = cardiovascular system; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation.

Table 2 Symptoms and signs before admission

Variables	All (n = 110)	ICU group (n = 19)	Non-ICU group (n = 91)	p
Symptoms				
Duration of fever (d), mean (SD)	2.9 (2.7)	1.7 (1.7)	3.1 (2.8)	0.05
Vomiting	37 (34)	5 (26)	32 (35)	0.60
Cough	85 (77)	13 (68)	72 (79)	0.37
Shortness of Breath	28 (25)	7 (37)	21 (23)	0.25
Seizure	8 (7)	5 (26)	3 (3)	0.004
Abdominal pain	16 (15)	1(5)	15 (16)	0.30
Myalgia	16 (15)	2 (11)	14 (15)	0.73
Change of consciousness	4 (4)	3 (16)	1 (1)	0.02
Decreased oral intake	54 (49)	8 (42)	46 (51)	0.62
Rhinorrhea	70 (64)	8 (42)	62 (68)	0.03
Signs				
Rales	24 (22)	6 (32)	18 (20)	0.36
Wheezing	23 (21)	5 (26)	17 (19)	0.53
Retraction	12 (11)	3 (16)	9 (10)	0.43
Rhonchi	21 (19)	4 (21)	17 (19)	0.76
Decreased Breathing Sound	1 (1)	1 (5)	0 (0)	0.17
Tonsil exudate	6 (5)	1 (5)	5 (5)	1.00
Neck lymphadenopathy	3 (3)	0 (0)	3 (3)	1.00
Injected throat	52 (47)	6 (32)	45 (49)	0.21
Peak temperature (°C), mean (SD)	39.2 (0.7)	39.1 (0.8)	39.2(0.7)	0.95
Peak RR (/min)[a] mean (SD)	38 (11.1)	41 (13.7)	37 (10.4)	0.38
RR > 95th of age limit	90 (82)	16 (84)	74 (81)	0.76
SpO2 at admission (%),[b] mean (SD)	97 (5.2)	93 (8.8)	97 (3.6)	0.001
SpO2 <90% at admission	5 (5)	3 (16)	2 (2)	0.04

[a] Data of peak RR are missing in one patient.
[b] Data of SpO2 at admission are missing in five patients of the non-ICU group.
Data are presented as n (%) unless otherwise indicated.
ICU = intensive care unit; RR = respiratory rate; SpO2 = peripheral oxygen saturation.

lower peripheral oxygen saturation (SpO_2) than those in the non-ICU group. However, only lower SpO_2 reached statistical significance (p = 0.004).

Table 3 shows the laboratory data and radiographic characteristics on the 1st day of hospitalization. A significantly higher percentage of children in the ICU group had high absolute neutrophil count (defined as absolute neutrophil count > 97th quartile) than the non-ICU group (47% vs. 22%; p = 0.02), but the difference of the CRP value was not significant between the two groups. Therefore, a higher absolute neutrophil count seemed a better predictor than CRP level for severe influenza virus infection. Also, either patchy lesion or pleural effusion on chest X-ray occurred significantly more often in the ICU group than the non-ICU group (33% vs. 8%; p = 0.02). All of the patients with pleural effusion also had patchy lesion and all required ICU care.

Clinical course, treatment, and outcome

Table 4 shows the clinical course, treatment, and outcome of the patients. Of the 110 patients, 19 (17%) were admitted to the ICU and 2 died. Among these 19 patients with severe influenza virus infections, 13 had influenza A virus infection, five had influenza B virus infection, and one did not have a record of influenza type. Almost all the patients received antiviral therapy with either oseltamivir or peramivir. Five patients did not receive antiviral therapy because they did not receive an influenza rapid test and the diagnosis of influenza was confirmed by viral culture several days later. The median time from the onset of illness to the initiation of antiviral therapy was 2.3 days (SD, 2.2); 63 (57 %) patients received antiviral therapy within 48 hours of onset of the symptoms. Most of the patients (n = 15; 79%) in the ICU group received antiviral therapy within 48 hours, whereas only about one half of the patients (n = 48; 53%) in the non-ICU group did (p = 0.02). Delayed administration (> 48 hours) of antiviral therapy was not associated with a higher rate of requiring intensive care. About one half of the patients received antibiotic treatment. Of the patients in the ICU group, six patients had the total TISS score in the highest class, Class IV (defined as a total score ≥ 40) and all of them required mechanical ventilation. Three patients required extracorporeal membrane oxygenation (ECMO) support; one patient survived and the other two died.

Risk factors associated with severe influenza virus infections

Table 5 shows the results of multivariable analysis of the predictors for severe influenza virus infection. In the multivariable analysis of demographic and underlying diseases, only digestive tract disease reached statistical significance as an independent risk factor for severe influenza

Table 3 Laboratory data and radiographic characteristics

Variables	All (n = 110)	ICU group (n = 19)	Non-ICU group (n = 91)	p
Flu type (n), A/B/undetermined	58/48/4	13/5/1	45/43/2	0.12
WBC (/μL), mean (SD)	10257 (4999)	11935 (6593)	9895 (4550)	0.26
WBC >15000/μL[a]	16 (15)	5 (26)	11 (12)	0.11
WBC <5000/μL	12 (11)	1 (5)	11 (12)	0.39
ANC (/μL),[a] mean (SD)	6146 (4133)	8251 (4998)	5691 (3803)	0.04
ANC >8800/μL	29(26)	9 (47)	20 (22)	0.02
ANC <1000/μL	4 (4)	0 (0)	4 (4)	0.35
Platelet count (/μL),mean (SD)	261,182 (98,115)	254,368 (101,906)	259,972 (98,343)	0.86
Hemoglobin (g/dL),[a] mean (SD)	12.4 (1.5)	11.7 (1.6)	12.6 (1.4)	0.06
CRP (mg/dL), mean (SD)	3.0 (4.3)	4.2 (6.2)	2.7 (3.8)	0.59
CRP >5 mg/dL[b]	21 (19)	5 (26)	16 (18)	0.38
Chest X-ray taken	101 (92)	18 (95)	83 (91)	
Patch or effusion	13 (13)	6 (33)	7 (8)	0.02
Infiltrate	58 (57)	8 (44)	50 (60)	0.22
Normal	30 (30)	4 (22)	26 (31)	<0.05

[a] Data of WBC, ANC, and hemoglobin are missing in three patients in the non-ICU group.
[b] Data of CRP are missing in four patients of the non-ICU group.
Data are presented as n (%) unless otherwise indicated.
ANC = absolute neutrophil count; CRP = C-reactive protein; ICU = intensive care unit; WBC = white blood cell.

disease (p = 0.03; adjusted OR, 12.37; 95% CI, 1.28—119.43). As for the clinical features, laboratory and radiographic data, seizure (p = 0.001; adjusted OR, 49.54; 95% CI, 4.61—532.76) and conscious disturbance (p = 0.006; adjusted OR, 131.61; 95% CI, 4.18—4141.64) were significant independent predictors for requirement of intensive care.

Discussion

A total of 110 children were hospitalized during the 2013 to 2014 influenza season, and 19 patients required ICU care in our study. Digestive tract disease, seizure, and conscious disturbance were independent predictors for severe influenza virus infection.

In Taiwan, influenza is reported year round with the "influenza season" occurring from early winter to late spring. According to data from the Taiwan CDC, there were 1193 influenza isolations from reported severe cases between September 2013 and May 2014. Influenza type A H1N1 accounted for 321 cases, H3N2 for 639 cases, and influenza type B for 333 cases.[2] In our study, among those admitted to ICU, more had influenza A virus infection, with an influenza A to B ratio of 2.6. This observation was consistent with higher virulence of influenza A as reported previously.[1] The influenza type A to B ratio from the Taiwan CDC report was 2.58, with all H1N1 viral isolates matched with the vaccine strain, 98% of H3N2 viral isolates matched, whereas only 19% of influenza B isolates matched with the vaccine strain during the 2013—2014 influenza season.[2] In our study, only two of the 13 ICU patients with influenza A virus infection received the 2013—2014 seasonal influenza vaccine; whereas three of the five patients with influenza B virus infection received the influenza vaccine. Ten patients did not even receive seasonal influenza vaccination and four patients did not have available records of influenza vaccination. Although the sample size was too small to

Table 4 Clinical course

Variables	All (n = 110)	ICU group (n = 19)	Non-ICU group (n = 91)	p
Receive antiviral medication	105 (96)	19(100)	86 (95)	0.59
Start within 48 h	63 (57)	15 (79)	48 (53)	0.02
Receive antibiotics	59 (54)	12 (63)	47 (52)	0.45
Macrolide only	4 (7)	0 (0)	4 (9)	
Beta-lactam only	41 (69)	9 (75)	32 (68)	
Macrolide + beta-lactam	14 (24)	3 (25)	11 (23)	
Total duration of fever (d), mean (SD)	4.42 (4.06)	4.74 (4.75)	4.35 (3.93)	0.88
Length of Stay (LOS; d), mean (SD)	6 (7.7)	16 (15)	4 (2.2)	<0.001
LOS >5 d	43 (39)	13 (68)	20 (22)	<0.001
Outcome				<0.001
Recovery	108 (98)	17 (89)	91 (100)	
Death	2 (2)	2 (11)	0 (0)	

Data are presented as n (%) unless otherwise indicated.
ICU = intensive care unit.

Table 5 Multivariate analysis of the predictors for severe influenza virus infection

Variables	All (n = 110)	ICU group (n = 19)	Non-ICU group (n = 91)	Adjusted OR (95% CI)	p
Age (y), median (IQR)	2.6 (1.0–6.3)	2.3 (1.4–10.4)	2.7 (1.0–5.9)	0.82 (0.66–1.02)	0.08
Male/female	57/53	13/6	44/47	2.22 (0.45–11.08)	0.33
Underweight	11 (10)	5 (26)	6 (7)	1.97 (0.69–5.65)	0.21
Neuromuscular disease	20 (18)	8 (42)	12 (13)	4.41 (0.62–13.36)	0.14
Digestive tract disease	8 (7)	4 (21)	4 (4)	12.37 (1.28–119.43)	0.03
Duration of fever (d), mean (SD)	3 (2.7)	2 (1.7)	3 (2.8)	0.77 (0.47–1.26)	0.30
Seizure	8 (7)	5 (26)	3 (3)	49.54 (4.61–532.76)	0.001
Change of consciousness	4 (4)	3 (16)	1 (1)	131.61 (4.18–4141.64)	0.006
SpO2 <90% at admission	5 (5)	3 (16)	2 (2)	13.00 (0.71–239.18)	0.08
ANC >8800/μL	29 (26)	9 (47)	20 (22)	2.26 (0.44–11.66)	0.33
Patch or effusion	13 (13)	6 (33)	7 (8)	3.38 (0.50–22.87)	0.21

Data are presented as n (%) unless otherwise indicated.
ANC = absolute neutrophil count; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation; SpO2 = peripheral oxygen saturation.

reach statistical significance, seasonal influenza vaccine seemed to protect children from contracting severe influenza A infection but not severe influenza B infection, which might be due to mismatched influenza vaccine type.

As shown by numerous previous studies and ACIP recommendations for the seasonal influenza vaccination, children with comorbidities or immunocompromisation were a susceptible population.[3–11] Our study also demonstrated that children with comorbidities had a significantly higher rate of requiring intensive care. Using multivariable analysis (Table 5), we identified the digestive tract disease as an independent risk factor of requiring ICU care. Four children in the ICU group had digestive tract disease, three of them had gastroesophageal reflux disorder and one had impaired swallowing coordination secondary to previous cardiac surgery and required a nasogastric tube for feeding, which might lead to increased reflux episodes. Four children in the non-ICU group had digestive tract diseases; only one had gastroesophageal reflux disorder. Gastroesophageal reflux is identified to have a role in upper airway diseases, such as chronic sinusitis, pharyngolaryngitis, otitis media with or without effusion, and bronchitis.[18–20] Patients with the above conditions might have airway mucosal immune dysfunction, resulting in increased frequency and severity of airway infection. Thus, we observe that children with reflux disorder are prone to have influenza virus infection with increased severity.

In contrast to the fact that many previous studies recognized morbid obesity (BMI $\geq$ 40) as a risk factor for severe H1N1 infection,[9,11] we found that underweight children had increased risk for severe disease in univariable analysis (Table 1). Previous studies in both mice and humans demonstrated that malnutrition might decrease immunity and increase the severity of influenza virus infection.[21–23] We still need to pay special attention to malnutrition children in resource-abundant Taiwan.

The symptoms and clinical signs of influenza virus infection were non-specific. Lower initial oxygen saturation at admission predicted the need of intensive care in the univariable analysis (Table 2), which was similar to previous studies during novel H1N1 pandemics both in Taiwan and the United States, in which shortness of breath was an indicator for poor outcome.[6,24] However, only seizure attack and disturbed consciousness were independent predictors of requiring intensive care in the multivariable analysis. The occurrence rate of seizure was 7.3% for all hospitalized children, which was the same as a previous report during a 2009 novel H1N1 pandemic in Taiwan,[6] but higher within the ICU group in our study.

Severe inflammation predicts a worse outcome. Both absolute neutrophil count and elevated CRP level were indicators for severe inflammation. However, in our study, CRP level at admission alone was not a good predictor for severe influenza disease, in contrast to the findings of the 2009 H1N1 pandemic[6] and also the influenza study of both adults and children in 2013 in Taiwan.[13] In this study, a higher absolute neutrophil count had better predictive value in the multivariable analysis (Table 5). It was likely that CRP level may take longer to reach a significantly high level compared to the reaction of absolute neutrophil count, as CRP may take 6–12 hours to be synthesized.[25]

Diffuse bilateral infiltrates on chest radiography were more commonly seen in patients with primary influenza viral pneumonia,[26] whereas consolidation on initial chest radiographs predicts the requirement of intensive care and use of a mechanical ventilator.[14] We noticed that patients without ICU care tended to present as infiltrates but patients who required ICU care tended to have pneumonia patch or pleural effusion on chest radiography, in accordance with the previous report during the 2009 H1N1 pandemic.[6] Although the secondary bacterial infection is a great concern, all patients did not have confirmed positive bacterial culture results from sterile sites such as blood, pleural effusion, or cerebrospinal fluid.

Receipt of antiviral drugs within 2 days of the onset of illness and early presentation to medical care predict better outcome as previously known.[7,24] However, in our study, the patients in the ICU group presented to medical care about 1 day earlier than those in the non-ICU group. Also, a higher percentage of patients in the ICU group received antiviral medication within 48 hours of the onset of illness (79% vs. 53%). Due to the universal insurance coverage in Taiwan and medical accessibility, parents take children to medical care much earlier, especially those with more comorbidities. During the influenza season, physicians are also more likely to use influenza rapid tests and initiate

antiviral medication when facing patients with many comorbidities or presenting with higher severity.

There are several limitations of our study. Firstly, this is a retrospective chart review study. The related medical history, such as the underlying comorbidities, presenting symptoms and signs, might not be accurately recorded by medical staff. In our analysis, we did not include the items with $>$ 20% of missing data. Some items in our study still had missing data as shown in Tables 1—3. Secondly, this study is conducted in a tertiary medical center, in which the patients may have higher disease severity and more complicated comorbidities than those in other local hospitals. Thirdly, the severity scores of ICU patients varied in our study. Some of the patients in the ICU group may have less severe disease conditions, which may confound the analytical results.

Conclusion

In our study, we found 110 children hospitalized due to influenza viral infection during the 2013—2014 influenza season and the rate of severe cases was 17%. We identified digestive tract disease, seizure, and conscious disturbance to be independent predictors for severe influenza infection in children. Close monitoring of the risk factors was recommended during the influenza season.

Conflicts of interest

The authors have no conflicts of interest to declare.

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