



RESEARCH ARTICLE

Outcome predictors of influenza for hospitalization and mortality in children

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Abstract

Severity of disease caused by influenza virus and the influencing factors that may be different. Moreover, the disease course actually may not be determined specifically in children because of lower seroprotection rates of children. Herein, the results clinic and outcome data of children with influenza from Turkey were reported. We present here the results from 2013 to 2017. Nasopharyngeal swab samples of the children with influenza were investigated via multiplex polymerase chain reaction. A total of 348 children were diagnosed with influenza; 143 (41.1%) were influenza A, 85 (24.4%) were influenza B, and 120 (34.5%) were mixt infection with other respiratory viruses. Fifty-four percent of children admitted to intensive care unit (ICU) were under 2 years of age ($p = .001$). Having an underlying disease was detected as the main predictor for both hospitalization and ICU stay according to multiple logistic regression analysis (odds ratio [OR], 11.784: 95% confidence interval [CI], 5.212–26.643; $p = .001$ and OR, 4.972: 95% CI, 2.331–10.605; $p = .001$, respectively). Neurological symptoms most frequently seen in cases who died (44.4%; $p = .02$). Lymphopenia was relatively higher (55.6%) and thrombocytopenia was most frequently seen in cases who died (77.8%) with a significant ratio ($p = .001$). Underlying diseases was found a risk factor for influenza being hospitalized and being admitted to ICU. Children under 2 years of age and with underlying diseases should be vaccinated particularly in countries where the influenza vaccination is still not routinely implemented in the immunization schedule.

Highlights Underlying diseases is a risk factor for influenza to be hospitalized and admitted to ICU. Influenza vaccination is of great importance to prevent life-threatening complications of influenza, particularly in children require ICU admission. The possibility to reduce the outpatient visit number by vaccination has a great impact on disease burden in addition to the underestimated crucial social benefits, as well.

KEYWORDS

influenza, infection, pediatric, outcome

1 | INTRODUCTION

The two influenza viruses, A and B, cause epidemics in humans and they are one of the main reasons of morbidity and mortality due to a virus in worldwide. An estimated 5%–10% of adults and 20%–30% of children are infected with influenza virus despite a significant variation of illness rates in year-to-year, which causing 3–5 million severe cases besides 250,000 to 500,000 deaths annually.^{1–4} Although many of infections have mild clinical course, requiring no hospital admission, a proportion of cases present with severe complications, mainly in people with underlying health conditions and in young children and the elderly.³ A couple of risk factors have been found to be associated with intensive care unit (ICU) admission and mortality in hospitalized cases^{3,5}; there are scarce data from Turkey, particularly from children. Investigating and understanding those factors associated with poor outcomes might be crucial to prepare health resources accurately.^{6,7} The aim of this study was to investigate factors associated with hospitalization, ICU admission, and death in children infected with influenza.

2 | MATERIALS AND METHODS

This retrospective study was performed by the Department of the Pediatric Infectious Diseases, Hacettepe University Faculty of Medicine in Turkey between December 2013 and December 2017. The medical records of patients diagnosed with influenza infection were reviewed. Relevant information including demographics, clinical, and laboratory findings were recorded on prepared forms. (The study was approved by the Ethical Committee of the Hacettepe University (number: GO 17/88). All laboratory tests had been performed in our local laboratory. Children's vaccination status was determined by parental report retrospectively.

Patients with influenza infection were classified into four groups as (1) intensive care unit (ICU) group; severe patients who required admission to an ICU,⁸ (2) non-ICU group; patients who did not need an ICU stay, (3) ex-patients; patients who died during the treatment were included in the assessment as infection-related mortality if the death had been caused by the infection,⁹ and (4) outpatients; patients who were followed in outpatient clinics that did not need hospitalization.

2.1 | Respiratory virus analysis

Respiratory viruses were isolated from nasopharyngeal specimens, and the samples were analyzed for 15 viruses including influenza A-B, parainfluenza 1–2–3, adenovirus, respiratory syncytial virus (RSV) A-B, coronavirus, enterovirus, human rhinovirus, human bocavirus, coronavirus 229/NL63, and coronavirus OC43/HKU1 via multiplex reverse transcription polymerase chain reaction (RT-PCR) to detect the etiological viral agent. Nucleic acid isolation was performed with a GeneAll Ribospin vRD II Isolation Kit (Seoul, Korea

and RT-PCR were performed by a Seegene RV16 Detection Kit as reported in our previous studies.^{8,10} One nasopharyngeal swab collected from each enrolled child. A specimen was defined as being influenza positive if RT-PCR assay was positive for influenza A or B.

2.2 | Statistical analysis

Statistical analyses were performed using SPSS for Windows version 20.0. Descriptive statistics used to define baseline characteristics of cases were mean, median, minimum–maximum, and interquartile ranges for continuous variables and percentages besides numbers for categorical variables. The χ^2 test and Kruskal–Wallis test were performed to compare categorical variables and continuous variables, respectively. Logistic regression was used to determine the adjusted effect of the influenza infection on each of the outcomes, including hospitalization, ICU stay, and infection-related mortality. Variables for which the *p* value was less than .20 in bivariate analysis were included in a full multiple logistic model according the magnitude of their effect. In all the analysis, *p* < .05 was considered significant.

3 | RESULTS

Total of 348 children infected with influenza virus were enrolled in this retrospective study during 4 years period. Nasopharyngeal swabs were collected from all the patients. We compared patients among four groups as patients (*n* = 33) who admitted to ICU, patients (*n* = 195) who hospitalized to pediatric inpatient clinics except ICU, patients (*n* = 9) who died, and patients (*n* = 111) who did not need hospitalization and were followed in outpatient clinics. The most patients were males (53.7%) and the median age of the cases were 3 years (min–max, 0–17). No statistically significant differences were found between the groups in terms of gender (*p* = .30) and overall age (*p* = .11). However, the distribution of cases under 2 years of age according to groups were 54.5%, 43.1%, 33.3%, and 20.7%, respectively (*p* = .001; Table 1).

Seasonal distribution of the influenza types was analyzed. Of the all diagnosed cases, 99 (28.4%) of the patients were diagnosed in January, 92 (26.4%) in December, 65 (18.6%) in February, and the others in November, March, and April. Among children with influenza, 143 (41.1%) were influenza A, 85 (24.4%) were influenza B, and 120 (34.5%) were mixt infection with other respiratory viruses. There was no any statistically significance between the groups in terms of the distribution of cases infected with influenza A and B as well as mixt viral infection (*p* = .32). Overall mixt viral infection ratio was 34.5% and the most coinfecting viruses were RSV, followed by rhinovirus, influenza A and B, and bocavirus (Figure 1). Mixt viral infection ratio was relatively higher in cases who died (Table 1) and the most coinfecting virus was RSV (Table 2). The most commonly clinical diagnosis of the cases who died were pneumonia and myocarditis (Table 2).

TABLE 1 Demographic and clinical data of all patients

	ICU group (n = 33)	Non-ICU group (n = 195)	Ex (n = 9)	Outpatients (n = 111)	p value
Age, years (median, IQR)	1 (0–6)	2 (0–8)	4 (0–7.5)	4 (2–6)	.11
<2 years, n (%)	18 (54.5)	84 (43.1)	3 (33.3)	23 (20.7)	.001
2–5 years, n (%)	5 (15.2)	49 (25.1)	3 (33.3)	55 (49.5)	
6–12 years, n (%)	7 (21.2)	42 (21.5)	2 (22.2)	28 (25.2)	
≥13 years, n (%)	3 (9.1)	20 (10.3)	1 (11.1)	5 (4.5)	
Female, n (%)	12 (36.3)	86 (44.1)	5 (55.6)	58 (52.2)	.30
Underlying diseases, n (%)					NA
No disease	9 (27.3)	101 (51.8)	3 (33.3)	99 (89.2)	
Pulmoner	2 (6.1)	12 (6.2)	0	1 (0.9)	
Neurologic	3 (9.1)	11 (5.6)	1 (11.1)	2 (1.8)	
Immunodeficiency	3 (9.1)	13 (6.7)	1 (11.1)	1 (0.9)	
Cardiac	5 (15.2)	4 (2.1)	1 (11.1)	3 (2.7)	
Malignancy	1 (3)	23 (11.8)	1 (11.1)	1 (0.9)	
Prematurity	3 (9.1)	6 (3.1)	0	1 (0.9)	
Metabolic	3 (9.1)	6 (3.1)	0	1 (0.9)	
Others*	4 (12.1)	19 (9.7)	2 (22.2)	2 (1.8)	
Clinical symptoms, n (%)					
Fever	22 (66.7)	150 (76.9)	2 (22.2)	104 (93.7)	.001
Respiratory	27 (81.8)	180 (92.3)	4 (44.4)	106 (95.5)	.001
GIS symptoms	8 (24.2)	27 (13.8)	3 (33.3)	27 (24.3)	.06
Neurological	4 (12.1)	14 (7.2)	4 (44.4)	12 (10.8)	.02
Length of hospitalization day, median, (IQR)	22 (11–73)	10 (5–17)	21 (8.5–28)	–	.001
White blood cell cell/mL, median (IQR)	10,100 (5600–18,150)	7800 (4200–11,700)	9700 (7300–16,550)	6900 (4700–9200)	.05
Platelets	247 (183–420)	260 (185–383)	63 (53–121)	231 (180–330)	.002
Neutropenia, n (%)	7 (21.1)	46 (23.7)	1 (11.1)	13 (11.7)	.46
Lymphopenia, n (%)	14 (42.2)	86 (43.6)	5 (55.6)	28 (25.2)	.37
Thrombocytopenia n (%)	5 (15.1)	29 (14.9)	7 (77.8)	11 (9.9)	.001
CRP mg/dl, median (IQR)	1.4 (0.2–11.2)	1 (0.4–4.1)	2.1 (0.6–17)	0.8 (0.3–1.6)	.17
Sedimentation mm/hour, median (IQR)	6 (2–40)	17 (3–45)	5 (5–)	12 (6.5–22)	.3
Virus type					.32
Influenza A	11 (33.3)	90 (46.2)	2 (22.2)	40 (36)	
Influenza B	9 (27.2)	41 (21)	2 (22.2)	33 (29.7)	
Multiple virus	13 (39.3)	64 (32.8)	5 (55.6)	38 (34.2)	
Antiviral treatment, n (%)	20 (60.6)	93 (47.7)	5 (55.6)	25 (22.5)	.001

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

In ICU group, 27.3% of patients had no underlying diseases, the most frequent underlying disease was cardiac conditions (15.2%). In non-ICU group, 51.8% of patients had no underlying disease, the most frequent underlying disease was malignancies (11.8%). In exitus group (n = 9), three patients (33.3%) who died and in outpatient group, 89.2% of cases had no any underlying conditions. Fever and respiratory symptoms were most significantly seen in outpatients (p = .001 in each). Neurological symptoms most frequently seen in

cases who died (44.4%, n = 4) with a significant ratio as compared with other groups (p = .02; Table 1).

Although no statistically significant differences were found between the groups in terms of white blood cell (WBC; p = .05), neutropenia (p = .46), and lymphopenia (p = .37), lymphopenia was relatively higher (55.6%) in cases who died as compared with the other groups. In addition, thrombocytopenia was most frequently seen in cases who died (77.8%) with a significant ratio as compared the others (p = .001).

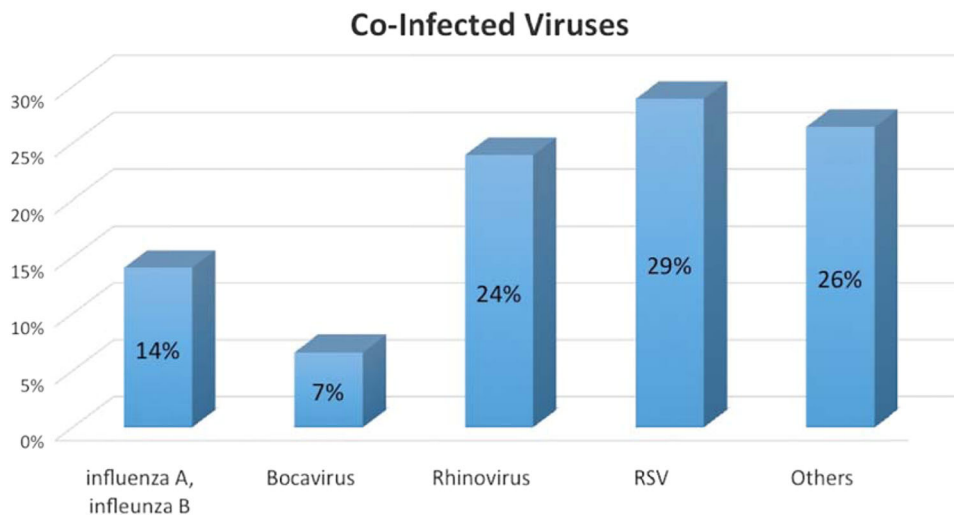


FIGURE 1 Coinfected viruses

According to the results of the multiple logistic regression analysis as shown in Table 3, the main predictor for both hospitalization and ICU stay was underlying diseases (odds ratio [OR], 11.784; 95% confidence interval [CI], 5.212–26.643; $p = .001$ and OR, 4.972; 95% CI, 2.331–10.605; $p = .001$, respectively).

None of the children were vaccinated with an available influenza vaccine.

4 | DISCUSSION

Influenza virus is an important cause of respiratory illness among children. Children younger than two years of age have a high hospitalization and complication ratio because of the infections caused by influenza virus^{11–13} as in our study. More than 50% of children admitted to ICU were under 2 years of age in the current study. Many children with influenza have commonly some clinical symptoms including fever, cough, and rhinorrhea. Poehling et al.¹⁴ reported that children younger than 6 months of age have significantly lower cough and fever and cough ratio as compared with children aged 6–59 months of age. In outpatient setting of the present study, the most common symptoms were fever and respiratory symptoms with the ratios more than 90% consistently with the literature.¹⁴ Vice versa, fever response and respiratory symptoms were not significantly seen in inpatients as compared with the outpatients. The age of the patients and existence of clinical symptoms such as fever and respiratory may be important to predict the severity of disease course. That is, these findings may possibly be explained by age-dependent immune maturation of children. In light of the data of our current and past studies about viral disease process, we learned that children have different pro-inflammatory/anti-inflammatory response network and need repeated antigenic stimulation and sequential changes in the functional capacity lymphocytes to reach the final maturation phase.¹⁵

Neurological findings were mostly seen in those who died in current study. Again, low platelet count was mostly seen in the death cases. Even though the total number of white blood cells was the same, the death cases had a lymphopenia but not statistically significant. In light of these data, it can be predicted that prognosis is worse in patients infected with influenza virus in the presence of neurological findings, lymphopenia and thrombocytopenia. Centers for Disease Control and Prevention (CDC) reported that children with neurologic/neurodevelopmental conditions have a higher risk for severe influenza, including death.¹⁶ On the other hand, there is a temporal relation of the neurological events and influenza illness in the absence of other identifiable causes.¹⁷ However, pediatric literature is quite limited on both the management of children with neurological complications caused by influenza and effects of neurological involvement on disease process in pediatric patients. Moreover, there was no difference between the distribution of influenza A and B viruses in patients who died, while the rate of mixed viral infection was relatively higher compared with other groups. Given that RSV, which cause influenza-like illness and pneumonia is the most common co-infecting virus in the cases who died in the current study and impose a substantial burden of hospitalization, which was estimated to cause 60%–80% more deaths than influenza in one study from England and Wales.^{18,19} Goka et al.²⁰ reported that co-infection is a significant predictor of disease outcome and rhinovirus and RSV were the most coinfecting viruses in this study as in our study. Therefore, the effects of these coinfecting viruses on the prognosis of the patient should not be ignored as well.

The annual rates of hospitalization attributable to influenza have ranged from 0.6 to 2.7 per 1000 children younger than 5 years of age.^{11,12,21–23} Underlying diseases was found a risk factor for influenza, having 11 times more risk of being hospitalized with influenza and about five times more risk of being admitted to ICU with influenza for children with underlying conditions. Particularly cardiac diseases are one of the leading causes for a patient with an underlying

TABLE 2 Demographic and clinical data of died patients

Patient no	Season/ Year	Age/Sex	Virus type	Underlying disease	Clinic	Physical examination	WBC (/mm ³)	ANS (/mm ³)	ALS (/mm ³)	Thrombocytopenia dL	CRP (mg/	Complication	Antiviral drug
1	2015	6 years/ female	Influenza A	Neurologic	Pneumonia	Kussmaul breathing, crepitant rales	19,900	16,400	1500	Yes	0.9	No	No
2	2017	2 mont- hs/ male	Influenza A, Bocavirus	Immunodeficiency	Myocarditis	Rough rales, hepatomegaly	9900	9300	100	Yes	0.2	Myocarditis	Yes
3	2017	2 years/ male	Influenza A, RSV-A	Cancer	GI bleeding	Abdominal tenderness	8400	6900	500	Yes	17	No	No
4	2017	5 years/ female	Influenza A+B	No	Myocarditis	Superficial respiration, peripheral pulse filiform, tachycardia	19,200	15,600	2800	Yes	0.2	Myocarditis	Yes
5	2017	17 years/ female	Influenza A, parainfluen- za-1, RSV-A	Hematologic	Myocarditis	Rough breath sounds	800	600	100	Yes	3.7	Myocarditis	Yes
6	2017	9 years/ female	Influenza B	No	Sepsis	Jaundice, organomegaly, encephalopathy	9700	4600	1000	Yes	2.1	No	No
7	2017	9 months/ female	Influenza B, RSV	Cardiac	Pneumonia	Rough rales, pansystolic murmur	13,900	1900	10,600	No	-	No	No
8	2017	10 mont- hs/ male	Influenza B	No	Sepsis	Bilateral rales	6300	4100	1700	Yes	38	Hemophagocytic syndrome	Yes
9	2017	4 years/ male	Influenza A	LHH	Pneumonia	Decreased breath sounds in left lung	8800	5200	3300	No	0.6	Pneumothorax	Yes

Abbreviation: RSV, respiratory syncytial virus.

TABLE 3 Multiple logistic regression models

Outcome and variable	OR (95% CI)	p value
Hospitalization		
Age <2 years,	0.317 (0.156–0.645)	.02
Age 2–5 years	0.339 (0.148–0.778)	.01
Age 6–12 years	1.264 (0.31–5.151)	.734
Fever	0.215 (0.084–0.548)	.001
Respiratory symptoms	0.248 (0.065–0.947)	.04
Underlying diseases	11.784 (5.212–26.643)	.001
ICU stay		
Fever	0.38 (0.178–0.826)	.014
Respiratory symptoms	0.232 (0.089–0.603)	.003
WBC count	1.0 (1.0–1.0)	.29
Underlying diseases	4.972 (2.331–10.605)	.001
Mortality		
Fever	0.029 (0.004–0.217)	.001
WBC count	1.0 (1.0–1.0)	.011
Thrombocyte count	1.0 (1.0–1.0)	.001

Abbreviations: CI, confidence interval; OR, odds ratio; WBC, white blood cell.

condition to be hospitalized in ICU in the present study. Flannery et al.²⁴ reported that more than one-half of the pediatric deaths in their study had one or more underlying medical condition with the severe influenza-associated complications. Therefore, American Academy of Pediatrics recommend a special effort to vaccinate individuals with chronic medical conditions which increase the risk of complications caused by influenza, including pulmonary, metabolic, and cardiac diseases, immunosuppression, renal, hepatic, and neurologic disorders.²⁵ Furthermore, 30% of the patients who died had no underlying health problems. Fifty percent of children hospitalized in nonintensive care units had no underlying disease, as well. Influenza virus played an important role for a healthy child to be hospitalized in ICU according to the result of the present study. In fact, school-aged children bear a large influenza disease burden and have a higher chance of need influenza-related medical care compared with healthy adults.^{13,25} Healthy children may also develop complications such as sepsis and myocarditis, which may lead to death. Especially, considering that 30% of the cases are lost from myocarditis, it is necessary to be very vigilant against this complication which may also have very subtle findings. Influenza myocarditis is not common; moreover, few pediatric cases were reported because of the various clinical presentation from asymptomatic electrocardiographic changes to heart failure with fatal arrhythmias. Two (40%) of the five patients died in one our case series despite the aggressive treatment including intravenous immunoglobulin and extracorporeal membrane oxygenation with the diagnosis of myocarditis caused by influenza virus, consistently with a national Japanese survey.^{10,26}

These information show us once again the importance of protection rather than treatment of this viral disease, which has very serious consequences in healthy children as well as children with underlying disease. Unfortunately, Turkey is still one of the countries

where the influenza vaccination is not routinely implemented in the National immunization schedule. There are very few reports about influenza vaccination rate in Turkey and vaccination ratio change between 5% and 27% in adult studies.^{27–29} Overall influenza vaccination coverage rate was 4.2% according to data of Public Health Institute of Turkey, which is really not sufficient to control the burden of influenza,³⁰ although the Global Influenza Hospital Surveillance Network included pediatric cases from Turkey reported that vaccination seemed to confer better protection against influenza B and in children under 4 years of age and prevent approximately one in four hospitalizations with influenza.³¹

Several limitations should be noted. Firstly, these data are small and local; which would not enhance generalizability of the findings. However, Hacettepe University İhsan Doğramacı Children's Hospital is a tertiary care hospital with approximately 270 acute-care beds and average 220.000 admissions each year. Influenza is still not included in National immunization schedule of Turkey; moreover, vaccination ratio with available influenza vaccines is quite low. Therefore, these data may give a valuable information to shed light on the situation of pre-vaccine era in countries such as Turkey. Second, we could not perform a cost analysis to reveal the actual burden of the disease, which might lead us realize the real impact of the virus from a detailed perspective in the world without vaccines.

As a conclusion, influenza illnesses cause a substantial health burden despite the many clinically unrecognized cases infected with influenza virus; therefore, since testing is not routinely performed in every center in Turkey, influenza testing is one of the major steps to increase the awareness of the physicians as well as public. Increased use of rapid testing may improve infection-control activities and increase the need for influenza vaccine as mentioned in literature.¹⁴ The other important step is prevention; that is, influenza vaccination reduces life-threatening influenza in children require ICU admission.³² When the realities of Turkey taken into consideration, particularly children under 2 years of age and children with underlying diseases should be driven to be vaccinated on account of the high hospitalization rates with a high ICU admission as a first step on the way of national immunization. In addition, although the vaccination against influenza in children has been primarily dependent on the ratio of hospitalization from a logical perspective, reducing the outpatient visit number via vaccination would have a great impact on disease burden with the underestimated crucial social benefits.³³

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Yasemin Ozsurekci: study design, manuscript writing, and review. **Kubra Aykac:** study design, data collection, and manuscript writing. **Fatma Bal:** data collection. **Cihangul Bayhan:** data collection. **Sevgen T. Basaranoglu:** data collection. **Alpaslan Alp:** study design, data collection. **Ali B. Cengiz:** results and discussion. **Ates Kara:** results and discussion. **Mehmet Ceyhan:** results, discussion. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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