

Predictors of complicated influenza infection in children presenting in a tertiary hospital in a tropical country: A case-control study

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Dear Editor,

Influenza causes significant healthcare burden globally¹ with highest risks in children and the elderly. In children, multiple studies have identified risk factors for severe influenza such as young age (<5 years), presence of comorbidities, abnormal vital signs (e.g. hypoxia, shock) and bacterial coinfections.²⁻⁴ We found similar findings in our centre which included children during the influenza A (H1N1) 2009 pandemic with age <2 years and comorbidity as risk factors for complicated influenza.⁵

We conducted a retrospective case-control study of hospitalised paediatric patients (<17 years old) with laboratory-confirmed (respiratory immunofluorescence antigen testing or multiplex polymerase chain reaction [PCR] testing) influenza infection admitted to our hospital over 7 years between January 2011 and October 2017. Cases were defined as severe influenza requiring intensive care unit (ICU) or high-dependency (HD) care anytime during their hospitalisation. Three unmatched controls were selected per case; controls were admitted into the general ward with laboratory-confirmed influenza infection within 3 days of the admission of their corresponding cases.

Our primary outcome was to compare the risk factors that predispose children to severe complicated course requiring ICU/HD care. Our secondary outcome was to study the risk factors associated with mortality.

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB number: 2015/2453) for a waiver of consent.

A total of 209 patients (55 cases, 154 controls) were included in this study, with a median age of 2.9 years (interquartile range [IQR] 0.9–5.8

years); there were 17 deaths reported (8.1%). Only 33 of the patients (15.8%) had 1 underlying comorbidity, and 9 patients (4.3%) had ≥2 comorbidities. Influenza A (n=161, 77.0%) was more common than Influenza B. There was no difference between Influenza A and Influenza B when comparing for HD/ICU admission or mortality risks. Concurrent viral infections occurred in 6.2 % (n=13) of patients, most commonly adenovirus (n=5, 38.5%) infection. Proven bacterial infections—either from positive mycoplasma PCR, respiratory cultures from endotracheal tube if intubated or from positive blood cultures—were found only in a minority of patients (n=20, 23.0%). There was no statistical difference for bacterial coinfection rates between cases or controls.

Mortality occurred in 8.1% (n=17) of patients. Among them, all required inotropic support; 52.9% (n=9) required intubation; 29.4% (n=5) required extra-corporeal membrane oxygenation, or ECMO support; and 11.8% (n=2) needed dialysis. A high proportion (n=7, 41.2%) had underlying comorbidities with neurological conditions being the most prevalent (n=4, 23.5%).

By univariate analysis (Table 1), risk factors for HD/ICU admission or mortality were drowsiness (odds ratio [OR] 5.81, $P<0.001$; OR 10.49, $P<0.001$, respectively), any comorbidities (OR 4.46, $P<0.001$; OR 3.14, $P=0.02$, respectively) and viral coinfections (OR 7.34, $P=0.001$; OR 6.26, $P=0.002$, respectively). Additional risk factors for HD/ICU admission were age >5 years old (OR 2.17, $P=0.02$), presence of seizure (OR 3.00, $P=0.01$) or tachypnoea (OR 6.86, $P<0.001$). By multivariate logistic regression analysis, risk factors for HD/ICU admission were tachypnoea (multivariate OR 9.27, $P<0.001$), viral coinfections (multivariate OR 10.42, $P=0.002$), seizure (multivariate OR 7.42, $P<0.001$), comorbidity (multivariate

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Table 1. Univariate comparison of cases admitted to ICU/HD versus controls admitted to general ward and univariate comparison of mortality cases versus survivors of paediatric Influenza infection.

Clinical characteristics	ICU/HD admissions/ cases (n=55) (%)	GW admissions/ controls (n=154) (%)	Univariate analysis				Univariate analysis			
			Odds ratio		P value		Odds ratio		P value	
Age, median (years)	4.5 (IQR 1.83–7.9)	2.6 (IQR 0.8–4.95)			0.02	4.3 (IQR 2.29–4.33)			2.8 (IQR 0.83–5.80)	0.2
Age category										
0–5 years	32 (58.2)	116 (75.3)				11 (64.7)			137 (71.4)	
>5 years	23 (41.8)	38 (24.7)			0.02	6 (35.3)			55 (28.6)	0.56
Race										
Chinese	33 (60.0)	86 (55.8)			0.6	12 (70.6)			107 (55.7)	0.54
Malay	12 (21.8)	44 (28.6)				4 (23.5)			52 (27.1)	
Indian	5 (9.1)	16 (10.4)				1 (5.9)			20 (10.4)	
Others	5 (9.1)	8 (5.2)				0 (0.0)			13 (6.8)	
Influenza type										
Influenza A	43 (78.2)	118 (76.6)			0.81	12 (70.6)			149 (77.6)	0.51
Influenza B	12 (21.8)	36 (23.4)				5 (29.4)			43 (22.4)	
Presenting symptoms										
Fever	51 (92.7)	145 (94.2)			0.71	16 (94.1)			180 (93.8)	0.95
Cough	33 (60.0)	121 (78.6)			0.007	12 (70.6)			142 (74.0)	0.76
Poor feeding	23 (41.8)	55 (35.7)			0.42	7 (41.1)			71 (37.3)	0.73
Rhinorrhoea	22 (40.0)	112 (72.7)			<0.001	8 (47.1)			126 (65.6)	0.13
Sore throat	3 (5.5)	6 (3.9)			0.63	1 (5.9)			8 (4.2)	0.91

Table 1. Univariate comparison of cases admitted to ICU/HD versus controls admitted to general ward and univariate comparison of mortality cases versus survivors of paediatric Influenza infection. (Cont'd)

Clinical characteristics	ICU/HD admissions/ cases (n=55) (%)	GW admissions/ controls (n=154) (%)	Univariate analysis		Mortality (n=17) (%)		Survivors (n=192) (%)		Univariate analysis	
			Odds ratio	P value					Odds ratio	P value
Any tachypnoea	19 (34.5)	11 (7.1)	6.86 (3.0–15.7)	<0.001	5 (29.4)		25 (13)			0.07
Vomiting	16 (29.1)	45 (29.2)		0.99	7 (41.2)		66 (34.4)			0.57
Diarrhoea	9 (16.4)	21 (13.6)		0.62	3 (17.6)		27 (14.1)			0.69
Any seizure	22 (40.0)	28 (18.2)	3.00 (1.52–5.90)	0.01	7 (41.2)		43 (22.4)			0.08
Drowsiness	23 (41.8)	0 (0.0)	5.81 (4.24–7.97)	<0.001	8 (47.1)		15 (7.8)	10.49 (3.53–31.15)		<0.001
Any significant comorbidities	22 (40.0)	20 (13)	4.46 (2.18–9.17)		7 (41.2)		35 (18.2)	3.14 (1.12–8.85)		0.02
No high risk comorbidity	33 (60.0)	134 (87.0)			10 (58.8)		157 (81.8)			
1 high risk comorbidity	17 (30.9)	16 (10.4)			4 (23.5)		29 (15.1)			
≥2 high risk comorbidity	5 (9.1)	4 (2.6)			3 (17.6)		6 (0.03)			
High risk factors										
Respiratory	6 (10.9)	9 (5.8)		0.21	1 (5.9)		14 (7.3)			0.83
Neurology	10 (18.2)	6 (3.9)	5.48 (1.88–15.91)	<0.001	4 (2.4)		12 (6.3)	4.62 (1.30–16.33)		0.01
Cardiac	4 (7.3)	1 (0.6)	12.00 (1.21–109.84)	0.006	2 (11.8)		3 (1.6)	8.40 (1.30–54.22)		0.01
Immunology	3 (5.5)	1 (0.6)	8.83 (0.898–86.73)	0.03	2 (11.8)		2 (1.0)	12.67 (1.67–96.37)		0.002

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Clinical characteristics	ICU/HD admissions/ cases (n=55) (%)	GW admissions/ controls (n=154) (%)	Univariate analysis		Mortality (n=17) (%)		Survivors (n=192) (%)		Univariate analysis	
			Odds ratio	P value					Odds ratio	P value
Abnormal chest radiograph	19 (34.5)	6 (3.9)	13.02 (4.85–34.95)	<0.001	8 (47.1)		17 (8.9)		9.15 (3.12–26.80)	<0.001
Normal chest radiograph	36 (65.5)	148 (96.1)			9 (52.9)		175 (91.1)			
Median duration of stay (days)	12 (IQR 6–31)	2 (IQR 2–3)		<0.001	11 (IQR 4.5–31.0)		3 (IQR 2–5)			0.001
Use of oseltamivir										
Yes	41 (74.5)	7 (4.5)	61.5 (23.29–162.41)	<0.001	14 (82.4)		34 (17.7)		21.69 (5.91–79.64)	<0.001
No	14 (25.5)	147 (95.5)			3 (17.6)		158 (82.3)			
Concurrent viral infections										
Present	9 (16.4)	4 (2.6)	7.34 (2.16–24.93)	0.001	4 (23.5)		9 (4.7)		6.26 (1.70–23.10)	0.002
Absent	46 (83.6)	150 (97.4)			13 (76.5)		183 (95.3)			
Bacterial cultures*	49 (89.1)	38 (24.7)			17 (100.0)		70 (36.5)			
Negative	35 (71.4)	32 (84.2)		0.16	11 (64.7)		56 (80.0)			0.18
Positive	14 (28.6)	6 (15.8)			6 (35.3)		14 (20.0)			

GW: general ward; HD: high dependency; ICU: intensive care unit; IQR: interquartile range

* Bacterial coinfections include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Escherichia coli*, *Moraxella catarrhalis*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Pseudomonas aeruginosa*.

OR 3.86, $P=0.002$) and age >5 years (multivariate OR 3.34, $P=0.005$). Multivariate logistic regression analysis for mortality showed drowsiness (multivariate OR 7.97, $P<0.001$) and abnormal chest radiograph (multivariate OR 6.88, $P=0.001$) as risk factors.

Our study showed that children >5 years had a higher risk of severe influenza complications (OR 3.34) resulting in ICU/HD admissions. This is unlike previous studies^{6,7} which showed that the highest rate of complications was more common in children ≤ 5 years of age. A previous study conducted by our hospital's emergency department (ED) could explain this phenomenon.⁸ The study showed that the patient's age was inversely proportional to the reattendance rate in ED. Interestingly, older paediatric patients were more likely to be admitted on their reattendance compared to younger patients. Extrapolating from this paper, we could infer that older patients are admitted when they have significant clinical progression or deterioration; and thus, the risk factors of severe influenza and its complications are more likely to be seen in hospitalised children who are older. In younger children, most are admitted earlier during the infection as parents tend to be more anxious regarding their symptoms, and this is reflected in our study with younger age groups having lower risk for severe influenza infection.

There may be residual confounders in our current study such as influenza vaccination status, which we would need to explore in future studies. Important risk factors for HD/ICU admission and influenza mortality were symptoms suggestive of neurological involvement, such as seizures and drowsiness. The presence of drowsiness was a significant risk factor for mortality (OR 7.97, $P<0.001$) with acute encephalitis as the commonest complication ($n=9$, 52.9%) among mortality cases in our study. This is consistent with previous studies showing higher mortality once the patient develops neurological complications.^{2,6,9}

Interestingly, viral coinfections were seen in a small minority (6.2 %) of patients, but was the greatest risk factor for HD/ICU admission (OR 10.42, $P=0.002$) similar to previous studies.^{2,10} Surprisingly, our study did not demonstrate a bacterial coinfection as a risk factor for complications or mortality. This is likely attributed to the small proportion with proven bacterial infection ($n=20$, 9.6%) and the empiric use of antibiotics in a large proportion of patients ($n=92$, 44.0%).

Similar to previous studies,^{11,12} this study showed an increased risk (HD/ICU admission OR 12.00, $P=0.006$, mortality OR 8.40, $P=0.01$) in patients with cardiac conditions; immunodeficiency (HD/ICU admissions OR 8.83, $P=0.03$, mortality OR 12.67, $P=0.002$); and neurological conditions (HD/ICU admission OR 5.48, $P=0.001$, mortality OR 4.62, $P=0.01$). This highlights the need for the attending physician to be hypervigilant and preempt any possible deterioration in the clinical status of patients who have influenza infection especially when they have significant comorbidities.

Our study has several limitations including knowledge of patients' influenza vaccination status. Such additional data could help us to ascertain if prior vaccination reduces the risks of complicated influenza or mortality especially in high-risk patients. We also acknowledge that testing strategy has changed during the period of this study from respiratory immunofluorescence (IF) to multiplex PCR. The detection of concomitant viral infections is higher when using multiplex PCR preferentially. Since the attending physician determined the method of testing; we may have under-estimated the presence of viral coinfections in patients whose testing was performed using IF. Another limitation was the inability to study obesity as a risk factor as height measurements were not recorded consistently. Future studies should include obesity as recent papers have highlighted obesity as an emerging risk factor for severe influenza.^{4,13}

In conclusion, influenza infection can result in severe complications that may lead to mortality especially in patients with neurological presentation of seizures and drowsiness. For clinical applicability, if there are suggestions of any neurological involvement, the attending physician should escalate care and be vigilant for the progression of symptoms and preempt the possible deterioration of the patient.

Keywords: *drowsiness, influenza, morbidity, mortality, paediatric, seizure*

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