Increased Mortality in Seasonal H3N2 Patients Compared with those with Pandemic 2009 H1N1 in Taiwan, 2009–2010

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Abstract. We conducted a retrospective study to compare clinical and laboratory findings between 1) severe influenza A and mild influenza A and 2) pandemic 2009 H1N1 (pdm09 A/H1) and seasonal H3N2 (A/H3) from 2009 to 2010. A total of 526 (mean age, 13.6 years; 447 pdm09 A/H1, 79 seasonal A/H3) patients were included, 41 (7.8%) with severe influenza (mean age, 28.1 years; 26 pdm09 A/H1, 15 seasonal A/H3). Influenza-associated complications were pneumonia (75.6%), meningoenzephalitis (14.6%), acute kidney injury (14.6%), and acute respiratory distress syndrome (12.2%). Patients with seasonal A/H3 were significantly less likely to experience sore throat ($P < 0.001$), malaise ($P < 0.001$), and muscle pain ($P < 0.001$); they were significantly more likely to have hypertension ($P < 0.001$), diabetes mellitus ($P = 0.001$), and chronic obstructive pulmonary disease ($P < 0.001$), delayed hospital presentation ($P = 0.001$), delayed oseltamivir treatment ($P < 0.001$), and higher in-hospital mortality ($P = 0.02$) than patients with pdm09 A/H1. Further comparison between severe pdm09 A/H1 and severe seasonal A/H3 revealed that severe seasonal A/H3 patients (median age, 71 years) were significantly older than patients with severe pdm09 A/H1 (median age, 7 years) ($P < 0.001$). Comparison between severe influenza and mild influenza, regardless of influenza A subtypes, by multivariate analysis, found that tachypnea (odds ratio [OR] = 44.3, 95% confidence interval [CI] = 15.7–124.6) and delayed oseltamivir therapy ≥ 48 hours after illness onset (OR = 3.7, 95% CI = 1.3–10.5) were independent risk factors for severe influenza. The findings of this study will improve the understanding of the clinical differences between pdm09 A/H1 and seasonal A/H3, and of influenza-associated complications and predictors for severe outcomes that can help to direct clinicians toward the most effective management of influenza patients to reduce the preventable mortality and morbidity.

INTRODUCTION

Influenza viruses often spillover from the animal reservoir into human populations, resulting in a novel zoonosis.¹ Influenza A subtypes H1N1 (A/H1) and H3N2 (A/H3) are the most common cause of human influenza (flu). Both gave rise to pandemics after they evolved into generally seasonal infections worldwide.² In the United States, influenza results in approximately 200,000 hospitalizations and 36,000 deaths in an endemic season.³ In April 2009, an outbreak of swine origin influenza A (pandemic 2009 A/H1N1) (pdm09 A/H1) started in Mexico^{4,5} and caused a global pandemic. An outbreak of pdm09 A/H1 occurred in Taiwan after the first patient was identified on May 20, 2009.⁶ Between June 19, 2009 and January 23, 2010, 39 out of 884 patients with pdm09 A/H1 infection died in Taiwan.⁷ The all-cause mortality of pdm09 A/H1 in Taiwan is higher than the estimated global deaths due to pdm09 A/H1 (4.4% versus 0.03%).^{7–9} Worldwide, influenza activity continued to increase in most countries. Between January 20, 2013 and February 2, 2013, the World Health Organization (WHO) Global Influenza Surveillance and Response System laboratories tested over 70,349 specimens from 87 countries. Of these, 20,711 were positive for influenza viruses (73% were positive for influenza A virus and 27% for influenza B). Of the 15,121 specimens positive for influenza A, 4801 (48%) were positive for pdm09 A/H1 and 5137 (52%) were positive for seasonal A/H3.¹⁰ Most of the patients with pdm09 A/H1 virus infection had clinical symptoms comparable with those of patients with seasonal A/H3 virus infection, such

as fever, cough, sore throat, headache, rhinorrhea, myalgia, and arthralgia, and the clinical course was self-limited.^{11,12} However, some patients developed severe influenza, potentially resulting in pneumonia, multiorgan failure, or even death.¹³ An important issue for clinicians is to identify patients at high risk of developing severe complications, so that timely management can be delivered to avoid otherwise preventable morbidity and mortality. We retrospectively reviewed the medical records of 526 patients with laboratory-confirmed pdm09 A/H1 virus infection and seasonal A/H3 virus infection diagnosed between 2009 and 2010. The objective of this study was to improve our understanding of the clinical and laboratory characteristics of patients with severe influenza A and mild influenza A, caused by pdm09 A/H1 virus or seasonal A/H3 virus, and highlight the range of clinical features in patients with pdm09 A/H1 infection and seasonal A/H3 infection, particularly those with severe disease. This report may offer valuable information to clinicians, particularly in countries where medical resources are limited.

MATERIALS AND METHODS

Ethics statement. The study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (KSCGMH) (Document no. 99–2654B). Informed consent was not required as the data were analyzed anonymously.

Patients and definitions. Clinical, laboratory, and imaging data of 526 patients with influenza A presenting to KSCGMH, a 2,700-bed primary care and tertiary referral medical center in Taiwan, between 2009 and 2010, were retrospectively analyzed. The data were mainly retrieved from the hospital electronic medical records and supplemented by a secondary manual search. Data collected included demographic

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characteristics, signs/symptoms on admission, commencement of oseltamivir therapy, laboratory tests results, radiography examination results, and outcome. Patients with influenza infection were defined as patients with a laboratory-positive test for influenza with influenza-like illness. Influenza-like illness was defined, according to the WHO guidelines, as fever ($\geq 38.0^{\circ}\text{C}$), cough, or sore throat.¹⁴ All patients included in this study were confirmed positive for influenza A virus-specific ribonucleic acid by nasopharyngeal swab and/or pharyngeal swab by a real-time reverse transcriptase-polymerase chain (RT-PCR) (TAIGEN Bioscience Corporation, Taiwan), as previously described.^{15,16} All influenza A positive samples were further subtyped using primers and probes for A/H1 (pdm09) and A/H3, according to the Centers for Disease Control and Prevention protocol.¹⁶

Severe influenza was defined as influenza complicated by symptoms and signs of lower respiratory tract infection (hypoxemia, pneumonia, and/or acute respiratory distress syndrome) and/or cardiovascular system involvement, central nervous system involvement as well as acute exacerbations of preexisting chronic medical conditions, for example, chronic lung disease, asthma, cardiovascular disease, or diabetes. Mild influenza was defined as influenza-like illness that recovers fully within 2 weeks, without any complications. Acute hepatitis was defined as serum alanine aminotransferase levels $> 1,000$ U/L (reference value, < 40 U/L). Rhabdomyolysis was defined as a 5-fold increase in the serum concentration of creatine phosphokinase (CPK) above the upper limit of the normal range (reference value, 13–130 U/L), with a CPK-muscle fraction of $> 95\%$ after hospitalization for influenza illness. An acute kidney injury was defined as having a rapid increase in serum creatinine level of > 0.5 mg/dL above baseline within 48 hours of hospital admission. Meningoencephalitis was defined as an altered mental status lasting ≥ 24 hours and fulfilling at least two of the following criteria: 1) fever $\geq 38^{\circ}\text{C}$, 2) generalized or partial seizures, 3) focal neurologic findings, 4) cerebrospinal fluid white blood cell count of $\geq 5/\text{mm}^3$, 5) abnormality of the brain parenchyma on neuroimaging suggestive of encephalitis, and 6) abnormality on electroencephalography that is consistent with encephalitis.¹⁷ The administration of oseltamivir was based on the personal experience and clinical judgment of the attending physicians. Delayed oseltamivir therapy was defined as commencement ≥ 48 hours after the onset of influenza illness.

Statistical analysis. Patients were divided into two groups: 1) severe influenza A and mild influenza A, regardless of influenza A subtypes and 2) pdm09 A/H1 and seasonal A/H3. Univariate analysis was performed to compare demographic, clinical, laboratory characteristics, and outcomes between the two groups. Further analyses were performed to investigate the differences in clinical and laboratory features among patients with severe pdm09 A/H1 and severe seasonal A/H3. Categorical variables were compared using the χ^2 or Fisher exact test, and continuous variables were compared using the Student's *t* or Mann-Whitney *U* test, where applicable. A two-tailed $P < 0.05$ was considered statistically significant. Significant variables between severe influenza A and mild influenza A in univariate analysis were entered into a multivariate logistic regression model to identify independent risk factor(s) for severe influenza.

RESULTS

Patient characteristics. Out of a total of 526 (mean age, 13.6 ± 13.5 years) patients, 447 patients had pdm09 A/H1 and 79 had seasonal A/H3. Forty-one (7.8%) patients had severe influenza A (26 [5.8%] patients with pdm09 A/H1, and 15 [19%] with seasonal A/H3) while 485 (92.2%) patients had mild influenza A (421 [86.8%] with pdm09 A/H1, and 64 [13.2%] with seasonal A/H3). Information regarding influenza vaccination was not obtained. The mean interval between symptom onset and hospital presentation was $1.7 (\pm 1.2)$ days. As shown in Table 1, fever (98.6%) and cough (87.8%) were the most common symptoms at the time of presentation. Rhinorrhea and sore throat were reported in 63.1% and 39.2% of the patients, respectively. Tachypnea was found in 43 (8.2%) patients. Less common symptoms included altered consciousness (2.5%), seizure (1.5%), and skin rash (0.9%). Five patients of the 526 patients died, accounting for a mortality rate of 0.9%.

TABLE 1
Patient characteristics

Variable	Total cases (N = 526)
Demographic features	
Mean age ($\pm$ SD), years	13.6 (± 13.5)
Age group	
≤ 18 years	458 (87)
> 18 years	78 (13)
Female	211 (40)
Pregnant, no./female no. (%)	1/211 (0.5)
Underlying condition	
Bronchial asthma	14 (2.6)
Hypertension	15 (2.8)
Diabetes mellitus	10 (2)
Chronic obstructive pulmonary disease	7 (1.3)
Influenza A subtype	
Pdm09 A/H1	447 (85)
Seasonal A/H3	79 (15)
Clinical features and outcome	
Mean day from the onset of symptoms to hospital presentation ($\pm$ SD)	1.7 (± 1.2)
Mean duration of fever, day ($\pm$ SD)	2.9 (± 1.5)
Antibiotic use	89 (17)
Oseltamivir ≥ 48 hours after onset of illness, no./total no. received oseltamivir therapy (%)	107/364 (29)
In-hospital mortality	5 (0.9)
Symptoms/signs at presentation	
Fever	519 (98.6)
Rhinorrhea	332 (63.1)
Cough	462 (87.8)
Sore throat	206 (39.2)
Malaise	183 (34.8)
Muscle pain	167 (31.7)
Headache	148 (28.1)
Vomiting/nausea	116 (22.1)
Diarrhea	57 (10.8)
Abdominal pain	48 (9.1)
Chest pain	24 (4.6)
Skin rash	5 (0.9)
Altered consciousness	13 (2.5)
Seizure	8 (1.5)
Tachypnea	43 (8.2)
Laboratory characteristics at presentation	
Mean WBC ($\pm$ SD) ($\times 10^9$ cells/L) (no.) (reference value $3.0\text{--}10 \times 10^9$ cells/L)	7.1 (± 2.9) (N = 283)
Mean platelet count ($\pm$ SD) ($\times 10^9$ cells/L) (no.)	202.1 (± 60.9) (N = 277)
Mean C-reactive protein ($\pm$ SD) (mg/L) (no.) (reference value < 5 mg/L)	25.2 (± 50.2) (N = 273)

Pdm = pandemic; WBC = white blood cell. Data are no. (%) unless otherwise indicated.

Characteristics of patients with severe influenza A. Of the 41 (mean age, 28.1 ± 30.1 years) patients with severe influenza A (26 pdm09 A/H1 and 15 seasonal A/H3), 22 were female, and among them, one was pregnant. The following complications were reported in the 41 patients with severe influenza A (one patient might have more than one complication): pneumonia in 31 (75.6%) patients; meningoencephalitis and acute kidney injury each in 6 (14.6%) patients; respiratory distress syndrome in 5 (12.2%) patients; intracranial hemorrhage, acute hepatitis, and myocarditis each in 2 (4.9%) patients; and hyperosmolar hyperglycemia, pneumothorax, and rhabdomyolysis each in 1 (2.4%) patient. Arterial blood gas was measured in 22 severe influenza cases at the time of hospital presentation; eight of these patients required ventilatory support, with average arterial oxygen saturation 80% at the time of initiation of ventilatory therapy. A cranial magnetic resonance imaging was carried out in six patients with meningoencephalitis; leptomeningeal enhancement was found in four. Cerebrospinal fluid pleocytosis

was noted in three of six patients with meningoencephalitis. All of these six patients had abnormality on electroencephalography that is consistent with encephalitis. All patients with severe influenza A were treated with oseltamivir, and 65.9% of patients were treated with antiviral therapy ≥ 48 hours after the onset of symptoms. Five (median age, 24 years [range, 2–72]) patients died, three with seasonal A/H3 and two with pdm09 A/H1. The following conditions were reported among the deceased patients (one patient may have developed more than one complication): pneumonia (five cases), acute respiratory distress syndrome (three cases), intracranial hemorrhage (two cases), acute kidney injury (two cases), hyperosmolar hyperglycemia (one case), myocarditis (one case), and gastrointestinal bleeding (one case).

Comparison between severe influenza A ($N = 41$) and mild influenza A ($N = 485$), independent of influenza A subtypes (Table 2). The prevalence of the following conditions was significantly higher among patients with severe influenza A than among patients with mild influenza A:

TABLE 2

Comparison of clinical and laboratory features between severe influenza patients and mild influenza patients, regardless of influenza A subtypes

Variable	Severe influenza A ($N = 41$)	Mild influenza A ($N = 485$)	P
Demographic features			
Mean age ($\pm$ SD), years	28.1 (± 30.1)	12.3 (± 10.2)	0.23
Age group	—	—	> 0.99
≤ 18 years	23 (56)	425 (87.6)	—
> 18 years	18 (44)	60 (12.4)	—
Female	22 (53.7)	189 (39)	0.07
Pregnant, no./female no. (%)	1/22 (4.5)	0	0.10
Underlying condition			
Bronchial asthma	2 (4.9)	12 (2.5)	0.29
Hypertension	10 (24.4)	5 (1.0)	< 0.001
Diabetes mellitus	6 (14.6)	4 (0.8)	< 0.001
Chronic obstructive pulmonary disease	7 (17.1)	0	< 0.001
Influenza A subtype	—	—	> 0.99
Pdm09 A/H1	26 (63.4)	421 (86.8)	—
Seasonal A/H3	15 (36.6)	64 (13.2)	—
Clinical features and outcome			
Mean day from onset of symptoms to hospital ($\pm$ SD)	3 (± 2.0)	1.6 (± 1.1)	< 0.001
Mean length of fever ($\pm$ SD), day	3.5 (± 2.5)	2.8 (± 1.3)	0.45
Antibiotic use	28 (68.3)	61 (12.6)	< 0.001
Oseltamivir ≥ 48 hours after onset of illness, no./total no. received oseltamivir therapy (%)	27/41 (65.9)	80/323 (24.8)	< 0.001
In-hospital mortality	5 (12.2)	0	< 0.001
Symptoms/signs at presentation			
Fever	41 (100)	478 (98.6)	> 0.99
Rhinorrhea	16 (39)	316 (65.2)	0.001
Cough	36 (87.8)	426 (87.8)	> 0.99
Sore throat	9 (21.9)	197 (40.6)	0.02
Malaise	16 (39)	167 (34.4)	0.60
Muscle pain	5 (12.2)	162 (33.4)	0.005
Headache	6 (14.6)	142 (29.3)	0.04
Vomiting/nausea	11 (26.8)	105 (21.6)	0.01
Diarrhea	3 (7.3)	54 (11.1)	0.60
Abdominal pain	5 (12.2)	43 (8.9)	0.40
Chest pain	3 (7.3)	21 (4.3)	0.42
Skin rash	1 (2.4)	4 (0.8)	0.33
Altered consciousness	13 (31.7)	0	< 0.001
Seizure	8 (19.5)	0	< 0.001
Tachypnea	33 (80.5)	10 (2)	< 0.001
Laboratory characteristics at presentation			
Mean WBC ($\pm$ SD) ($\times 10^9$ cells/L) (no. (reference value $3.0\text{--}10 \times 10^9$ cells/L))	8.5 (± 3.8) ($N = 41$)	6.9 (± 2.7) ($N = 242$)	0.006
Mean platelet count ($\pm$ SD) ($\times 10^9$ cells/L) (no.)	196.9 (± 78.5) ($N = 41$)	203 (± 57.5) ($N = 236$)	0.41
Mean C-reactive protein ($\pm$ SD) (mg/L) (reference value < 5 mg/L)	71.0 (± 97.7) ($N = 38$)	17.8 (± 31.9) ($N = 235$)	0.005

Pdm = pandemic; WBC = white blood cell. Data are no. (%) unless otherwise indicated.

hypertension ($P < 0.001$), diabetes mellitus ($P < 0.001$), and chronic obstructive pulmonary disease ($P < 0.001$). Furthermore, delayed hospital presentation ($P < 0.001$), higher frequency of antibiotic treatment ($P < 0.001$), delayed oseltamivir treatment ≥ 48 hours after onset illness ($P < 0.001$), and higher in-hospital mortality ($P < 0.001$) were also significantly more frequent among patients with severe influenza A. Clinical manifestations, such as vomiting/nausea ($P = 0.01$), tachypnea ($P < 0.001$), altered consciousness ($P < 0.001$), and seizures ($P < 0.001$) were also reported significantly more frequently among patients with severe influenza A. Conversely, significantly lower frequencies of rhinorrhea ($P = 0.001$), sore throat ($P = 0.02$), muscle pain ($P = 0.005$), and headache ($P = 0.04$) were noted in patients with severe influenza A compared with patients with mild influenza A. Patients with severe influenza A had a significantly higher white blood cell count ($P = 0.006$) and C-reactive protein level ($P = 0.005$) compared with patients with mild influenza A. Multivariate analysis revealed that tachypnea (odds ratio [OR] = 44.3, 95% confidence interval [CI] = 15.7–124.6; $P < 0.001$) and delayed oseltamivir therapy ≥ 48 hours after illness onset

(OR = 3.7, 95% CI = 1.3–10.5; $P = 0.01$) were independent risk factors for severe influenza.

Comparison between pdm09 A/H1 (N = 447) and seasonal A/H3 (N = 79). As shown in Table 3, significantly higher proportions of patients with pdm09 A/H1 experienced a sore throat ($P < 0.001$), malaise ($P < 0.001$), and muscle pain ($P < 0.001$) compared with patients with seasonal A/H3. Compared with patients with pdm09 A/H1, patients with seasonal A/H3 had a significantly higher prevalence of hypertension ($P < 0.001$), diabetes mellitus ($P = 0.001$), and chronic obstructive pulmonary disease ($P < 0.001$); they also had a shorter fever duration ($P = 0.02$), delayed presentation to hospital ($P = 0.001$), higher prevalence of antibiotic use ($P < 0.001$), and delayed oseltamivir treatment ≥ 48 hours after illness onset ($P < 0.001$). Furthermore, an increased white blood cell count ($P = 0.02$), C-reactive protein level ($P = 0.03$), and in-hospital mortality ($P = 0.02$) were observed in this group.

Comparison between severe pdm09 A/H1 (N = 26) and severe seasonal A/H3 (N = 15) (Table 4). Patients with severe seasonal A/H3 were found to be significantly older ($P < 0.001$), with a higher prevalence of hypertension

TABLE 3
Comparisons of clinical and laboratory features between pdm09 A/H1 and seasonal A/H3

Variable	Pdm09 A/H1 (N = 447)	Seasonal A/H3 (N = 79)	P
Demographic features			
Mean age ($\pm$ SD), years	12.1 (10.1)	18.8 (24.9)	0.15
Age group	—	—	> 0.99
≤ 18 years	392 (87.7)	56 (70.9)	—
> 18 years	55 (12.3)	23 (29.1)	—
Female	179 (40)	32 (40.5)	> 0.99
Pregnant, no./female no. (%)	1/14 (7.1)	0	—
Underlying condition			
Bronchial asthma	13 (2.9)	1 (1.3)	0.70
Hypertension	5 (1.1)	10 (12.6)	< 0.001
Diabetes mellitus	4 (0.9)	6 (7.6)	0.001
Chronic obstructive pulmonary disease	1 (0.2)	6 (7.6)	< 0.001
Clinical features and outcome			
Mean day from onset of symptoms to hospital ($\pm$ SD)	1.6 (1.0)	2.2 (1.8)	0.001
Mean length of fever ($\pm$ SD), day	2.9 (1.5)	2.5 (1.4)	0.02
Antibiotic use	47 (10.5)	42 (53.2)	< 0.001
Oseltamivir ≥ 48 hours after onset of illness, no./total no. received oseltamivir therapy (%)	81/316 (25.6)	26/48 (54.2)	< 0.001
Severe influenza	26 (5.8)	15 (19)	> 0.99
In-hospital mortality	2 (0.4)	3 (3.8)	0.02
Symptoms/signs at presentation			
Fever	440 (98.4)	79 (100)	0.60
Rhinorrhea	285 (63.7)	47 (49.5)	> 0.99
Cough	405 (90.6)	57 (72.2)	> 0.99
Sore throat	189 (43)	17 (21.5)	< 0.001
Malaise	176 (39.4)	7 (8.9)	< 0.001
Muscle pain	162 (36.2)	5 (6.3)	< 0.001
Headache	137 (30.6)	11 (13.9)	0.40
Vomiting/nausea	88 (19.7)	28 (35.4)	> 0.99
Diarrhea	48 (10.7)	9 (11.4)	> 0.99
Abdominal pain	38 (8.5)	10 (12.6)	> 0.99
Chest pain	21 (4.7)	3 (3.8)	> 0.99
Skin rash	5 (1.1)	0	> 0.99
Altered consciousness	10 (2.2)	3 (3.8)	> 0.99
Seizure	7 (1.6)	1 (1.3)	> 0.99
Tachypnea	30 (6.7)	13 (16.4)	> 0.99
Laboratory characteristics at presentation			
Mean WBC ($\pm$ SD) ($\times 10^9$ cells/L) (no.) (reference value $3.0\text{--}10 \times 10^9$ cells/L)	6.8 (2.7) (N = 224)	8.3 (4.5) (N = 59)	0.02
Mean platelet count ($\pm$ SD) ($\times 10^9$ cells/L) (no.)	205.7 (60.3) (N = 223)	190 (91.6) (N = 54)	0.42
Mean C-reactive protein ($\pm$ SD) (mg/L) (no.) (reference value < 5 mg/L)	19.6 (35.76) (N = 214)	45.6 (81.1) (N = 59)	0.03

Pdm = pandemic; WBC = white blood cell. Data are no. (%) unless otherwise indicated.

($P = 0.002$), diabetes mellitus ($P = 0.01$), and chronic obstructive pulmonary disease ($P = 0.006$), as well as higher C-reactive protein levels ($P = 0.03$).

DISCUSSION

Influenza is a highly infectious viral illness causing moderate to severe illness and affecting all age groups.^{2,3,18} Herein, we describe a series of 526 Taiwanese patients with RT-PCR confirmed influenza virus A infection between 2009 and 2010. Severe influenza was found in 41 out of 526 patients with influenza A infection, accounting for a 7.8% incidence rate. Classic symptoms of influenza included sudden onset of

high fever, sore throat, cough, headache, myalgia, and malaise.^{12,19} In an earlier study, describing 642 patients with confirmed pdm09 A/H1 infection, the most frequently reported symptoms were fever (94%), cough (92%), sore throat (66%), diarrhea (25%), and vomiting (25%).²⁰ In our series, the comparison of clinical features between patients infected with pdm09 A/H1 and those infected with seasonal A/H3 showed that sore throat, malaise, and muscle pain were more frequently associated with pdm09 A/H1 virus infection. A similar finding has been reported in a study from Nicaragua, with sore throat being significantly more frequently associated with pdm09 A/H1 virus infection than patients with seasonal A/H3 infection.²¹ A study from Singapore found that rhinorrhea and

TABLE 4
Comparisons of clinical and laboratory features between severe pdm09 A/H1 and severe seasonal A/H3

Variable	Severe pdm09 A/H1 (N = 26)	Severe seasonal A/H3 (N = 15)	P
Demographic and clinical features			
Median age, year (range)	7 (0.4–47)	71 (1–90)	< 0.001
Age group	–	–	< 0.001
≤ 18 years	22 (84.6)	1 (6.7)	–
> 18 years	4 (15.4)	14 (93.3)	–
Female	14 (53.8)	8 (53.3)	> 0.99
Pregnant, no./female no. (%)	1/14 (7.1)	0	> 0.99
Underlying condition			
Bronchial asthma	2 (7.7)	0	0.52
Hypertension	2 (7.7)	8 (53.3)	0.002
Diabetes mellitus	1 (3.8)	5 (33.3)	0.01
Chronic obstructive pulmonary disease	1 (3.8)	6 (40)	0.006
Median day from onset of symptoms to hospital (range)	3 (1–9)	2 (1–7)	> 0.99
Median length of fever, day (range)	3 (0–10)	3 (1–4)	0.52
Antibiotic use	18 (69.2)	10 (66.7)	> 0.99
Oseltamivir ≥ 48 hours after onset of illness	17 (65.4)	10 (66.7)	> 0.99
Symptoms/signs at presentation			
Fever	26 (100)	15 (100)	> 0.99
Rhinorrhea	13 (50)	3 (20)	0.09
Cough	23 (88.5)	13 (86.7)	> 0.99
Sore throat	6 (23.1)	3 (20)	> 0.99
Malaise	12 (46.2)	4 (26.7)	0.32
Muscle pain	3 (11.5)	2 (13.3)	> 0.99
Headache	5 (19.2)	1 (6.7)	0.38
Vomiting/nausea	6 (23.1)	5 (33.7)	0.49
Diarrhea	2 (7.7)	1 (6.7)	> 0.99
Abdominal pain	3 (11.5)	2 (13.3)	> 0.99
Chest pain	1 (3.8)	2 (13.3)	0.54
Skin rash	1 (3.8)	0	> 0.99
Altered consciousness	10 (38.5)	3 (20)	0.30
Seizure	7 (26.9)	1 (6.7)	0.22
Tachypnea	20 (76.9)	13 (86.7)	0.68
Laboratory characteristics at presentation			
Median WBC (range) ($\times 10^9$ cells/L) (reference value $3.0\text{--}10 \times 10^9$ cells/L)	7.4 (3.2–18.6)	10 (2.2–15.9)	0.24
Median platelet count (range) ($\times 10^9$ cells/L)	196 (78–374)	174 (24–337)	0.71
Median C-reactive protein (range) (mg/L) (no.) (reference value < 5 mg/L)	9.6 (0.2–249.9) (N = 24)	54.4 (1.2–340.7) (N = 14)	0.03
Complications during the entire clinical course and outcome			
Meningoencephalitis	6 (23)	0	0.07
Pneumonia	18 (14)	13 (86.7)	0.27
Acute respiratory distress syndrome	4 (15.4)	1 (6.7)	0.63
Acute kidney injury	2 (7.7)	4 (26.7)	0.16
Intracranial hemorrhage	2 (7.7)	0	0.52
Gastrointestinal bleeding	1 (3.8)	1 (6.7)	> 0.99
Hyperosmolar hyperglycemia	1 (3.8)	0	> 0.99
Myocarditis	1 (3.8)	1 (6.7)	> 0.99
Acute hepatitis	0	2 (13.3)	0.12
Pneumothorax	0	1 (6.7)	0.36
Rhabdomyolysis	0	1 (6.7)	0.36
In-hospital mortality	2 (7.7)	3 (20)	0.36

Pdm = pandemic; WBC = white blood cell. Data are no. (%) unless otherwise indicated.

dyspnea occurred more frequently with seasonal influenza virus (A/H3, A/H1, and influenza B) infection, while cough and sore throat were more frequently associated with pdm09 A/H1 infection.²² Comparison between influenza A and influenza B were not performed in this series. Nevertheless, our analysis and previous studies have shown that it is difficult to distinguish between pdm09 A/H1 and seasonal A/H3 on the basis of clinical signs and symptoms.

Our data showed that most severe influenza cases occur among adults with a mean age of 28 years (Table 2). Further analysis revealed that patients with severe seasonal A/H3 were significantly older than patients with severe pdm09 A/H1 (median age, 71 years versus 7 years; $P < 0.001$) (Table 4). This finding is supported by previous studies reporting that pdm09 A/H1 virus infection preferentially affects children and teenagers,²³ unlike seasonal A/H3, which has the greatest impact on adults, and specifically, the elderly.²² Our data suggest that children with pdm09 A/H1 infection are at risk of developing severe influenza. By contrast, among elderly patients, more severe respiratory disease and increased mortality were observed with seasonal A/H3. Our study demonstrates the age-specific differences in clinical outcomes for pdm09 A/H1 and seasonal A/H3 infection. These findings may have important implications for prioritizing vaccination policies to prevent severe disease and death in influenza seasons.

Remarkably, the mean white blood cell count and C-reactive protein levels were significantly higher among seasonal A/H3 patients than among pdm09 A/H1 patients. Also, most of the patients with seasonal A/H3 were treated with antibiotics and oseltamivir therapy was delayed to ≥ 48 hours after illness onset (Table 3). We believe that this delay is caused by clinicians' lack of awareness to influenza infection. This finding underscores the challenges faced by physicians to differentiate between influenza and other infections on the basis of the early clinical manifestations, particularly in elderly patients with seasonal A/H3 who do not present with obvious respiratory tract symptom, or high white blood cell count and C-reactive protein level.

The analysis of the prevalence of underlying diseases in severe influenza cases revealed bronchial asthma (7%) and hypertension (7.7%) among patients with pdm09 A/H1, whereas hypertension (53.3%), chronic obstructive pulmonary disease (40%), and diabetes mellitus (33.3%) were observed among patients with seasonal A/H3 (Table 4). Patients with severe seasonal A/H3 were older and had a higher prevalence of comorbidities than those with severe pdm09 A/H1. In our series, despite no significant difference was found in the occurrence of severe influenza between seasonal A/H3 and pdm09 A/H1, the in-hospital mortality among patients with seasonal A/H3 virus infection was significantly higher than among those with pdm09 A/H1 (Table 3). Higher rates of mortality in seasonal A/H3 may be the result of delayed oseltamivir therapy as well as aging and comorbidities that lead to immune dysfunction in addition to concomitant immunosenescence.²⁴⁻²⁶

This study found that the presentation to the hospital of patients with severe influenza was significantly delayed compared with patients with mild influenza (mean, 3 days versus 1.6 days). This finding suggests that there are delays in the timely commencement of antiviral therapy in severe cases. Remarkably, 65.9% of patients with severe infection were

treated with antiviral therapy ≥ 48 hours after the onset of illness. Previous reports have demonstrated that early antiviral treatment is effective in reducing virus load compared with without antiviral treatment.²⁷ Our study established that early antiviral treatment significantly reduces the risk of developing a severe disease, regardless of influenza A subtypes and this is consistent with previous studies.²⁸ As the influenza viruses remain a major health threat in both endemic and pandemic forms, our series underscore the important role of timely antiviral treatment.

In the present study, altered consciousness, seizure, and tachypnea were found to be significantly associated with severe outcomes; in contrast, the typical clinical manifestations of influenza illness, such as rhinorrhea, sore throat, muscle pain, and headache, were found less frequently with severe influenza compared with mild influenza in univariable analysis. Remarkably, tachypnea at the presentation was the only symptom present in multivariate analysis. This suggests that tachypnea is the strongest risk factor of severe influenza. As diffuse alveolar injury, tracheitis, and necrotizing bronchiolitis are consistent histopathological findings in severe cases of influenza that the physical sign of tachypnea is an important predictive factor is not surprising.^{29,30}

The findings regarding influenza-associated complications demonstrated that either pdm09 A/H1 or seasonal A/H3 can cause severe illness, including pneumonia (75.6%), acute respiratory distress syndrome (12.2%), meningoencephalitis (14.6%); furthermore, 82.9% of severe influenza patients required admission to an intensive care unit, with 12.2% of in-hospital mortality. Remarkably, in our series, extrapulmonary complications, such as central nervous system involvement (19.5%), myocarditis (4.9%), acute hepatitis (4.9%), and rhabdomyolysis (2.4%), were not uncommon in severe influenza.³¹⁻³⁵ Physicians should have a high index of suspicion for influenza-associated extrapulmonary complications when caring for influenza patients and these should be managed accordingly.

Our study has several limitations. First, it was conducted in a single medical center setting, and the disease severity may have been biased by the referral pattern. Second, the decision to perform a test for the diagnosis of influenza was based on the expertise of the individual physicians; therefore, some patients with influenza may not have been tested. Third, confounding may have occurred as a result of the administration of antiviral therapy on the basis of clinical decisions. Despite these limitations, this study has several strengths. First, our study performed detailed descriptions and comparisons between severe influenza A and mild influenza A and between severe pdm09 A/H1 and severe seasonal A/H3. Second, as influenza affects all populations, the range of outcomes and risk factors examined in our series complement earlier studies which analyzed specific age groups.

In conclusion, the results of this study will allow a better understanding of the clinical characteristics of pdm09 A/H1 and seasonal A/H3, the patterns of influenza-associated complications, and the risk factors for severe outcomes in influenza. As the impact of influenza will continue in the future, such information would be important for risk stratification, resource allocation, and clinical disposition in future pandemics and therefore, highly relevant to emergency department and primary care clinicians.

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