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Predictors of fatality in influenza A virus subtype infections among inpatients in the 2015–2016 season

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ABSTRACT

Background: Infection with the influenza A virus can cause severe disease and mortality. The effect of the different subtypes of influenza on morbidity and mortality is not yet known in Turkey. The aim of this study was to describe the predictors of fatality related to influenza A infection among hospitalized patients in Istanbul during the 2015–2016 influenza season, and to detail the differences between infections caused by H3N2 and H1N1.

Methods: This was a multicenter study performed by the Istanbul Respiratory Infections Study Group of The Turkish Society of Clinical Microbiology and Infectious Diseases (KLİMİK), among patients hospitalized for influenza in Istanbul during the 2015–2016 influenza season.

Results: A total of 222 patients hospitalized with laboratory-confirmed influenza during the 2015–2016 season were included in the study, of whom 25 (11.2%) died. The fatality rate was significantly higher among patients older than 65 years of age and those with chronic heart and kidney diseases ($p < 0.001$), chronic neurological diseases ($p = 0.009$), and malignancies ($p = 0.021$). Thrombocyte counts were lower in those who died than in those who survived ($p < 0.004$). The median alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatinine phosphokinase, and C-reactive protein levels were higher among fatal cases. In the multivariate analysis for the prediction of fatality, being >65 years old (odds ratio (OR) 6.9, 95% confidence interval (CI) 2.07–23.08, $p = 0.002$), being infected with influenza A (H3N2) (OR 4.2, 95% CI 1.27–14.38, $p = 0.019$), and a 1-day delay in antiviral use (OR 1.28, 95% CI 1.01–1.63, $p = 0.036$) were found to be associated with an increased likelihood of fatality.

Conclusions: The case fatality rate of influenza A(H3N2) was significantly higher than that of influenza A (H1N1). Detection of the infection, allowing the opportunity for the early use of antiviral agents, was found to be important for the prevention of fatality. The vaccination should be prioritized for at-risk groups.

Introduction

Influenza is an acute viral infection with a clinical range from self-limiting respiratory symptoms characterized by fever, cough, and headache in healthy individuals to complications such as bronchitis, acute otitis media, secondary bacterial pneumonia,

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and death, particularly among adults over 65 years old and patients with chronic diseases (Reed et al., 2015). It is usually diagnosed clinically on the basis of characteristic symptoms and seasonal epidemiology (Treanor, 2015). Early antiviral treatment (oseltamivir or zanamivir) is recommended for patients at risk of complications (Louie et al., 2012). Some studies have reported that a higher proportion of hospitalized patients with severe disease during the 2010–2011 season had influenza A(H1N1) (Lehners et al., 2013; Chaves et al., 2013), but it remains unclear which influenza virus types and subtypes are more virulent. In another study, the authors suggested that hospitalized patients with influenza A(H1N1) were younger and developed more respiratory complications, acute respiratory distress syndrome (ARDS), and septic shock than patients with influenza A(H3N2) (Minchole et al., 2016).

Based on the authors' experience of the A(H1N1)pdm outbreak in Turkey (Ergonul et al., 2014), the aim of the present study was to describe the predictors of fatality related to influenza A infection among hospitalized patients in 11 different hospitals in Istanbul during the 2015–2016 influenza season, and to determine the differences in morbidity and mortality according to the influenza virus subtypes.

Methods

Study population

The study was performed by the Istanbul Respiratory Infections Study Group of The Turkish Society of Clinical Microbiology and Infectious Diseases (KLİMİK). Patients who were hospitalized for an influenza-like illness (ILI) in Istanbul during the 2015–2016 influenza season and who were positive for influenza A by PCR were included. The largest 11 hospitals in Istanbul participated in the study. Three of these hospitals are university hospitals and eight are training and research hospitals of the Ministry of Health of Turkey. Patients who were diagnosed with influenza B and influenza A by rapid antigen test (ELISA) were excluded.

A case of influenza-associated hospitalization was defined as a person who was admitted with suspected influenza and who presented at least one of the Infectious Diseases Society of America (IDSA) conditions (Harper et al., 2009) and had a positive PCR test.

Oseltamivir was initiated before PCR results were obtained, within 24 h after admission. If the results of PCR were negative, then oseltamivir was withdrawn. In positive cases, antiviral therapy was continued for at least 5 days at the usual dose.

Statistical analysis

In the univariate analysis, comparing patients who died and those who survived, categorical data were tested by Chi-square test and the means of the two groups were compared by *t*-test (Tables 1 and 2). Parameters found to be statistically significant in the univariate analysis were tested by logistic regression to predict the risk of fatality (Table 3). The independent variables included in the model were age >65 years, detection of influenza A(H3N2) versus influenza A(H1N1), early use of neuraminidase inhibitors, secondary bacterial infection, and having a malignant disease. Stata version 11 software (StataCorp, College Station, TX, USA) was used for the statistical analysis, and statistical significance was set at $p < 0.05$.

Results

A total of 222 patients hospitalized in the 11 hospitals with laboratory-confirmed influenza during the 2015–2016 season were included in the study. The population of Istanbul in the 2016 census was 14 800 000 (http://www.tuik.gov.tr), and during the 2015–2016 season, influenza A virus was detected in 2196 out of 5509 samples (40%). The influenza attack rate was 14.8/100 000 (2196/14 800 000). The hospitalization rate for influenza A in the population was 1.4/100 000 (222/14 800 000), and 10% (222/2196) among the diagnosed patients.

The mean age of the 222 patients hospitalized with influenza A was 39 years (standard deviation (SD) 27 years); 47 patients (21%) were older than 65 years. One hundred and twenty-six patients (57%) were female. Among the hospitalized patients, 25 (11.2%) died. Thirteen of the 25 fatal cases (54%) had influenza A(H3N2) and 11 (45%) had influenza A(H1N1); the virus was untyped for one patient ($p < 0.001$). There were no deaths under age 16 years. The mean age of the patients who died was 65 years; the mean age of those who survived was 36 years ($p < 0.001$) (Table 1). The fatality rate was significantly higher among patients with chronic heart and kidney diseases ($p < 0.001$), chronic neurological diseases ($p = 0.009$), and malignancies ($p = 0.021$) (Table 1).

Among the study patients, 115 (69.6%) were infected with influenza A(H1N1) and 52 (23.4%) with influenza A(H3N2); the virus was untyped for 15 influenza A virus-infected patients. Compared to patients with influenza A(H3N2), patients with

Table 1
Demographic characteristics of the patients infected with influenza A and their risk factors for mortality.

	Died $n = 25$, n (%)	Survived $n = 197$, n (%)	p-Value
Sex, female	10 (40)	116 (59)	0.073
Age (years), mean ± SD	65 ± 22	36 ± 26	<0.001
Age ≥65	14 (56)	33 (17)	<0.001
Age ≤16	0 (0)	58	0.002
Obese	1 (4)	13 (7)	0.615
Pregnant women	1 (5)	6 (5)	0.939
Comorbid chronic diseases			
Chronic heart disease	9 (36)	19 (10)	<0.001
Diabetes mellitus	5 (24)	23 (12)	0.085
Chronic renal disease	6 (24)	8 (4)	<0.001
Chronic neurological disease	5 (20)	11 (6)	0.009
Chronic obstructive lung disease	3 (12)	24 (12)	0.979
Malignancy	5 (20)	13 (7)	0.021
Vaccinated	0	4 (2)	0.472
Laboratory findings			
Leukocyte count ($\times 10^9$/l), median	5.84	7.39	0.146
Thrombocyte count ($\times 10^9$/l), median	123	197	0.004
AST (U/l), median	112	34	<0.001
ALT (U/l), median	44	27	<0.001
CPK (μg/l), median	239	120	0.001
LDH (IU/l), median	478	320	0.025
CRP (mg/l), median	91	22	0.004
Influenza A H3N2	13 (54)	39 (21)	<0.001
Influenza A H1N1	11 (45)	144 (79)	<0.001
Chest X-ray findings			
Lobar	2 (8)	9 (5)	0.456
Interstitial	11 (44)	44 (22)	0.018
Bilateral involvement	17 (71)	52 (39)	<0.001
Days to starting oseltamivir after disease onset, mean ± SD	4 ± 3	2.6 ± 2	0.025
Secondary bacterial infection	3 (12)	7 (4)	0.055
Days from onset to hospital admission, mean	3.8	2.7	0.04
ICU stay	20 (80)	20 (10)	<0.001
Use of invasive mechanical ventilation	17 (94)	12 (11)	<0.001
Use of non-invasive mechanical ventilation	6 (33)	15 (13)	0.023
Length of hospital stay (days), mean ± SD	7 ± 6	8 ± 10	0.664
Antibiotic use	18 (78)	122 (64)	0.171

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; SD, standard deviation.

Table 2
Comparison of the characteristics of patients with a diagnosis of influenza between those with H1N1 and those with H3N2.

	H1N1 $n=155$, n (%)	H3N2 $n=52$, n (%)	p-Value
Sex, female	84 (54)	31 (60)	0.496
Age (years), mean ± SD	35 ± 25	47 ± 30	0.005
Age ≥65	25 (16)	18 (35)	0.004
Age ≤16	45 (29)	13 (25)	0.575
Morbidly obese	8 (5)	3 (6)	0.866
Pregnant women	3 (3)	2 (6)	0.358
Comorbid chronic diseases			
Chronic heart disease	17 (11)	11 (21)	0.063
Diabetes mellitus	19 (12)	7 (13)	0.821
Chronic renal disease	7 (5)	7 (13)	0.026
Chronic neurological disease	12 (8)	4 (8)	0.991
Chronic obstructive lung disease	19 (12)	5 (10)	0.607
Malignancy	8 (5)	5 (10)	0.252
Vaccinated	2 (4)	2 (0.37)	0.247
Laboratory findings			
Leukocyte count ($\times 10^9$/l), median	7.25	6.60	0.201
Thrombocyte count ($\times 10^9$/l), median	188.0	191.5	0.973
AST (U/l), median	42	38	0.547
ALT (U/l), median	27	32	0.480
CPK (μg/l), median	123	166	0.113
LDH (IU/l), median	316	309	0.468
CRP (mg/l), median	22	22	0.467
Chest X-ray findings			
Lobar	9 (6)	2 (4)	0.586
Interstitial	42 (27)	13 (25)	0.767
Bilateral involvement	49 (32)	17 (33)	0.885
Days to starting oseltamivir after disease onset, mean ± SD	2.6 ± 2	3 ± 2	0.386
Secondary bacterial infection	3 (6)	7 (5)	0.715
Days from onset to hospital admission, mean ± SD	2.8 ± 2.6	3 ± 2.6	0.654
ICU stay	25 (16)	14 (27)	0.085
Use of invasive mechanical ventilation	19 (23)	9 (32)	0.33
Use of non-invasive mechanical ventilation	13 (14)	8 (25)	0.174
Length of hospital stay (days), mean ± SD	8.5 (10)	7 (8.5)	0.329
Antibiotic use	95 (62)	34 (74)	0.141

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; SD, standard deviation.

Table 3
Univariate and multivariate analyses for the predictors of mortality among the adult inpatients.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age >65 years	6.3	2.63–15.15	<0.001	6.9	2.07–23.08	0.002
H3N2 vs. H1N1	4.3	1.81–10.49	0.001	4.2	1.27–14.38	0.019
One day delay of oseltamivir	1.2	1.01–1.39	0.032	1.3	1.01–1.63	0.036
Secondary bacterial infection	3.7	0.89–15.35	0.07	2.8	0.4–20.55	0.294
Presence of malignancy	3.5	1.14–10.95	0.028	1.25	0.19–8.22	0.811

OR, odds ratio; CI, confidence interval.

influenza A(H1N1) were significantly older (47 (SD 30) years vs. 35 (SD 25) years, $p=0.005$) (Table 2).

Thrombocyte counts were lower in the patients who died than in the surviving patients ($p<0.004$). The median alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and C-reactive protein (CRP) levels were higher among fatal cases (Table 1). Pulmonary findings were common among fatal cases, and the bilateral involvement rate was significantly higher in these patients than in those who survived ($p<0.001$) (Table 2).

The mean number of days before the start of oseltamivir after disease onset was higher among patients who died than among those who survived; the difference was statistically significant ($p=0.025$). A secondary bacterial infection was detected in three (12%) fatal cases and seven (4%) surviving cases, with no statistically difference between them ($p=0.055$).

In total, 140 patients (65%) received antibiotics. The most frequently ordered antibiotics were beta-lactams (41%), respiratory fluoroquinolones (20%), and macrolides (13%); 19% received combined antibiotics. Among the patients who received antibiotics, only 6% had a suspected secondary bacterial infection. The rate of vaccination against influenza A(H1N1) was 4%.

In the univariate analysis of the risk factors for mortality among the adult inpatients, age ($p<0.001$), being infected with A(H1N1) or A(H3N2) ($p=0.001$). In the multivariate logistic regression model for the predictors of fatality among the adult inpatients, being older than 65 years (odds ratio (OR) 6.9, 95% confidence interval (CI) 2.07–23.08, $p=0.002$), being infected with influenza A (H3N2) (OR 4.2, 95% CI 1.27–14.38, $p=0.019$), and a 1-day delay in antiviral use (OR 1.28, 95% CI 1.01–1.63, $p=0.036$) significantly increased the likelihood of fatality (Table 3).

Discussion

This multicenter study involved 222 patients with laboratory-confirmed influenza A who were hospitalized in 11 hospitals in Istanbul during the 2015–2016 season. The case fatality rate of influenza A was high at 11.2% (Table 1). In the multivariate analysis, age >65 years, being infected with influenza A(H3N2), and delayed use of oseltamivir were found to be associated with fatality. Approximately one-fifth of the patients were over 65 years of age, and no fatality occurred in those <16 years of age. It was also found that adults with chronic heart and kidney diseases, chronic neurological diseases, and malignancies were at increased risk of greater disease severity and fatality. High rates of hospitalization (Cox et al., 2012) and severe cases (Reed et al., 2014) have been reported particularly in persons with underlying medical conditions.

The morbidity and mortality associated with the A(H3N2) and A (H1N1) subtypes of influenza were compared (Table 2). The fatality rate for the patients infected with A(H3N2) was higher than that for patients infected with A(H1N1) (OR 4.2, 95% CI 1.27–14.38, $p=0.019$; Table 3). In contrast, Chaves et al. reported that influenza A(H1N1) caused more severe disease than influenza A(H3N2) or influenza B in hospitalized patients (Chaves et al., 2013). In the present study, patients hospitalized with influenza A(H1N1) were younger than those hospitalized with influenza A(H3N2) (Table 2), in parallel with previous reports (Reed et al., 2015; Minchole et al., 2016). Minchole et al. reported that patients with influenza A (H1N1) infection were younger, as found in the present study, but that the virulence of influenza A(H1N1) was very high compared with influenza A(H3N2) in hospitalized patients (Minchole et al., 2016). The decreasing morbidity and mortality for influenza A (H1N1) compared to influenza A(H3N2) could be explained by changing immunity.

The unnecessary use of antimicrobial agents should be emphasized. In this study, less than one in 10 patients had a suspected secondary bacterial infection, but antibacterials were ordered in nearly a quarter of the cases. One of the reasons for such a high rate of unnecessary antibiotic use was because obtaining the PCR test results in many centers requires an average of 2–3 days; this confirms a previous report from Turkey (Ergonul et al., 2014). Early diagnosis of influenza virus infection will decrease the unnecessary use of antibiotics. It is difficult to consider bacterial

co-infection in some cases, such as pregnant women and immunosuppressed patients or people over 65 years of age with chronic diseases. This may be another reason for antibiotic use even in those with positive influenza results.

Empiric oseltamivir treatment has been reported to be beneficial when influenza is suspected, even before confirmed laboratory results (Fiore et al., 2011). The results of the present study emphasize the importance of the early use of oseltamivir, in parallel with our findings during the influenza A pandemic (Ergonul et al., 2014). Some studies have shown a reduction in severe complications and mortality among influenza patients who have received antivirals (Lee et al., 2010; Hiba et al., 2011). A study from Denmark reported the failure of combined oral oseltamivir and inhaled zanamivir in ventilator- and extracorporeal membrane oxygenation (ECMO)-treated critically ill patients with pandemic influenza A(H1N1) virus (Petersen et al., 2011).

In conclusion, the case fatality rate of influenza A(H3N2) was significantly higher than that of influenza A(H1N1). Early detection of the infection, allowing the opportunity for the early use of antiviral agents, was found to be important for the prevention of death. Vaccination should be provided to at-risk groups.

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Ethical approval

The Institutional Review Board of Koç University approved the study.

Informed consent

Not applicable.

Conflict of interest

None to declare.

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