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Original Article

General Characteristics and Prognostic Factors of Pneumonia Cases Developed During Pandemic (H1N1) Influenza-A Virus Infection in Turkey

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ABSTRACT

Objective: Unlike seasonal influenza, seen in previous years, the strain identified in the 2009 influenza-A pandemic involved high mortality. In this study, prognostic factors and general characteristics of pneumonia cases developed in Turkey during the H_1N_1 pandemic between October 2009 and January 2010 were analyzed.

Study Design: Multicenter retrospective study.

Material and Methods: This multicentric retrospective study was conducted between August and October 2010 and patients' data were collected by means of standard forms.

Results: The study included 264 pneumonia cases, collected from 14 different centers. Mean age was 47.5±18.6 years. Nineteen patients (7.2%) were pregnant or had a new birth and comorbid diseases were detected in 52.3% of all patients. On admission, 35 (13.8%) cases had altered mental status. Overall, 32.6% were treated in intensive care units (ICU) and invasive/non-invasive mechanical ventilation was performed in 29.7%. The mean duration of ICU stay was 2.9±6.2 and total hospital stay was 12.0±9.4 days. Mortality rate was 16.8% (43-cases). The length of ICU treatment, total hospital stay, and mortality were significantly higher in H1N1-confirmed patients. Mortality was significantly higher in patients with dyspnea, cyanosis, and those who had altered mental status on admission. Patients who died had significantly higher rate of peripheral blood neutrophils, lower platelet counts, higher BUN, and lower SaO_2 levels.

Conclusion: This study showed that pneumonia developed during H_1N_1 pandemic in our country had resulted in a high mortality. Mortality was especially high among patients with cyanosis, altered mental state and those with lower SaO_2.

Key Words: Influenza, Pandemic influenza A, H_1N_1 pandemic, mortality, pneumonia, intensive care unit

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Introduction

After the detection of first H_1N_1 influenza-A case in May 2009 in Turkey, the disease spread rapidly and reached a plateau during October to December 2009. Unlike seasonal flu seen in previous years, pandemic (H_1N_1) influenza-A virus infection was reported to affect populations under 65 years of age and to cause more complications, especially in patients with chronic disease, pregnant women, and obese patients (1-5). The disease has also led to a severe infection and mortality in young adults and those patients without risk factors (2, 6). This multicenter study was performed to describe prognostic factors and general characteristics of pneumonia cases identified in Turkey during the influenza-A (H_1N_1) pandemic between October 2009 and January 2010.

Material and Methods

Study Setting and Population

The study was conducted between August and October 2010 with the participation of 14 different centers from Tur-

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key and the study protocol was approved by the local institutional board review. The study was announced to pulmonologists in Turkey via e-mail by the Turkish Thoracic Society Respiratory Infections Study Group (TTS-RISG) and physicians who agreed to participate in the study were included. Patient data were collected through the standard data collection forms developed by TTS-RISG and consisted of comprehensive questions related to patient demographics, clinical and laboratory characteristics and patient treatment. In each center, data collection forms were completed retrospectively, using patients' hospital records. Pandemic influenza-A diagnosis was made according to the guidelines issued by the Health Ministry of Turkey at that time and diagnosis of H_1N_1 was confirmed using real-time polymerase chain reaction (PCR) method (7). All patients with pneumonia admitted to study centers during the pandemic period, and showing suitable clinical and radiographic features, were included in the study irrespective of whether H_1N_1 was confirmed. Patients with appropriate symptoms and findings of lower respiratory tract infection (e.g. temperature >38°C, productive cough, chest pain, shortness of breath, crackles on auscultation and consolidation findings); or those with infiltrates on chest radiography were diagnosed as pneumonia (8, 9). Patients not meeting this definition were excluded from the study. Confirmed pandemic (H_1N_1) influenza-A pneumonia was defined as pneumonia plus a positive real-time PCR. Patients who were diagnosed with pneumonia during the pandemic period, who had similar clinical and radiographic findings but with a negative PCR for H_1N_1 were defined as unconfirmed pandemic (H_1N_1) influenza-A pneumonia.

Data Analysis

The chi-square test was used for comparison of quantitative data between patient subgroups. The Mann-Whitney U test, Student's t test and analysis of variance (ANOVA) were used for qualitative data. Factors (demographic, clinical and laboratory data) likely to predict the mortality were evaluated using logistic regression analysis and p values <0.05 were considered to be significant.

Results

From 14 different centers, a total of 285 cases were included in the study. Of the patients, 20 cases not meeting pneumonia definition criteria and 1 duplicate case were excluded. The remaining 264 patients were included in the statistical analysis. Of the patients, 51.1% were women, 48.9% were men and combined mean age was 47.5±18.6 years. Comorbid diseases were detected in 52.3% of cases and 7.2% were pregnant or had recently given birth. H_1N_1 was confirmed in 151 (57.4%) of cases using PCR method. On admission, 45.8% of the patients had fever (≥38.0°C), 24.4% had tachypnea, 13.8% had altered mental status, and 3.5% had hypotension. Patients with confirmed pandemic (H_1N_1) influenza-A did not differ from the unconfirmed cases in terms of demographic characteristics, symptoms and radiographic infiltrates (Table 1). However, altered mental status, high fever (≥38.0°C) and tachypnea (≥30/min.) were significantly higher in patients with confirmed pandemic (H_1N_1) influenza-A.

Of the patients, 32.6% were treated in an intensive care unit (ICU) and invasive/non-invasive mechanical ventilation was performed in 29.7% of patients. The length of ICU stay was 2.9±6.2 days and total hospital stay was 12.0±9.4 days. Overall mortality rate was 16.8%. Mortality was significantly higher in patients with dyspnea, cyanosis, and those who had altered mental status on admission. ICU admission rates and duration, total duration of treatment, and mortality rates were all significantly higher in confirmed H_1N_1 cases (Table 1). The rates of tachycardia (≥100) and tachypnea (≥30) were significantly higher in patients who died (Table 2). Patients who died had also a significantly higher rate of peripheral blood neutrophils, lower platelet counts, higher BUN, and lower SaO_2 levels. Univariate logistic regression analysis showed that dyspnea, cyanosis, altered mental state, hypotension, tachycardia (≥100), tachypnea (≥30), a positive test for H_1N_1 and ICU-need was directly related to mortality in all cases. Using multivariate logistic regression analysis, altered mental state, cyanosis, and lower SaO_2 were found to be correlated with mortality (Table 3).

Discussion

In this study, pneumonia cases developed during influenza-A (H_1N_1) pandemic of winter 2009-2010 were evaluated using data collected from 14 different geographical regions of Turkey. However, although H_1N_1 was confirmed in 57.4% of cases, all patients were accepted as having pandemic influenza-A pneumonia because of similar clinical and radiographic findings during the pandemic season. Moreover it is known that nasopharyngeal aspirates or swabs taken early after the onset of symptoms are suitable samples, but endotracheal or bronchoscopic aspirates have higher yields in patients with lower respiratory tract illness especially for some mutations such as D222G (10, 11). One study showed that among patients with detectable H_1N_1 viral RNA in bronchoscopic samples, 19% had negative upper respiratory tract samples (11). We think that the confirmation rate of H_1N_1 remained low in our study because nasopharyngeal swabs were mostly used for the detection of viral RNA, and due to possible delayed presentation of some patients to study center.

In previous studies, it was reported that pneumonia due to pandemic (H_1N_1) influenza-A developed in relatively young patients (2, 12), and showed similarities as pneumonia irrelevant to H_1N_1 cases in terms of the distribution of comorbid diseases (3, 12). However, obesity, pregnancy, and comorbid conditions such as chronic obstructive pulmonary disease (COPD) were shown to increase the severity of the disease in pandemic (H_1N_1) influenza-A pneumonia (3, 4). In the current study, the average age of the cases was 47.5±18.6 years and 52.1% had co-morbid diseases. A study in the USA found that 73% of hospitalized pandemic influenza-A patients had a single co-morbidity on admission, of which asthma was the most common (28%), followed by obesity (29%) and diabetes (15%) (13).

In the current study, classic symptoms of pneumonia like fever, cough, sputum and shortness of breath was observed in 76.9%, 89.8%, 59.1% and 74.6% of the cases, respectively, and no difference was observed between confirmed H_1N_1 and

Table 1. Demographic, clinical and laboratory findings of pneumonia patients with confirmed and unconfirmed pandemic (H1N1) influenza-A virus infection

Variable	H1N1 Confirmed (No: 151)	H1N1 Unconfirmed (No: 113)	p
Age (Mean±SD)	48.6±19.1	46.6±18.1	0.377
Age>65 yrs (No: 264)	31 (20.5%)	30 (26.5%)	0.251
Gender (F/M) (No: 264)	74/77	61/52	0.424
Smoker (No: 231)	55 (43.0%)	45 (43.7%)	0.913
Comorbid Diseases (No: 264)	80 (53.0%)	58 (51.3%)	0.790
Pregnancy/New birth (No: 263)	11 (7.3%)	8 (7.1%)	0.937
Symptoms (No: 264)			
- Fever	117 (77.5%)	86 (76.1%)	0.793
- Cough	132 (87.4%)	105 (92.9%)	0.144
- Sputum	93 (61.6%)	63 (55.8%)	0.340
- Dyspnea	116 (76.8%)	81 (71.7%)	0.342
Physical Examination			
- Altered mental state (No: 254)	27 (18.8%)	8 (7.3%)	0.009*
- Hypotension (TA<90/60) (No: 255)	7 (4.9%)	2 (1.8%)	0.174
- Fever ≥38.0°C (No: 253)	79 (55.2%)	37 (33.6%)	0.001*
- Pulse ≥100 (No: 229)	55 (44.7%)	51 (48.1%)	0.607
- Respiratory rate ≥30 (No: 197)	31 (30.4%)	17 (17.9%)	0.041*
- Cyanosis (No: 259)	21 (14.3%)	8 (7.2%)	0.071
Laboratory			
- Leucocyte (/µL)	8712.2±7245.2	10703.0±5993.4	0.020*
- Lymphocyte (%)	16.6±12.0	14.9±9.7	0.245
- Neutrophil (%)	73.7±16.2	77.3±12.6	0.059
- Platelet (/µL)	209.6±116.9	255.6±100.8	0.001*
- Sedimentation rate (mm/h)	48.4±30.2	41.6±28.4	0145
- BUN (mg/dL)	21.7±17.7	17.9±16.2	0.101
- Creatinine (mg/dL)	1.2±0.9	0.9±0.4	0.070
- SaO_2 (%)	86.4±11.2	87.9±9.6	0.257
Chest Radiograph (No: 256)			
- Lober consolidation	20 (13.7%)	18 (16.4%)	0.532
- Segmenter consolidation	22 (15.1%)	19 (17.3%)	0.661
- Bronchopneumonic infiltration	72 (49.3%)	54 (49.1%)	0.913
- İnterstitial infiltration	8 (5.5%)	13 (11.9%)	0.064
- Pleural effusion	18 (12.3%)	22 (20.2%)	0.088
Treatment			
- ICU required (No: 230)	56 (41.5%)	19 (20.2%)	0.001*
- Length of ICU stay (day)	3.7±7.2	1.6±4.0	0.005*
- Length of total hospitalization (day)	13.3±11.1	10.4±6.2	0.008*
- Bill (TL)	4131.5±6596.4	2190.9±2906.2	0.003*
Mortality (No: 256)	34 (23.0%)	9 (8.3%)	0.002*

* Statistically significant p<0.05

Table 2. Demographic, clinical and laboratory findings of pneumonia patients who died or survived

Variable	Mortality (+) (No: 43)	Mortality (-) (No: 123)	p
Age (Mean±SD)	44.3±19.8	47.9±18.1	0.238
Age>65 yrs (No: 256)	9 (20.9%)	49 (23.0%)	0.767
Gender (F/M) (No: 256)	26/43	99/213	0.094
Smoker (No: 225)	17 (53.1%)	80 (41.5%)	0.217
Comorbid Diseases (No: 256)	21 (48.8%)	114 (53.5%)	0.575
Pregnancy/New birth (No: 255)	5 (11.6%)	12 (5.7%)	0.138
H_1N_1 confirmed (No: 256)	34 (79.1%)	114 (53.5%)	0.002*
Symptoms (No: 256)			
- Fever	32 (74.4%)	164 (77.0%)	0.716
- Cough	41 (94.3%)	189 (88.7%)	0.149
- Sputum	31 (72.1%)	122 (57.3)	0.071
- Dyspnea	38 (88.4%)	151 (70.9%)	0.017*
Physical Examination			
- Altered mental state (No: 248)	19 (50.0%)	15 (7.1%)	<0.001*
- Hypotension (TA<90/60) (No: 247)	5 (12.2%)	4 (1.9%)	0.008*
- Fever ≥38.0°C (No: 245)	21 (52.5%)	91 (44.4%)	0.346
- Pulse ≥100 (No: 221)	27 (73.0%)	74 (40.2%)§	<0.001*
- Respiratory rate ≥30 (No: 190)	17 (54.8%)	30 (18.9%)	<0.001*
- Cyanosis (No: 251)	14 (32.6%)	13 (6.3%)	<0.001*
Chest Radiograph (No: 248)			
- Lober consolidation	7 (16.7%)	30 (14.6%)	0.727
- Segmenter consolidation	3 (7.1%)	36 (17.5%)	0.094
- Bronchopneumonic infiltration	24 (57.1%)	100 (48.5%)	0.310
- İnterstitial infiltration	2 (4.8%)	16 (7.8%)	0.494
- Pleural effusion	4 (9.5%)	35 (17.0%)	0.226
Laboratory			
- Leucocyte (/u L)	9778.2±10818.1	9454.1±5676.3	0.849
- Lymphocyte (%)	13.3±9.2	16.7±11.5	0.077
- Neutrophil (%)	79.4±13.6	74.0±15.1	0.033*
- Platelet (/u L)	194.3±120.5	237.7±110.7	0.022*
- Sedimentation rate (mm/h)	41.5±29.3	46.9±29.7	0.382
- BUN (mg/dL)	32.6±28.7	17.6±12.9	0.007*
- Creatinine (mg/dL)	1.4±1.3	1.0±0.6	0.071
- SaO_2 (%)	78.1±14.6	88.8±8.7	<0.001*
-ICU required (No: 229)	28 (90.3%)	47 (23.7%)	<0.001*

* Statistically significant p<0.05

the unconfirmed cases. In another study from Turkey, as well as fever and shortness of breath, extrapulmonary symptoms such as fatigue, muscle and joint-aches, nausea, vomiting, and headache were observed more frequently in pandemic (H_1N_1) influenza-A patients with pneumonia (12). Perez-Padilla and colleagues in Mexico evaluated the demographic and clinical characteristics of patients with pandemic (H_1N_1) influenza-A pneumonia and respiratory failure and found that all patients had fever, cough, and shortness of breath (14). In the present study, altered mental state, fever ≥38°C and tacypnea (≥30/

Table 3. Evaluation of factors determining pneumonia mortality by multivariate logistic regression analysis in all cases

Variable	Mortality		
	OR	95.0% CI	p
- H_1N_1 confirmed	6.277	0.920-42.844	0.061
- Dyspnea	3.804	0.467-30.981	0.212
- Altered mental state	48.230	4.164-558.695	0.002*
- Hypotension (TA<90/60)	1.984	0.078-50.468	0.678
- Pulse ≥100 /min	2.445	0.427-13.997	0.315
- Respiratory rate ≥30 /min	1.462	0.233-9.167	0.685
- Cyanosis	7.004	1.412-34.740	0.017*
- Leucocyte (/uL)	1.000	1.000-1.000	0.069
- Platelet (/uL)	0.996	0.984-1.007	0.444
- BUN (mg/dL)	1.000	0.962-1.039	0.988
- Creatinine (mg/dL)	1.037	0.514-2.095	0.918
- SaO_2 (%)	0.906	0.830-0.988	0.026*

* Statistically significant p<0.05

min) were found to be significantly more common in confirmed pandemic (H_1N_1) influenza-A pneumonia. In a study of 1046 patients, Bewick et al. (15) similarly reported that the presence of ≥38°C fever and altered mental state was associated with pandemic (H_1N_1) influenza-A pneumonia.

Unlike seasonal influenza, seen in previous years, thrombocytopenia have been experienced in pandemic (H_1N_1) influenza-A in some studies from Turkey and internationally (3, 12, 16-19). Leukopenia and lymphopenia, which is an indicator of viral infection, is a common finding in pandemic (H_1N_1) influenza-A pneumonia (3, 15). Cunha et al. (20) have shown that lymphopenia, and thrombocytopenia may play a key role in the diagnosis of pandemic (H_1N_1) influenza-A pneumonia in hospitalized cases. Reyes et al. (6) showed lower counts of leukocytes in A/H1N1(+) than in bacterial pneumonia. In the present study, white blood cells and platelet counts were also significantly lower in patients with confirmed pandemic (H_1N_1) influenza-A pneumonia. However, similar to findings by Cunha et al. (20) no relationship was found between the degree of these parameters and clinical severity disease.

There are limited studies defining radiological findings of pandemic (H_1N_1) influenza-A pneumonia in the literature. In the current study, bronchopneumonia was the most common radiological finding, followed by segmental and non-segmental consolidation in confirmed pandemic (H_1N_1) influenza-A pneumonia cases. Radiological findings were the same in confirmed and unconfirmed patients. According to the literature, some patients may have a normal chest radiograph at first presentation, but may develop alveolar opacities and bilateral interstitial infiltrates on chest radiographs in the following days (12, 21). It was reported that radiological findings were more often bilateral in patients who underwent mechanical ventilation due to severe respiratory failure (4, 21, 22). Even where no radiological evidence of disease is initially detected, radiological findings may subsequently emerge and serious respiratory failure may develop over a short period. Therefore, patients who presented with clinical findings of influenza should carefully followed-up in terms of rapid radiographical progression.

Our study showed that 32.6% of the patients needed ICU support, required longer ICU and ward hospitalization and as a result increased the cost of treatment and caused higher mortality rates. A study by Saidel-Odes and colleagues reported that 18.7% of cases with pandemic (H_1N_1) influenza-A pneumonia required ICU follow-up (3). This proportion was reported as 25.0% by Gurgun and colleagues (12). In contrast, in a study from spain, Rello and colleagues reported that 62.5% of 32 pandemic (H_1N_1) influenza-A pneumonia cases required ICU support (23). ARDS, multiple organ failure and mortality rate was high as expected among patients requiring ICU support. Therefore, mortality rate may differ in ICU patients and was reported to vary between 15% and 62.5% according to the centers (4, 23, 24). However, in some studies, the mortality rate of pandemic (H_1N_1) influenza-A pneumonia cases not requiring ICU support did not differ from that of CAP with no H_1N_1 infection (3, 15).

In the present study, mortality rate was significantly higher among patients with dyspnea, cyanosis, hypotension, a heart rate ≥100, a respiratory rate ≥30 and in patients with altered mental status. In addition, the peripheral blood neutrophil counts were high, platelet counts were low, blood urea nitrogen (BUN) levels were significantly elevated and oxygen saturation (SaO_2) level was lower in mortal cases. Similarly, Kirakli and colleagues found higher levels of lactic dehydrogenase (LDH) and creatinine and lower level of PaO_2/FiO_2 to be associated with mortality in pandemic (H_1N_1) influenza-A pneumonia patients who required ICU support (4). We also found that ICU admission rates and duration, total duration of treatment and mortality rates were significantly higher in confirmed pandemic (H_1N_1) influenza patients. Similar to our results, Reyes et al. reported that H_1N_1 positivity was a risk factor for mortality in CAP (6).

We think our results broadly reflect the clinical characteristics of the pandemic (H_1N_1) influenza-A pneumonia outbreak in Turkey between October 2009 and January 2010, because the patient group contained a significant number of cases from different geographic regions of the country. However, the present study has a number of limitations, since it was designed retrospectively and lacked information about antiviral response to therapy, concomitant bacterial agents, and laboratory markers of infection.

Our study showed that physical examination and laboratory findings might be important parameters in differentiating pandemic (H_1N_1) influenza-A pneumonia from other forms of pneumonia in cases lacking specific symptoms and radiological findings. Therefore, pandemic (H_1N_1) influenza-A pneumonia should be considered in patients with classic symptoms of pneumonia but also have an altered mental state, a high fever, tachypnea, leucopenia, and thrombocytopenia in influenza season. We also concluded that pneumonia that developed during the H_1N_1 pandemic in Turkey resulted in high mortality. Mortality was particularly high among patients with altered mental state, cyanosis, and those with lower SaO_2 levels.

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