Clinical characteristics of 74 pandemic H1N1 influenza patients from Turkey

Risk factors for fatality

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ABSTRACT

الأهداف: تقييم الصفات السريرية والعوامل التي تزيد من خطر الوفاة عند المرضى المصابين بإنفلونزا الخنازير (H1N1).

الطريقة: تم إجراء هذه الدراسة الاسترجاعية خلال الفترة من أكتوبر إلى ديسمبر 2009م في قسم الأمراض المعدية والميكروبولوجيا بمستشفى إس بي ديسكابي يلدريم بيازيت للأبحاث والتدريب، أنقرة، تركيا. لقد تمت مراجعة الصفات السريرية والوبائية لـ 74 حالة منومة بالمستشفى بعد تأكيد إصابتها بأنفلونزا (H1N1).

النتائج: كان متوسط عمر المرضى 49 عاماً (18–83 عاماً)، ووصل عدد الذكور إلى 34 مريضاً (46%). لقد كان السعال (91.9%) وارتفاع درجة الحرارة عن 38 درجة مئوية (71.7%) من أكثر العلامات والأعراض شيوعاً عند دخول المستشفى. و عانى أكثر من ثلثي المرضى (68.9%) من مرض خفي واحد على الأقل والذي غالباً ما كان من الأمراض التنفسية المزمنة كالأزمة، هذا بالإضافة إلى مرض السكري، فيما عانى (77%) من المرضى من التهاب الرئة الذي كان واضحاً في الأشعة الصوتية. تم إدخال 16 مريضاً (21.6%) من أصل 74 وحدة العناية المركزة، فيما توفي 10 مرضى (13.5%). لقد كانت السمنة وانخفاض نسبة امتصاص الأوكسجين في الدم عن 92% عند دخول المستشفى مرتبطين بشكل كبير مع معدل الوفيات. ولقد عانى المرضى المتوفين من ارتفاع كبير في معدل كل من: ناقلة أمين الآلانين (ALT)، وناقلة أمين الأسبارتات (AST)، ونازعة هيدروجين الاكتات (LDH)، واليوريا، والكرياتينين، والبروتين الذي يُنتج وقت التجلط (D–dimer)، وقياس وقت البروثرومبين (PT)، وقياس وقت الثرومبوبلاستين الجزئي النشط (APTT)، وكذلك زيادة النسبة الطبيعية الدولية (INR) عن معدلها الطبيعي.

خاتمة: قد يساعد التعرف على المصابين بأنفلونزا (H1N1) والمعرضين أكثر من غيرهم للوفاة وكذلك مراقبتهم بالوقت المناسب في تلافي خطر الوفاة.

Objectives: To evaluate the clinical characteristics and certain risk factors that may be associated with fatal outcome in patients with H1N1 influenza.

Methods: This retrospective study was conducted between October and December 2009 in the Department of Infectious Diseases and Clinical Microbiology, SB Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey. Data regarding the epidemiological and clinical characteristics of 74 hospitalized cases of confirmed pandemic H1N1 influenza were reviewed.

Results: The median age was 49 (18-83) years, and 34 (46%) were males. The most common symptom and signs on admission were cough (91.9%) and fever >38ºC (71.7%). More than two-thirds of patients (68.9%) had at least one underlying condition; most frequently chronic respiratory disease, including asthma and diabetes. Seventy-seven percent had evidence of pneumonia on their chest x-rays at presentation. Of the 74 cases, 16 (21.6%) were followed up in the Intensive Care Unit, and 10 (13.5%) died. Obesity and oxygen saturation below 92% at the time of admission were found to be significantly related with fatal outcome. In addition, fatal patients had significantly higher levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, creatinine, d-dimer on admission and prothrombin time (PT), activated partial thromboplastin time, and the international normalized ratio (INR) was longer.

Conclusion: Timely identification and management of patients with higher risk for fatality may improve outcomes.

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Influenza is a self-limited, uncomplicated, and acute febrile respiratory illness that is caused mainly by 2 influenza viruses; influenza A and B. The ability of these viruses to change their antigenic structure may result in the emergence of a new virus that can cause influenza epidemic. It has been well known that influenza is associated with substantial mortality and morbidity, particularly during epidemics and pandemics.[1,2] In March and early April 2009, Mexico has experienced outbreaks of respiratory illness in certain areas of the country. Subsequently in late April 2009, a novel influenza virus infection was confirmed in the United States and Mexico. The World Health Organization (WHO) declared a phase 6 pandemic on 11 June 2009.[3-5] The first case of the 2009 pandemic influenza A (H1N1) in Turkey was diagnosed in May 15, 2009.[6] Although pandemic influenza cases were mostly imported at the beginning, admissions to outpatient clinics and hospitals significantly rose by November. We described the epidemiological and clinical characteristics of 74 confirmed cases of 2009 pandemic H1N1 virus infection followed up in our institution to identify risk factors for fatality.

Methods. We conducted this retrospective study between October and December 2009 in the Department of Infectious Diseases and Clinical Microbiology, SB Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey. We reviewed data regarding the epidemiological and clinical characteristics of 74 hospitalized cases of confirmed pandemic H1N1 influenza. The Pandemic Influenza Plan was developed by the Turkish Ministry of Health (MoH) since 2006, and case definitions were described in line with the United States Centers for Disease Control and Prevention (CDC) definitions and recommendations.[7] A nationwide hospital-based surveillance system was implemented. In addition, algorithms for hospitalization criteria, follow-up, and therapy were developed and distributed throughout the country. These algorithms were intended to define persons who have risk factors for complications such as pregnancy or chronic underlying diseases, and to define patients who will possibly have severe or complicated disease course. Influenza-like illness is defined as fever (temperature >38ºC), and either cough or sore throat in the absence of another known cause. Probable pandemic H1N1 influenza case is defined as fever or history of fever, and any one of the following; cough, sore throat, myalgia, headache, rhinorrhea, shortness of breath, diarrhea, and vomiting. A confirmed case of pandemic H1N1 influenza is defined as probable case with positive test results for the 2009 H1N1 virus by real-time reverse transcriptase polymerase chain reaction (RT-PCR), or viral culture. Shortness of breath, oxygen saturation less than 92% by pulse oximeter, arterial hypotension, tachypnea, tachycardia, mental changes (such as, confusion), convulsions, severe dehydration, fever lasting for more than 3 days, and infiltration on chest x-ray (CXR) are considered as hospitalization criteria.[7]

Nasopharyngeal and nasal swabs were obtained within 2 hours following admission, and were sent to the reference laboratory Refik Saydam National Public Health Agency, Ankara, Turkey. The diagnosis was confirmed in 74 cases by positive real-time RT-PCR assay. Names, epidemiologic data, clinical characteristics, symptoms and signs on admission, underlying medical conditions, vaccination status, laboratory data, treatments, and outcome of all hospitalized patients were recorded. A total of 37,868 patients with influenza symptoms applied to the outpatient clinics of our hospital during the period of October and December 2009. Two hundred and five (0.54%) patients with influenza like illness were hospitalized. Only laboratory-confirmed 74 cases of pandemic H1N1 influenza were included in the analysis. This study was approved by the institutional research ethics committee.

Descriptive statistics were calculated for all study variables. Percentages were reported for categorical variables and means (±standard deviation), or medians (minimum-maximum) were reported for continuous variables. Patients were categorized according to outcomes, and all descriptive statistics were calculated for fatal and non-fatal patients. Differences between the 2 groups were determined with the use of chi-square and the Mann-Whitney U-test, as appropriate. Statistical analyses were performed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results. Of the hospitalized 74 confirmed cases of pandemic H1N1 influenza, 34 were males. There were 2 pregnant women and one health care worker. Two cases were regarded to be nosocomial. The median age of cases was 49 years (minimum-maximum; 18-83). None of the patients had been previously vaccinated for pandemic H1N1 influenza. Median time between symptom onset and hospital admission was 4 (1-12) days, and the median time between hospitalization and intensive care unit (ICU) admission was 1 (0-8) days. Epidemiologic data and co-existing medical conditions are presented in **Table 1**. Fifty-one patients had at least one underlying condition. Forty-one patients were smokers. The most frequent reported symptoms were cough, fatigue and myalgia, and the most frequent signs on admission were; fever of >38ºC, tachypnea, and presence of rales and/or ronchi on oscultation. Patient's symptoms and signs are presented

Table 1 - Epidemiological characteristics and underlying medical conditions of 74 confirmed pandemic H1N1 influenza cases (n=74).

Characteristics	n (%)
Gender	
Male	34 (45.9)
Female	40 (54.1)
Age, years	
Mean ± standard deviation	47.9 ± 18.12
Median (minimum-maximum)	49 (18-83)
Age group, years	
18-40	23 (31.1)
41-65	34 (45.9)
Over 65	17 (23)
Co-existing conditions	
Diabetes mellitus	19 (25.7)
Chronic obstructive pulmonary disease	16 (21.6)
Coronary heart disease	15 (20.3)
Asthma	11 (14.9)
Immunsupression	6 (8.1)
Pregnancy	2 (2.7)
Chronic renal failure	1 (1.4)
Patients with co-existing conditions	
None	23 (31.1)
One	24 (32.4)
More than one	27 (36.5)
Smoking	41 (55.4)
Time from symptom onset to admission (days)	
Median (minimum-maximum)	4 (1-12)
Time from hospitalization to ICU admission (days)	
Median (minimum-maximum)	1 (0-8)

Table 2 - Symptoms and signs of infection on admission in 74 confirmed pandemic H1N1 influenza cases (n=74).

Variables	n (%)
Symptoms	
Cough	68 (91.9)
Fatigue	66 (89.2)
Myalgia	50 (67.6)
Shortness of breath	47 (63.5)
Headache	34 (45.9)
Sore throat	27 (36.5)
Nausea and/or vomiting	25 (33.8)
Rhinorrhea	15 (20.3)
Chest pain	12 (16.2)
Diarrhea	6 (8.1)
Signs	
Fever, °C	
36-37.9	21 (28.3)
38-38.9	41 (55.4)
>39	12 (16.3)
Tachypnea	45 (60.8)
Rales and/or ronchi	43 (58.1)
Pharyngitis	34 (45.9)
Cyanosis	10 (13.5)
Body mass index	
<30	60 (81.1)
≥30	14 (18.9)

Body mass index - weight in kilograms divided by the square of the height in meters

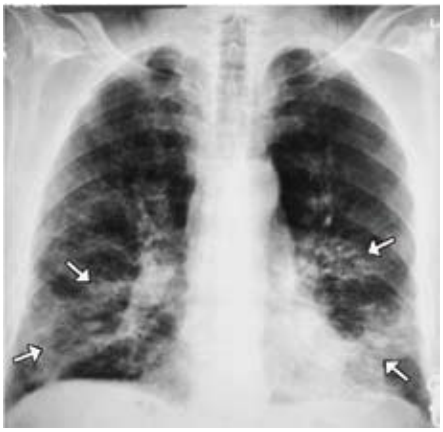

Figure 1 - Chest x-ray showing concomitant bilateral reticular interstitial infiltrates and airspace consolidation(arrows).

in **Table 2**. Nineteen patients had leucopenia (white blood cells <4500/mm^3) on admission, whereas 22 had leucocytosis. Thirty patients were thrombocytopenic, and 29 had lymphomonocytosis. All patients had undergone CXR on admission, and 57 patients had evidence of pneumonia on their CXR. Findings on these CXR were mainly patchy infiltrations, and diffuse reticular densities, or ground glass opacifications. The airbronchogram pattern was rare. The patchy infiltration pattern was mainly located in the lower zones of the lungs unilaterally, while reticular densities were seen on both lungs diffusely (**Figure 1**). Oxygen saturation by pulse oximeter was found to be below 92% in 32 patients. All patients were given oseltamivir (75 mg orally, twice a day) after nasopharyngeal and/or nasal specimens were obtained for the diagnosis. Median duration of oseltamivir therapy was 5 (1-14) days. No serious adverse effects due to oseltamivir were recorded during follow-up. Similarly, all patients with infiltration on CXR received either intravenous ceftriaxone 2x1 g, and oral clarithromycin 2x500 mg combination, or oral levofloxacin 2x500 mg in terms of antimicrobial therapy. Median duration of antimicrobial therapy was 7 (1-26) days. Of the 74 cases, 16 (21.6%) were followed up in the ICU and required respiratory support. Among the patients followed up in the ICU, 10 (13.5%) had died. The mean ± standard deviation (SD) duration of hospitalization was 14.57 ± 11.52 days for patients followed in the ICU, and 6.55 ± 4.32 days for patients not requiring ICU follow-up (p=0.019). When the fatal and non-fatal cases were compared, there was no difference in terms of gender and age. Median age of fatal patients was 51 years. Four (40%) fatal patients were under the age of 40, and 3 were over 65 years old. Time from onset of symptoms to hospital admission was not found to be different in fatal and non-fatal groups. Eight of the 10 fatal patients had at least one underlying

disease. Five died (18.5%) among the 27 patients with more than one underlying diseases. On the other hand, only 2 out of the 23 (8.7%) died in the group of patients without any underlying diseases. Although it was remarkable, the difference was not significant (p=0.590). The most frequent underlying diseases in the fatal group were diabetes (40%) and obesity (50%). The mean ± SD body mass index (BMI) of fatal cases was 30.55 ± 4.9, and non-fatal cases was 25.84 ± 3.96, and the difference was significant (p=0.004). In addition, case fatality rate was significantly higher in obese patients (5/14 versus 5/60, p=0.007). All fatal patients had infiltration on CXR on admission, whereas none of the patients without infiltration had died during follow-up. The mean ± SD oxygen saturation of fatal cases was 67 ± 14%, and non-fatal cases was 91 ± 8% by pulse oximeter on admission, and the difference was significant (p=0.000). All fatal cases had oxygen saturations below 92% on admission.

Comparison of laboratory data in fatal and non-fatal groups is presented in **Table 3**. When the 2 groups were compared, the fatal cases had significantly higher levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea and creatinine on admission. Also these patients had elongated prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). Fibrinogen levels were lower and d-dimer levels were higher in the fatal group. The differences between the 2 groups were significant for all, except fibrinogen and creatine kinase (CK) levels.

Discussion. Most cases of pandemic H1N1 influenza are relatively mild and uncomplicated.[8] It was reported that the clinical manifestations and severity of pandemic and seasonal influenza were similar for hospitalized patients.[9] However, a broad range of clinical characteristics was described from different countries. It was reported that ICU support was required in up to 25% of patients hospitalized in the United States,[10] and mortality rates up to 58% in the ICU in Mexico.[11] Most patients hospitalized for seasonal influenza are less than 2 or over 65 years of age, and more than 90% of influenza-related deaths occur in patients 65 years of age and older.[12,13] In contrast, pandemic H1N1 influenza mainly affects younger age groups. Our hospital only serves patients over 16 years of age. Only 23% of patients were over 65 years of age. The median age of fatal cases in a study by van 't Klooster[14] was 52 years, and 42 years by Fuhrman et al,[15] and it was found 51 years in our patients as well. The most frequently reported symptoms and signs were cough and fever, which was very similar to seasonal influenza. Diarrhea and/or vomiting were found in 41.9% of our patients. Although these symptoms were reported in less than 3% of patients in China,[16] our results were in line with reports from Australia and the US.[9,10] At least one underlying risk factor was determined in 69% of patients in this study, and 37% had at least 2 such conditions. Chronic respiratory disease including asthma and diabetes were most frequently found. Similarly chronic pulmonary diseases and asthma were reported as the most frequent underlying medical conditions in a number of different studies,[10,14,15,17,18] and diabetes was reported to be the

Table 3 - Comparison of fatal and nonfatal cases.

Characteristic	Fatal (n=10)	Nonfatal (n=64)	*P*-value
Age in years, mean ± standard deviation	49.6 ± 17.82	47.64 ± 18.29	0.981
Gender, n (%)			0.077
Male	2 (6.25)	32 (93.75)	
Female	8 (20)	32 (80)	
Time from symptom onset to admission (mean days)	5.7 (±3.09)	4.56 (±3.02)	0.231
Body mass index, mean ± standard deviation	30.55 ± 4.9	25.84 ± 3.96	0.004
Oxygen saturation <92% (%)	67 (±13.96)	91.27 (±8.13)	<0.001
Alanine aminotransferase (0-41 U/L)	230.2 (±308.69)	31.05 (±23.86)	0.024
Aspartate aminotransferase (0-40 U/L)	365.8 (±541.27)	37.02 (±28.83)	<0.001
Lactate dehydrogenase (207-414 U/L)	703.1 (±388)	469.61 (±242.88)	0.023
Creatine kinase (0-180 U/L)	399.7 (±389.34)	396.41 (±699.7)	0.18
Urea (10-50 mg/dL)	75.3 (±26.61)	35.97 (±17.04)	<0.001
Creatinine (0.9-1.3 mg/dL)	1.57 (±0.59)	0.97 (±0.39)	0.004
Prothrombin time (10.5-14.5 sec)	21.48 (±10.43)	14.47 (±12.45)	0.006
Activated partial thromboplastin time (21-36)	34.72 (±12.21)	26.73 (±5.22	0.032
International normalized ratio (0.8-1.2)	1.48 (±0.56)	1.06 (±0.12)	0.007
Fibrinogen (150-400 mg/dL)	454 (±152)	528 (±197)	0.359
D-dimer* (0-500 ng/ml)	6430 (±3027)	1174 (±856)	<0.001

All data for biochemical parameters are expressed as mean ± standard deviation.*Data were available for 47 patients

most frequent underlying condition by Vaillant et al.[19] In this study, the presence of at least one co-existing condition was found to be 80% in fatal cases. The most frequent underlying conditions were diabetes and obesity. There was a documented underlying disease in 90% of the fatal cases in the study by Vaillant et al,[19] and the most frequently reported conditions were also diabetes and obesity.[19] Whether obesity itself contributes to the risk of acquiring H1N1 influenza, or to the risk of severe disease or death remains unclear.[18] Data from the US and France underlined the importance of obesity in pandemic H1N1 influenza. Jain et al[10] reported that 45% of hospitalized patients were either obese or morbidly obese. Obesity was one of the most frequently identified underlying conditions in other studies as well.[15,19,20] The BMI was ≥30 in 14 (18.9%) patients in this study, and most importantly, the mean BMI of fatal cases was significantly higher than that of non-fatal cases. In addition, we have found that obese patients had higher case fatality rates. Seventy-seven percent of patients in this study had findings on CXR that were consistent with pneumonia. This was considerably higher than it was reported elsewhere,[10,16] and may be related with our high fatality rates. Antiviral treatment is recommended for all hospitalized patients with confirmed, probable, or suspected pandemic influenza, and patients at high risk of complications. Treatment benefit is greatest if antiviral medications are started within 48 hours of the illness' onset especially in patients with underlying conditions.[18,21,22] It was suggested that delayed initiation of antiviral therapy may contribute to an increased severity of illness,[10] and median interval from symptom onset to antiviral treatment was found to be significantly longer for severe cases.[15] However, it was also suggested that hospitalized patients would benefit from treatment initiation even after 48 hours.[23] All patients in our study group received oseltamivir. Therapy was initiated after hospital admission, a median of 4 (1-12) days after the onset of symptoms. Only 25.6% of patients received antiviral therapy within 48 hours from symptom onset. Although it can be concluded that a 4-day interval is too long for an effective antiviral treatment, and in this study, we have found no difference between fatal and non-fatal patients in terms of antiviral treatment before or after 48 hours. Oseltamivir therapy is generally recommended for 5 days, but longer duration of antiviral treatment may be considered depending on clinical response.[22,24] Bacterial co-infections should be considered during, or after influenza. Evidence of bacterial co-infection was discovered in 29% of cases by means of histopathologic, molecular, and immunohistochemical analyses in the evaluation of postmortem lung specimens of 77 fatal pandemic influenza cases.[25] It is recommended that empirical treatment of community acquired pneumonia during influenza season should include both oseltamivir and antibacterial drugs.[22,26]

A study from Mexico revealed that non-survivors were more likely to present with severe organ dysfunction and hypoxia than survivors.[20] In our group of patients, oxygen saturation of fatal patients on admission was significantly lower than that of the non-fatal patients. Elevated levels of LDH, CK, AST, ALT on admission were reported in another study from Mexico,[11] but the difference between fatal and non-fatal cases was not significant. Elevated d-dimer levels in 4 patients were also reported in the same study.[11] We have found that when fatal and non-fatal patients were compared, fatal cases had significantly higher levels of ALT, AST, LDH, urea, and creatinine on admission. This may be explained by that all fatal patients were severely ill and had multi-organ failure on admission. Indeed, median duration between hospitalization and ICU admission was found to be one day in this study. All fatal patients also had longer PT, aPTT and INR. Fibrinogen levels were lower and d-dimer levels were higher in the fatal group. Elongated PT, aPTT times and INR, low levels of fibrinogen and elevated levels of fibrin degradation products raise the possibility that disseminated intravascular coagulation and/or pulmonary embolism may have played a role in the pathogenesis of pandemic H1N1 influenza in fatal cases.

Fatality rate was 13.5% for hospitalized confirmed pandemic H1N1 influenza cases in this study. During pandemics, more severe cases with a higher probability of dying tend to be detected initially.[19] Our hospital is a tertiary reference hospital and severe cases were more likely to be referred to our clinic. These factors may have contributed to the high fatality rate in our patients: the longer time from the onset of symptoms to hospital admission and hence, the delay in antiviral therapy; high presence of underlying conditions; high proportion of radiologically confirmed pneumonia; low levels of oxygen saturation on admission, and presentation of patients with organ dysfunctions.

The major limitation of this study was that this high fatality rate due to following more complicated and severe cases as a tertiary reference hospital cannot be generalized because of the small number of the study population.

In conclusion, our findings indicate that certain patients groups, such as obese patients and patients with underlying conditions are at increased risk for fatality. Oxygen saturation and biological parameters may be used to identify patients who are high-risks. Early recognition of patients with higher risk for fatality and appropriate management of these patients such as

ICU follow up and/or early intervention of respiratory support may result in better outcomes. Further research should be carried out to better understand the risk factors and pathogenesis of influenza virus infection.

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