Predictive factors for fatality in pandemic influenza A (H1N1) virus infected patients

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ABSTRACT

الأهداف: تحديد المعايير التنبؤية التي تزيد من خطر الوفاة بين المرضى المصابين بوباء أنفلونزا الخنازير وذلك اعتماداً على النتائج السريرية ونتائج المختبر عند الدخول إلى المستشفى.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في كلية الطب التابعة لجامعة كارادينيز التقنية، ترابزون، تركيا. لقد قمنا بمراجعة وتحليل البيانات السريرية والمختبرية والديموغرافية للحالات التي شُخصت بوباء أنفلونزا الخنازير خلال الفترة من أكتوبر 2009م إلى مايو 2010م. وبعد ذلك قُسم المرضى إلى مجموعتين وهما: مجموعة المرضى الموتى (المجموعة1)، ومجموعة المرضى ممن كانوا على قيد الحياة (المجموعة2)، وعلى هذا قمنا بمقارنة البيانات السريرية والديموغرافية والمختبرية للمجموعتين.

النتائج: أشارت نتائج الدراسة إلى أن 10 مرضى (20%) من أصل 50 مريض شملتهم الدراسة قد توفوا، ولقد كان متوسط العمر للمرضى في المجموعة1 كبيراً بصورة واضحة من الناحية الإحصائية مقارنة بالمجموعة2. ولم يكن هناك اختلافاً واضحاً من الناحية الإحصائية بين المجموعتين وذلك فيما يخص الحمل والإصابة بالأمراض المزمنة. ولقد لوحظ ارتفاع معدلات الحمى، والبلغم، وضيق التنفس، وتسارع التنفس، والزراق في المجموعة1 مقارنة بالمجموعة2. وكانت مستويات الهيموغلوبين، والغلوكوز، والألبومين، وامتصاص الأوكسجين الشرياني أقل في المجموعة1 منها لدى المجموعة2، فيما كانت مستويات أسبارتات ترانسامينار، وناقلة أمين الألانين، وبروتين سي التفاعلي، وبروكالسيتونين، ونيتروجين اليوريا في الدم، والوقت الفاصل بين بداية أعراض المرض والبدء بالعلاج المضاد للفيروس مرتفعة في المجموعة1 مقارنةً بالمجموعة2.

خاتمة: أظهرت هذه الدراسة بأنه بالإضافة إلى الخصائص السريرية والديموغرافية التي يتميز بها مرضى أنفلونزا الخنازير فإنه يمكن التنبؤ بسير المرض عن طريق نتائج المختبر. ويمكن لهذه المقاييس جميعها أن تدل الأطباء على كيفية التعرف على هذا المرض ونتائجه المميتة، بالإضافة إلى تحديد العلاج المناسب واحتمال إدخال هؤلاء المرضى إلى وحدة العناية المركزة.

Objectives: To determine predictive fatality criteria based on clinical and laboratory findings on admission to hospital in patients diagnosed with pandemic influenza A (H1N1) virus infection.

Methods: The study was conducted at the School of Medicine, Karadeniz Technical University, Trabzon, Turkey. Demographic, clinical, and laboratory data for hospitalized cases with a diagnosis of A (H1N1) virus infection between October 2009 and May 2010 were analyzed retrospectively. Patients were divided into 2 groups: fatal (group I) and non-fatal (group II). The 2 group's demographic, clinical, and laboratory data were compared on admission.

Results: Ten (20%) of the 50 patients included in the study died. The average age of group I was significantly higher than that of the group II. No significant difference was observed between the groups in terms of underlying chronic diseases and pregnancy. Fever, phlegm, shortness of breath, tachypnea, cyanosis were observed at significantly higher levels in group I compared to group II. Serum hemoglobin, glucose, albumin levels, arterial oxygen saturation were significantly lower in group I compared to group II; aspartate transaminase, alanine aminotransferase, C-reactive protein, procalcitonin, blood urea nitrogen levels, time between onset of symptoms and commencement of antiviral treatment were all significantly higher in group I.

Conclusion: This study shows that in addition to demographic characteristics and clinical findings, prognosis of patients with A (H1N1) virus infection can be determined beforehand with various laboratory tests. But these parameters, which can guide the clinician in the prior identification of potentially fatal A (H1N1) cases will contribute to the provision of supporting treatment and, when necessary, intensive care services for such patients.

Saudi Med J 2012; Vol. 33 (2): 146-151

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Received 12th September 2011. Accepted 10th December 2011.

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The first cases infected with pandemic influenza A (H1N1) were described in the United States of America and Mexico in April 2009, following which the virus spread rapidly to other parts of the world.[1-6] This new virus appeared as a hybrid consisting of a compound of human, swine and avian flu viruses.[7-9] When transmission from human to human had been demonstrated in a number of countries, the World Health Organization (WHO) raised the pandemic alarm to level 6 on 11 June, 2009.[10] The rapid spread of the infection caused concern and these cases were monitored with great care across the world. The majority of pandemic influenza A (H1N1) cases undergo the disease as outpatients, while some patients require hospitalization or admission to intensive care, and the disease can prove fatal.[11-13] Metabolic factors such as advanced age, pregnancy and obesity and factors such as severe respiratory difficulty/organ insufficiency on admission to hospital, APACHE II score, and elevated serum aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatine, d-dimer, prothrombin time (PT) and active partial thromboplastin time (aPTT) have been reported as risk factors correlated with fatality.[14-17] Considering the factors that determine prognosis in patients infected with pandemic influenza A (H1N1) virus makes it possible to obtain an early idea of the course of these cases and gain time for treatment. Some of these factors are parameters that have already been more intensively studied, though there are few studies in the literature examining the effect on prognosis of clinical findings together with laboratory results. Our study investigated the effect on fatality in association with pandemic influenza A (H1N1) virus of the above-mentioned clinical and laboratory findings.

Methods. The study was conducted according to the principles of Helsinki Declaration at the School of Medicine, Karadeniz Technical University, Trabzon, Turkey. The Ethical Committee of the hospital approved the study and was obtained before commencement.

Demographic, clinical and laboratory data for cases hospitalized with a diagnosis of pandemic influenza A (H1N1) virus infection between October 2009 and May 2010 were analyzed retrospectively. Respiratory/organ insufficiency was determined as intensive care hospitalization criteria, and the patients with hospitalization indication with a diagnosis of pandemic influenza A (H1N1) virus infection were monitored at the chest diseases intensive care unit, and patients not requiring intensive care were followed-up at the infectious diseases department. Hemogram, biochemical parameters, blood gases, C-reactive protein (CRP), procalcitonin and hemorrhage-clotting values were investigated in all cases during the admission procedure. Phlegm/tracheal aspirate cultures taken from all of cases and pulmonary radiographs were also taken. Patients were divided into 2 groups, fatal (group I) and non-fatal (group II). The 2 group's demographic, clinical and laboratory data were compared on admission.

Case definition for pandemic influenza A (H1N1) virus infection in our study was based on the Centers for Disease Control and Prevention (CDC) recommendations.[18] Nasal and/or nasopharyngeal samples from suspected cases were transported to the national reference center (Refik Saydam Hygiene Center Virology Laboratory in a viral transport medium) (Virocult, Medical Wire & Equipment, Corsham, Wiltshire, UK). Diagnosis of pandemic influenza A (H1N1) virus in cases described was confirmed using the in-house real-time PCR method at this laboratory.

Descriptive statistical analysis was performed for all the studied variables. The data obtained in measurements of the normal distribution were analyzed using the Kolmogorov Smirnov test. Data in conformity with normal distribution were analyzed using Students-t test, and those not conforming to normal distribution using the Mann Whitney-U test. Data obtained by measurements are given as mean ± standard deviation and those obtained by counting are given as numbers (%); analyses were performed using the Chi-square test. The results of the analysis were presented as P values, odds ratio (OR) and 95% confidence interval (95% CI). $P<0.05$ was regarded as statistically significant. Logistic regression analysis was used to assess whether risk factors for the development of fatality were independent.

Results. Fourteen (28%) patients with a diagnosis of pandemic influenza A (H1N1) virus infection were monitored at the chest diseases intensive care unit, and other (72%) patients followed-up at the infectious diseases department. Data for 50 patients with a confirmed diagnosis of pandemic influenza A (H1N1) virus were evaluated during the study. Twenty-two (44%) patients were males and 28 (56%) females. Ages ranged between 12 and 84, with a mean age of 48.8±16.5 in group I and 34.5±18.4 in group II (p=0.008). When the risk factors for the 10 (20%) patients who died were examined, an underlying chronic disease was determined in 3 (30%). In the non-fatal group, pregnancy was present in 7 (17.5%) of the 40 patients and with an underlying chronic disease in 8 (20%). No statistically significant difference was determined between the groups in terms of pregnancy and underlying chronic disease.

The most common complaints in our cases were cough-phlegm (84%), headache (74%), muscle-joint pain (58%), fever (56%), shortness of breath (54%), while other symptoms and findings included confusion

(26%), sore throat (20%), nausea-vomiting (16%), cyanosis (14%) and diarrhea (12%). Compared in terms of complaints, fever, phlegm, shortness of breath, tachypnea, confusion and cyanosis were significantly more evident in group I than in group II ($p<0.05$). In terms of baseline laboratory findings, serum hemoglobin, glucose, albumin levels and arterial oxygen saturation (SaO_2) were significantly lower in group I than in group II ($p<0.05$). Serum AST, ALT, serum creatinine phosphokinase (CPK), BUN, CRP and PCT levels in group I were significantly higher compared to those in group II ($p<0.05$). No bacterial reproduction was observed in the phlegm/tracheal aspirate cultures taken from our cases in group I, while bacteria were only isolated in 2 (5%) cases in group II. Streptococcus pyogenes was isolated in one case and *Haemophilus influenza* and *Streptococcus pneumonia* together in the other.

Infiltration was determined in 92% of our cases at pulmonary radiography. Six (60%) of the cases with bilateral infiltration at pulmonary radiography were in group I and 8 (20%) in group II. There was a statistically significant difference between the groups in terms of bilateral pulmonary infiltrations ($p=0.020$). Four (8%) cases in which no infiltration was determined were discharged in a healthy condition. Oseltamivir at a dosage of 2x75/150 mg was administered independently to all our cases from the onset of symptoms for 7-14 days. The period from the onset of symptoms to commencement of oseltamivir was 5.7±0.9 days in group and 2.8±1.7 days in group II ($p<0.0005$). There was also detected a markedly relationship along with this parameter and fatality in logistic regression analysis.

Clinical, laboratory, and demographic characteristics of patients with pandemic influenza A (H1N1) virus infection at the time of admission are shown in **Table 1**.

Discussion. Although this can vary between countries and regions, most fatal cases of pandemic influenza A (H1N1) virus infection fall within the age range 20-49 years, and these are known to have a higher average age compared with non-fatal cases.[14,15] Average age of fatal cases in our study, approximately 48.8, was significantly higher than that of survivors. Individuals infected with pandemic influenza A (H1N1) virus and with underlying chronic diseases such as bronchial asthma, chronic obstructive pulmonary disease, immunosuppression, diabetes mellitus, obesity or chronic coronary disease and pregnant patients have a greater mortality risk than others.[11,12] One in 5 of our cases diagnosed with pandemic influenza A (H1N1) followed a fatal course, though in terms of underlying chronic disease/pregnancy there was no significant difference between the fatal and non-fatal groups. However, we thought this might be attributed to the low number of pregnant cases or those with underlying chronic disease.

Clinically, fever, headache, sore throat, rhinorrhea, trembling and muscle pain were most frequently observed in cases with pandemic influenza A (H1N1) virus infection in our study. Nausea, diarrhea, dyspnea, joint pain and abdominal pain are relatively less common.[2,11] The most common symptoms and findings in our cases were fever, headache, cough-phlegm, shortness of breath and muscle-joint pain; fever, cough-phlegm, shortness of breath, confusion and tachypnea were significantly more observed in the fatal group. Severe hypoxemia and organ dysfunction at first arrival at hospital indicate the need for intensive care and a potentially fatal course.[11] In our fatal group, in addition to SaO_2, Hb, glucose and albumin levels were all significantly lower compared to the non-fatal group, while AST, ALT, LDH, BUN, CRP and PCT levels were all significantly higher in the fatal group. We thought that the low Hb and SaO_2 levels in the fatal group might lead to a rise in AST, ALT and LDH levels by impairing hepatic oxygenation. AST and LDH can also rise as an indicator of muscle tissue inflammation in such cases. A similar study conducted in Turkey investigated the relationship between laboratory values and fatality in pandemic influenza cases; it reported that SaO_2 below 92% at initial admission, high AST, ALT, LDH, urea, creatinine and d-dimer values and prolonged prothrombin time and international normalization ratio (INR) values were correlated with fatality.[16] Another study performed in Mexico reported that cases of pandemic influenza A (H1N1) had high AST, ALT, LDH and creatinine kinase (CK) levels at admission to hospital; however, it also reported no significant difference between fatal and non-fatal cases.[19] CRP and PCT are important parameters used in differentiating between bacterial infections and those of viral origin.[20,21] However, elevated CRP and PCT values are not only encountered in bacterial infections. These parameters can also rise in such situations as severe course viral and parasitic infections and non-infection conditions.[22,23] The significant elevation in CRP and PCT values in group I compared with group II in our study was thought to be correlated with infection severity. Since no bacterial agent was determined in any fatal cases, this elevation in CRP and PCT values may be attributed to the direct effect of the influenza virus on the pulmonary tissue. The high BUN and low glucose levels in these cases was thought to be correlated with an increase in metabolic rate seen as a result of severe infection and the low albumin with lung dysfunction and oral administration. Pulmonary radiography findings are also

Table 1 - Demographic, clinical, and laboratory characteristics of patients with pandemic influenza A (H1N1) infection at the time of admission.

Characteristics	Group I	Group II	*P*-value	Odds ratio	Confidence intervals	Normal values
Age (years) (mean±SD)	48.8 ± 16.5	34.5 ± 18.4	0.008			
Gender (%)						
Male	7 (70)	15 (37.5)	0.08	3.90	0.73 - 22.85	
Female	3 (30)	25 (62.5)				
Underlying chronic disease	3 (30)	8 (20)	0.670	1.71	0.27 - 10.15	
The period from the onset of symptoms to commencement of oseltamivir (days)	5.7 ± 0.9	2.8 ± 1.7	<0.0005			
Clinical findings (%)						
Fever (>38 ºC)	9 (90)	19(47.5)	0.029	9.95	1.08 - 229.6	
Lethargy	9 (90)	29 (72.5)	0.416	3.41	0.36 - 8.38	
Headache	6 (60)	31 (77.5)	0.420	0.44	0.08 - 2.37	
Myalgia-arthralgia	5 (50)	29 (72.5)	0.256	0.38	0.07 - 1.92	
Sore throat	3 (30)	24 (60)	0.155	0.29	0.05 - 1.51	
Shortness of breath	9 (90)	18 (45)	0.014	11.00	1.20 - 254.16	
Tachypnea	9 (90)	14 (35)	0.003	16.71	1.79 - 389.73	
Cough	7 (70)	12 (30)	0.03	5.44	1.0 - 32.8	
Confusion	8 (80)	5 (12.5)	<0.00001	28.00	3.72 - 274.45	
Nausea-vomiting	2 (20)	9 (22.5)	0.618	0.86	0.10 - 5.79	
Cyanosis	6 (60)	1 (2.5)	0.00009	58.50	4.61 - 1704.1	
Diarrhea	2 (20)	4 (10.0)	0.586	2.25	0.23 - 18.95	
Laboratory findings						
White blood cell (μL^{-1})	7750 ± 5566	10460 ± 7021	0.07			4000-10000μL^{-1}
Hemoglobin (g/dL)	14.1 ± 1.4	12.8 ± 1.9	0.043			12-18g/dL
Hematocrit (%)	40.3 ± 3.9	37.4 ±5.5	0.116			42-52
Platelet (μL^{-1})	206000 ± 73000	187000 ± 79000	0.495			140000-500000μL^{-1}
Prothrombin time (s)	14.2 ± 1.3	14.0 ± 1.4	0.740			11.5-15.5s
Active partial thromboplastin time(s)	33.7 ± 5.0	33.5 ± 2.9	0.880			20-34s
International normalization rate	1.5 ± 0.6	1.1 ± 0.2	0.101			0.8-1.2
Glucose (mg/dL)	165.6 ± 65.5	109 ± 28.3	0.024			70-100 mg/dL
Total protein (g/dL)	6.8 ± 1.0	7.2 ± 1.3	0.398			6.6 - 8.7 g/dL
Albumin (g/dL)	3.2 ± 0.6	4.0 ± 0.6	0.001			3.4 - 5.0 g/dL
Sodium (Na) (mmol/L)	139.2 ± 5.3	137.2 ± 2.9	0.278			136 - 147 mmol/L
Potassium (K) (mmol/L)	3.6 ± 0.8	3.9 ± 0.5	0.140			3.5 - 5.5 mmol/L
Aspartate aminotransferase (U/L)	104 ± 93	45 ± 52	0.004			5-40U/L
Alanine aminotransferase (U/L)	84 ± 80	38 ± 63	0.004			0-40U/L
Lactate dehydrogenase (U/L)	772 ± 434	435 ± 169	0.038			123-243U/L
Creatinine phosphokinase (U/L)	394 ± 373	319 ± 463	0.126			25-200U/L
Blood urea nitrogen (mg/dL)	7750 ± 5566	14.3 ± 10.9	0.012			4.7-23 mg/dL
Creatinine (mg/dL)	14.1 ± 1.4	0.8 ± 0.4	0.053			0.6-1.2 mg/dL
Sedimentation (mm/h)	40.3 ± 3.9	25.9 ± 19.6	0.265			0 - 20 mm/h
C-Reactive Protein (mg/dL)	33.8 ± 20.6	8.3 ± 9.3	0.001			0 - 0.3 mg/dL
Procalcitonin (ng/mL)	21.1 ± 12.1	0.6 ± 0.9	0.004			0 - 0.5 ng/mL
Partial oxygen pressure (mmhg)	6.9 ± 10.8	75.2 ± 20.4	0.367			75-100 mm Hg
Arterial oxygen saturation (%)	67.4 ± 18.3	92.9 ± 6.5	0.002			92 - 98.5
Radiological findings (%)						
Bilateral pulmonary infiltration	6 (60)	7 (17.5)	0.020	6.00	1.11 - 34.6	

important in terms of prognosis in cases of pandemic influenza A (H1N1) virus infection. One study reported abnormal pulmonary radiography findings in all cases requiring intensive care hospitalization, that 72% had patchy alveolar infiltration involving 3 out of 4 quadrants and that there was a high respiratory insufficiency-associated fatality rate in these cases.[17] Another study retrospectively analyzing radiological findings of 147 cases with pandemic influenza A (H1N1) virus infection, reported normal pulmonary radiography findings in the majority of cases, and that abnormal findings were mainly seen in the form of alveolar opacities in cases with advanced age, comorbid factors and a fatal course.[24] In our study, infiltration was determined at pulmonary radiography in 92% of cases, all of which were hospitalized in either departmentally or in the intensive care unit. The cases in group I were seen to have significantly greater bilateral pulmonary

Table 2 - Risk factors for fatality in pandemic influenza A (H1N1) infection (logistic regression).

Variables	Odds ratio	95% confidence interval
Age	1.001	0.92 - 1.09
Bilateral pulmonary infiltration	1.001	0.92 - 1.09
Time to commencement of antiviral treatment of symptoms (days)	5.31	1.19 - 23.64
C-reactive protein	1.178	0.99 - 1.39
Albumin	0.107	0.01 - 1.37

infiltration compared to those in group II. In the cases with widespread bilateral parenchymal involvement, we thought that tissue oxygenation was impaired as a result of decreased SaO_2 levels and that the oxygenation problem contributed to organ dysfunction thus having a negative influence on disease prognosis.

Commencement of antiviral treatment is advised for all patients hospitalized with pandemic influenza A (H1N1) virus infection and all patients in the high risk group for influenza complications.[11] When these patients are started on antiviral treatment within 48 hours of onset of symptoms, the effect is reported to be at a maximum level. However, antiviral treatment still needs to be initiated for hospitalized patients without regard to disease days.[25,26] For this reason, those patients in group I were not applied to the our hospital at first of the starting their symptoms, treatments were delayed in most of them. The importance of early antiviral treatment was also detected with logistic regression analysis in our study. It was shown that, one day delay on the antiviral treatment would result 5 times increase in the fatality (**Table 2**).

In conclusion, it may be possible to predict a fatal course in cases of pandemic influenza A (H1N1) virus infection from time of presentation. Several laboratory tests capable of being performed on a routine basis will assist the clinician on this subject, in addition to clinical and radiological findings alone. It is most important in terms of prognosis for antiviral treatment to be administered as quickly as possible, especially in cases requiring hospitalization, with underlying chronic

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