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Clinical characteristics of 75 pandemic H_1N_1 influenza patients from Turkey; risk factors for fatality

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Background/aim: The 2009 influenza A (H_1N_1) pandemic caused mild to severe illnesses and led to death in some cases. In this study, we aimed to evaluate the relationship between the serum D-dimer levels, CURB-65 scores, and the severity of pneumonia among patients with H_1N_1 infections.

Materials and methods: Sixty-eight patients who had probable H_1N_1 infections were evaluated by clinical, radiological, and laboratory methods. The H_1N_1 strain was specified by reverse transcription-polymerase chain reaction. Of 55 patients diagnosed with pneumonia, 18 exhibited H_1N_1 positivity and 37 patients did not.

Results: CURB-65 scores of pneumonia patients with H_1N_1 (group 1) were higher than those of patients without H_1N_1 (group 2) ($P = 0.02$). The D-dimer levels of group 1 were higher than those of group 2 ($P = 0.001$). Moreover, there was a positive correlation between D-dimer levels and CURB-65 scores in patients with H_1N_1-associated pneumonia ($P = 0.001$; $r = 0.89$).

Conclusion: Increased D-dimer levels were observed in pneumonia patients with H_1N_1 infection, which predicted the severity of pneumonia.

Key words: H_1N_1, pneumonia severity index, pneumonia, D-dimer

1. Introduction

In 2009, the influenza-A H_1N_1 strain (H_1N_1) caused diseases ranging from influenza-like illness to pneumonia, which led to acute respiratory distress syndrome (ARDS). The patients with influenza-like illnesses were admitted to health care units and cough, headache, and fatigue were the prominent symptoms, especially among young adults. However, pneumonia patients that were hospitalized in the clinics or intensive care units (ICUs) were generally infants or adults older than 65 years of age (1–3). For all that, severe H_1N_1 pneumonia also affected some young adults without any underlying comorbidities in both the United States and Turkey (4).

H_1N_1 patients in critical condition were transported to ICUs in the 2009 pandemic alert (4,5). Patients who developed acute respiratory failure were followed up with the best of care and cautions (6,7). Some of the patients were young and frequently did not have any accompanying health problems. Physicians had to diagnose and treat the infection immediately and evaluate the severity of the illness in order to prevent acute respiratory progression and possible fatality. Therefore, investigators were in need of new prognostic tools.

The Pneumonia Severity Index, or CURB-65, was reported to be effective in assessment of the severity of community-acquired pneumonia (CAP). However, it is not clear whether these evaluation scales are sufficient to assess the severity of pneumonia with H_1N_1 infection. Thus, we investigated an indicator in order to assess the severity of pneumonia in H_1N_1-positive patients (8).

Serum D-dimer values may increase in inflammatory conditions, such as pneumonia, sepsis, and septic shock (3,8). We hypothesized that D-dimer levels might be used as an assessment tool to evaluate the severity of pneumonia. In this study, we aimed to assess the relationship between CURB-65 scores and serum D-dimer levels in evaluating the severity of pneumonia among patients infected with H_1N_1. In this way, we planned to evaluate if the serum

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D-dimer values and CURB-65 scores reflected the prognosis of pneumonia in H_1N_1-positive patients.

2. Materials and methods

2.1. Patients

The study was conducted in the Ankara Atatürk Research and Training Hospital during the 2009 pandemic. Seventy-five patients with a high probability of H_1N_1 infection were evaluated. The study protocol was approved by the ethical committee of our institution. The study was designed as retrospective cohort.

Patients who had pulmonary embolism, malignancy, chronic renal failure, deep venous thrombosis, and hematologic disorders were excluded from the study. Those that were infected after the confirmation of the H_1N_1 infection were also excluded.

The following data were recorded: age, sex, duration of the symptoms (in days), fever, C-reactive protein (CRP), sedimentation rate, white blood cell counts, platelet counts, existence of monocytosis, existence of leukocytosis, median D-dimer levels (reference serum D-dimer values: 0–500 ng/mL), CURB-65 scores, comorbid illnesses, and radiological findings.

Nasopharyngeal swab samples were taken from all of the patients. H_1N_1 was diagnosed via real-time polymerase chain reaction (RT-PCR) assay as recommended by the World Health Organization (WHO) (4,9). The chest X-rays were evaluated by a radiologist and a pulmonologist. The clinical, radiological, and laboratory findings were evaluated by the pulmonologist.

A suspected case was defined as a case with at least one of the following symptoms: a temperature ≥37.5 °C, sore throat, cough, rhinorrhea, or nasal congestion. A confirmed case was defined by a positive result of a RT-PCR assay.

Patients with pneumonia were divided into two groups: H_1N_1-positive cases (group 1) and H_1N_1-negative cases (group 2).

Acute infections of the lung parenchyma, with symptoms such as cough, sputum, breathlessness, infiltration on a chest X-ray, and crackling during chest examination were defined as CAP according to the Infectious Diseases Society of America criteria (10).

The CURB index, as defined by the British Thoracic Society guidelines, was used to evaluate the severity of pneumonia. Criteria were: confusion of new onset, serum urea >7 mmol/L, respiratory rate ≥30/min, and systolic blood pressure <90 mmHg, or diastolic blood pressure ≤60 mmHg. Severe pneumonia was defined as at least two criteria positivity (11).

The CURB index was modified by adding age ≥65. A CURB-65 score was considered severe when the patients met three or more of the five variables (12).

2.2. Statistical analysis

Statistical analyses were performed using SPSS 16. In order to test whether the data were normally distributed, the Kolmogorov–Smirnov or Shapiro–Wilk tests were used. To compare groups, Student's t-test or the Mann–Whitney U-test were used for continuous variables and the chi-squared test was used for categorical variables. Homogeneities of variances were tested through Levene's test. Degree of association between continuous and ordinal variables were calculated by Spearman's correlation coefficient and graphed in scatter plots. Frequencies (percentages), mean ± standard deviation, and median (interquartile range) were provided as descriptive statistics. $P < 0.05$ was considered statistically significant.

3. Results

We evaluated 75 hospitalized patients with symptoms of the common cold or pneumonia in whom H_1N_1 infection was suspected via clinical, radiological, or laboratory methods. H_1N_1 diagnosis was confirmed by RT-PCR. Multislice computed tomography of the thorax was performed for patients with suspected pulmonary embolism. Subsequently, pulmonary embolism was diagnosed in 7 of the cases. Moreover, we excluded 13 patients with tracheobronchitis because of the absence of pneumonia signs and symptoms. A total of 55 patients consistent with a diagnosis of pneumonia were included in the study.

According to RT-PCR results, 18 H_1N_1-positive patients were classified as group 1 and 37 H_1N_1-negative patients were classified as group 2. There were no significant differences regarding the demographic parameters of group 1 and group 2 (Table 1). Risk factors associated with H_1N_1 were evaluated in all patients. Twenty-seven patients had chronic obstructive pulmonary disease (COPD), 1 patient had asthma, 2 patients had bronchiectasis, and 1 patient had obstructive sleep apnea syndrome. Fifteen patients had congestive heart failure, 7 patients had atrial fibrillation, and 28 patients had hypertension. Twelve patients had diabetes mellitus and 16 patients were obese. The incidence of obesity was significantly higher in group 1 than in group 2 ($P = 0.001$). However, congestive heart failure presence was significantly higher in group 2 than in group 1 ($P = 0.04$). Other comorbidities were similar between group 1 and group 2 ($P > 0.05$). There were no significant differences in terms of smoking status and pathogen microorganisms (Table 2) between group 1 and 2 cases ($P = 0.25$).

Seventy-two percent (n = 13) of group 1 and 56% (n = 21) of group 2 had multilobar involvement on the chest X-ray. The radiological difference between the 2 groups was statistically significant ($P < 0.005$). There was a positive correlation between the D-dimer levels and CURB-65

Table 1. Characteristic features and patient outcomes included in the study.

	H_1N_1-positive cases (n: 18) Median (min–max)	H_1N_1-negative cases (n: 37) Median (min–max)	P
Age	56.5 (17–85)	62.0 (18–88)	0.71
Female/Male	15/3	21/16	0.24
Duration of symptoms (days)	6 (1–15)	11 (1–60)	0.01
Fever	36.9 (37.9–39)	37.0 (36–39.4)	0.91
C-reactive protein (mg/L)	84.5 (4–254)	90.3 (0–209)	0.79
Sedimentation (mm/h)	44.5 (12–140)	26 (0–129)	0.11
White blood cell count (/μL)	7650 (2700–20,800)	12,000 (2700–28,700)	<0.001
White blood cell percent (%)	14	28	0.66
Monocyte count (/μL)	5.7 (1–17)	5.6 (2.3–17)	0.62
Monocyte percent (%)	9	15	0.88
Platelet count (/L)	222 (111–371)	261 (83–461)	0.03
Serum d-dimer level ng/mL	2805 (620–9007)	1160 (17–6295)	0.0001
Curb-65 score	3 (2–5)	2 (2–4)	0.02

Table 2. Pathogen microorganisms in the study group.

Material	Group 1	Group 2
Blood	Meticillin-resistant *Staphylococcus aureus* (MRSA)	
Sputum, Urine	*Streptococcus pneumoniae*	
Sputum		*Enterobacter cloacae*
Blood	*E. coli*	
Bronchial Lavage		*Klebsiella pneumoniae*
Urine		*Enterobacter aerogenes*
Urine		*E. coli*
Sputum		*Streptococcus pneumoniae*
Blood	MRSA	
Sputum, Urine	*Streptococcus pneumoniae*	
Blood	MRSA	
Sputum, Urine	*Streptococcus pneumoniae*	

scores of group 1 cases (P = 0.00; r = 0.89) (Figure 1). The D-dimer levels in group 1 were higher than those in group 2 [median (IQR): 3420 (4709.50) and 1245 (1637) ng/mL, respectively; P = 0.001] (Figure 2). CURB-65 scores of group 1 were higher than those of group 2 [median (IQR): 3 (2) and 2 (1), respectively; P = 0.02] (Figure 3).

Eight patients required ICU treatment in follow-up, 5 required mechanic ventilation, and 1 required hemodialysis. Five (6.6%) of the patients did not survive. Of those, 4 were confirmed H_1N_1 cases. The D-dimer levels of patients that died during follow-up were higher than those of the survivors (P = 0.001). In addition, the

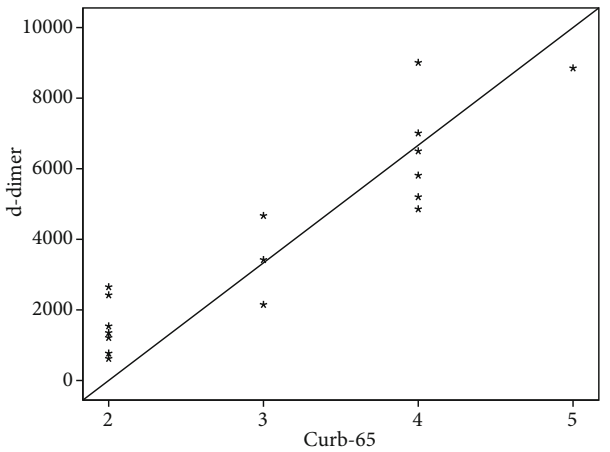

Figure 1. The correlation between the D-dimer and CURB-65 scores of H1N1-positive pneumonia patients.

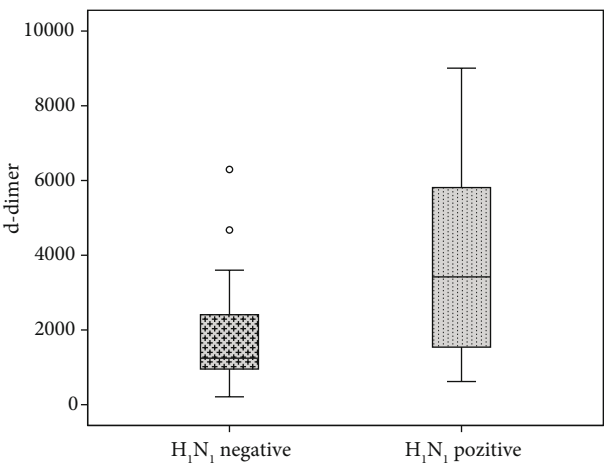

Figure 2. Serum D-dimer levels in H_1N_1-positive pneumonia patients and in H_1N_1-negative pneumonia patients.

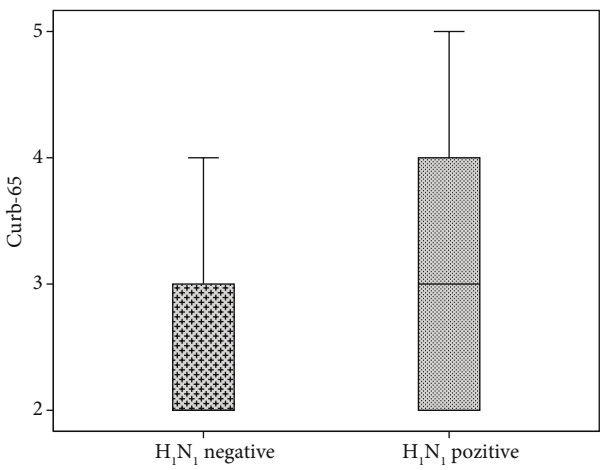

Figure 3. CURB-65 figures in H_1N_1-positive pneumonia patients and with H_1N_1-negative pneumonia patients.

deceased patients' CURB-65 scores were significantly higher than the scores of the survivors (P = 0.001).

Pneumonia cases were sorted into mild and severe groups according to CURB-65 scores. CURB-65 scores of 1–2 were defined as mild pneumonia, and scores of over 2 defined as severe pneumonia. Thirty-three patients were diagnosed with mild pneumonia and 22 patients with severe pneumonia. There were 12 (36.2%) patients with H_1N_1-negative severe pneumonia. However, while 10 (58.8%) H_1N_1-positive patients had severe pneumonia, 8 (41.2%) H_1N_1-positive patients had mild pneumonia. We analyzed CURB-65 scores and age, white blood cell count, CRP count, and serum D-dimer values by regression analysis. Only serum D-dimer values were related to the severity of pneumonia (risk ratio: 1.002, 95% confident interval; 1.001–1.004: P = 0.001). The D-dimer levels of severe pneumonia were higher than those of mild pneumonia (4134 and 1160 ng/mL respectively; P = 0.001). We did not define the relation between serum D-dimer values and CRP (P > 0.05).

4. Discussion

In this study, we demonstrated that D-dimer levels in patients with pneumonia and H_1N_1 positivity were higher than those in the H_1N_1-negative group. There was a positive correlation between the D-dimer levels and CURB-65 scores in patients with H_1N_1- positive pneumonia.

The H_1N_1 virus infection originated from North America in April 2009 and rapidly spread worldwide in the following months. Before the WHO declared a pandemic due to H_1N_1, the adenovirus was frequently isolated in adults. After the WHO emphasized the pandemic, reported cases reached a peak in June 2009. Patients with H_1N_1 infections had mostly respiratory signs and symptoms in Turkey. The clinical spectrum of illness has been reported as ranging from upper respiratory tract infection to ARDS in patients with H_1N_1 infection in a previous study (9). The patients in our study reflected a clinical spectrum similar to that mentioned in the literature.

In this study, the most common symptoms were recorded as cough (69.5%) and fever (67.4%), similar to a previous study (9). Moreover, the median length of time duration of positive RT-PCR was 6 days, which is the same as Cao et al.'s study. We determined that the admission period to a hospital in group 2 was longer than that of group 1.

Serum D-dimer values indicate fibrin turnover in the body (13). Intraalveolar fibrin can be deposited during inflammatory lung diseases. Thus, increased serum D-dimer levels reflect the severity of disease. It was determined to be higher in pneumonia patients who required ICU treatment than in CAP patients (14).

It was reported in previous studies that D-dimer levels were correlated with the mortality and the need for ICU admission in patients with CAP (15–17). Two other studies indicated an association between D-dimer levels and pneumonia severity index class (18,19). It was revealed that the CURB-65 pneumonia score is a predictor of 30-day mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia (20). In the current study, D-dimer levels and the CURB-65 pneumonia scores were found to be higher in 5 of the deceased patients than in the survivors. For this reason, it was speculated that serum D-dimer levels and CURB-65 pneumonia scores are important in evaluating pneumonia's severity.

H_1N_1–CAP has a high complication rate. Therefore, early estimation of the diagnosis and prompt treatment are lifesaving. Appropriate clinical evaluation, effective antiviral and antibacterial treatment, and monitoring the pneumonia's severity are critical for survival (1,21–23). For these reasons, while we were monitoring CAP patients with H_1N_1 infections, it was important to evaluate the severity of pneumonia. In the literature, there are rare studies evaluating pneumonia severity with CURB-65 scoring in order to predict the severity of pneumonia with H_1N_1 infection. No correlation was found between CURB-65 scoring and the severity of pneumonia in their study (24). In the current study, we showed that both CURB-65 scores and serum D-dimer levels were correlated with the severity of pneumonia in H_1N_1-positive patients. Five of the patients (6.6%) died in our study. D-dimer levels of these patients were higher than the levels of the patients who survived. D-dimer levels could reflect the prognosis in this population.

Both MRSA and *Streptococcus pneumoniae* were frequently detected in pneumonia patients with H_1N_1 infections, similar to the literature. However, these microorganisms were not observed in patients without H_1N_1 infection.

Our study had some limitations. First, this study is retrospectively designed. It may not be enough to evaluate the severity of pneumonia with other parameters. Second, we did not apply any other severity indices or compare CURB-65 with other scoring systems. Third, we did not record the follow-up serum D-dimer values.

In light of the current results, higher D-dimer levels among patients with H_1N_1-associated pneumonia compared with the other cases were determined in this study. The D-dimer levels correlated with CURB-65 scores of the patients. In conclusion, increased D-dimer levels were detected in the large majority of pneumonia patients with H_1N_1, and it was observed that they could even be higher in mortal cases and could predict the severity of pneumonia. We conclude that serum D-dimer levels might be an important marker in the follow-up treatment of H_1N_1-positive pneumonia patients. Although serum D-dimer value is a nonspecific marker, a high D-dimer value could indicate a high grade of inflammation in pneumonia. When the patients were admitted to the hospital, high D-dimer values indicated to the clinician that a more aggressive approach was necessary. The importance of CURB-65 scores in the evaluating of severity of pneumonia is known in the literature. Furthermore, high CURB-65 scores might be able to predict fatality and poor prognosis in H_1N_1-positive pneumonia patients. As a result, clinicians might follow up and treat patients exhibiting high serum D-dimer levels and CURB-65 scores on admission with an aggressive approach in clinical practice.

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