ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 23(3): 168-176, 2018
DOI: 10.5505/ejm.2018.04834

Mortality and severity related factors during the admission: H1N1 pneumonia

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ABSTRACT

In our country, fatal cases of H1N1 pneumonia were detected between 2015-2016 years. Our aim is to analyze the mortality and severity related factors, during admission of these patients.

By conducting a retrospective analysis, 17 cases, confirmed to have H1N1 pneumonia, included in the study. Findings were compared in terms of ARDS and mortality.

ICU and hospital mortality rates were 50% and 30%. The mean age of patients was 50 years. Serum LDH, CK, CK-MB, CRP AST, ALT levels, and the neutrophil-to-lymphocyte ratio (NLR) were found to be increased. In terms of co-infections, there wasn't a significant difference between died and survived patients. The mortality rate was 50% in patients with ARDS. There was no relationship between hospital stay with mortality. The symptom of restlessness was related to mortality, and presence of ARDS (P<.05). In died and alive patients, the mean-ranks of PaO2, SpO2, and CURB-65 scores were 3.5, 9.7, 4.3, 10.96, 14.6, and 6.6, respectively (P<.05). PaO2 and SpO2 values were lower, and CURB-65 scores were higher in dead patients. SpO2 <79.5, PaO2 <62.5, and CURB-65 scores ≥2 were related to mortality (P<.05). However, CURB-65 <2 did not exclude severe pneumonia. There was no relationship between comorbid diseases and mortality. The main radiographic finding was bilateral infiltrates.

This study suggests that PaO2, SpO2, and CURB scores of ≥2 and the presence of restlessness can be used to predict the severity and mortality in patients suspected to have H1N1 pneumonia, during admission.

Key Words: Influenza A Virus H1N1 Subtype, Pneumonia Viral, Severe Acute Respiratory Syndrome, Signs and Symptoms

Introduction

Influenza viruses have caused pandemics with morbidity and mortality in the recent years. Numerous studies have been carried out on the influenza A viruses (1-9). It is known that the clinical course of influenza infection varies depending on the interaction between the virus and the host's immune system (6,8).

Since H1N1 pneumonia may result in death, it is important to know the factors that are related with the mortality and severity during admission. Therefore, we evaluated the outcomes and the mortality-related factors in patients having H1N1 pneumonia between 2015 and 2016 years.

Materials and Methods

Subjects: This study was carried out at Chest Diseases Clinic (14 bed) and Anesthesiology Intensive Care Unit (15 bed) of Dursun Odabaş Medical Center of Yüzüncü Yıl University and Chest Diseases Department (10 bed) and Intensive Care Unit (12 bed) of Lokman Hekim Hospital in Van, Turkey. The approval of Ethics Committee of Yüzüncü Yıl University was obtained.

The records of 77 adult patients, who have been hospitalized with suspicion of swine H1N1 virus pneumonia, were retrospectively evaluated. By using the reverse transcriptase-polymerase chain reaction (RT-PCR) assay in their pharyngeal swab, 17 patients, who have been confirmed to have

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Received: 28.01.2018, **Accepted:** 30.03.2018

H1N1 virus, were involved in this study. Patients were not vaccinated against the flu and were treated with broad-spectrum antibiotics and oseltamivir. Positive pressure ventilation and corticosteroids were applied to the patients having ARDS. Age, gender, complaints, mental state, pulse, systolic blood pressure, and respiratory rate, CRP, Na, urea, creatinine, glucose, AST, ALT, LDH, CK, CK-MB, NLR, SpO_2, PaO_2, radiological findings, RT-PCR results, hospitalization states, underlying comorbidities, presence of ARDS, restlessness state, and treatment results were obtained from patient records.

ARDS: Berlin definition criteria were used in our centers in order to define the ARDS (10).

H1N1 Pneumonia: The patients were considered to have H1N1 pneumonia according to the Infectious Diseases Society of America, if they had complaints and symptoms (fever≥ 38°C; tachypnea; cough; and/or findings of crackles, bronchial breathing, or diminished breath sounds on auscultation) consistent with respiratory infections, and radiologically pulmonary infiltrations compatible with pneumonia (11). **The CURB-65** (confusion, urea, respiratory rate, blood pressure, age ⩾65 years) scores were calculated at the moment of admission to the hospital, and these scores to identify the severity of pneumonia (12).

Detection of the viral RNA: According to the CDC criteria, nasopharyngeal swab specimens had been taken at the moment of admission and then have been kept at a temperature ranging between 4 and 8°C. The specimens have been sent to the laboratory center of TR Ministry of Health for detection of the type of the viruses by RT-PCR (13).

Restlessness: According to 2 case studies, the symptom of restlessness was defined as a state of distress and discomfort that can be noticed by the physician during respiration of the patient (14, 15).

Statistical Assessment: The Mann-Whitney U-test was used in order to compare the non-normally distributed variables. Categorical variables were compared by using Chi-Square test. The agreement was calculated using Cohen's Kappa coefficient. The relationship between the PaO_2, SpO_2 with mortality was evaluated with ROC analysis. The results were considered to be statistically significant if P value was <0.05. Statistical analysis was carried out by using SPSS for Windows version 20 (SPSS Inc., Chicago, IL).

Results

Demographic characteristics of all patients are presented in Table 1. The mean age of patients was 50 years. In died and survived patients, the mean ranks of ages were 7.8 and 9.5 years (p .52). There was no statistical difference between died and survived patients' ages (p .52). Although patients with ARDS had a longer stay in hospital and ICU, there was no relationship between hospital stay with mortality.

The laboratory results are shown in Table 2. The Serum LDH (1096), CK (642), CK-MB (40), CRP (124), AST (197), and ALT (208) levels were higher than the normal upper limit and the NLR (8.8) ratio was higher than the normal value which was found in the literature. The leukocyte counts (11456) were increased slightly (Table 2). There was no difference between the levels of sodium and potassium with the mortality.

The symptoms and clinic states of patients are shown in Table 3. Of 17 patients, 100% patients had the fever, cough, myalgia and fatigue, 94% dyspnea and headache, 66% restlessness, 30% abdominal pain, and 18% rhinorrhea and sore throat (Table 3).

Receiving positive pressure support (60% invasive, 40% noninvasive) due to ARDS (10 patients, 60%), the patients' mortality rate was 50%. Of the 11 patients with restlessness, six patients were survived, and five patients were dead. The presence of ARDS was significantly accompanied by the symptom of restlessness (Figure 1, p<0 .05).

The symptom of restlessness was present in 10 patients with ARDS and in one patient without ARDS. As a risk factor for ARDS, the risk ratio was found to be 7 times higher in patients with restlessness, compared with patients who were not restlessness. The Cohen's Kappa coefficient was 0.87 (95% confidence interval (CI): 1.1–42.9; P< 0.01, Figure 1). Furthermore, restlessness and ARDS were found to be associated with mortality. The mortality risk was more than 2-fold in patients having restlessness, and in these patients, the Kappa coefficient was 0.37 (95% CI: 1.13–3.5; P= .049, Figure 1). The mortality risk was more than 2-fold among the patients having ARDS, and the Kappa coefficient was 0.45 (95% CI; 1.2–4.6; P= .026, Figure 1).

In the dead and surviving patients, there was no significant difference between the NLR ratios. In

Table 1. The table shows the descriptive physical findings and the duration of stay

Descriptive Characteristics of all patients		Counts	Mean	*SD.	**Min.	***Max.
Physical	Age, Year	17	50	16	30	80
Findings	Systolic Blood Pressure, mmHg	17	95	19	60	140
	Pulse /min	17	113	21	75	140
	Breaths per minute	17	28	7	16	42
Times	Stay in ICU, Day	10	9	14	0	43
	Stay in hospital, Day	17	12	15	1	49
	From beginning to the treatment	17	5	2,3	2	10

Findings of physical examination, the time from the beginning of complaints to starting of the treatment, the length of intensive care unit stay and the hospital stay are presented in the table. Abbreviations: *SD; Standard Deviation, *Min; **Minimum, Max; Maximum

Table 2. The table shows the laboratory results

Laboratory results	Counts	Mean	*SD.	Minimum	Maximum
Potassium, mmol/L	16	4	0.6	2.9	5.5
Glucose, mg/dL	16	153	63	65	328
Creatinine, mg/dL	16	1	0.3	0.6	1.81
Urea, mg/dL	16	49	32	18	139
CK , U/L	9	642	683	53	2241
CK-MB, U/L	10	40	19	13	75
AST, U/L	14	197	449	17	1775
ALT, U/L	13	208	452	14	1645
LDH, U/L	7	1096	660	346	2000
Leucocyte count /mm^3	17	11456	8854	1600	39000
Neutrophil/Lymphocyte ratio	17	8.8	6.6	1.17	23
****CRP, mg/L	17	124	94	1	339
***PaO2, mmHg	14	61.5	7.8	50	78
**SpO2	17	82.5	14.5	50	98
Sodium, mmol/L	16	136	2.4	131	141

The table shows the results of laboratory parameters. Abbreviations: *SD, Standart Deviation **SpO2; Oxygen saturation measured by pulse oximeter, ***Pao2; Partial pressure of oxygen in arterial blood gases, ****CRP; C-reactive protein

dead and alive patients there was no difference in terms of the pathogenic bacterial growth. There were not any pathogenic bacteria isolated from the cultures within the first three days of the hospitalization. After the first three days of the hospitalization, the pathogenic bacteria were isolated in three cultures taken from three patients. Klebsiella was isolated from a dead patient's bronchial aspiration culture. Additionally, the Klebsiella and Acinetobacter were isolated in one survivor patient's sputum culture at different times. The Acinetobacter was also isolated from one another patient's sputum culture.

The mean arterial PaO_2 and SpO_2 values were 61.5 and 82.5 on room air (Table 2). Among the dead patients, the mean levels of PaO2 and SpO2 were significantly lower while compared to the levels of survived patients ($P< .05$). For this relation the cut-off value of arterial PaO_2 was 62.5. The PaO2 values which were lower than 62.5 were related to mortality (100% sensitivity, 78% specificity) (Figure 2).

The area under the curve was 0.94 for PaO_2. The SpO2 values lower than 79.5 were related to mortality with 80% sensitivity and 83% specificity. The area under the curve was 0.89 for SpO_2 (Figure 2).

The CURB-65 scores <2 were unable to predict severe pneumonia and the CURB-65 scores ≥2 were associated with mortality (Table 4).

Among 6 patients having ARDS, the CURB-65 was equal two or less than two. In terms of

Table 3. The table shows the symptoms and clinic states of patients

Symptoms and clinic states	Counts	Percentage	Mortality rate	P Value
● Respiratory system				
*ARDS	10	60%	50%	0,026
Fever	17	100%	30%	indeterminable
Cough	17	100%	30%	indeterminable
Dyspnea	16	94%	31%	0.5
Rhinorrhea	3	18%	33%	0.8
Sore throat	3	18%	21%	0.1
Restlessness	11	66%		0.049
● Gastrointestinal system				
Abdominal pain	5	30%	40%	0.5
● Cardiovascular system				
Tachycardia	14	84%		0.5
● Neuromuscular system				
Headache	16	94%		0.5
Fatigue	17	100%	30%	indeterminable
Myalgia	17	100%	30%	indeterminable

*: Acute respiratory distress syndrome (ARDS) Symptoms and clinic states

Table 4. The table shows the PaO2, CURB-65, and SpO2 values according to the states

Admission Parameters	The patient state	Numbers	Mean Ranks	P-Values
PaO2	In died patients	5	3.5	0.008
	In survived patients	9	9.7	
	In patients with ARDS	10	7.4	0.88
	In patients without ARDS	4 *	7.75	
CURB-65	In died patients	5	14.6	0.002
	In survived patients	12	6.67	
	In patients with ARDS	10	10	0.31
	In patients without ARDS	7	7.57	
SpO2	In died patients	5	4.3	0.013
	In survived patients	12	10.96	
	In patients with ARDS	10	5.5	0.001
	In patients without ARDS	7	14	

Note: * Indicates that arterial blood gases weren't taken in three patients without ARDS. There is no difference between the mean ranks of PaO2 and CURB-65 score in the patient with and without ARDS

CURB-65 scores, there was no significant difference between patients with and without ARDS (Table 4, P= 0.31). However, the mean CURB-65 scores were 14.6 and 6.67 for died and survived patients, respectively (Table 4, P< 0.01).

The comorbidities were reported to be COPD (18%), asthma, immunosuppressive drug use and hypertension (12%), coronary artery disease, diabetes mellitus and substance abuse (6%). There wasn't any difference between survived and died patients in terms of the underlying comorbid conditions. A survived patient was using the methylprednisolone at a dose of 18 mg per day due to asthma and one died patient was using the infliximab treatment at a dose of 3mg/kg every 8 weeks.

Radiologically, fourteen patients (84%) had bilateral and three patients (18%) had unilateral infiltrates, mainly located in the lower and peripheral area (Figure 3).

Fig. 1. Mortality rates and coexistence of ARDS and restlessness

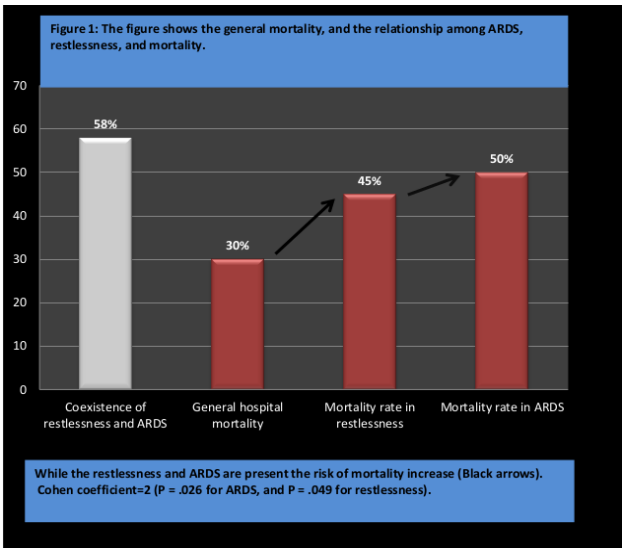


Figure shows that the risk of the presence of ARDS is 7 times higher in patients with restlessness, compared patients without restlessness. The mortality rate is more than 2-fold (45%-50%) in patients with restlessness and ARDS (P<0,05)

Discussion

In our country, between 2015 and 2016 years a mild outbreak of H1N1 viruses has emerged, and lethal cases were detected as seen in Nepal and India in early 2015 (16). During the admission to the hospital, a prediction for severity and mortality should be assessed in patients with H1N1 pneumonia since some factors may have resulted in death. Therefore, we evaluated the clinical, laboratory, and radiological findings of our patients having H1N1 pneumonia during the admission to the hospital.

Early initiation of the oseltamivir is recommended for hospitalized patients with H1N1 pneumonia (1-3). Low degree of drug resistance has been reported for Oseltamivir (1-3, 17). In our study, the Oseltamivir has been given to all patients at the dose of 75 mg twice a day for approximately five days (2–10 days) after the onset of the complaints. However, we could not analyze the effect of the absence ore delayed of Oseltamivir since all patients received the Oseltamivir treatment.

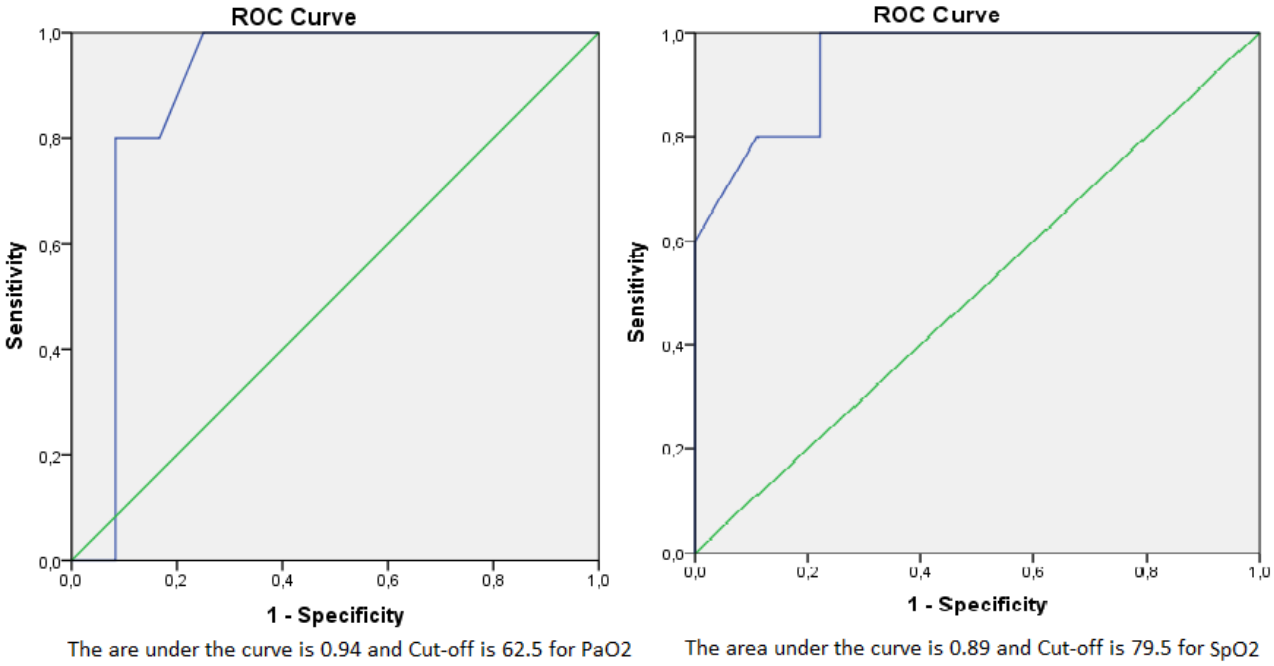
The WHO's writing committee report supports that the young and middle-aged people have been frequently affected by the H1N1 viruses (1). Similar to our study, most of the studies have shown that H1N1 pneumonia can be more severe among the young and middle-aged people (1-3,18-20). In our study, 24% of the mortality cases consisted of patients aged 44 years or less than 44 years. Nonetheless, there was no significant difference between our dead and surviving patients' mean ages.

In our study, the main complaints of the patients were fever, cough, and myalgia sometimes accompanied by a sore throat and the rhinorrhea and, like being seen in 2009 H1N1 pandemic (1-3,21). However, unlike the pandemic in 2009, the nausea, vomiting, and diarrhea were not seen in any of our patients. There wasn't any relation between mortality and our patients' complaints or symptoms except for the symptom of restlessness. The symptom of restlessness, considered to be a condition of distress in the respiration is mentioned as the symptom of central nervous system in severe H1N1 infection (1). Except for two case studies, the relationships between restlessness and severe disease have not been adequately discussed in literature from the aspect of the patients having H1N1 pneumonia (14,25). In our study, the presence of restlessness was related to the mortality and presence of ARDS. Furthermore, the pulmonary involvement was more severe in patients with restlessness compared with patients who are not having restlessness. This result suggests that the symptom of restlessness reflects the severity of pneumonia or ARDS as a simple physical examination finding during the admission.

During the admission, the normal or below-normal counts of leukocytes together with lymphocytopenia, elevations in levels of serum AST, LDH, CK, and creatinine have been reported among the patients having severe H1N1 pneumonia (1,2,9,18-21). Similarly, among our patients, there was a significant elevation in the levels of serum LDH, CK, CK-MB, CRP AST, ALT in addition to the slight increase in the counts of leukocyte. Nevertheless, in our study, there was no relationship between these laboratory findings with mortality. This may have resulted from the small size of our study population.

The neutrophil counts increases and the number of lymphocytes decreases among the patients having H1N1 virus infection (1,2). It has been shown that NLR can be used as an indicator of inflammatory or infectious diseases (22). The normal NLR value has been found between 0.78 and 3.53 in the good healthy adult population (23). Deng et al (24) were found the leukocytosis and lymphopenia in patients with H1N1 infection. However, few studies have examined the NLR ratio in patients with H1N1 pneumonia. In our

Fig. 2. Figure shows the relationship between mortality with PaO2 and SpO2



The figure shows that the SpO2 values <79.5 and PaO2 values <62.5 are related to mortality on Receiver Operating Characteristic (ROC) Curve Analysis

study, the NLR was 8.8 and this value was higher than the normal level of good healthy population. However, there was no difference between our dead and surviving patients in terms of the NLR ratio. On the contrary with our study, Indavarapu et al (25) reported that NLR lower than 2 is related to the presence of H1N1 infection at the moment of admission.

The H1N1 pneumonia can be accompanied by bacterial infections (1-3,17-19,21,26). Furthermore, it has reported that the risk of mortality increases due to bacterial co-infections (1). However, in cultures, there wasn't any bacterial growth seen within the first three days of our patients, and after the three days of the hospitalization, there was no difference between our died and surviving patients in terms of pathogenic bacterial growth.

In the literature, the mortality rates have been found to be 0-47% among the patients, who had been followed up in ICU (1-3,17-19,21,27). A positive correlation has been shown between the respiratory failure and mortality among the patients having H1N1 pneumonia (1-3,19,21). Our hospital and ICU mortality rates were similar to the values observed in pandemic of year 2009. Moreover, in our study, the presence of the respiratory insufficiency and ARDS, and the need for positive pressure were correlated with the mortality and severity of pneumonia.

Since the presence of severe H1N1 pneumonia has been found to be associated with the mortality, the investigators have evaluated various severity scales of pneumonia at the admission in order to enable the early prediction of severity and mortality (28,29). However, it is not well known whether CURB-65 scoring, which is useful in community-acquired pneumonia, is effective in H1N1 pneumonia. In a multicenter study, Pereira et al (28) evaluated the mortality-predicting values of pneumonia severity scores such as PIRO-CAP, PSI and CURB 65 in patients with H1N1 pneumonia. They found that pneumonia-specific scores could not estimate the severity and should not be used as instruments to guide decisions in the ICU (28). In a multicenter study, Fujikura and et al (29) reported that PSI, CURB-65, and A-DROP scores (age, dehydration, respiration, disorientation, and blood pressure) are useful predictors of the mortality regardless of the pneumonia patterns. However, they also found that these pneumonia prediction models might underestimate the severity and inaccurately determine the appropriate site of care for the patients having influenza pneumonia. Similarly, in our study, CURB-65 scores equal 2 or higher than 2 were associated with the increased mortality rate, but the lower scores weren't sufficient for efficiently predicting the need for hospitalization due to hypoxemia during the admission. In our study, the CURB-65 scores were found to be equal

Fig. 3. The figure shows radiological findings

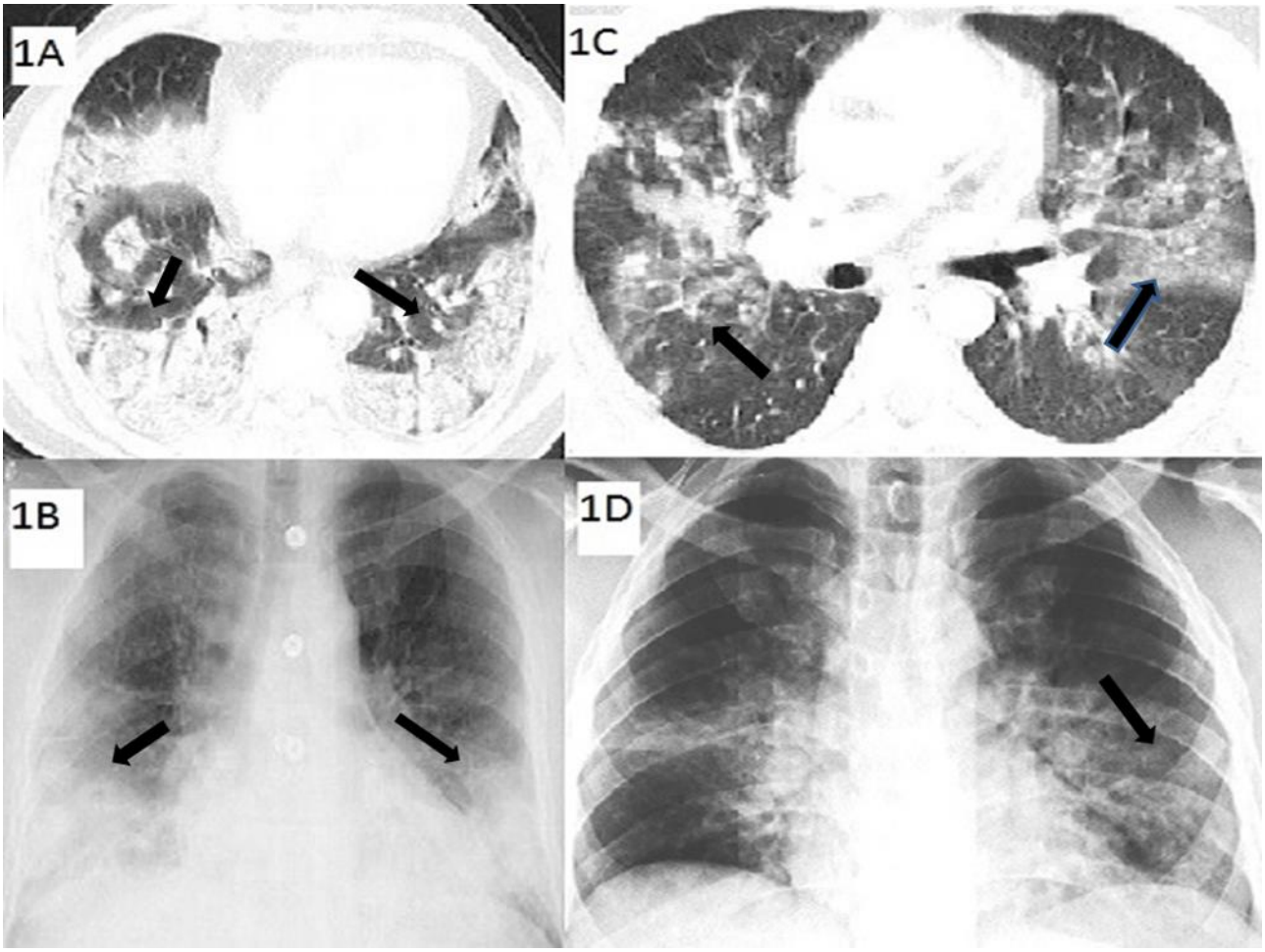


Figure shows computed tomography and chest x-ray images of one died (1A, 1B) and another one survived (1C, 1D) patients. The arrows show localization of infiltrates on radiography

2 or less than 2 in the six patients and these patients, having been radiologically bilateral ground glass infiltrates, were hospitalized due to ARDS. This finding suggests that H1N1 pneumonitis may be severe even if the CURB-65 score is ≤ 2.

In case of the failed non-invasive ventilation, the delayed diagnosis and antiviral therapy were found to be associated with the mortality (28). Likewise, the late diagnosis, late antiviral therapy, and failure of noninvasive ventilation were present in our one dead patient. During 2009 H1N1 pandemic, the main clinical syndrome resulting in the hospitalization and intensive care was the diffuse viral pneumonitis, which was associated with severe hypoxemia and ARDS (1). Similarly, among our patients, SpO_2 levels lower than 79.5 and PaO_2 levels lower than 62.5 were related with the mortality and the severity of pneumonia, as seen in the previous study (1,2,30).

H1N1 pneumonia can be severe and mortal depending on the presence of comorbidities (1,2). Uses of immunosuppressive drugs are a factor related to the severity of pneumonia (1). Our one patient, having Infliximab treatment because of ankylosing spondylitis died within one hour after the admission to the ICU. However, in our study, there was no relation between comorbid diseases and mortality. This may be due to the low number of patients in our study. Bilateral ground-glass infiltrates located mainly in middle and lower zones have been reported (1-3,14-15,17). Additionally, the bilateral infiltrates also were found to be related to severe pneumonia (1-3,17-19). Likewise, there were bilateral infiltrates in the majority of our patients and all of the dead patients.

The level of AST, ALT, LDH, CK, and CK-MB and the NLR increase in patients with H1N1 pneumonia during the admission. The H1N1 pneumonia can be fatal in patients, who use immunosuppressive treatment. The CURB-65

score of ≥2, SpO2 <79.5 and PaO2 <62.5 can be used as indicators of ARDS during the admission. The CURB-65 <2 couldn't exclude severe pneumonia. During such an H1N1 outbreak, the clinicians must be careful about possible ARDS in patients with restlessness and such clinical, laboratory parameters, and bilateral infiltrates.

Our Study limitations: One limitation of our study was that cases in H1N1 viruses couldn't be detected in the nasopharyngeal swab were excluded from the study. Therefore, few cases with the H1N1 virus have been evaluated. Secondly, the actual effect of comorbid conditions may be overlooked due to the limited number of cases.

Since the study was done retrospectively, no additional fund was needed. The authors do not have any conflict of interest.

Acknowledgement: All authors would like to thank Dr. Sıddık KESKİN for his statistical calculations of the study.

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