Spectrum of clinical and imaging findings in patients with serological diagnosis of H1N1 and its correlation with clinical severity

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Aims and objectives

Influenza A H1N1 virus is the subtype of influenza virus that typically leads to a more severe infection than the usual seasonal influenza virus. It was the cause of the last influenza global outbreak in 2009, which resulted in thousands of deaths worldwide, principally among young individuals and pregnant woman. Since then, the H1N1 influenza virus has assumed a seasonal spreading similar to other influenza types and continues to cause substantial morbidity, although it is controlled with the immunization programs.[1] Nevertheless, an atypical outbreak occurred in South America in 2016, which started before the vaccination campaign, and caused approximately 800 deaths and 500 intensive care unit internments in a single country.[2]

Since the first outbreak of H1N1, many studies have been conducted to identify an imaging pattern [3, 4] or clinical features that indicate a worse prognosis.[1, 5, 6] The identification of clinical and radiographic findings in patients with H1N1 infection that correlate with the clinical severity is of key importance in the management of these patients. Previous studies have demonstrated that all patients with H1N1 admitted to an intensive care unit had at least an abnormal CR at diagnosis. However, there is a relative lack of studies in the literature that have examined predictive tools in the evaluation of patients with H1N1.[7, 8]

In this scenario, the purpose of this study was to evaluate the correlation between clinical and imaging findings with a worse clinical outcome in patients with a confirmed diagnosis of H1N1 influenza A virus.
Methods and materials

The institutional review board approved this retrospective study and waived the requirement for informed consent. The database from our institution was searched for consecutive patients with a diagnosis of influenza A H1N1 in 2016 as assessed via the upper airway by nasopharyngeal swabbing or a washing test with polymerase chain reaction. The inclusion criteria were a positive test for influenza A H1N1 and chest radiograph (CR) and/or chest computed tomography (CT) within 48 hours before or after the positive test. The exclusion criteria were another confirmed concomitant pulmonary infection and the absence of follow-up data in the medical records.

Clinical and laboratorial data were obtained from a detailed medical record review conducted by two radiologists with 2 and 3 years of experience, using a standardized form. The following clinical data of the patients were assessed: gender, age, symptoms at admission (such as flu-like symptoms, dyspnea, thoracic pain, hemoptysis, and sepsis), and presence of comorbidities (including systemic hypertension, diabetes mellitus [DM], tobacco smoke, asthma, chronic obstructive pulmonary disease [COPD], and immunodeficiency). Information regarding the physical examination at admission was also evaluated, including the heart rate (HR), temperature, oxygen saturation (O₂), and blood pressure (BP). Regarding the laboratory data, the white blood count, lymphocytes, and C-reactive protein (CRP) obtained at admission were assessed.

The CR were performed in posteroanterior and lateral incidences during maximal inspiration with the following parameters: 70-120kV and 1-10mAS.

CT scans were performed on a dual-source 256 row or a 128 row detector CT system. The acquisition parameters were the same for both devices as follows: 115-160mAs; 120kVp; tube rotation time 0.5s; pitch 1.2; and field of view (FOV), 400-430mm. When contrast was required, it was performed with 1.0-1.5ml/kg injected at a flow rate of 4.0-5.5ml/s. Images were reconstructed in the axial view using a slice thickness of 1mm and an increment of 0.7mm.

Two board-certificated chest radiologists blinded to the clinical data independently reviewed the radiological exams and analyzed the imaging features according to the Fleischner Society glossary.[9] Figures 1 and 2 exemplifies the imaging features.

The following imaging features were evaluated on CR: pulmonary infiltrate, consolidation, and pleural effusion.[10] The distribution of the features was defined as follows: none, one field, two fields unilateral, three or more fields bilateral, and diffuse.

The following imaging features were assessed on CT: ground glass opacity (GGO), consolidation, bronchial wall thickening, and pleural effusion. The distribution of the imaging features on CT was defined as indicated for CR.
The patients were classified into two groups: good clinical outcome and worse clinical outcome. A good clinical outcome was defined as hospital discharge after evaluation in the emergency department without the need for hospitalization. Patients who were hospitalized, admitted to the intensive care unit (ICU) or died were determined to have a worse clinical outcome.

Statistical Analysis

Continuous variables were tested for normality with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The values are expressed as median and percentiles 25 and 75 or as the mean and standard deviation for parametric and non-parametric data respectively. The categorical data are presented as absolute values and percentages and were tested using Pearson $^2$ test and Fisher exact test, if applicable. The McNemar test was used by compare two methods. Nonparametric data was compared using the Mann-Whitney U test for two independent samples. The logistic regression models included calculations of corresponding crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI). Two-tailed p-values $<0.05$ were considered significant. Hierarchical cluster analysis was performed to identify individual similarities in the diagnostic model through analysis of clusters to try to determine from each of the groups to which they belong. Statistical significance was considered with $p<0.05$. 
**Fig. 1**: Forty-five-year-old man without comorbidities with H1N1 virus infection who was admitted to the intensive care unit with acute respiratory distress syndrome. (A) Anteroposterior chest radiography demonstrates bilateral diffuse pulmonary infiltrates and consolidations. (B and C) Chest computed tomography on coronal and axial planes also show consolidations and bilateral ground-glass opacities.

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**Fig. 2:** Sixty-five-year-old woman without comorbidities with H1N1 infection who did not have a worse outcome. Normal chest radiography performed at emergency department.

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Results

Our study population (Figure 3.) consisted of 160 patients, including 80/160 (50%) men and 80/160 (50%) women, with a median age of 43 years (IQR: 32-56). 49/160 (30.6%) patients had comorbidities, 12/160 (7.5%) had DM, 29/160 (18.1%) had systemic hypertension, 4/160 (2.5%) had COPD, 6/160 (3.8%) had another pneumopathy and 8/160 (5.0%) had immunosuppression. Five of 160 (3.1%) patients were smokers. None of the patients had asthma. The vast majority of the included patients (147/160, 91.8%) were diagnosed in March and April.

Concerning the clinical manifestations at admission, 144 patients had this information written in the medical records. Based on this subpopulation, 141/144 (97.9%) patients had flu-like symptoms, 25/144 (17.4%) had dyspnea, and 7/144 had thoracic pain. None of the patients were septic or had hemoptysis. On physical examination, the median oxygen saturation was 96% (IQR: 95-98), the median HR was 92 bpm (IQR: 80-107), 49/141 (34.7%) patients had high temperature levels, with a median temperature of 37ºC (IQR: 36.3-37.7), the median systolic BP was 125.5 mmHg (IQR: 113-138), and the median diastolic BP was 78.5 mmHg (IQR: 69-87). Regarding the laboratory data, the median white blood cell count and lymphocytes were 5990/mm³ (IQR: 4610-7560) and 950/mm³ (IQR: 680-1400), respectively, and the median of CRP was 1.90 mg/dL (IQR: 0.96-3.88).

Considering outcome, 37/160 (23.1%) patients were hospitalized and classified as having a worse clinical outcome. Four of these patients (4/37, 10.8%) required ICU admission, and none of these patients died. The mean age of this subpopulation was 50 years old (IQR: 34-66). All patients who were hospitalized had an abnormality on CR and/or CT. Table 1 summarizes the patients’ characteristics and radiological findings.

113 patients underwent CR, and 8/113 (7.1%) of them were abnormal. Pulmonary infiltrate was detected in 5/8 (62.5%) patients, consolidation was identified in 2/8 (25.0%) patients and pleural effusion was found in 1/8 (12.5%) patients.

60 patients underwent chest CT, and 43/60 (71.7%) patients showed some abnormality. 27/60 (45.0%) patients had GGO, 9/60 (15%) patients had consolidation, 26/60 (43.3%) patients had bronchial thickening, and 5/60 (8.3%) patients had pleural effusion.

13 patients underwent both CR and chest CT (Table 2). There was a significant correlation between an abnormal CR and abnormal chest CT (p=0.031) and between the presence of pulmonary infiltrate on CR and GGO on CT (p=0.016). In contrast, there was no significant correlation between consolidation and pleural effusion on CR and CT (p=0.501 and p=0.999, respectively).

Considering the clinical data, the presence of DM, systemic hypertension, dyspnea, thoracic pain, temperature levels and CRP levels were significantly different between
the groups (Table 1). The frequency of DM (7/37, 18.9% vs 5/123, 4.1%; p=0.003), systemic hypertension (12/37, 32.4% vs 17/106, 13.8%; p=0.010), dyspnea (12/25, 32.4% vs 13/107, 12.1%; p=0.005), and thoracic pain (5/37, 13.5% vs 2/107, 1.9%; p=0.005) were significantly higher in the patients who required hospitalization. The temperature was significantly lower in the patients with worse clinical outcomes (36.4ºC vs 37.4ºC, respectively, p<0.001), and the C-reactive protein levels were significantly higher (3.05 vs 1.75, respectively, p=0.026).

Regarding the imaging features on CR, the presence of an abnormality, pulmonary infiltrate, consolidation, and pleural effusion were significantly more frequent in the patients with worse outcomes ([4/14, 28.6% vs 4/99, 4%; p=0.001], [2/14, 14.3% vs 1/99, 1%; p=0.004], [2/14, 14.3% vs 0/99, 0.0%; p<0.001], and [1/14, 7.1% vs 0/99, 0.0%; p=0.008], respectively).

With regards to the imaging features on CT, the presence of an abnormality, GGO and consolidation were significantly more frequent in the patients with worse outcomes ([26/30, 86.7% vs 17/30, 56.7%; p=0.010], [18/30, 60% vs 9/30, 30%; p=0.020], and [8/30, 26.7% vs 1/30, 3.3%; p=0.011]). Furthermore, the distribution of the imaging features on CR and CT were correlated with outcome, in which a diffuse pattern was more related to worse clinical outcomes.

In the logistic regression, the following data predicted worse outcomes: DM (OR: 8.3; 95% CI 1.4-50.2, p=0.020), body temperature (OR: 0.4; 95% CI 0.3-0.8, p=0.005), thoracic pain (OR: 20.3; 95% CI 2.2- p<0.001), alteration on CR or CT (OR: 22.7, p<0.001), pulmonary infiltrate on CR or GGO on CT (OR: 6.9, p=0.002), and pleural effusion on CT or CR (OR: 10.3, p=0.045).

Figures 1 and 2 show patients with and without worse clinical outcomes.

In the hierarchical cluster analysis, three clusters were identified (Figure 4). The cluster that better correlated with worse clinical outcomes contained the following variables: GGO on CT or CR, consolidation on CT or pulmonary infiltrate on CR and the extension of the disease.
Fig. 3: Flowchart of patient selection.

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Fig. 4: Dendrogram showing hierarchical clustering of variables in predicting worse clinical outcomes. The variables with higher correlations with worse clinical outcomes are highlighted in green, with moderate correlations in yellow and variables with low correlations in red.

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Table 1: Patient characteristics.

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Table 2: Intertest agreement of chest X-ray and chest computed tomography.

<table>
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<th>Abnormality</th>
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<th>Chest CT</th>
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<td></td>
</tr>
<tr>
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<td>Pleural effusion</td>
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Conclusion

Our study population was obtained from our database throughout the year of 2016; however, all patients selected had the H1N1 infection diagnosed between the three months before winter in the south hemisphere, which configured an atypical and early outbreak of H1N1 infection.[11]

The major clinical findings among our population were flu-like symptoms (97.9%) as expected for a respiratory infection.[12] DM, systemic hypertension, dyspnea, thoracic pain, temperature and CRP levels were the clinical features associated with worse clinical outcomes. Moreover, the radiological findings were the presence of pulmonary infiltrate, consolidation, and pleural effusion on CR, presence of GGO and consolidation on CT, and diffuse pattern of imaging abnormality on CT or CR. In the logistic regression, the presence of DM, thoracic pain, levels of body temperature, an alteration on CR or CT, diffuse pattern of distribution of any abnormality on CR or CT; pulmonary infiltrate on CR, GGO on CT, and pleural effusion on CT or CR were the variables that predicted worse clinical outcomes. In the hierarchical cluster analysis, the cluster that better correlated with worse clinical outcomes contained GGO on CT, pulmonary infiltrate on CR, consolidation and distribution on CT or CR.

Regarding the clinical features, our results are in line with similar studies that evaluated symptoms associated with a worse outcome, as they demonstrated that fever and dyspnea may predict hospitalization.[12] Studies that have analyzed only patients with severe H1N1 admitted to an ICU have also demonstrated that symptoms were similar to typical seasonal H1N1, such as cough, dyspnea, fever, myalgia and headache.[1] The results are also comparable to studies that have analyzed mild and severe infections.[7]

Our study also demonstrated chest pain as a predictor of worse outcome, a feature that was not found in previous studies and may be related to the institution sample or type of H1N1 virus. Therefore, despite minor differences among studies, H1N1 infection exhibits similar clinical features that predict severity over the years regardless of the genotype. In contrast to previous studies, we did not identify death due to H1N1 infection. The average mortality among adult patients in the United States was 26%.[13]

With regards to imaging features, the CR and CT findings in our study population are comparable to the most representative studies over the years since the first H1N1 outbreak in 2009.[5, 12, 14] All 37 patients with worse outcomes had at least a pulmonary abnormality in an imaging exam, and we identified significant differences among the groups with and without hospitalization.

The imaging features detected in our population are in line with previous data of viral pneumonia, including pulmonary infiltrate, GGO, consolidation and pleural effusion.[10, 15] Comparable to other studies, we found that diffuse distribution on an imaging abnormality was associated with worse clinical outcomes.[5, 12, 14]
The clinical relevance of our results essentially relies on the management of patients with H1N1 infection. Informing the multidisciplinary team of the potential for a worse clinical outcome based on easily accessible information, such as the presence of DM, thoracic pain, body temperature, and an abnormality on CR or CT, may add value in the setting of emergency departments. If clinicians know in advance the possibility of a worse outcome, they may consider a closer evaluation, and the emergency discharge decision may be postponed. This type of guidance may be valuable, particularly at noncomprehensive centers and during epidemic situations.

There are several potential limitations of this study. First, it is a single-center retrospective study, which is thus subjected to selection bias. Second, the study population seemed to have a milder infection than previous studies. No deaths or sepsis at admission were found, and 92.9% of the chest CRs were normal. These results may be related to the earlier outbreak of 2016 in the early autumn or with a less severe H1N1 genotype. Although our study population was relatively large compared to other imaging studies, a larger sample would have resulted in a greater generalizability of our imaging findings, particularly for patients admitted to the ICU. Consequently, further studies, particularly prospective cohorts, are necessary to overcome these limitations and provide a better generalization of our results.

In conclusion, our study demonstrates that the presence of DM, hypertension, dyspnea, thoracic pain, or an abnormal CR or CT on admission were associated with worse clinical outcomes in patients with H1N1 influenza A virus infection. Consolidation and ground glass opacities on CT were also associated with the clinical severity in these patients. Thus, the use of readily accessible clinical and imaging features on admission may have a role in the evaluation of patients with H1N1 infection.
References


