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Comparison of patients with avian influenza A (H7N9) and influenza A (H1N1) complicated by acute respiratory distress syndrome

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Abstract

The aim of this study was to compare the clinical features of patients with avian influenza A (H7N9) and influenza A (H1N1) complicated by acute respiratory distress syndrome (ARDS).

The clinical data of 18 cases of H7N9 and 26 cases of H1N1 with ARDS were collected and compared in the respiratory intensive care unit (RICU) of Fuzhou Pulmonary Hospital of Fujian from March 2014 to December 2016.

Patients with H7N9 had a higher acute physiology and chronic health evaluation-II score ($P < .05$) and lung injury score ($P < .05$). The rates of coexisting diabetes mellitus, hyperpyrexia, and bloody sputum production were significantly higher in the H7N9 group than in the H1N1 group ($P < .05$). The H7N9 group had a longer duration of viral shedding from the onset of illness ($P < .05$) and from the initiation of antiviral therapy ($P < .05$) to a negative viral test result than the H1N1 group. Patients with H7N9 had higher rates of invasive mechanical ventilation; serious complications, including alimentary tract hemorrhage, pneumothorax or septum emphysema, hospital-acquired pneumonia (HAP) and multiple organ dysfunction syndrome (MODS); and hospital mortality ($P < .05$). At the 6th month of follow-up, the rates of bronchiectasia, reticular opacities, fibrous stripes, and patchy opacities on chest computed tomography (CT) were significantly higher in the H7N9 group than in the H1N1 group ($P < .05$). Based on multiple logistic regression analysis, H7N9 influenza viral infection was associated with a higher risk of the presence of severe ARDS than H1N1 influenza viral infection (odds ratio 8.29, 95% confidence interval [CI] 1.53–44.94; $P < .05$).

Compared to patients with H1N1, patients with H7N9 complicated by ARDS had much more severe disease. During long-term follow-up, more changes in pulmonary fibrosis were observed in patients with H7N9 than in patients with H1N1 during the convalescent stage.

Abbreviations: APACHE-II = acute physiology and chronic health evaluation-II, ARDS = acute respiratory distress syndrome, CI = confidence interval, CPAP = continuous positive airway pressure, CT = computed tomography, FiO_2 = fraction of inspiration oxygen, GGOs = ground-glass opacities, HAP = hospital-acquired pneumonia, IQR = interquartile range, MODS = multiple organ dysfunction syndrome, NPPV = noninvasive positive pressure ventilation, OR = odds ratio, PaO_2/FiO_2 = the ratio of arterial partial pressure of oxygen to inspiratory oxygen fraction, PCT = procalcitonin, PEEP = positive end expiratory pressure, RICU = respiratory intensive care unit, RT-PCR = reverse transcription polymerase chain reaction.

Keywords: acute respiratory distress syndrome, avian influenza A (H7N9), influenza A (H1N1), tomography, x-ray computed

1. Introduction

Humans infected with either avian influenza A (H7N9)[1] or influenza A (H1N1)[2–4] can exhibit severe respiratory disease. Acute respiratory distress syndrome (ARDS) has a high incidence in severe cases and is the main cause of avian influenza-related death.[5–7] To date, data regarding comparisons between patients with H7N9 and those with H1N1 have been reported,[8–11] but specific studies comparing the 2 diseases in terms of ARDS are rare. Herein, the clinical features and prognoses of patients with H7N9 avian influenza and those with H1N1 influenza were retrospectively and comparatively analyzed to further improve the understanding of ARDS caused by influenza viruses.

2. Methods

2.1. Patients

This study was established in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fuzhou Pulmonary Hospital of Fujian, Educational Hospital of Fujian Medical University. The Ethics Committee waived the requirement for informed consent for this study, but all patient data were analyzed anonymously. The clinical data, including epidemiology, clinical manifestations, imaging examinations, and laboratory examinations, were collected from 18 patients with avian influenza A (H7N9) and 26 patients with influenza A (H1N1)

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The authors declare that they have no conflict of interest.

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Table 1

Epidemiological features in the H7N9 and H1N1 groups.

	H7N9 (n = 18)	H1N1 (n = 26)	*P*
Age, yr	59 (48–73)	53 (40–62)	.152
Subgroup			
0–20 yr	0	2 (7.7)	.505
21–40 yr	3 (16.7)	5 (19.2)	1.000
41–64 yr	7 (38.9)	16 (61.5)	.139
≥65 yr	8 (44.4)	3 (11.5)	.031
Female	2 (11.1)	10 (38.5)	.083
APACHE-II score	20.0 (16.5–24.3)	13.0 (12.0–15.3)	.001
Lung injury score	3.7 (2.8–4.0)	2 (1.5–2.6)	.001
Coexisting underlying diseases	9 (50.0)	11 (42.3)	.614
Hypertension	5 (27.8)	6 (30.8)	.738
Coronary heart disease	3 (16.7)	2 (7.7)	.386
Arrhythmia	3 (16.7)	0	.062
Diabetes	7 (38.9)	2 (7.7)	.021
ASC/CHB	1 (5.6)	2 (7.7)	1.000
Chronic gastrointestinal diseases	1 (5.6)	2 (7.7)	1.000
Schizophrenia	3 (16.7)	1 (3.9)	.289
COPD	1 (5.6)	2 (7.7)	1.000

Data are presented as the median (IQR) or No. (%).

Coexisting underlying diseases include any of the following (one or more): hypertension, coronary heart disease, arrhythmia, diabetes, ASC/CHB, chronic gastritis, schizophrenia, or COPD.

APACHE-II = acute physiology and chronic health evaluation-II, ASC = hepatitis B virus carriers, CHB = chronic viral hepatitis, COPD = chronic obstructive pulmonary disease, IQR = interquartile range.

complicated by ARDS in the respiratory intensive care unit (RICU) of the Fuzhou Pulmonary Hospital of Fujian from March 2014 to December 2016. All patients with H7N9 or H1N1 were diagnosed according to the diagnosis and treatment programmes for influenza issued by the Chinese Ministry of Health (National Health and Family Planning Commission).[12,13] The respiratory specimens (nasopharyngeal swab, sputum, extracted tracheal aspirate, or bronchoalveolar lavage fluid) in all clinically suspected cases of influenza viral infection were positive for avian influenza A (H7N9) virus or influenza A (H1N1) virus by reverse transcription polymerase chain reaction (RT-PCR), which was performed as a qualitative assay. After admission, serial sampling of all respiratory secretions mentioned above (nasopharyngeal swab or lower respiration sample) was performed daily for viral monitoring until the clinical specimens were consistently negative twice during a time interval of 24 hours. Patients with ARDS were diagnosed according to the diagnostic criteria of the Berlin definition[14] as follows: the timing was within 1 week of a known clinical insult or new/worsening respiratory symptoms; chest imaging (chest x-ray or computed tomography [CT] scan) showed bilateral opacities that were not fully explained by effusions, lobar/lung collapse, or nodules; hypoxemia (positive end expiratory pressure [PEEP] or continuous positive airway pressure [CPAP] ≥5 cm H_2O) was classified as mild (the ratio of arterial partial pressure of oxygen to inspiratory oxygen fraction [PaO_2/FiO_2] 201–300 mmHg), moderate (PaO_2/FiO_2 101–200 mmHg), or severe (PaO_2/FiO_2 ≤100 mmHg); and the origin of edema was assessed as respiratory failure that was not fully explained by cardiac failure or fluid overload, and an objective assessment (e.g., echocardiography) was necessary to exclude hydrostatic edema if no risk factor was present.

2.2. Statistical analysis

Data were described as the median (interquartile range, IQR) or number (%). The comparisons of the features between the different subtypes of influenza (H7N9 and H1N1) were performed with the Wilcoxon signed-rank test to compare the medians of continuous variables and Fisher exact test or the chi-squared test to compare proportions. The association between the different subtypes of influenza viral infection (H7N9 and H1N1) and the risk of severe ARDS presentation and death was assessed using multivariable logistic regression analysis, adjusted for age, sex, and coexisting diabetes. All analyses were performed with SPSS 19.0 statistical analysis software (IBM, Armonk, NY). A *P*-value <.05 was considered statistically significant.

3. Results

3.1. Epidemiological characteristics

The epidemiological characteristics of the 2 groups are shown in Table 1. The number of patients aged ≥65 years, the acute physiology and chronic health evaluation-II (APACHE-II) score and the lung injury score were higher in the H7N9 group than in the H1N1 group ($P < .05$) on admission. The rate of diabetes mellitus was statistically higher in the H7N9 group than in H1N1 group ($P < .05$).

3.2. Clinical manifestations, laboratory results, and imaging findings

The clinical characteristics of the patients in the 2 groups are shown in Table 2. The 2 groups were mainly characterized by fever, shortness of breath, cough, hemoptysis, poor appetite, and fatigue, and hyperpyrexia (>39.0 °C) and bloody sputum were more common in the H7N9 group than in the H1N1 group ($P < .05$).

The procalcitonin (PCT) level, elevated lactic acid, and D-dimer rates on admission and PCT >0.5 ng/mL rate after onset were significantly higher in the H7N9 group than in the H1N1 group ($P < .05$). The severity of ARDS was more serious in the H7N9 group than in the H1N1 group ($P < .05$).

The typical chest CT characteristics of the 2 groups were similar. A nodular shadow was extremely rare, and bronchiecta-

Table 2

Clinical symptoms, laboratory results, and imaging features of the H7N9 and H1N1 groups.

	H7N9 (n = 18)	H1N1 (n = 26)	*P*
Clinical symptoms			
Fever	18 (100)	26 (100)	1.000
Maximal temperature, °C	39.6 (38.9–40.3)	38.9 (38–39.0)	.001
Subgroup			
37.3–38 °C	1 (5.6)	8 (30.8)	.060
38.1–39 °C	5 (27.8)	12 (46.15)	.218
39.1–41 °C	12 (66.7)	6 (23.1)	.004
Shortness of breath	18 (100)	26 (100)	1.000
Cough	18 (100)	26 (100)	1.000
Hemoptysis sputum	14 (77.8)	10 (38.5)	.010
Anorexia	14 (77. 8)	14 (53.9)	.105
Weakness	12 (66.7)	20 (76.9)	.506
Runny nose	7 (38.9)	10 (38.5)	.977
Gastrointestinal symptoms	7 (38.9)	3 (11.5)	.064
Nausea	2 (11.1)	1 (3.9)	.558
Vomiting	2 (11.1)	1 (3.9)	.558
Diarrhea	3 (16.7)	1 (3.9)	.289
Laboratory results			
Leukocyte count (10^9/L)	3.4 (2.2–6.9)	4.5 (2.7–7.0)	.535
Subgroup			
<4 (10^9/L)	10 (55.6)	10 (38.5)	.263
>10 (10^9/L)	2 (11.1)	4 (15.4)	1.000
Lymphocyte count (10^9/L)	0.6 (0.4–0.8)	0.6 (0.5–0.8)	.504
Lymphocyte count <1.5 (10^9/L)	18 (100)	24 (92.3)	.505
Hemoglobin, g/L	139.5 (125.8–145.5)	132.0 (121–144.5)	.459
HCT	39.6 (36.9–42.5)	40.4 (37.9–41.2)	.949
Platelet count (10^9/L)	155.5 (109.8–189.3)	158.0 (114.5–183.3)	.981
Platelet count <100 (10^9/L)	4 (22.2)	2 (7.7)	.615
C reactive protein, mg/L	137.6 (81.0–176.5)	129.2 (114.7–188.8)	.740
ALT >40 (U/L)	13 (72.2)	14 (53.9)	.218
AST >40 (U/L)	16 (88.9)	16 (61.5)	.083
LDH >250 (U/L)	18 (100)	22 (84.6)	.133
CK >200 (U/L)	10 (55.6)	12 (46.2)	.540
Lactic acid >2.0, mmol/L	7 (38.9)	2 (7.7)	.021
D-dimer >500, mg/L	9 (50.0)	2 (7.7)	.003
PCT >0.5, ng/mL	17 (94.4)	10 (38.5)	<.001
PCT on admission, ng/mL	5.6 (4.3–8.5)	0.26 (0.13–2.19)	<.001
PaO_2/FiO_2	85.5 (64.75–190.5)	144 (97–185)	.032
Subgroup			
201–300 (slight ARDS)	3 (16.7)	4 (15.4)	1.000
101–200 (moderate ARDS)	3 (16.7)	14 (53.9)	.013
<100 (severe ARDS)	12 (66.7)	8 (30.8)	.019
Imaging features, no (%)			
Consolidation	18 (100)	26 (100)	1.000
Ground-glass opacity	17 (94.4)	26 (100)	.409
Air bronchogram	17 (94.4)	26 (100)	.409
Pleural effusion	16 (88.9)	2 (7.7)	<.001
Interlobular septal thickening	7 (38.9)	13 (50.0)	.467
Lymph node enlargement	7 (38.9)	4 (15.5)	.093
Nodular shadow	1 (5.6)	0	.409

Data are presented as the median (IQR) or No. (%).

ALT = alanine aminotransferase, ARDS = acute respiratory distress syndrome, AST = aspartate amino transferase; CK = creatine kinase, HCT = haematocrit, IQR = interquartile range, LDH = lactate dehydrogenase, PaO_2/FiO_2 = the ratio of arterial partial pressure of oxygen to inspiratory oxygen fraction, PCT = procalcitonin.

sis was not observed. The pleural effusion rate was higher in the H7N9 group than in the H1N1 group ($P < .05$).

3.3. Treatment and prognosis

All patients were treated with antiviral drugs and other treatment measures (Table 3). The rate of invasive mechanical ventilation was significantly higher in the H7N9 group than in the H1N1 group ($P < .05$). The H7N9 group had longer durations of viral shedding from the onset of illness and from the initiation of antiviral therapy to a negative viral test result ($P < .05$) than the H1N1 group.

Over the course of the viral infections, the 2 groups presented with a variety of serious accompanying complications, of which the occurrence rates of alimentary tract hemorrhage, pneumothorax or septum emphysema, hospital-acquired pneumonia (HAP) and multiple organ dysfunction syndrome (MODS) were significantly higher in the H7N9 group than in the H1N1 group

Table 3

Treatment and prognosis of the H7N9 and H1N1 groups.

	H7N9 (n = 18)	H1N1 (n = 26)	*P*
Mechanical ventilation	18 (100)	22 (84.6)	.133
Noninvasive ventilation	7 (38.9)	18 (81.8)	.005
Invasive ventilation	11 (61.1)	4 (18.2)	
ECMO treatment	3 (16.7)	0	.062
Timing from onset to hospitalization, d	5 (4–6)	5 (5–7)	.264
Timing from onset to diagnosis of ARDS, d	6 (5–7)	6 (5–8)	.761
Timing from onset to administration of antiviral therapy, d	4 (2–6)	4 (2–6)	.443
Timing from onset to a negative viral test result, d	24 (17–29)	10 (8–12)	<.001
Timing from administration of antiviral therapy to a negative viral test result, d	19 (11–24)	6 (4–8)	<.001
Timing from onset to fever relief, d	13 (12–16)	12 (10–14)	.062
Timing from the administration of antiviral therapy to fever relief, d	8 (7–11)	8 (6–10)	.176
RICU stay, d	26 (20–37)	13 (11–15)	<.001
Severe complications			
Lower-extremity vein thrombosis	1 (5.6)	0	.409
Pulmonary embolism	3 (16.7)	0	.062
Digestive tract bleeding	10 (55.6)	4 (15.4)	.005
Pneumothorax or mediastinal emphysema	8 (44.4)	2 (7.7)	.008
HAP	8 (44.4)	3 (11.5)	.031
MODS	11 (61.1)	4 (15.4)	.002
Hospital mortality	7 (38.9)	2 (7.7)	.021
Imaging features at the 6th month of follow-up			
Bronchial dilation	4 (22.2)	0	.023
Grid shadow	4 (22.2)	0	.023
Filament shadow	6 (33.3)	1 (3.9)	.013
Patchy consolidation	7 (38.9)	2 (7.7)	.021

Data are presented as the median (IQR) or No. (%).

ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation, HAP = hospital-acquired pneumonia, IQR = interquartile range, MODS = multiple organ dysfunction syndrome, RICU = respiratory intensive care unit.

($P < .05$). The hospital mortality rate of the H7N9 group was significantly higher than that of the H1N1 group ($P < .05$).

During follow-up, residual lesions on chest CT could be observed in both groups. At the 6th month of follow-up, the rates of bronchiectasia, reticular opacities, fibrous stripes, and patchy opacities in the H7N9 group were significantly higher than those in the H1N1 group ($P < .05$). Most residual lesions were adjacent to the pleura and obvious pulmonary fibrosis changes with collapsed lung could be detected in some survivors in the H7N9 group.

3.4. Different subtypes of influenza viral infection correlate with the presence of severe ARDS and death

After the adjustments for baseline variables (age, sex, and coexisting diabetes), H7N9 influenza viral infection was associated with a higher risk of the presence of severe ARDS than H1N1 influenza viral infection (odds ratio [OR] 8.29, 95% confidence interval [CI] 1.53–44.94; $P < .05$; Table 4). The differences remained significant when the corrections for only age and sex were made and when no corrections for baseline variables were made (OR 10.20, 95% CI 1.97–52.40; $P < .05$ and OR 4.50, 95% CI 1.24–16.28; $P < .05$, respectively; Table 4).

After the adjustments for baseline variables (age, sex, and coexisting diabetes), the risk of death between the 2 subtypes of influenza viral infection (H7N9 and H1N1) was not significantly different (OR 5.09, 95% CI 0.67–38.65; $P > .05$; Table 4), though the differences were significant when corrections for only age and sex were made and when no corrections for baseline variables were made (OR 8.06, 95% CI 1.21–53.92; $P < .05$; OR 7.64, 95% CI 1.36–42.90; $P < .05$; Table 4).

4. Discussion

In our study, the proportions of underlying diseases in the patients with H7N9 and those with H1N1 complicated by ARDS were high at 50.0% and 42.3%, respectively, which indicated that the combination of underlying diseases had a significant effect on the severities of H7N9 and H1N1.[5,15] Interestingly, 3 cases (16.7%) with coexisting schizophrenia were found in the

Table 4

The association between the different subtypes of influenza viral infection and the risk of the presentation of severe ARDS and death.

Dependent Variable	Subtypes of Influenza Virus	OR (95% CI)	*P*	OR (95% CI)[a]	*P*[a]	OR (95% CI)[b]	*P*[b]
Severe ARDS	H7N9	4.50 (1.24–16.28)	.022	10.20 (1.97–52.40)	.005	8.29 (1.53–44.94)	.014
	H1N1	1		1		1	
Death	H7N9	7.64 (1.36–42.90)	.021	8.06 (1.21–53.92)	.031	5.09 (0.67–38.65)	.116
	H1N1	1		1		1	

ARDS = acute respiratory distress syndrome, CI = confidence interval, OR = odds ratio.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex, and coexisting diabetes.

H7N9 group. To our knowledge, there was no specific association between schizophrenia and the presence of H7N9 influenza viral infection, and the coexistence of the 2 diseases was considered coincidental.

The presentation of ARDS in both the H7N9 and H1N1 patients was rapid after viral infection, along with a series of clinical symptoms. Notably, large amounts of bloody sputum production showing diffuse alveolar hemorrhage were more common among the H7N9 patients, which indicated that the viral injury to the H7N9 patients was more severe.[16] In addition, H7N9 patients had similar patterns of leukopenia, lymphopenia, and thrombocytopenia and similar levels of creatine kinase, lactic dehydrogenase, alanine aminotransferase, and aspartic transaminase to those observed in the H1N1 patients. These experimental indexes were considered to be closely related to the severities of the H7N9 and H1N1 infections.[12,17]

The main manifestations on chest CT for both diseases were characterized by consolidations, ground-glass opacities (GGOs), and air bronchograms. Pleural effusion, interlobular septal thickening, and mediastinal or hilar lymphadenectasis were the second most common imaging abnormalities. The pleural effusion rate in the H7N9 group reached 88.9%, while the pleural effusion rate in the H1N1 group was only 7.7%, suggesting that the combination with pleural effusion might have a certain value in the differential diagnosis of the 2 diseases. During the follow-up period of the survivors, chest CT showed that the resolution of the lesions among the H7N9 patients was slow, which was consistent with the previously reported rate in the literature[18] and which was similar to the rate among the patients with avian influenza A (H5N1) viral infection.[19] In addition, pulmonary fibrosis changes were much more commonly observed in the H7N9 survivors. The main cause might have been the obviously prolonged viral shedding time during the H7N9 infection, which may have produced more severe damage to the lung tissue.[20] More observations are needed to clarify further imaging changes in such patients.

Notably, H7N9 influenza viral infection was associated with a significantly higher risk of the presence of severe ARDS. Specifically, as observed in our study, ARDS in the H1N1 group was mainly light and moderate, while ARDS in the H7N9 group was mainly severe, suggesting the relatively moderate conditions of the H1N1 patients.[21] Since ARDS in the H7N9 group was much more severe, the necessity for mechanical ventilation was much higher, but the treatments for mild and moderate ARDS of the 2 groups were mainly based on noninvasive positive pressure ventilation (NPPV). A multiple-center survey[22] indicated that when NPPV was applied as the first-line intervention for ARDS, intubation was avoided for 54% of treated patients, with less ventilator-associated pneumonia and a lower intensive care unit mortality rate. In addition, the multicenter trial reported by Zhan et al[23] showed that the early application of NPPV for mild ARDS improved PaO_2/FiO_2 with time and decreased the proportion of patients requiring intubation with a lower number of organ failures and a trend towards reducing inhospital mortality. In our research, most of the patients with mild and moderate ARDS and some with severe ARDS in both groups were treated with NPPV and ultimately cured, indicating that the use of NPPV for mild and moderate ARDS had a good curative effect. However, additional prospective and comparative trials that address the need for intubation and the mortality rate as the outcomes of interest for patients with viral pneumonia and ARDS are required.

5. Conclusions

The patients with H7N9 complicated by ARDS had much more severe diseases with worse outcomes than the patients with H1N1. More changes in pulmonary were observed in the patients with H7N9 at the convalescent stage, and thus, these patients should be carefully followed up to further clarify their outcomes. Additional studies are needed to further the understanding of ARDS in patients with influenza.

Author contributions

Conceptualization: J. Huang.
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