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Comparison of acute respiratory distress syndrome in patients with COVID-19 and influenza A (H7N9) virus infection

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ABSTRACT

Objectives: We aimed to compared the clinical features of acute respiratory distress syndrome (ARDS) induced by COVID-19 and H7N9 virus infections.
Methods: Clinical data of 100 patients with COVID-19 and 46 patients with H7N9 were retrospectively analyzed.
Results: Elevated inflammatory indices and coagulation disorders were more common in COVID-19-ARDS group than in the H7N9-ARDS group. The median interval from illness onset to ARDS development was shorter in H7N9-ARDS. The PaO_2/FiO_2 level was lower in H7N9-ARDS, whereas the Sepsis-related Organ Failure Assessment score was higher in COVID-19-ARDS. The proportion of patients with disseminated intravascular coagulation and liver injury in COVID-19-ARDS and H7N9-ARDS was 45.5% versus 3.1% and 28.8% versus 50%, respectively ($P < 0.05$). The mean interval from illness onset to death was shorter in H7N9-ARDS. A total of 59.1% patients with H7N9-ARDS died of refractory hypoxemia compared with 28.9% with COVID-19-ARDS ($P = 0.014$). Patients with COVID-19-ARDS were more likely to die of septic shock and multiple organ dysfunction compared with H7N9-ARDS (71.2% vs 36.4%, $P = 0.005$).
Conclusion: Patients with H7N9 were more susceptible to develop severe ARDS and showed a more acute disease course. COVID-19-ARDS was associated with severe inflammatory response and coagulation dysfunction, whereas liver injury was more common in H7N9-ARDS. The main causes of death between patients with the two diseases were different.

Introduction

Since December 2019, SARS-CoV-2, which is a highly pathogenic respiratory infectious virus, has caused a global pandemic. Patients with SARS-CoV-2 infection, which was named COVID-19, presented with mild illness during the early stage of disease but subsequently developed severe pneumonia, respiratory failure, and multiple organ dysfunction (MODS) in a relatively short time since illness onset (Huang *et al.*, 2020; Zhu *et al.*, 2020). The reported incidence of acute respiratory distress syndrome (ARDS) in patients with COVID-19 is approximately 41.8%, with a mortality rate of 52.4%. Patients with advanced age or underlying diseases are at a high risk of death, and ARDS is the main cause of death in these patients (Burki, 2020; Wu *et al.*, 2020).

Since March 2013, there have been five waves of H7N9 epidemics in mainland, China, presenting a high mortality of 40% (Wang *et al.*, 2017). Most cases presented severe disease, and moderate-severe ARDS was the most common complication. Refractory hypoxemia was the main cause of death reported in patients with H7N9 virus infection (Gao *et al.*, 2013).

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As two respiratory infectious viruses, we speculate that ARDS caused by different viruses may exhibit different characteristics. Thus, in this study, we compared and analyzed the clinical features of ARDS induced by the two viruses. To the best of our knowledge, this is the first study on this subject.

Materials and methods

Subjects and data collection

Clinical data of 100 patients with COVID-19 (including 66 ARDS cases) who were admitted to Tongji Hospital of Huazhong University of Science and Technology from February 2020 to March 2020 and 46 patients with H7N9 (including 32 ARDS cases) who were admitted to the First Affiliated Hospital of Soochow University from March 2013 to May 2017 were retrospectively reviewed. In all cases, the diagnosis was confirmed by polymerase chain reaction assay from pharyngeal swab, sputum, tracheal aspirate, or bronchoalveolar lavage fluid.

Definitions and diagnoses of ARDS and MODS and severity assessment of disease

The definitions and diagnostic criteria for ARDS, cardiac injury, septic shock, acute kidney injury, and disseminated intravascular coagulation (DIC) have been described in a previous study (Wang *et al.*, 2021). Owing to variability among studies, with respect to the criteria for liver injury, in the present study, liver injury was defined as levels of alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN) level or total bilirubin levels >2 times the ULN level (Siddiqui *et al.*, 2022). Gastrointestinal bleeding was defined as evidence of hematemesis, coffee-ground emesis, melena, maroon stools, or hematochezia (Martin *et al.*, 2020). The ratio of partial pressure of arterial oxygen and concentration of inspired oxygen (PaO_2/FiO_2) was used to evaluate respiratory failure. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sepsis-related Organ Failure Assessment (SOFA) score were used for the assessment of illness severity.

Statistical analysis

As our study was based on data obtained from different hospitals, there were differences with respect to detection methods used for laboratory tests and the normal reference range of various indexes; therefore, most laboratory indexes have been analyzed as a categorical variable (percentage of patients with deranged indexes, according to the respective reference levels). Other continuous variables are presented as mean ± standard deviation or median with interquartile range. Between-group differences with respect to continuous variables were assessed using the independent samples *t*-test or the Mann-Whitney *U* test. Between-group differences with respect to categoric variables were assessed using the chi-square test or Fisher's exact test. *P*-values less than 0.05 were considered indicative of statistical significance. All statistical analyses were performed using SPSS version 23.0 software.

Results

Clinical features of patients with COVID-19 and patients with H7N9 at admission

Data pertaining to the 100 patients with COVID-19 (including 66 ARDS and 34 non-ARDS cases) and 46 patients with H7N9 (including 32 ARDS and 14 non-ARDS cases) are summarized in Table 1. Elderly patients were significantly more common in the ARDS group than that in the non-ARDS group in both patients with COVID-19 and patients with H7N9. Interestingly, the proportion of male patients in H7N9 virus-induced ARDS group was significantly greater than that in the COVID-19-induced ARDS group (78.1% vs 50%, $P = 0.008$). The percentage of patients with high-grade fever and expectoration was higher in H7N9-ARDS group, whereas dry cough was more prevalent in the COVID-19-ARDS group. Other symptoms, such as fatigue, myalgia, and dyspnea, seemed more prevalent in H7N9-ARDS than in COVID-19-ARDS; however, the between-group difference was not statistically significant. The median time from onset of illness to admission in the COVID-19-ARDS group was significantly longer than that in the H7N9-ARDS group (11.0 vs 7.0 days, $P = 0.002$).

Laboratory indexes of patients with COVID-19 versus H7N9 infection at admission

The percentage of patients with leukocytosis and neutrophilia in COVID-19-ARDS group was significantly higher than that in COVID-19-non-ARDS group, as well as higher than that in H7N9-ARDS group; however, the percentage of patients with leukopenia was lower in the COVID-19-ARDS group (Table 2). The COVID-19-ARDS group had significantly more patients with lymphopenia and thrombocytopenia than the COVID-19-non-ARDS group. However, there was no significant difference with respect to these two indexes in H7N9 patients with or without ARDS.

Comparing the COVID-19-ARDS and H7N9-ARDS groups, the incidence of elevated alanine aminotransferase level was higher in the former group, and elevated aspartate aminotransferase level was higher in the latter group. The incidence of elevated lactate dehydrogenase, elevated C-reaction protein with 10 times the ULN, and elevated procalcitonin with 10 times the ULN was higher in patients with COVID-19 with ARDS than in patients with COVID-19 without ARDS; however, there was no significant difference in these respects between patients with H7N9 with or without ARDS.

Coagulation indexes, such as elevated prothrombin time, elevated fibrinogen, and elevated D-dimer were more prevalent in patients with COVID-19 with ARDS than in patients with COVID-19 without ARDS, and this difference were also observed between COVID-19-ARDS and H7N9-ARDS. However, there was no significant difference between patients with H7N9 with or without ARDS in these respects.

Interval from illness onset to ARDS development and severity of ARDS

The median time from onset of illness to ARDS development in patients with H7N9 was significantly shorter than in patients with COVID-19 (7.0 vs 9.5 days, $P = 0.018$) (Table 3). Notably, the SOFA score in patients with COVID-19-ARDS was higher than in patients with H7N9-ARDS; however, the APACHE II score showed no significant difference between the two groups. The PaO_2/FiO_2 level in patients with H7N9-induced ARDS was significantly lower in patients with COVID-19-induced ARDS (73.55 vs 144 mm Hg, $P < 0.001$). Comparing the severity of ARDS between the two groups, severe ARDS was found to be more common in patients with H7N9, whereas mild ARDS was more common in patients with COVID-19.

Complications of COVID-19 and H7N9 virus-induced ARDS

There was no significant difference between COVID-19-ARDS and H7N9-ARDS groups with respect to the proportion of patients with septic shock, cardiac injury, or gastrointestinal bleeding (Table 4). Notably, the proportion of patients with DIC was significantly higher in the COVID-19-ARDS group, whereas the incidence of liver injury was significantly higher in H7N9-ARDS group (45.5% vs 3.1%, $P < 0.001$; 28.8% vs 50%, $P = 0.04$).

Table 1
Clinical and epidemiological features of patients with COVID-19 versus patients with H7N9 virus infection at admission

Variables	COVID-19-ARDS (n = 66)	COVID-19-non-ARDS (n = 34)	P1 value	H7N9-ARDS (n = 32)	H7N9-non-ARDS (n = 14)	P2 value	P[a] value
Age (≥65 years)	39(59.1%)	13(38.2%)	0.048	16(50%)	2(14.3%)	0.011	0.395
Sex (male)	33(50%)	19(55.9%)	0.577	25(78.1%)	7(50%)	0.119	0.008
Clinical symptoms							
Temperature >39.0 °C	2(3.0%)	0(0%)	0.547	24(75%)	14(100%)	0.102	<0.001
Fatigue	43 (65.2%)	17(50%)	0.143	24(75%)	10(71.4%)	1	0.326
Anorexia	25(37.9%)	4(11.8%)	0.006	15(46.9%)	5(35.7%)	0.482	0.395
Myalgia	10(15.2%)	4(11.8%)	0.874	8(25%)	3(21.4%)	1	0.238
Dry cough	47(71.2%)	24(70.6%)	0.948	6(18.8%)	5(35.7%)	0.387	<0.001
Expectoration	25(37.9%)	14(41.2%)	0.749	20(62.5%)	8(57.1%)	0.732	0.022
Dyspnea	49(74.2%)	22(64.7%)	0.319	29(90.6%)	8(57.1%)	0.026	0.059
Abdominal pain	7(10.6%)	3(8.8%)	1	0(0%)	0(0%)	/	0.135
Diarrhea	17(25.8%)	11(32.4%)	0.487	4(12.5%)	1(7.1%)	0.982	0.134
Nausea	3(4.5%)	3(8.8%)	0.683	3(9.4%)	0(0%)	0.543	0.627
Vomiting	3(4.5%)	2(5.8%)	1	3(9.4%)	0(0%)	0.543	0.627
Underlying disease							
Hypertension	32(48.5%)	13(38.2%)	0.329	15(46.9%)	3(21.4%)	0.104	0.08
Diabetes	11(16.7%)	8(23.5%)	0.407	9(28.1%)	0(0%)	0.071	0.187
Chronic lung disease	7(10.6%)	1(2.9%)	0.342	5(15.6%)	0(%)	0.293	0.702
Chronic heart disease	10(15.2%)	3(8.8%)	0.564	1(3.1%)	0(0%)	1	0.153
Chronic renal disease	1(1.5%)	0(0%)	1	1(3.1%)	0(0%)	1	1
Chronic liver disease	1(1.5%)	0(0%)	1	2(6.3%)	0(0%)	1	0.248
Malignancies	4(6.1%)	1(2.9%)	0.846	1(3.1%)	0(0%)	1	0.897
Immunocompromised	1(1.5%)	1(2.9%)	1	1(3.1%)	0(0%)	1	0.549
Days from illness onset to admission	11.00 (5.75-16.00)	11.50 (9.75-15.25)	0.702	7.00 (5.00-9.75)	7.50 (5.00-9.00)	0.646	0.002

[a] Comparison between COVID-19-ARDS and H7N9-ARDSARDS: Acute respiratory distress syndrome.

Table 2
Laboratory indices of patients with COVID-19 versus H7N9 virus infection at admission

Indices	COVID-19-ARDS (n = 66)	COVID-19-non-ARDS (n = 34)	P1 value	H7N9-ARDS (n = 32)	H7N9-non-ARDS (n = 14)	P2 value	P[a] value
Blood counts							
Leukocytosis	31(47.0%)	3(8.8%)	<0.001	5(15.6%)	0(0%)	0.293	0.003
Leukopenia	3(4.5%)	3(8.8%)	0.683	10(31.3%)	8(57.1%)	0.098	0.001
Neutrophilia	44(66.7%)	9(26.5%)	<0.001	10(31.3%)	2(14.3%)	0.4	0.001
Neutropenia	1(1.5%)	2(5.9%)	0.553	3(9.4%)	2(14.3%)	1	0.194
Lymphopenia	57(86.4%)	21(61.8%)	0.002	30(93.8%)	13(92.9%)	1	0.586
Thrombocytopenia	21(31.8%)	4(11.8%)	0.028	14(43.8%)	5(35.7%)	0.611	0.248
Anemia	19(28.8%)	6(17.6%)	0.223	15(46.9%)	5(35.7%)	0.482	0.078
Serum biochemistry							
Albumin<30 g/L	24(36.4%)	3(8.8%)	0.003	14(43.8%)	4(28.6%)	0.332	0.482
Elevated TBIL	10(15.2%)	1(2.9%)	0.131	2(6.3%)	0(%)	1	0.351
Elevated ALT	34(51.5%)	10(29.4%)	0.035	9(28.1%)	6(42.9%)	0.523	0.029
Elevated AST	40(60.6%)	14(41.2%)	0.065	26(81.3%)	10(71.4%)	0.723	0.041
Elevated BUN	28(42.4%)	4(11.8%)	0.002	20(62.5%)	4(28.6%)	0.034	0.062
Elevated creatinine	27(40.9%)	10(29.4%)	0.259	8(25%)	5(35.7%)	0.699	0.123
Elevated LDH	59(89.4%)	25(73.5%)	0.04	31(96.9%)	13(92.9%)	0.521	0.382
Inflammatory markers							
CRP: 10 times the ULN	26(39.4%)	3(8.8%)	0.001	11(34.4%)	5(35.7%)	1	0.631
PCT: 10 times the ULN	16(24.2%)	0(0%)	0.002	4(12.5%)	0(0%)	0.415	0.176
Coagulation condition							
Elevated PT	44(66.7%)	6(17.6%)	<0.001	14(43.8%)	2(14.3%)	0.111	0.03
Elevated APTT	31(47.0%)	15(44.1%)	0.786	9(28.1%)	2(14.3%)	0.524	0.075
Elevated Fib	45(68.2%)	30(88.2%)	0.028	3(9.4%)	0(0%)	0.543	<0.001
Elevated D-dimer	58(87.9%)	23(67.6%)	0.015	18(56.3%)	6(42.9%)	0.403	<0.001

[a] Comparison between COVID-19-ARDS and H7N9-ARDSARDS: acute respiratory distress syndrome; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; CRP: C-reaction protein; PCT: procalcitonin; ULN: upper limit of normal; PT: prothrombin time; APTT: activated partial prothrombin time; Fib: fibrinogen.

Table 3
Development and severity of ARDS in patients with COVID-19 versus H7N9 virus infection

Indices	COVID-19-ARDS (n = 66)	H7N9-ARDS (n = 32)	*P*-value
Duration from onset to ARDS development	9.5(6-13)	7.0(5-9.75)	0.018
APACHE II score	22.19±6.91	20.44±5.08	0.159
SOFA score	10.06±2.88	8.34±4.01	0.017
PaO_2/FiO_2 (mm Hg)	144(98-224)	73.55(60.75-128.85)	<0.001
Mild ARDS	18(27.3%)	2(6.3%)	0.031
Moderate ARDS	31(47.0%)	11(34.4%)	0.237
Severe ARDS	17(25.8%)	19(59.4%)	0.001

COVID-19: Coronavirus disease 2019; ARDS: acute respiratory distress syndrome; PaO_2/FiO_2: partial pressure of arterial oxygen and the concentration of inspired oxygen; APACHE II: Acute Physiology and Chronic Health Evaluation-II; SOFA: Sepsis-related Organ Failure Assessment.

Table 4
Complications of patients with COVID-19-ARDS versus H7N9-ARDS

Indices	COVID-19-ARDS (n = 66)	H7N9-ARDS (n = 32)	*P*-value
Septic shock	48(72.7%)	21(65.6%)	0.47
Cardiac injury	52(78.8%)	23(71.9%)	0.449
Acute kidney injury	35(53.0%)	17(53.1%)	0.993
Liver injury	19(28.8%)	16(50.0%)	0.04
DIC	30(45.5%)	1(3.1%)	<0.001
Gastrointestinalbleeding	14(21.2%)	4(12.5%)	0.296

ARDS: Acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation.

Table 5
Treatment details and outcomes of patients with COVID-19-ARDS versus H7N9-ARDS

Variables	COVID-19-ARDS (n = 66)	H7N9-ARDS (n = 32)	*P*-value
Antiviral agents	46(69.7%)	32(100%)	<0.001
Antibacterial agents	63(95.5%)	32(100%)	0.549
Antifungal agents	7(10.6%)	21(65.6%)	<0.001
Glucocorticoids	56(84.8%)	30(93.8%)	0.351
Immunoglobulin	56(84.8%)	21(65.6%)	0.03
HFNC	16(24.2%)	2(6.3%)	0.031
NIV	19(28.8%)	12(37.5%)	0.384
IV	52(78.8%)	26(81.3%)	0.777
ECMO	4(6.1%)	3(9.4%)	0.858
14-day mortality	7(10.6%)	6(18.8%)	0.425
28-day mortality	29(43.9%)	18(56.3%)	0.253
Days from onset to death	25.50±9.52	19.86±8.90	0.02
Main cause of death			
Refractory hypoxemia	15(28.9%)	13(59.1%)	0.014
Acute heart failure	0(0%)	1(4.5%)	0.655
Malignant arrhythmia	0(0%)	1(4.5%)	0.655
Septic shock and MODS	37(71.2%)	8(36.4%)	0.005

ARDS: acute respiratory distress syndrome; HFNC: high-flow nasal cannula; NIV: noninvasive ventilation; IV: invasive ventilation; ECMO, extracorporeal membrane oxygenation; MODS: multiple organ dysfunction.

Treatment and outcome of patients with COVID-19 and H7N9 virus-induced ARDS

All patients in the H7N9-ARDS group were administered antiviral agents as against 69.7% in the COVID-19-ARDS group (P <0.001) (Table 5). A significantly greater proportion of patients in the H7N9-ARDS group were administered antifungal agents compared with that in the COVID-19-ARDS group (65.6% vs 10.6%, P <0.001). However, the proportion of patients who were administered immunoglobulins and high-flow nasal cannula in the COVID-19-ARDS group was significantly higher than in the H7N9-ARDS group.

A total of 52 patients in the COVID-19-ARDS group and 23 patients in the H7N9-ARDS group died. One patient in H7N9-ARDS group died 10 months after illness onset, and we excluded this case because the cause of death was not related with H7N9 virus infection. The 14-day mortality and 28-day mortality in the H7N9-ARDS group seemed higher than that in COVID-19-ARDS group, but the between-group difference was not statistically significant. The mean interval from onset of illness to death in the H7N9-ARDS group was significantly shorter than in the COVID-19-ARDS group (19.86 vs 25.5 days, $P = 0.02$). Refractory hypoxemia was a significantly more common cause of death in H7N9-ARDS than COVID-19-ARDS (59.1% vs 28.9%, $P = 0.014$). In the COVID-19-ARDS group, septic shock and MODS were the main cause of death and seemed more common than in the H7N9-ARDS group (71.15% vs 36.36%, $P = 0.005$).

Discussion

In a previous study, patients with H7N9 were found to have more obvious symptoms, such as fever, fatigue, myalgia, and sputum production; whereas dry cough was the most common symptom in patients with COVID-19, with incidence rates ranging from 59.4-82% (Deng *et al.*, 2020; Li and Ma, 2020). Gao *et al* reported that hospitalized patients with H7N9 mainly presented with fever and cough, and 55.9% patients had expectoration (Gao *et al.*, 2013). Consistent with previous study, high-grade fever and expectoration were more common in patients with H7N9-ARDS in our study, whereas dry cough was more common in patients with COVID-

19-ARDS. Dry cough during viral infection likely indicates less severe vascular endothelial injury and less severe exudation in the alveolar space (Li and Ma, 2020), which partly explains the higher PaO_2/FiO_2 level and more mild ARDS in patients with COVID-19-ARDS in our study than in patients with H7N9-ARDS. In our study, the interval from onset of illness to admission in the COVID-19-ARDS group was longer than that in the H7N9-ARDS group. This was likely attributable to the milder symptoms of COVID-19 in the early stage of disease; moreover, the sudden outbreak of COVID-19 in Wuhan City, China caused shortage of medical resources, which may have prevented timely hospitalization of some patients.

The median time from onset of illness to ARDS development in our study was 9.5 days for COVID-19 versus 7 days for patients with H7N9. This suggests that there may be an extra therapeutic time window in COVID-19 and that comprehensive treatment including antiviral therapy, should be administered as early as possible. In the absence of timely treatment, some patients with mild disease may develop severe pneumonia, ARDS, and even death. The time window for ARDS prevention and therapy in patients with H7N9 seems to be shorter than for patients with COVID-19. In a study by Yang *et al* (Yang *et al.*, 2015), 24 of 26 patients with H7N9 developed ARDS (14 severe ARDS) over a median time of 6 days after onset of illness. In another study, moderate-severe ARDS was found to be common respiratory complication in patients with H7N9 (Li *et al.*, 2018; Wang *et al.*, 2016). Studies have shown that H7N9 virus infection is more likely to cause damage to both capillary endothelial cells and alveolar epithelial cells, resulting in increased permeability of alveolar membrane, deteriorating pulmonary interstitial edema and alveolar edema (Bein *et al.*, 2016; Zheng *et al.*, 2020). These pathologic changes can lead to severe pulmonary shunt and impaired diffusion, causing refractory hypoxemia. In our study, severe ARDS was more common in patients with H7N9 than in patients with COVID-19. The mean time from onset of illness to death in the H7N9-ARDS group was approximately 5 days shorter than that in the COVID-19-ARDS group, and refractory hypoxemia was the leading cause of death in the H7N9-ARDS group.

In our study, the proportion of patients with liver injury in the H7N9-ARDS group (50%) was higher than that in the COVID-19-ARDS group (28.8%). Liver injury has been commonly reported in previous studies of patients with H7N9 (Zhang *et al.*, 2014). Liver is extremely sensitive to hypoxic environment due to its multiple and complex biological and metabolic processes (Gonzalez *et al.*, 2018). We considered that severe refractory hypoxemia mainly accounted for the high incidence of liver injury in H7N9-ARDS. Moreover, excessive inflammatory response to viral infection and ARDS development can also be an important contributor. Notably, we found that patients with COVID-19-ARDS had significantly higher incidence of coagulation disorders, and that these patients were more prone to develop DIC than patients with H7N9. Coagulation disorders are common in patients with COVID-19, especially in severe disease, and a previous study indicated definitive evidence of DIC in fatal cases (Jiang *et al.*, 2021). During the process of ARDS and sepsis, uncontrollable inflammatory response is a trigger for DIC (Asakura and Ogawa, 2021). Abnormal coagulation indexes, such as thrombocytopenia, prolonged prothrombin time, and activated partial prothrombin time and elevated D-dimer levels, were relatively common in patients with severe H7N9. However, DIC in patients with H7N9 has rarely been reported to date, which is probably attributable to the limited number of H7N9 cases worldwide (1568 laboratory-confirmed cases) (Wang *et al.*, 2020) and the low incidence of DIC in patients with H7N9 generally (Chen *et al.*, 2013a; Chen *et al.*, 2013b).

The percentage of patients with H7N9 who were administered antiviral therapy (100%) was significantly higher than that in patients with COVID-19 p (69.7%). As one of the influenza A virus, neuraminidase inhibitors are effective against H7N9 in most cases. Therefore, antiviral therapy was extensively used in early stage during the influenza epidemic seasons in suspected and confirmed cases. However, to date, there is no robust evidence of the efficacy of any specific antiviral against SARS-CoV-2 infection. In our study, the percentage of patients who received antifungal treatment in the H7N9 group (65.6%) was greater than that in COVID-19 group (10.6%). The complication of fungal infection during the annual influenza virus epidemics has aroused considerable attention. According to a study, the incidence of pulmonary aspergillosis in patients with severe influenza was 19%, with a 90-day mortality of 51% (Schauwvlieghe *et al.*, 2018). The patients with COVID-19 enrolled in our study were from the early phase of the first wave of the COVID-19 pandemic (February to March 2020), during which the possibility of superimposed fungal infection may not have received great attention. According to a recent study, the incidence of COVID-19 associated pulmonary aspergillosis ranges from 11.1-34.4%, with a high mortality of 55.2%. This prompted increased attention to the risk of fungal infection in patients with severe COVID-19 (Feys *et al.*, 2021; Lahmer *et al.*, 2021).

Patients with COVID-19-ARDS in our study showed a higher incidence of increased inflammatory indices, coagulation disorders, and higher SOFA scores. A previous study indicated that patients with COVID-19 are prone to MODS (Wu *et al.*, 2020). Angiotensin-converting enzyme 2, a functional receptor on cell surface, which facilitates the entry of SARS-CoV-2 into host cells, plays an important role in the pathogenesis of COVID-19. Angiotensin-converting enzyme 2 is widely expressed in human tissues and organs (e.g., nasal mucosa, lung, heart, and kidney), which enhances the organ susceptibility to this viral infection (Beyerstedt *et al.*, 2021). Patients with severe COVID-19 also develop conspicuous and complex immune disorders, which facilitates the occurrence of secondary infection in clinical settings (Giamarellos-Bourboulis *et al.*, 2020). Kreitmann *et al* reported high incidence of coinfections in patients with COVID-19; however, this phenomenon has not been found in influenza virus infection (Kreitmann *et al.*, 2020). These previous studies may partly explain why more patients with COVID-19 in our study died of septic shock and MODS than patients with H7N9-ARDS.

Some limitations of our study should be considered while interpreting the results. First, we mainly performed rate comparisons between groups because the data were retrieved from different hospitals. Comparison of mean and median values is also very important in data analysis; however, this approach is not viable if the indexes are obtained using different test methods. Second, owing to the retrospective study design, the effect of some missing data on our results cannot be ruled out. Comparison of inflammatory cytokine levels at admission and their dynamic changes during hospitalization between patients with COVID-19 and H7N9 would provide important clinical and pathophysiologic information. However, cytokine levels in sputum or bronchoalveolar lavage fluid were not routinely measured at our center during the past five waves of H7N9 epidemic. Third, the sample in our study was relatively small, especially in the H7N9 group, which may have limited the generalizability of our results. However, to the best of our knowledge, this study has the largest sample size (46 cases) in a study of clinical features in patients with H7N9 virus-induced ARDS to date (Li *et al.*, 2018). Despite these limitations, our results may further improve the understanding and management of ARDS caused by SARS-CoV-2 and H7N9 viruses.

Conclusion

In this study, we retrospectively investigated the clinical features of ARDS induced by COVID-19 and H7N9 virus infection. We found that ARDS induced by H7N9 virus infection can occur in a

relatively shorter timer after illness onset than ARDS induced by COVID-19. Moreover, H7N9-ARDS was associated with greater aggravation of PaO_2/FiO_2 level and higher risk for severe ARDS. DIC was more common in patients with COVID-19-ARDS, whereas liver injury was more common in H7N9-ARDS. Refractory hypoxemia was a leading cause of death in H7N9-ARDS, whereas septic shock and MODS were the main causes of death in COVID-19-ARDS. The mean interval from illness onset to death in H7N9-ARDS was significantly shorter than in COVID-19-ARDS.

Consent for publication

Not applicable.

Conflicts of interest

The authors have no competing interests to declare.

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Ethical approval

This study was exempted from institutional review board assessment because of the retrospective design and lack of interference with the diagnosis and treatment.

The ethics commission of the First Affiliated Hospital of Soochow University and the Tongji Hospital of Huazhong University of Science and Technology approved this study.

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