

Comparison of Hospitalized Patients with Severe Pneumonia Caused by COVID-19 and Highly Pathogenic Avian Influenza (H7N9): A Retrospective Study from A Designated Hospital

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Research

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Abstract

Background: Considerable attention has been focused on clinical features of Coronavirus Disease 2019 (COVID-19), it is also important for clinicians to differentiate it from influenza virus infections.

Methods: The clinical data of 23 cases of H7N9 and 23 cases of COVID-19 with severe pneumonia were collected. The comparisons were performed with the *t* test, Mann-Whitney U test, Fisher exact test or the chi-squared test, and multivariable logistic regression analysis.

Results: All of the cases were under the circumstance of sufficient medical staff and medical supplies. Radiologically, severe COVID-19 patients had less consolidation and pleural effusion, but more crazy-paving pattern than severe H7N9 patients ($p < 0.05$). Clinically, compared to severe H7N9, severe COVID-19 patients were more inclined to suffer to relative better disease severity score, less secondary bacterial infection, a shorter time to beginning absorption on CT, but a longer duration of viral shedding from the admission ($p < 0.05$). Although more severe H7N9 patients needed non-invasive respiratory support, these two groups ultimately yielded comparable mortality. Based on multiple logistic regression analysis, severe COVID-19 infection was associated with a lower risk of the presence of severe ARDS (OR 0.964, 95% [CI] 0.931-0.998, $p = 0.040$), but exhibited longer duration of viral shedding (OR 0.734, 95% [CI] 0.550-0.980, $p = 0.036$) than severe H7N9 infection.

Conclusion: Although the conditions of severe H7N9 patients seemed to be more critical than those of severe COVID-19 patients, the relatively lower mortality of these two severe cases is to be expected in context of sufficient medical supplies.

Introduction

The coronavirus disease 2019 (COVID-19), which is caused by 2019 novel coronavirus (2019-nCoV) imposes a grand immediate challenge for global public health. So far, COVID-19 has spread to many other countries with thousands of infected cases.

Despite many articles have established the clinical features of COVID-19 patients [1–3], comparison of hospitalized patients with severe pneumonia caused by COVID-19 and highly pathogenic avian influenza (HPAI) has not been reported yet. Because of distinct treatments and prognoses, it is important for clinicians to accurately identify these two respiroviral infections via their differential clinical manifestations [4–5].

In this study, we systematically compared severe pneumonia patients infected with COVID-19 versus H7N9 viruses in terms of clinical presentations, laboratory tests, virologic shedding, image characteristics, complication and clinical outcome in context of critical bundle and intensive management, in order to provide some guidance for their differential consideration.

Methods

Patients

All of the severe COVID-19 pneumonia and severe H7N9-induced pneumonia subjects were confirmed by laboratory tests and were hospitalized at The Fifth People's Hospital of Suzhou. The date of disease onset and hospital admission date, as well as the severity of disease were recorded. The severe COVID-19 pneumonia cases were hospitalized from January 2020 to March 2020, who was defined according to the diagnostic and treatment guideline for COVID-19 pneumonia issued by the National Health and Family Planning Commission of P.R.China (Version 1–7). The severe H7N9 cases were hospitalized from 2014 to 2016, who met the following criteria published by the National Health and Family Planning Commission of P.R.China (the 2nd edition, 2013).

Data collection

The data of all patients were collected from an electronic case report form and included the following: demographic characteristics (age and sex), comorbidities, clinical symptoms, laboratory tests (blood routine test, arterial blood gas analysis (ABG), and blood chemistry), virologic test, microbiological findings and images of the lung (chest CT). Antimicrobiological therapy, respiratory support, complications and outcomes were also recorded. The Ethics Committee of The Fifth People's Hospital of Suzhou approved this study (2020-005).

Study design

This was a retrospective case-control study. We compared two independent cohorts of patients infected with either COVID-19 or H7N9 in terms of initial onset, further course and outcome, which included clinical presentations at diagnosis, virologic shedding, peak values of laboratory tests, time course of image characteristics, the worst SOFA and PSI score, extrapulmonary complication, secondary bacterial infection, intensive therapy, and clinical outcome.

Definitions

Septic shock was defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock [6]. Secondary bacterial infection was diagnosed when patients showed clinical symptoms or signs of pneumonia or bacteraemia and a positive culture of a new pathogen was obtained from lower respiratory tract specimens (qualified sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples after admission [7]. Extrapulmonary complication was defined as: i acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines; ii acute cardiac injury was diagnosed if serum levels of cardiac biomarkers (eg, high-sensitive cardiac troponin I) were above the 99th percentile upper reference limit; iii acute liver injury was diagnosed if serum levels of ALT or TBIL was above the 2-fold of upper reference limit; iv coagulopathy was defined as a 3-second extension of Prothrombin time (PT) [8–9]. RNA shedding duration was defined the interval from admission to the date of the first RNA negative result before discharge.

Statistical analysis

Data were described as the mean \pm sd, median (interquartile range, IQR) or number (%). The comparisons of the features between the different subtypes of virus (H7N9 and COVID-19) were performed with the *t* test to compare the mean \pm sd of continuous variables, Mann-Whitney U test to compare the medians of continuous variables, and Fisher exact test or the chi-squared test to compare proportions. To identify risk factors associated with severe COVID-19 infection, we performed a multivariable logistic regression analysis adjusted for baseline covariates. Statistical analyses were performed using SPSS, version 24.0 for Windows, probabilities were 2-tailed, and a 2-tailed *p* value of < 0.05 was considered significant.

Results

Dermatologic feature

As shown in Table 1, the median age of severe COVID-19 patients was 49 years old, which was comparable to that of severe H7N9 patients (54 years old, $p > 0.05$). The proportion of males in severe COVID-19 patients was 69.57%, which was also comparable to that of severe H7N9 patients (65.22%, $p > 0.05$). 26.09% of severe COVID-19 patients has a history of underlying diseases, whereas that of severe H7N9 patients was significantly higher, at 56.52% ($p = 0.04$). The majority of severe H7N9 patients suffered to hypertension ($p < 0.01$). There was no significant difference in the history of diabetes, chronic-airway diseases between the two groups ($p > 0.05$).

Table 1
Characteristics of subjects.

	H7N9	COVID-19	<i>p</i> value
Age (median, ys)	54 (35–66)	49 (38–60)	0.38
Male (%)	65.22	69.57	0.75
Underlying disease (%)	56.52	26.09	0.04
Hypertension	52.17	8.70	< 0.01
HBV	8.70	0	0.47
Diabetes	13.04	13.04	1.00
Chronic-airway diseases	0	4.34	1.00
Clinical manifestations (%)			
Fever	100	100	NA
Cough	100	82.61	0.12
Dyspnea	86.96	30.43	< 0.01
Myalgia	47.82	17.39	0.03
Nasal congestion	30.43	0	0.01
Pharyngodynia ()	21.74	8.70	0.41
Gastrointestinal symptoms	17.39	8.70	0.66
Hemoptysis	0	0	NA

Clinical manifestations at diagnosis

At admission (Table 1), almost all severe H7N9 and severe COVID-19 patients presented with fever and cough (100% vs 100%, 100% vs 82.61%, $p > 0.05$ for each). Furthermore, 86.96%, 47.82% and 30.43% of severe H7N9 patients had dyspnea, myalgia and nasal congestion, which was significantly more than those of severe COVID-19 patients (30.43%, 17.39%, 0, $p < 0.05$ for each). The proportions of pharyngodynia (21.74%) and gastrointestinal symptoms (17.39%) in with severe H7N9 patients were comparable to those of severe COVID-19 patients (8.70%, 8.70%), whereas hemoptysis was less common in both two groups.

Laboratory results

Over the course of the hospitalization (Table 2), acute kidney injury, acute liver injury occurred in 8.07% and 69.57% of patients with severe H7N9, which was comparable to those of severe COVID-19 patients

(13.04%, 78.26%, $p > 0.05$ for each). However, 69.57% of severe H7N9 patients suffered to acute cardiac injury, which was significantly higher than the proportion of 4.34% in severe COVID-19 patients ($p < 0.01$). Following biochemical testing, the peak level of alanine aminotransferase (ALT), total bilirubin (TBIL), creatinine (Cr), and troponin I (TnI) in severe COVID-19 patients were comparable to those in severe H7N9 patients ($140.9.7 \pm 19.11$ vs 132.7 ± 19.64 U/L, 22.18 ± 2.80 vs 21.19 ± 1.62 $\mu\text{mol/L}$, 79.52 ± 5.22 vs 71.74 ± 3.72 $\mu\text{mol/L}$, 18.65 ± 9.36 vs 286.50 ± 181.1 pg/ml, respectively, $p > 0.05$ for each).

Table 2 Over disease's course between of severe H7N9 and COVID-19 patients.

	H7N9	COVID-19	p value
Onset to confirm diagnosis (d)	8.39±0.59	8.09±0.72	0.74
Severity*			
Sepsis shock (%)	13.04	0	0.23
SOFA score	5.35±0.77	3.57±0.31	0.03
PSI score	89.96±7.72	61.22±3.00	<0.01
OI	133.70±11.18	228.30±11.01	<0.01
Complication (%)			
Lymphopenia	100	82.61	0.12
Thrombocytopenia	65.22	47.83	0.23
Acute kidney injury	8.70	13.04	1.00
Acute liver injury	69.57	78.26	0.50
Acute cardiac injury	69.57	4.34	<0.01
Coagulation	21.74	0	0.06
Laboratory test*			
Ly ($\times 10^9/\text{ml}$)	0.44±0.39	0.71±0.06	<0.01
PLT ($\times 10^9/\text{ml}$)	149.2±18.67	157.8±11.34	0.69
ALT (U/L)	132.7±19.64	140.9±19.11	7.67
TBIL (mmol/l)	21.19±1.62	22.18±2.80	0.76
TnT (ng/ml)	286.5±181.1	18.65±936	0.15
D-dimer ($\mu\text{g/ml}$)	5447±1094	1914±426.5	<0.01
PT (s)	14.67±0.74	12.47±0.36	<0.01
Cr ($\mu\text{mol/l}$)	71.74±3.72	79.52±5.22	0.23
Positive bacterial culture (%)			
Gram-pos	34.78	4.34	0.03
Gram-neg	4.34	4.34	1.00
Radiologic findings			
Ground-glass opacity	60.87	43.48	0.24
Crazy-paving pattern	0	26.09	0.03
Consolidative	100	60.87	<0.01
Pleural effusion	47.83	0	<0.01

*, minimal or peak value of the index over disease's course.

Both severe COVID-19 and severe H7N9 patients exhibited impairments in coagulation. However, significantly increase of peak levels of D-dimer and Prothrombin time (PT) were associated with severe

H7N9 patients compared to severe COVID-19 patients (5447 ± 1094 vs 1914 ± 426.5 mg/L, 14.67 ± 0.74 vs 12.47 ± 0.17 sec, $p < 0.05$ for each).

In terms of blood cell counting, lymphopenia was observed in most severe COVID-19 (86.96%) and severe H7N9 patients (100%, $p > 0.05$), but the minimal level of lymphocytes in severe COVID-19 patients were higher than those in severe H7N9 patients (0.71 ± 0.06 vs $0.44 \pm 0.39 \times 10^9/L$, $p < 0.05$).

Thrombocytopenia was observed in 47.82% of severe COVID-19 and 65.28% of severe H7N9 patients ($p < 0.05$), but the minimal level of platelet in severe COVID-19 patients were comparable to those in severe H7N9 patients (157.80 ± 11.34 vs $149.20 \pm 18.67 \times 10^9/L$, $p = 0.69$).

Worst Oxygenation Index (OI) during the hospitalization predicts deteriorated respiratory failure. The minimal level of OI in severe COVID-19 patients was 228.30 ± 11.01 mmHg, which was significantly higher than the 113.7 ± 11.18 mmHg of severe H7N9 patients ($p < 0.05$).

Imaging findings

In terms of imaging characteristics (Table 2), ground-glass opacity in initial chest CTs was common in COVID-19 patients (43.48%) and in H7N9 patients (60.87%, $p > 0.05$). In contrast, consolidation and pleural effusion were more common in H7N9 patients than in COVID-19 patients ($p < 0.05$ for each), crazy-paving pattern was less seen in H7N9 patients ($p < 0.05$).

Further course and intensive treatment

Over the course of the viral infections (Table 3), septic shock occurred in 13.04% of patients with severe H7N9. There was no significant difference in the duration of onset to ARDS between severe H7N9 and severe COVID-19 patients (8.39 ± 0.59 days, 8.09 ± 0.72 days, $p = 0.74$). The highest sequential organ failure assessment (SOFA) score and pneumonia severity index (PSI) score of severe COVID-19 patients were 3.57 ± 0.31 and 61.22 ± 2.99 , respectively, which were lower than the scores of 5.35 ± 0.77 ($p = 0.04$) and 89.96 ± 7.72 ($p = 0.00$) for severe H7N9 patients.

Table 3
Treatment and prognosis of two groups.

	H7N9	COVID-19	<i>p</i> value
Respiratory support (%)	69.57	21.74	< 0.01
NPPV	13.04	0	0.23
IMV			
Respiratory support failure (%)			
NPPV	4.35	0	1.00
IMV	13.04	0	0.23
CRRT (%)	13.04	0	0.23
Duration of virus shedding (d)	9.86 ± 0.81	13.91 ± 1.56	0.03
The time to beginning absorption on CT (d)	11.64 ± 0.83	9.13 ± 0.70	0.02
Glucocorticoid (%)	95.65	82.61	0.34
LMWH (%)	34.78	43.48	0.55
Mortality (%)	13.04	0	0.23

All patients have received medical bundle intervention, including antimicrobial therapy, fluid administration, respiratory support, or steroid therapy.

The two groups presented with a variety of accompanying secondary bacterial infection. 39.13% of severe H7N9 patients had positive culture of pathogen isolated from qualified lower respiratory tract specimens, whereas that of severe COVID-19 patients was significantly lower (8.70%, $p < 0.05$).

In terms of respiratory support, during the entire process of treatment, the proportions of severe H7N9 patients who received non-invasive mechanical ventilation (NIV) was significantly higher than that of COVID-19 patients (69.57% vs 21.74%, $p < 0.05$). The failure rates of NIV in severe H7N9 patients were comparable to those in COVID-19 patients (4.35% vs 0%, $p > 0.05$).

In addition to treatments above, 82.61% of COVID-19 patients received glucocorticoids, which was comparable to the proportion of 95.65% in H7N9 patients ($p > 0.05$). Low-molecular-weight Heparin was administered in 43.48% of COVID-19 patients, which also was comparable to that administered to H7N9 patients (34.78%, $p < 0.001$).

Virologic outcomes and prognosis

All of the patients received antiviral therapies. Oseltamivir was administered in all of the H7N9 patients. However, COVID-19 patients had a variety of antiviral treatments, included 43.48% with lopinavir/ritonavir,

8.70% with arbidol, and 47.83% with combination. The duration of severe COVID-19 RNA shedding from the admission was 13.91 ± 1.56 days, which was longer than that of severe H7N9 patients (9.86 ± 0.81 days, $p = 0.03$).

Based on the follow-up of chest CT, the time to beginning absorption on chest CT (TTBAC) was established. Severe H7N9 patients have longer TTBAC than that in severe COVID-19 patients (11.64 ± 0.83 vs 9.13 ± 0.70 days, $p = 0.02$).

In terms of prognoses, although the in-hospital mortality of H7N9 patients with ARDS was 13.04%, it did not reach the statistical significance when compared to COVID-19 patients (0 , $p < 0.001$).

Multivariate analysis

Based on multiple logistic regression analysis, compared with parameters in severe H7N9 patients, severe COVID-19 patients were associated with a lower risk of the presence of severe ARDS (OR 0.964, 95% [CI] 0.931–0.998, $p = 0.040$), but exhibited longer duration of viral shedding (OR 0.734, 95% [CI] 0.550–0.980, $p = 0.036$) than severe H7N9 infection (Table 4).

Table 4 Multivariate analysis of independent risk factors for differentiating COVID-19 from H7N9.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, y	1.021(0.983-1.061)	0.286		
Male	0.820 (0.239-2.820)	0.753		
Duration of virus shedding (d)	0.883 (0.785-0.993)	0.038	0.734 (0.550-0.980)	0.036
SOFA score	1.361 (0.971-1.908)	0.074		
PSI score	1.059 (1.017-1.102)	0.005	0.970 (0.879-1.071)	0.546
OI	0.971 (0.956-0.987)	<0.001	0.964 (0.931-0.998)	0.040
Ly ($\times 10^9$ /ml)	0.007 (0.000-0.184)	0.003	0.004 (0.000-8.010)	0.153
PLT ($\times 10^9$ /ml)	0.998 (0.990-1.006)	0.687		
ALT (U/L)	0.999 (0.993-1.005)	0.761		
TBIL (mmol/l)	0.991 (0.939-1.047)	0.755		
D-dimer (μ g/ml)	1.000 (1.000-1.001)	0.012	1.001 (1.000-1.001)	0.086
TnT (ng/ml)	1.026 (1.004-1.048)	0.020	1.000 (0.983-1.018)	0.970
Cr (μ mol/l)	0.983 (0.955-1.011)	0.233		

Discussion

In this study, we compared the clinical features and courses of patients with severe pneumonia caused by COVID-19 and highly pathogenic avian Influenza (H7N9). As sufficient medical staff and medical supplies have affected the treatments and prognoses of severe cases, this retrospective study was conducted in a resident designated hospital, where medical resources reached standardized respiratory support in accordance with related guidelines.

Because of different therapies, it is important to differentiate these two diseases via clinical presentations. We found that compared with features in H7N9 patients, COVID-19 patients were less inclined to exhibit dyspnea, myalgia, and nasal congestion. Therefore, we speculate from previous research that severe H7N9 infection may present as more systemic and catarrh symptoms compared with the COVID-19 infection. Furthermore, based on the proportions of underlying diseases in these two groups, it was indicated that the combination of underlying diseases had a significant effect on the severities of H7N9 infection [1–5].

The main manifestations on chest CT for both diseases were characterized by ground-glass opacities (GGOs) [10]. Additionally, we found that crazy-paving pattern was more common in severe COVID-19 patients than in H7N9 patients, whereas consolidation and pleural effusion were more frequent in severe H7N9 patients. It was suggested that the combination of radiologic findings might have a certain value in the differential diagnosis of the two diseases.

Clinically, although severe COVID-19 patients had similar extra-pulmonary complication to those observed in the severe H7N9 patients, they were less inclined to suffer to secondary bacterial infection, severe thrombocytopenia, acute cardiac injury and impairments in coagulation. The majority of patients had increased coagulation activity, marked by increased D-dimer concentrations. High levels of D-dimer have a reported association with 28-day mortality in patients with infection or sepsis [11]. These experimental indexes were considered to be closely related to the severities of the severe infections [9, 12].

In term of disease severity, duration from the onset to confirmed diagnosis of ARDS in severe H7N9 and COVID-19 patients was comparable. However, severe COVID-19 patients were more inclined to suffer to relative better disease severity score. Also, according to the $\text{PaO}_2/\text{FiO}_2$ in severe COVID-19 patients, the corresponding OI was significantly higher than that of severe H7N9 patients, suggesting the relatively moderate conditions of the severe COVID-19 patients. As supported, serial chest CT showed that the absorption of the lesions among the H7N9 patients was slow. The main cause might have been more severe damage to the lung tissue.

There are still no specific antiviral medicines or vaccines recommended for COVID-19 infection. Under the circumstances, comparison of duration of virus shedding between severe COVID-19 and H7N9 infection may produce more interesting findings. Surprisingly, the severe COVID-19 group had longer duration of viral shedding from the admission than the severe H7N9 group. This has important implications for the guidance around the length of antiviral treatment.

We also found that severe COVID-19 patients received a wider variety of treatments that were similar to severe H7N9 patients. The application of glucocorticoids and LMWH were both common in COVID-19 and H7N9 patients in our present study. The treatments for ARDS of the two groups were mainly based on NPPV. More of the patients with severe H7N9 needed NPPV and ultimately cured. However, additional prospective and comparative trials that address the need for intubation and the mortality rate are required [13–14].

Taken together, compared to COVID-19, patients with H7N9 complicated by severe pneumonia had much more severe disease. Given sufficient medical staff and medical supplies, the relatively lower mortality rate of these two severe cases is to be expected. However, there were some limitations of our present study. First, this was a retrospective study that included data from one independent single-center cohorts, which may have resulted in unavoidable bias. Second, more observations are needed to clarify further clinical features by a large scale of investigation.

Abbreviations

ARDS: acute respiratory distress syndrome; CI: confidence interval; COVID-19: Coronavirus Disease 2019; CT: computed tomography; GGOs: ground-glass opacities; HAP: hospital-acquired pneumonia; HPAI: highly pathogenic avian influenza; ICU: intensive care unit; IQR: interquartile range; NPPV: noninvasive positive pressure ventilation; OR: odds ratio; PSI: pneumonia severity index; RT-PCR: reverse transcription polymerase chain reaction; SOFA: sequential organ failure assessment

Declarations

Acknowledgment

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Authors' contributions

T.P.J and C.C. conceived the idea, designed, and supervised the study, drafted the manuscript. G.B.B. and Y.L. collected data and had full access to all of the data and took responsibility for the integrity of the data. Z.X.Y. analyzed data and performed statistical analysis. All of the authors reviewed and approved the final version of the manuscript.

Finding

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Availability of data and materials

All data generated during this study are included in this article.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of our Institute of The Fifth People's Hospital of Suzhou (2020–005).

Consent for publication

In this retrospective small-scale study, written informed consent from the patients were waived, which was approved by the Ethics Committee of our Institute of The Fifth People's Hospital of Suzhou (2020–005).

Competing interests

The authors declare that they have no competing interests.

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