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Comparative analysis of elderly hospitalized patients with COVID-19 or influenza A H1N1 virus infections

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ABSTRACT

Objectives: This study aimed to investigate the differences between elderly patients hospitalized with COVID-19 or influenza A H1N1 virus infections.
Methods: We contrasted two absolute groups of patients (age ≥60 years) infected with either COVID-19 (n = 222) or influenza A H1N1 virus infections (n = 96). Propensity score matching was used to reduce the imbalance between the two matched groups. The clinical features, imaging presentations, therapies, and prognosis data were compared between the two groups.
Results: The patients with influenza showed higher proportions of cough, expectoration, fatigue, and shortness of breath. Higher counts of lymphocytes, hemoglobin, and creatine kinase and lower counts of white blood cells, neutrophils, blood urea nitrogen, and C-reactive protein were found in the patients with COVID-19. Regarding the imaging characteristics, bilateral pneumonia was the most abnormal pattern in the two groups of patients. The incidence of acute respiratory distress syndrome or death was lower among the patients with COVID-19.
Conclusion: The clinical manifestations of patients with COVID-19 are more concealed than those of patients with influenza. Fewer symptoms of sputum production, fatigue, and shortness of breath, combined with lower counts of white blood cells, neutrophils, and C-reactive protein are the possible predictive factors of COVID-19 among elderly patients.

Introduction

The SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and influenza A viruses are major pathogens that damage the respiratory system and can produce outbreaks of SARS, MERS, COVID-19, and influenza A H1N1 virus pneumonia, respectively. SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus are from the same genus and share many virological and epidemiological similarities. However, COVID-19 shows more similarities with influenza A H1N1 virus infections in the pattern and scale of spread than with SARS or MERS. For example, COVID-19 has higher proportions of asymptomatic and mild infections than SARS and MERS, which is similar to influenza A H1N1 virus infections. Both the COVID-19 and influenza A H1N1 viruses exhibit high viral shedding, which is essential for the spread of infection between hosts at an early stage of infection, which differs from SARS and MERS (Wu *et al.*, 2021).

In addition, the clinical manifestations and imaging manifestations of influenza A H1N1 virus pneumonia are similar to those of COVID-19 (Wu *et al.*, 2021). As the diseases develop, some patients may develop acute respiratory distress syndrome (ARDS) and multiorgan failure, leading to death. However, the rate of ARDS is higher in influenza pneumonia, and the fatality rate is lower in COVID-19 (World Health Organization, 2020). Thus, the complications and prognosis of the two pneumonias are diverse. Moreover, previous research has shown that both COVID-19 and influenza A H1N1 viral pneumonia have high morbidity and mortality in elderly individuals (Abdelrahman *et al.*, 2020; Chen *et al.*, 2020; Grasselli *et al.*, 2020). Primary data from Wuhan showed that the death rate among elderly patients (aged ≥60 years) infected with

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SARS-CoV-2 was 11.0% (Chen *et al.*, 2020). Italian statistics showed that COVID-19 is far more serious among elderly patients, with a mortality rate of 3.6% among those aged between 60 and 69 years, 8.0% among those aged between 70 and 79 years, 14.8% among those aged >80 years, and over 20.0% among those aged >90 years compared with 2.3% in the general population (Grasselli *et al.*, 2020). The mortality rates of H1N1 exhibit a J-shaped curve, and the mortality rate among elderly patients (aged ≥70 years) was 10.3% (Echevarría-Zuno *et al.*, 2009). Due to the different complications, prognoses, and therapies of the two diseases, it is important for clinicians to identify them quickly and administer proper treatments to patients. Therefore, the purpose of this study was to identify the differences between hospitalized elderly patients infected with SARS-CoV-2 or influenza viruses to provide some guidance for their differential diagnoses.

Materials and methods

Subjects and data

In total, 222 elderly (aged ≥60 years) patients infected with SARS-CoV-2 between January 17 and March 10, 2020 in Zhejiang, China were enrolled in this research. All confirmed patients were admitted to a designated hospital in accordance with the requirements of Zhejiang Province.

As a comparison group, 96 elderly (aged ≥60 years) patients confirmed to have H1N1 influenza virus infection between November 1, 2017 and March 31, 2018 in Zhejiang who were hospitalized at the First Affiliated Hospital, College of Medicine, Zhejiang University were enrolled.

Our study followed the ethical guidelines of the Declaration of Helsinki and obtained the approval of the medical ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Data collection

We retrospectively investigated the characteristics, underlying diseases, clinical symptoms, and lung images of the two groups. The treatments and prognosis were also recorded. All patients were diagnosed with COVID-19 or influenza A H1N1 viral pneumonia by positive polymerase chain reaction results, with a combination of clinical manifestations and imaging presentations.

Statistical analysis

All data were analyzed by SPSS (version 26.0), and a two-sided α <0.05 was considered statistically significant. Continuous variables with a normal or a non-normal distribution are described as the mean ± standard deviation or median (interquartile range), respectively. Numbers (%) and chi-square tests were used to describe the categorical variables and comparisons between the groups.

To reduce the imbalance between the two groups, we performed this research based on propensity score matching (PSM). PSM was performed to obtain a 1:1 matched cohort using the 'nearest-neighbor' approach without replacement, with a match tolerance of 0.05. The following factors were included in the PSM: age, sex, current smoking status, and coexisting conditions, such as hypertension, heart disease, diabetes, etc.

Results

Baseline characteristics and underlying diseases

The characteristics of the patients infected with COVID-19 or influenza A H1N1 virus before and after PSM are described in Table 1.

Table 1
Baseline characteristics and underlying diseases of patients with COVID-19 or influenza A H1N1 virus pneumonia.

Characteristics	Patients before PSM				Patients after PSM			
	COVID-19 (n = 222)	H1N1 (n = 96)	*P*-value	Estimated difference, (95% CI)	COVID-19 (n = 72)	H1N1 (n = 72)	*P*-value	Estimated difference, (95% CI)
Ages, years, median	66.00 (63.00-72.00)	71.00 (64.00-79.00)	<0.001	-3.29 (-5.32 to -1.26)	67.00 (62.00-74.00)	70.00 (64.00-77.00)	0.231	-1.79 (-4.74 to 1.15)
Male sex, n (%)	102 (45.6)	63 (65.6)	<0.001	-0.20 (-0.31 to -0.08)	44 (61.1)	44 (61.1)	1.000	0.00 (-0.16 to 0.16)
Current smoker, n (%)	21 (9.5)	24 (25.0)	<0.001	-0.16 (-0.25 to -0.06)	15 (20.8)	15 (20.8)	1.000	0.00 (-0.13 to 0.13)
Coexisting conditions, n (%)	113 (51.9)	71 (74.0)	0.117	-0.23 (-0.34 to -0.12)	40 (55.6)	49 (68.1)	0.123	-0.13 (-0.28 to 0.03)
Hypertension, n (%)	99 (44.6)	52 (54.2)	0.049	-0.10 (-0.21 to 0.02)	37 (51.4)	44 (61.1)	0.314	-0.10 (-0.26 to 0.06)
Heart disease, n (%)	31 (14.0)	22 (22.9)	0.291	-0.09 (-0.19 to 0.01)	14 (19.4)	16 (22.2)	0.837	-0.03 (-0.16 to 0.10)
Diabetes, n (%)	42 (18.9)	21 (21.9)	0.544	-0.03 (-0.13 to 0.07)	17 (23.6)	17 (23.6)	1.000	0.00 (-0.14 to 0.14)
Chronic obstructive pulmonary disease, n (%)	8 (3.6)	6 (6.3)	0.291	-0.03 (-0.08 to 0.03)	5 (6.9)	4 (5.6)	1.000	0.01 (-0.07 to 0.09)
Asthma, n (%)	4 (1.8)	1 (1.0)	0.617	0.01 (-0.02 to 0.03)	4 (5.6)	1 (1.4)	0.363	0.04 (-0.02 to 0.10)
Cancer, n (%)	4 (1.8)	7 (7.3)	0.014	-0.05 (-0.11 to 0.00)	2 (2.8)	3 (4.2)	1.000	-0.01 (-0.07 to 0.05)
Immunosuppression, n (%)	2 (0.9)	9 (9.4)	<0.001	-0.08 (-0.14 to -0.03)	2 (2.8)	1 (1.4)	1.000	0.01 (-0.03 to 0.06)
Blood disease, n (%)	1 (0.5)	10 (10.4)	<0.001	-0.10 (-0.16 to -0.04)	1 (1.4)	1 (1.4)	1.000	0.00 (-0.04 to 0.04)
Chronic liver disease, n (%)	10 (4.5)	10 (10.4)	0.046	-0.06 (-0.13 to 0.01)	6 (8.3)	6 (8.3)	1.000	0.00 (-0.09 to 0.09)
Chronic renal disease, n (%)	6 (2.7)	5 (5.2)	0.262	-0.03 (-0.07 to 0.02)	4 (5.6)	4 (5.6)	1.000	0.00 (-0.07 to 0.07)

PSM, propensity score matching

The influenza A H1N1 virus patients were older than the patients with COVID-19, with a median (interquartile range) age of 70.00 (64.00-77.00) versus 67.00 (62.00-74.00) years (P <0.001). The proportions of males and current smokers among the patients with COVID-19 were 46.0% and 9.5%, respectively, which were significantly lower than those among the patients with influenza A H1N1 virus (P <0.001, 95% confidence interval [CI], −0.31 to −0.08, P <0.001, 95% CI −0.25 to −0.06 for each).

The patients with influenza had more coexisting diseases than the patients with COVID-19, including heart diseases (22.9% vs 14.0%, P = 0.049, 95% CI, −0.19 to 0.01), cancers (7.3% vs 1.8%, P-value = 0.014, 95% CI, −0.11to 0.00), immunosuppressive diseases (9.4% vs 0.9%, P <0.001, 95% CI, −0.14 to −0.03), blood diseases (10.4% vs 0.5%, P <0.001, 95% CI, −0.16 to −0.04), and chronic liver diseases (10.4% vs 4.5%, P <0.001, 95% CI, −0.13 to 0.01). There were no obvious differences in coexisting hypertension (44.6% vs 54.2%, P-value = 0.117, 95% CI, −0.21 to 0.02), diabetes (18.9% vs 21.9%, P-value = 0.544, 95% CI, −0.13 to 0.07), chronic obstructive pulmonary disease (3.6% vs 6.3%, P-value = 0.291, 95% CI, −0.08 to 0.03), asthma (3.6% vs 6.3%, P-value = 0.617, 95% CI, −0.02 to 0.03), or chronic renal disease (2.7% vs 5.2%, P-value = 0.262, 95% CI, −0.07 to 0.02) between the two groups.

After PSM in the cohort, a 1:1 balanced cohort of 144 patients was obtained; in this cohort, 72 were patients with COVID-19, and 72 were patients with influenza. The distribution of the baseline characteristics between the two groups was similar for all covariates before and after PSM.

Clinical symptoms and laboratory examinations

In summary, the incidence of fever and cough was the highest in the two groups neither before and after the PSM analysis (shown in Table 2). After the PSM analysis, more concretely, the percentages of patients with COVID-19 with cough (72.2% vs 88.9%, P-value = 0.021, 95% CI, −0.29 to −0.04), sputum production (40.3% vs 86.1%, P <0.001, 95% CI, −0.60 to −0.32), fatigue (15.3% vs 50.0%, P <0.001, 95% CI, −0.49 to −0.20), and shortness of breath (15.3% vs 69.4%, P <0.01, 95% CI −0.68 to −0.41) were lower than those of patients with influenza. No apparent differences existed in the proportion of fever (86.1% vs 80.6%, P-value = 0.502, 95% CI, −0.07 to 0.18), hemoptysis (1.4% vs 4.2%, P-value = 0.612, 95% CI, −0.08 to 0.03), sore throat (12.5% vs 5.6%, P-value = 0.245, 95% CI, -0.02 to 0.16), nasal obstruction (1.4% vs 1.4%, P-value = 1.000, 95% CI, −0.04 to 0.04), headache (6.9% vs 9.7%, P-value =0.763, 95% CI, −0.12 to 0.06), muscle ache (12.5% vs 8.3%, P-value = 0.585, 95% CI, −0.06 to 0.14) and gastrointestinal symptoms (11.1% vs 13.9%, P-value = 0.801, 95% CI, −0.14 to 0.08) between the two groups. The results were similar to the data before the PSM analysis.

After the routine blood laboratory tests, before the PSM analysis, the counts of white blood cells (WBCs) (6.13 vs 11.93 10^9/l, P <0.001, 95% CI, −11.12 to 0.41), neutrophils (4.42 vs 7.19 × 10^9/l, P <0.001, 95% CI, −3.65 to −1.59), and lymphocytes (1.20 vs 3.99 × 10^9/l, P-value = 0.001, 95% CI, −7.99 to 2.91) in the patients with COVID-19 were all lower than those in the patients with influenza A H1N1 virus. However, the counts of hemoglobin (124.68 vs 115.68 g/l, P <0.01, 95% CI, 3.89 to 14.39) and platelets (203.30 vs 183.84 × 10^9/l, P <0.01, 95% CI, 6.89 to 59.14) were higher in the patients with COVID-19. After the PSM analysis, the lymphocyte counts (1.00 vs 0.82 × 10^9/l, P-value = 0.030, 95% CI, −0.19 to 0.91) in the patients with COVID-19 were higher, and the platelet counts (182.50 vs 1181.00 × 10^9/l, P-value = 0.575, 95% CI, −39.66 to 40.32) did not obviously differ between the two groups.

Regarding the blood biochemistry, there were no prominent differences in the counts of alanine transaminase, aspartate transaminase, total bilirubin, serum creatinine and C-reactive protein (CRP) between the two groups neither before or after the PSM analysis (P >0.05 for each). Blood urea nitrogen (4.54 vs 6.22 mmol/l, P <0.001, 95% CI, −4.34 to 2.21) in the patients with COVID-19 was lower than that in the patients with influenza, and compared with the patients with influenza, the patients with COVID-19 had higher counts of creatine kinase (67.50 vs 32.00 U/l, P <0.001, 95% CI, −25.39 to 60.36) after the PSM analysis.

Computed tomography (CT) scans play a key role in the identification and diagnosis. As shown in Table 2, after the PSM analysis, multiple mottling and ground-glass opacities (37.5% vs 0.0%, P <0.001, 95% CI, 0.26 to 0.49) and unilateral pneumonia (20.8% vs 0.0%, P <0.001, 95% CI, 0.11 to 0.30) were more easily observed in the patients with COVID-19, and bilateral pneumonia (41.7% vs 90.3%, P-value = 0.022, 95% CI, −0.62 to −0.35) was more evident in the patients with influenza.

Treatment and prognosis

Doctors prescribed antiviral therapy to 97.2% of the patients with COVID-19 and 87.5% of the patients with influenza A H1N1 virus (P-value = 0.060, 95% CI, 0.01 to 0.18). In addition, both groups of patients were administered antibiotics, antifungal drugs, glucocorticoids, and immunoglobulins when necessary. Smaller proportions of patients with COVID-19 received antibiotics (62.5% vs 95.8%, P <0.001, 95% CI, −0.45 to −0.21) and antifungal drugs (2.8% vs 40.3%, P <0.001, 95% CI, −0.49 to −0.26), but a higher proportion underwent immunoglobulin treatment (31.9% vs 12.5%, P-value = 0.009, 95% CI, 0.06 to 0.33). There was no difference in glucocorticoid treatment (40.3% vs 52.8%, P-value = 0.181, 95% CI, −0.29 to 0.04) between the two groups. Regarding respiratory support, 16.7% of the patients with COVID-19 and 23.6% of the patients with influenza received mechanical ventilation (including noninvasive and invasive ventilation) (P-value = 0.406, 95% CI, −0.20 to 0.06). There were no prominent differences in the use of extracorporeal membrane oxygenation or continuous renal replacement therapy (both P-values = 0.243, 95% CI, 0.00 to 0.09, 95% CI, −0.09 to 0.00 for each). Regarding complications, the rate of shock (1.4% vs 2.8%, P-value = 1.000, 95% CI, −0.06 to 0.03) did not significantly differ, but fewer patients with COVID-19 developed ARDS (16.7% vs 40.3%, P-value = 0.003, 95% CI, −0.38 to −0.09) than patients with influenza. In our research, the mortality rate among the patients with COVID-19 was 0.0% between January 17 and March 10, 2020, whereas seven patients with influenza died from November 1, 2017 to March 31, 2018. The mortality rate among the patients with COVID-19 was lower than that among the patients with influenza (0.0% vs 9.7%, P <0.01, 95% CI, −0.17 to −0.03; shown in Table 3).

Multivariate logistic regression

To further identify the differences between the two diseases, we performed a regression analysis of the significantly different data. A multivariate logistic regression was used to discern the main diverse factors of the two pneumonias.

Compared with the patients with COVID-19, the patients with influenza tended to have a higher proportion of sputum production (P-value = 0.001, 95% CI, 4.41-247.37), fatigue (P-value = 0.005, 95% CI, 1.64-16.00), and shortness of breath (P <0.001, 95% CI, 3.92-40.79) and the counts of WBC (P-value = 0.004, 95% CI, 1.99-39.67), neutrophils (P-value = 0.01, 0.95% CI, 0.30-0.62), lymphocytes (P-value = 0.012, 95% CI, 0.27-0.64) and CRP (P-value = 0.015, 95% CI, 1.00-1.03) were higher. Moreover, the patients with COVID-19 were less likely to present with an abnormal chest CT (P-value = 0.015, 95% CI, 0.16-0.82; shown in Table 4).

Table 2
Clinical symptoms and laboratory examinations of the patients with COVID-19 or influenza A H1N1 virus pneumonia.

Characteristics	Patients before PSM				Patients after PSM			
	COVID-19 (n = 222)	H1N1 (n = 96)	*P*-value	Estimated difference, (95% CI)	COVID-19 (n = 72)	H1N1 (n = 72)	*P*-value	Estimated difference, (95% CI)
Fever, n (%)	188 (84.7)	80 (83.3)	0.761	0.01 (-0.07 to 0.10)	62 (86.1)	58 (80.6)	0.502	0.06 (-0.07 to 0.18)
Cough, n (%)	152 (68.5)	83 (86.5)	<0.001	-0.18 (-0.27 to -0.09)	52 (72.2)	64 (88.9)	0.021	-0.17 (-0.29 to -0.04)
Sputum production, n (%)	86 (38.7)	81 (84.4)	<0.001	-0.46 (-0.55 to -0.36)	29 (40.3)	62 (86.1)	<0.001	-0.46 (-0.60 to -0.32)
Hemoptysis, n (%)	4 (1.8)	4 (4.2)	0.216	-0.02 (-0.07 to 0.02)	1 (1.4)	3 (4.2)	0.612	-0.03 (-0.08 to 0.03)
Sore throat, n (%)	23 (10.4)	8 (8.3)	0.576	0.02 (-0.05 to 0.09)	9 (12.5)	4 (5.6)	0.245	0.07 (-0.02 to 0.16)
Nasal obstruction, n (%)	3 (1.4)	2 (2.1)	0.630	-0.01 (-0.04 to 0.03)	1 (1.4)	1 (1.)4	1.000	0.00 (-0.04 to 0.04)
Headache, n (%)	11 (5.0)	8 (8.3)	0.243	-0.03 (-0.10 to 0.03)	5 (6.9)	7 (9.7)	0.763	-0.03 (-0.12 to 0.06)
Muscle ache, n (%)	24 (10.8)	6 (6.3)	0.201	0.05 (-0.02 to 0.11)	9 (12.5)	6 (8.3)	0.585	0.04 (-0.06 to 0.14)
Fatigue, n (%)	38 (17.1)	46 (47.9)	<0.001	-0.31 (-0.42 to -0.20)	11 (15.3)	36 (50.0)	<0.001	-0.35 (-0.49 to -0.20)
Shortness of breath, n (%)	20 (9.0)	67 (69.7)	<0.001	-0.61 (-0.71 to -0.51)	11 (15.3)	50 (69.4)	<0.001	-0.54 (-0.68 to -0.41)
Gastrointestinal symptoms, n (%)	22 (9.9)	11 (11.5)	0.691	-0.02 (-0.09 to 0.06)	8 (11.1)	10 (13.9)	0.801	-0.03 (-0.14 to 0.08)
Nausea/vomiting, n (%)	10 (4.5)	7 (7.3)	0.415	-0.03 (-0.09 to 0.02)	3 (4.2)	7 (9.7)	0.325	-0.06 (-0.14 to 0.03)
Diarrhea, n (%)	16 (7.2)	5 (5.2)	0.627	0.02 (-0.04 to 0.08)	7 (9.7)	4 (5.6)	0.530	0.04 (-0.04 to 0.13)
Blood routine								
White blood cell, ($\times 10^9$ per l)	6.13 (5.67-6.59)	11.93 (5.58-18.28)	<0.001	-5.35 (-11.12 to 0.41)	5.20 (4.10-7.46)	8.45 (5.18-12.03)	<0.001	-3.06 (-4.50 to -1.63)
Neutrophils, ($\times 10^9$ per l)	4.42 (4.00-4.84)	7.19 (6.16-8.22)	<0.001	-2.62 (-3.65 to -1.59)	3.40 (2.90-4.64)	6.43 (4.00-10.18)	<0.001	-3.29 (-4.58 to -2.01)
Lymphocytes, ($\times 10^9$ per l)	1.20 (1.00-1.40)	3.99 (2.02-10.01)	0.001	-2.54 (-7.99 to 2.91)	1.00 (0.70-1.40)	0.82 (0.45-1.24)	0.030	0.36 (-0.19 to 0.91)
Platelets, ($\times 10^9$ per l)	203.30 (191.75-214.85)	183.84 (154.60-213.08)	0.001	33.02 (6.89 to 59.14)	182.50 (142.50-225.50)	181.00 (112.75-261.75)	0.575	0.33 (-39.66 to 40.32)
Hemoglobin, (g/l)	124.68 (122.49-126.87)	115.68 (110.47-120.89)	0.001	9.14 (3.89 to 14.39)	129.50 (120.75-140.25)	117.50 (102.00-130.00)	0.001	11.13 (4.56 to 17.69)
Blood biochemistry								
Alanine aminotransferase, (U/l)	31.34 (27.14-35.54)	40.23 (26.69-53.77)	0.493	-8.22 (-21.24 to 4.80)	23.00 (16.00-31.50)	21.00 (14.00-44.50)	0.853	-15.79 (-33.08 to 1.50)
Aspartate aminotransferase, (U/l)	31.73 (28.18-35.28)	43.18 (33.98-52.40)	0.057	-11.22 (-20.33 to -2.10)	25.50 (19.25-32.50)	27.00 (20.00-45.00)	0.322	-15.86 (-27.53 to -4.19)
Total bilirubin, (mmol/l)	11.66 (10.05-13.27)	16.38 (8.67-24.09)	0.244	-4.53 (-11.74 to 2.68)	10.00 (7.00-13.20)	8.00 (6.00-12.00)	0.097	-5.64 (-15.26 to 3.99)
Blood urea nitrogen, (mmol/l)	6.13 (4.94-7.32)	7.98 (6.68-9.28)	<0.001	-1.74 (-3.63 to 0.14)	4.54 (3.55-6.26)	6.22 (4.57-9.37)	<0.001	-1.06 (-4.34 to 2.21)
Serum creatinine, (mmol/l)	75.61 (65.03-86.20)	102.59 (74.80-130.39)	0.031	-16.72 (-53.61 to 20.17)	68.00 (55.50-85.25)	69.50 (56.00-93.00)	0.431	17.31 (-65.83 to 3.03)
Creatine kinase, (U/l)	88.96 (68.60-109.31)	82.10 (46.13-118.07)	<0.001	4.00 (-36.10 to 44.10)	67.50 (41.25-108.25)	32.00 (15.00-50.00)	<0.001	17.49 (-25.39 to 60.36)
Lactate dehydrogenase, (U/l)	258.48 (241.38-275.59)	320.18 (281.86-358.51)	<0.001	-59.64 (-100.59 to -18.68)	233.00 (180.00-287.00)	256.00 (220.00-347.00)	0.088	-15.94 (-94.11 to 62.22)
C-reactive protein, (mg/l)	29.08 (24.27-33.89)	76.21 (58.06-94.36)	<0.001	-44.33 (-57.28 to -31.38)	18.08 (4.65-40.17)	50.50 (13.90-115.10)	<0.001	-46.60 (-68.70 to -24.50)
Computed tomography findings								
Unilateral pneumonia, n (%)	24 (10.8)	11 (11.5)	0.502	-0.01 (-0.08 to 0.07)	15 (20.8)	0 (0.0)	<0.001	0.21 (0.11 to 0.30)
Bilateral pneumonia, n (%)	110 (49.5)	60 (62.5)	0.022	-0.13 (-0.25 to -0.01)	30 (41.7)	65 (90.3)	<0.001	-0.49 (-0.62 to -0.35)
Multiple mottling and ground-glass opacity, n (%)	81 (36.5)	23 (24.0)	0.019	0.13 (0.02 to 0.23)	27 (37.5)	0 (0.0)	<0.001	0.38 (0.26 to 0.49)

PSM, propensity score matching

Table 3
Complications, treatments, and prognosis of the patients with COVID-19 or influenza A H1N1 virus pneumonia.

Characteristics	Patients before PSM				Patients after PSM			
	COVID-19 (n = 222)	H1N1 (n = 96)	*P*-value	Estimated difference, (95% CI)	COVID-19 (n = 72)	H1N1 (n = 72)	*P*-value	Estimated difference, (95% CI)
Treatments								
Antivirus- treatment, n (%)	213 (96.0)	96 (100.0)	0.004	-0.04 (-0.07 to -0.01)	70 (97.2)	63 (87.5)	0.060	0.10 (0.01 to 0.18)
Antibiotics- treatment, n (%)	116 (52.3)	92 (95.8)	<0.001	-0.44 (-0.51 to -0.36)	45 (62.5)	69 (95.8)	<0.001	-0.33 (-0.45 to -0.21)
Antifungal- treatment, n (%)	2 (0.9)	36 (37.5)	<0.001	-0.37 (-0.46 to -0.27)	2 (2.8)	29 (40.3)	<0.001	-0.38 (-0.49 to -0.26)
Glucocorticoids, n (%)	74 (33.3)	51 (53.1)	<0.001	-0.20 (-0.32 to -0.08)	29 (40.3)	38 (52.8)	0.181	-0.13 (-0.29 to 0.04)
Intravenous immunoglobulins therapy, n (%)	57 (25.7)	10 (10.4)	0.002	0.15 (0.07 to 0.24)	23 (31.9)	9 (12.5)	0.009	0.19 (0.06 to 0.33)
Mechanical ventilation, n (%)	26(11.7)	24 (25.0)	0.004	-0.13 (-0.23 to -0.04)	12 (16.7)	17 (23.6)	0.406	-0.07 (-0.20 to 0.06)
Extracorporeal membrane oxygenator, n (%)	5 (5.3)	0 (0.0)	0.194	0.02 (0.00 to 0.04)	3 (4.2)	0 (0.0)	0.243	0.04 (0.00 to 0.09)
Continuous renal replacement therapy, n (%)	3 (1.4)	5 (5.2)	0.057	-0.04 (-0.09 to 0.01)	0 (0.0)	3 (4.2)	0.243	-0.04 (-0.09 to 0.00)
Complications								
Acute respiratory distress syndrome, n (%)	26 (11.7)	37 (38.5)	<0.001	-0.27 (-0.37 to -0.16)	12 (16.7)	29 (40.3)	0.003	-0.24 (-0.38 to -0.09)
Shock, n (%)	3 (1.4)	3 (3.1)	0.371	-0.02 (-0.06 to 0.02)	1 (1.4)	2 (2.8)	1.000	-0.01 (-0.06 to 0.03)
Prognosis								
Death, n (%)	0 (0.0)	11 (11.5)	<0.001	-0.11 (-0.18 to -0.05)	0 (0.0)	7 (9.7)	0.020	-0.10 (-0.17 to -0.03)

PSM, propensity score matching

Table 4
Multivariate regression analysis of the patients with COVID-19 or influenza A H1N1 virus pneumonia.

Variable	Coefficient	95% CI	*P*-value
Sputum production	33.02	4.41-247.37	0.001
Fatigue	5.13	1.64-16.00	0.005
Shortness of breath	12.65	3.92-40.79	0.000
White blood cell	8.88	1.99-39.67	0.004
Neutrophils	0.14	0.30-0.62	0.010
Lymphocytes	0.13	0.27-0.64	0.012
C-reactive protein	1.01	1.00-1.03	0.015
Computed tomography findings	0.36	0.16-0.82	0.015

Discussion

Our study used real-world data from Zhejiang Province, China, and some of the data were obtained from the same hospital. To ensure data quality, the data were collected by the same group of doctors, which was helpful for reducing data collection errors and provided good comparability. COVID-19 and influenza A H1N1 virus have both caused severe pandemics worldwide and have many identical epidemiological characteristics and clinical and imaging manifestations (Huang *et al.*, 2020; Wang *et al.*, 2020a). Hence, it is possible to misdiagnose COVID-19 as influenza A H1N1 viral pneumonia, especially in the early phase of COVID-19. However, COVID-19 is far more contagious than influenza A H1N1 viral pneumonia (Li *et al.*, 2020; Wang *et al.*, 2020b). The basic reproduction number (R_0) of COVID-19 was estimated in the initial outbreak to be between 2.2 and 3.6 patients (Zhao *et al.*, 2020). It is estimated that the R_0 during the 2009 influenza outbreak in Mexico ranged from 1.3 to 1.7 (Yang *et al.*, 2009). Moreover, elderly patients have more underlying diseases and more easily progress to the critical disease stage (Lian *et al.*, 2020). Previous research has shown that both diseases have high morbidity and mortality in elderly individuals (Abdelrahman *et al.*, 2020; Chen *et al.*, 2020; Grasselli *et al.*, 2020). Therefore, it is very important for clinicians to accurately identify the two diseases, especially in the elderly population. The purpose of the current research was to contrast the distinct clinical manifestations between hospitalized elderly patients infected with COVID-19 and H1N1 to provide some guidance for their differential diagnoses.

The results of our research show that the proportion of males among patients with COVID-19 was lower than that among patients with influenza. However, most previous reports showed that the sex ratio of COVID-19 and patients with influenza were similar (Caruso *et al.*, 2020; Han *et al.*, 2020; Wang *et al.*, 2020a). Moreover, the patients with COVID-19 showed lower proportions of underlying diseases than the H1N1 patients, which is similar to previous results (Huang *et al.*, 2020), especially in heart disease, immunosuppression, and blood disease, which have differential diagnostic value. This may be associated with the inconsistent criteria for hospitalization. Therefore, a PSM analysis was used to reduce the imbalance to improve the reliability of our research.

Patients with COVID-19 and influenza A H1N1 virus have many similar clinical symptoms, which makes it difficult to distinguish the two only through clinical manifestations before pathogen detection. A previous study reported that fever, fatigue, cough, expectoration, muscular soreness, and rhinorrhea were the most common symptoms of viral pneumonia, with gastrointestinal features, such as diarrhea, nausea, and vomiting (Chen *et al.*, 2020; Han *et al.*, 2020; Wang *et al.*, 2020a). Our research found that patients with COVID-19 had lower rates of cough, expectoration, fatigue, and shortness of breath than those with influenza. Moreover, there was no differential diagnostic value in the digestive symptoms of the two groups in our research. However, previous studies have shown that the frequency of gastrointestinal symptoms is higher

in patients with COVID-19 than in patients with influenza (Chan *et al.*, 2020; Jin *et al.*, 2020), which may be related to the damage by the SARS-CoV-2 infection to the gastrointestinal tract (Holshue *et al.*, 2020).

As the disease progresses, dyspnea, chest pain, and even ARDS and shock may appear. We found that patients with influenza more easily developed ARDS, which is consistent with previous research (Pormohammad *et al.*, 2021). This result indicates that the clinical manifestation of COVID-19 is more concealed.

In addition, we showed that the counts of WBCs, neutrophils, lymphocytes, blood urea nitrogen, and CRP in patients with COVID-19 were lower, and the counts of hemoglobin and creatine kinase were higher, which is consistent with previous studies (Bai *et al.*, 2020; Kuang *et al.*, 2021; Pormohammad *et al.*, 2021; Yin *et al.*, 2020). Because of the limited data, other immunological and inflammatory markers (*e.g.,* erythrocyte sedimentation rate, tumor necrosis factor-α, interleukins [1, 6], coagulation parameters, prolonged prothrombin time, thrombocytopenia, and elevated d-dimer) were not evaluated. In further studies, the inclusion of these indicators may help better differentiate the two diseases.

In addition, the most common radiologic abnormalities in patients with COVID-19 were bilateral changes on chest X-rays (Pormohammad *et al.*, 2021). In our research, most patients with COVID-19 and influenza showed abnormal imaging, with the highest proportion of lung changes on both sides. Multiple mottling and ground-glass opacities and unilateral pneumonia were more frequently observed in the patients with COVID-19, whereas bilateral pneumonia was more common in the patients with influenza pneumonia. Previous research showed the same results as follows: ground-glass opacities were the most abnormal pattern in patients with COVID-19, and bilateral consolidation with or without ground-glass opacities was more common in critical cases of influenza pneumonia on chest CT scans (Marchiori *et al.*, 2011; Rohani *et al.*, 2016; Shi *et al.*, 2020). Therefore, these imaging characteristics may help distinguish the two diseases.

Regarding treatment, patients with COVID-19 or influenza A H1N1 virus received a wide variety of treatments, including antibiotics, antifungals, glucocorticoids, and mechanical ventilation, when necessary. Compared with the definitive treatment measures for patients with influenza pneumonia (Uyeki *et al.*, 2019), there is no solid evidence regarding the effectiveness of any remedy for COVID-19. In our research, patients with COVID-19 accepted more immunoglobulins than patients with H1N1. One study showed that glucocorticoids might reduce the death rate in patients with H1N1 (Li *et al.*, 2017), whereas another study showed that glucocorticoids increased the mortality and secondary infection rates in patients infected with SARS and MERS and even complicated corticosteroid therapies in survivors (Russell *et al.*, 2020). Therefore, the application of glucocorticoids should be cautiously assessed in patients with COVID-19, especially in elderly patients.

Regarding complications, the incidence of shock did not differ, but fewer patients with COVID-19 developed ARDS, which is similar to a previous research showing that the incidence of ARDS was higher in influenza type A (31.5%; 95% CI 26-38%, P <0.001) than in COVID-19 (26.6%; 95% CI 18-38%, P <0.001) (Pormohammad *et al.*, 2021). The death rate of COVID-19 was 0.00% in our research, which was lower than the fatality rate of H1N1 (9.7%, P-value = 0.020). However, other research found that the fatality rate of COVID-19 was higher (Pormohammad *et al.*, 2021). The previously mentioned differences may be related to the following possible reasons. First, patients with influenza A H1N1 pneumonia may be compared with patients with COVID-19 not necessarily having pneumonia, and there would be an obvious difference in fatality. Second, compared with the management of influenza A H1N1, the pandemic of SARS-CoV-2 triggered more comprehensive life-saving health systems. This, based on the lack of understanding of the spread and severity of SARS-CoV-2 in the early stage, once the pathogen detection was positive, the patients were immediately isolated and admitted to the hospital for good care, which may also be the reason for the zero death rate of the patients with COVID-19 in this study. In summary, in our research, elderly patients infected with H1N1 had a poorer prognosis than patients with COVID-19.

In conclusion, there are certain differences between elderly patients with COVID-19 and those with influenza. We report the differences in the clinical features and laboratory examinations between the two groups, including cough, expectoration, fatigue and shortness of breath, and diverse laboratory results. Dormant clinical symptoms of sputum production, fatigue, and shortness of breath, combined with lower counts of WBCs, neutrophils, lymphocytes, and CRP, are possible predictive factors of COVID-19 among elderly patients.

In summary, the clinical manifestations of patients with COVID-19 are more concealed than those of patients with influenza in elderly individuals. More attention is needed for elderly individuals, especially those with underlying diseases, which can have a large impact on the prognosis. Because of the lower immune response and concealed clinical manifestations in elderly patients, prevention is still the most important strategy to protect them from infection.

Our study had the following limitations. First, this study was retrospective, which may have an unavoidable bias because the data originated from two independent groups. Second, the information of the influenza and COVID-19 groups was collected from 1-year and 2-month time spans, respectively, which could introduce bias. Because of the limited data, other pathogens (*e.g.,* bacteria and parasites) that may result in similar symptoms or poorer prognosis were not analyzed, which is a limitation of this study. The differences between elderly patients with COVID-19 or influenza were not obvious. Therefore, a larger sample size is required for relevant verification in the future.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

The study was approved by the institutional ethical committee.

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Author contributions

Yida Yang supervised the project.Yan Lv, Guodong Yu, Xiaoli Zhang designed the study and Yan Lv drafted the manuscript.Yan Lv, Guodong Yu, Xiaoli Zhang, Jueqing Gu, Chanyuan Ye, Jiangshan Lian, Xiaoqing Lu, Yingfeng Lu participated in the collection of data.All authors scrutinized the manuscript and approved the final version for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.11.008.

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