Influence of influenza A virus in COVID-19 patients: A retrospective cohort study

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Abstract

Background and objective: Coronavirus disease (COVID-19) is currently an urgent global issue, but we cannot ignore the impact of influenza A since there is an overlap of infection time and region and similar clinical manifestations and chest computed tomography (CT) images for influenza A and COVID-19 infections. We compared patients who had a COVID-19 infection and co-infection with the influenza A virus.

Methods: We retrospectively reviewed patients who met the inclusion criteria for this study.

Results: There were 213 patients included in this study, of whom 106 were females and 107 were males, with a median age of 63 years. All patients were diagnosed with COVID-19 and were subsequently divided into influenza positive (n = 97) and influenza negative (n = 116) groups according to the serum test results for the influenza A IgM antibody. The two groups had similar symptoms, outcomes, CT manifestation and CT scores, except for lymphadenopathy (6.2% in the influenza positive group vs. 14.7% in the negative group, P = 0.047). However, in the subgroup analysis, male or younger patients (age <= 60 years) in the influenza negative group had higher CT scores than patients in the influenza positive group (P < 0.05).

Conclusions: COVID-19 patients who had co-infection with the influenza A virus showed similar symptoms, outcomes, CT manifestation and CT scores to influenza negative patients. However, male patients and younger patients had higher CT scores in the influenza negative group.

Introduction

Coronavirus disease (COVID–19) is currently an urgent global issue, but we cannot ignore the impact of influenza A. From October 2019 to February 2020, a large-scale influenza outbreak occurred in the United States, causing more than 20000 related deaths, followed by the COVID–19 epidemic. The same scenario occurred in Wuhan, China where the time period concerned coincided with the winter peak of influenza and other respiratory illnesses. The number of influenza-like illness (ILI) cases in all age groups increased dramatically starting in early December 2019 and reached the peak by the New Year of 2020. In addition, ILI data for the 2019–2020 winter season was significantly higher in comparison to previous years, suggesting the necessity to distinguish between influenza-infected and suspected COVID–19 patients[1].

Since there is an overlap of infection time and region between influenza and COVID–19, it is difficult to distinguish them on CT images. Currently we do not know the relationship between influenza A and COVID–19 and we therefore designed the following retrospective study to address this issue.

Methods

Study Design and Participants

This retrospective cohort study included adult inpatients (> = 18 years old) from five wards of Wuhan Tongji Hospital which were in the charge of the Peking University Medical Health Center during the study period. All patients who were diagnosed with COVID–19 based on SARS-CoV–2 RNA PCR detections in samples from the respiratory tract between January 28, 2020 and March 24, 2020 were included in our study.

Inclusion criteria were as follows: patients who were diagnosed with COVID–19 and age > = 18 years old. Exclusion criteria were as follows: patients had no local CT scan, did not undergo a serum influenza A IgM test, symptoms to day of CT scan was greater than 60 day, and history of pneumonectomy.

All the patients were divided into influenza positive and influenza negative groups according to the serum test for influenza A IgM antibody at admission. The first chest CT scan after admission was collected for analysis.

This study was approved by the Research Ethics Commission of Peking University First Hospital (2020□098□). The Ethics Committee approved access to patient records and patient confidentiality was maintained.

Data collection

Epidemiological, demographic, clinical, and outcome data were collected using a standardized data collection form. All data were checked by two physicians (CY and WX) and a third researcher (HZW) adjudicated any difference in interpretation between the two primary reviewers.

Statistical analysis

Continuous and categorical variables were presented as median (IQR) and n (%), respectively. We used the Mann-Whitney U test, χ^2 test, or Fisher's exact test to compare differences between the two groups.

Imaging evaluation

One experienced pulmonologist and one experienced radiologist (CY, WH) reviewed the images independently, with a final finding reached by consensus when there was a discrepancy. CT findings included ground glass opacity (GGO), consolidation, and fibrosis. GGO was defined as hazy areas of increased opacity or attenuation without concealing the underlying vessels. Consolidation was defined as homogeneous opacification of the parenchyma obscuring the underlying vessels, and fibrosis was defined as distorted consolidation, tractive bronchiectasis, and interlobular septal thickening. The presence of lymphadenopathy was defined as a lymph node larger than 1 cm in short-axis diameter.

The CT scans were scored on the axial images as previously reported [2,3]. Briefly, the extent of abnormality and distribution of affected lung parenchyma were independently recorded in upper, middle and lower

zone on each side. The CT findings were graded using a 3-point scale: score of 1, normal attenuation, score of 2, ground-glass attenuation, and score of 3, consolidation. According to the distribution of the affected lung parenchyma, each lung zone was scored as follows: 0 as normal, 1 as < 25% abnormality, 2 as 25–50% abnormality, 3 as 50–75% abnormality, and 4 as > 75% abnormality. The four-point scale of the lung parenchyma distribution was then multiplied by the three-point scale of abnormality. The scores from all 6 zones were added for final cumulative score that had a range from 0 to 72.

Results

There were 323 patients hospitalized in five wards of Tongji Hospital with suspected COVID–19 infection between January 28, 2020 and March 24, 2020. The following patients were excluded from the analysis: 40 patients who did not have a local chest CT scan, 35 patients who did not have a serum influenza A IgM test, one patient who had a history of pneumonectomy, two patients who did not test positive for COVID–19, and 32 patients where more than 60 days had elapsed from symptoms to the day of CT(Figure 1). Hence 213 patients were included in the final analysis, of which 106 were female and 107 male, with a median age of 63 years (interquartile range, IQR, 24–88 years). As of March 24 2020, eight patients had died in hospital. The median time from the onset of symptoms to local CT scan was 18 days (IQR, 0 to 60 days). All the patients were divided into influenza positive (n = 97) and influenza negative (n = 116) groups according to the serum test result of the influenza A IgM antibody at admission.

Table 1 shows a comparison of patient age, gender, coexisting medical conditions and symptoms between the influenza positive and influenza negative groups. There were no significant differences between the two groups with respect to patient age, gender, coexisting medical conditions, and symptoms or in the history of hypertension, diabetes, or chronic obstructive pulmonary diseases. Fever and cough were the most common symptoms and there was no significant difference in fever, cough, dyspnoea, expectoration, and gastrointestinal symptoms between the two groups.

Table 2 shows the outcome and CT manifestation of the patients. Twelve patients required non-invasive positive pressure ventilation, of which 5 were in the influenza positive group and 7 were in the influenza negative group (P = 0.782). Two patients required invasive mechanical ventilation, of which one was in the influenza positive group and one was in the influenza negative group (P = 0.899). Eight patients died, of which three were in the influenza positive group and five were in the influenza negative group (P = 0.899).

The median time from onset of symptoms to CT scan was similar in the two groups (20 days in the influenza positive group vs. 18 days in the influenza negative group, P = 0.487). The CT features, including the location, extent and distribution of each abnormality are shown in Table 2. CT scans of four patients were normal, two were in the influenza positive group and two were in the influenza negative group. Predominant CT characteristics consisted of GGO (45.8%), bilateral sides involved (88.8%), peripheral distribution (57.9%), and lower zone involved (90.2%). Lymphadenopathy and pleural effusion

were only occasionally observed (10.7% for lymphadenopathy, 1.9% for unilateral pleural effusion, and 3.3% for bilateral pleural effusion). Lymphadenopathy was more common in the influenza positive group. The median CT score of the influenza positive group was similar to the influenza negative group (15 vs. 19.5, P = 0.052), but in subgroup analysis, it was significant lower in patients < 60 years (12 vs. 18, P = 0.007) and males (12 vs. 24, P = 0.031). CT manifestation of fibrosis was observed in 21% of all the patients (16% in the influenza positive group vs. 25% in the influenza negative group, P = 0.130). Linear atelectasis was observed in 45.3% of all the patients, and was similar in the two groups (46.4% in the influenza positive group vs. 44.8% in the influenza negative group, P = 0.819). Linear atelectasis was typically manifested as linear soft tissue opacities ranging from 1 to 3 mm in thickness and 1 to 5 cm in length, located in subpleural regions. There were no significant differences in the manifestation of fibrosis and linear atelectasis between the two groups.

Discussion

COVID–19 has caused many deaths and critical cases all over the world. COVID–19 pneumonia is likely to have a peripheral distribution with bilateral lung. The CT findings of COVID–19 pneumonia reflected a typical lung injury of viral pneumonia. COVID–19 and influenza pneumonia have similar clinical presentations and radiological manifestations; hence, laboratory tests are critical for differential diagnosis.

Influenza A pneumonia may cause bronchogenic dissemination and bronchiolar impaction by mucus or pus, resulting in bronchial wall thickening, centrilobular nodules or tree-in-bud patterns[4]. We did not find these signs in COVID–19 pneumonia, but these findings cannot exclude co-existing influenza A pneumonia and COVID–19 pneumonia and it would be necessary to perform a lung biopsy or bronchoalveolar lavage to confirm the diagnosis. However, considering the danger of aerosol transmission, the bronchoscopy procedure is avoided. Influenza A is a common problem in Wuhan in winter, but the emergence of COVID–19 has covered over the presence of influenza.

Influenza infection is known to increase the host's susceptibility to bacteria, and bacterial co-infections following influenza infection result in morbidity and mortality[5], but there is limited data with co-existing respiratory viral infections. Detection of specific IgM antibodies against viruses and other atypical pathogens has been widely applied for the diagnosis of respiratory infections[6]. In a previous study, influenza was reported to have occurred a little earlier than the new coronavirus, but there are overlaps in the time windows[1].

There were no significant differences in clinical manifestations between the two groups; the requirements for non-invasive ventilation and invasive ventilation were similar, and mortality was similar. The presence of the influenza A virus did not seem to affect the symptoms or prognosis of COVID–19 patients. The CT scores of the two groups were similar, but analysis of the subgroups showed that the CT scores of men and subgroups younger than 60 years old were lower in the influenza positive group. We postulated that the influenza virus may cause a human immune response and immune protection, especially in males

and younger patients. Influenza viruses and coronaviruses utilize a common pathway of antagonism via interferon[7], which might interfere with anti-virus responses.Influenza A IgM may last for about 2 months[8], so it is suitable for a retrospective study, but it is not possible to ascertain the exact time of influenza infection, whether it occurred before or at the same time as COVID–19 infection.

We observed that COVID–19 patients may display early signs of fibrosis on CT scans. In a previous report, fibrosis in CT scans may decrease in the following few months. Autopsies from SARS patients in 2003 showed the formation of diffuse alveolar damage and fibrosis[9], which may indicate that coronavirus infection causes early lung fibrosis. Lymphadenopathy was reported in 4~8% of patients with COVID–19 and was considered one of the significant risk factors of severe COVID–19 pneumonia[10,11]. However, we found more lymphadenopathy in the influenza negative group, which may due to the immune protection effect. Linear atelectasis is typically seen both in and out of the pneumonia area. It is speculated that it may result from diminution of lung volume due to severe parenchymal scarring or to surfactant deficiency or dysfunction caused by infection.

In conclusion, influenza A infections were very common in Wuhan from January 2020 to March 2020. Co-infection in COVID–19 patients with influenza A resulted in similar comorbidity, symptoms, outcomes, CT scores, and most CT manifestations. Male or younger patients (age < = 60 years) in the influenza negative group had higher CT scores than patients in the influenza positive group. Co-infection of the influenza A virus had a limited impact on COVID–19 infection.

There are some limitations in the current study. First, the IgM concentrations might be affected by vaccination, thus influence of vaccination on antibody detection need to be taken into consideration when the influenza vaccination rate has reached 9.5% among adults in China[12]. In addition, antibody-based test might produce false negative results during the window period. Further research is warranted to understand the mechanism of correlation between influenza and COVID–19 infection in the future.

Declarations

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Author contributions

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Competing interests

The author(s) declare no competing interests.

Data availability

All data generated or analyzed during this study are included in this published article.

Ethics declarations

Due to the retrospective nature of the study, the need for obtaining the consent from the patient for participating in the study had been waive. This study was approved by the Research Ethics Commission of Peking University First Hospital (2020(098)).

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Tables

Table 1 Demographic and clinical characteristics of the population and comparison between influenza positive and influenza negative patients

	All	Influenza positive	Influenza negative	P-value
	n = 213	n = 97	n = 116	
Age, median, years	63	61	64	0.349
Gender				0.635
Female*	106(49.5%)	50(51.5%)	56(48.3%)	
Male*	107(50.0%)	47(48.5%)	60(51.7%)	
Coexisting medical conditions				
Hypertension*	70(32.7%)	31(32.0%)	39(33.6%)	0.797
Diabetes*	36(16.8%)	19(19.6%)	17(14.7%)	0.339
Coronary heart disease*	18(8.4%)	10(10.3%)	8(6.9%)	0.373
COPD*	6(2.8%)	3(3.1%)	3(2.6%)	0.824
Any*	26(12.1%)	9(9.3%)	17(14.7%)	0.233
Symptoms				
Fever*	188(87.9%)	86(88.7%)	102(87.9%)	0.869
Cough*	157(73.4%)	71(73.2%)	86(74.1%)	0.876
Dyspnea*	121(56.5%)	53(54.6%)	68(58.6%)	0.559
Expectoration*	95(44.4%)	46(47.4%)	49(42.2%)	0.449
GI symptoms*	109(50.9%)	52(53.6%)	57(49.1%)	0.516
Other*	34(15.9%)	13(13.4%)	21(18.1%)	0.351

*n(%)

COPD, chronic obstructive pulmonary disease; GI, gastrointestinal

Table 2 Outcomes and CT manifestations

		Total	Influenza positive	Influenza negative	P-value
		n = 213	n = 97	n = 116	
Outcomes					
	NIPPV*	12(5.6%)	5(5.2%)	7(6.0%)	0.782
	MV*	2(0.9%)	1(1.0%)	1(0.9%)	0.899
	Death*	8(3.7%)	3(3.1%)	5(0.9%)	0.642
Symptom onset before CT, days		18	20	18	0.487
CT manifestations					0.584
	GGO*	98(45.8%)	44(45.4%)	54(46.6%)	
	Consolidation*	26(12.1%)	15(15.5%)	11(9.5%)	
	Both*	85(39.7%)	36(37.1%)	49(42.2%)	
	None*	4(1.9%)	2(2.1%)	2(1.7%)	
CT score, median(IQR)			15	19.5	0.052
	<60 years		12	18	**0.007**
	>= 60 years		22	20	0.796
	Male		12	24	**0.031**
	Female		17	20	0.093
Fibrosis*		45(21.0%)	16(16.5%)	29(25.0%)	0.130
Linear atelectasis*		97(45.3%)	45(46.4%)	52(44.8%)	0.819
Lymphadenopathy*		23(10.7%)	6(6.2%)	17(14.7%)	**0.047**
Pleural effusions					0.618
	Unilateral*	4(1.9%)	1(1.0%)	3(2.6%)	
	Bilateral*	7(3.3%)	2(2.1%)	5(4.3%)	
	None*	202(94.4%)	94(96.9%)	108(93.1%)	
Sides involved					0.513
	Unilateral*	19(8.9%)	11(11.3%)	8(6.9%)	
	Bilateral*	190(88.8%)	84(86.6%)	106(91.4%)	
	None*	4(1.9%)	2(2.1%)	2(1.7%)	

Predominant distribution					0.060
	Central*	1(0.5%)	1(1.0%)	0	
	Peripheral*	124(57.9%)	62(63.9%)	62(53.4%)	
	Both central and peripheral*	83(38.8%)	31(32.0%)	52(44.8%)	
	None*	4(1.9%)	2(2.1%)	2(1.7%)	
Assessed zone					0.964
	Upper*	174(81.3%)	76(78.4%)	98(84.5%)	
	Middle*	182(85.0%)	81(83.5%)	101(87.1%)	
	Lower*	193(90.2%)	87(89.7%)	106(91.4%)	
	None*	4(1.9%)	2(2.1%)	2(1.7%)	

*n(%)

Figures

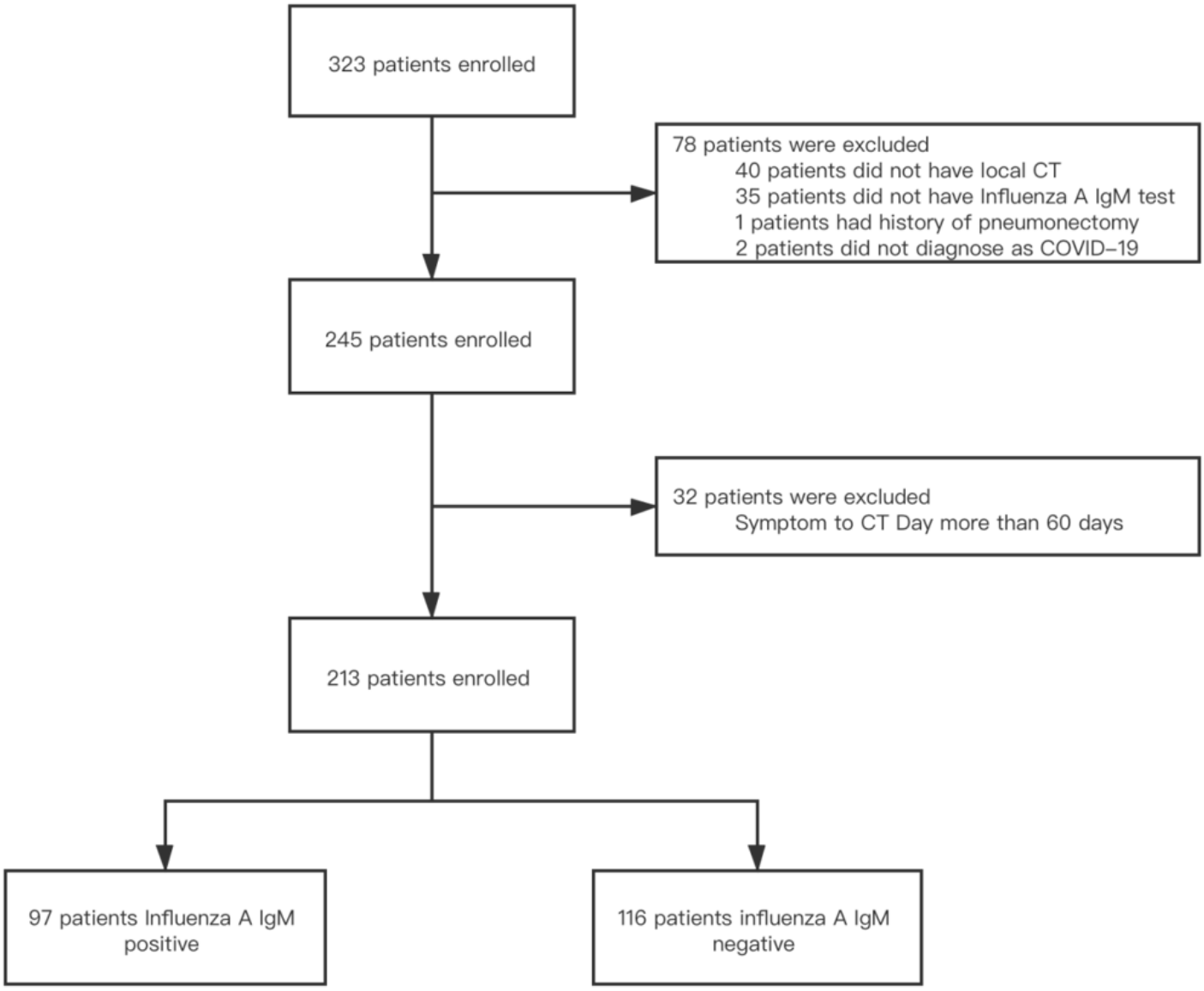

Figure 1

Flowchart of the participants