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Article

Clinical differences between hospitalized patients with COVID-19-related pneumonia and those with influenza-related pneumonia during the omicron variant surge

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Abstract ***Background:*** COVID-19-related pneumonia was initially rare, though influenza-related pneumonia is well known as a severe complication of influenza. However, COVID-19-related pneumonia may be increasing since the omicron variant of COVID-19 appeared. ***Methods:*** The clinical differences between COVID-19-related and influenza-related pneumonia patients were retrospectively investigated in patients hospitalized from January 2022 to December 2023. ***Results:*** COVID-19-related and influenza-related pneumonias were found in 46 of 285 (15.8%) and 6 of 12 (50.0%) patients, respectively ($p<0.001$). Their mean ages were 75.5 (45-93) years and 53.8 (19-73) years in COVID-19-related and influenza-related pneumonia cases, respectively ($p=0.002$). Aspiration pneumonia was more common in COVID-19-related pneumonia (28/46=60.9%) than in influenza-related pneumonia patients, and it was treated by sulbactam/ampicillin (31/46=67.4%). The influenza-related pneumonia patients were more often infected in the work place (2/6=33.3%) and not vaccinated (4/6=66.7%), compared with COVID-19-related patients. Death occurred in 7 of 46 (15.2%) COVID-19 patients, but none of 6 influenza-infected patients died. ***Conclusions:*** These data suggest that COVID-19-related pneumonia presented as aspiration pneumonia in older patients, although influenza-related pneumonia was more common in younger and non-vaccinated patients and might be associated with immune mechanisms during the omicron variant surge era.

Keywords: Aspiration pneumonia, Cytokine storm, Influenza virus, SARS-CoV-2, Secondary bacterial pneumonia

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1. Introduction

COVID-19 has had an enormous impact on societies worldwide, and it has recently increased again with some mutant lineages, although influenza and other respiratory virus infections have also been increasing during the omicron variant surge era[1].

Secondary bacterial pneumonia is well known as an important complication in these respiratory viral diseases[2, 3]. However, the rate of secondary pneumonia in COVID-19 was suggested to be around 3% before the omicron variant appeared[4, 5]; it was considered that pure viral pneumonia was predominant, although in influenza infection, secondary bacterial pneumonia was common, and more than 30% of influenza pneumonia patients were found to be co-infected with bacteria[6]. These data and comparisons so far have relied on data and mortality statistics obtained with disparate methods and at different times, because the pathogenesis of SARS-CoV-2 was very

different between the original Wuhan variant and the omicron variant[7, 8]. In general, the pathogenicity of SARS-CoV-2 became weaker with the omicron variant, compared with the original strain, and this may affect the occurrence rates and the conditions of pneumonia, as well as patients' outcomes.

In this study, the clinical features of patients with pneumonia related to COVID-19 and to influenza when the omicron variants were predominant and surging were evaluated and compared.

2. Methods

2.1. Patients and the definition of pneumonia

The data of patients who were hospitalized with either COVID-19 or influenza at Saitama Medical University International Medical Center from January 2022 to December 2023 were analyzed. Pneumonia was defined as the presence of symptoms of lower respiratory tract infection along with a new infiltrate on chest radiography and no emerging alternative diagnosis.

Aspiration pneumonia was defined as a new chest X-ray infiltrate in a dependent pulmonary segment in patients with risk factors for aspiration, including microaspiration, from the history of the presenting illness, medical history, and vital signs[9]. Aspiration of a small or large bacterial load of pathogens from the oral cavity or upper gastrointestinal tract into the lungs was usually suspected.

2.2. Ethics

This study was approved by the Committee for Clinical Scientific Research of Saitama Medical University International Medical Center on July 06, 2022 (No. ID2022-2-032) as a trial of treatment for viral pneumonia. All patients whose specimens were used and who participated in this study provided written, informed consent to have their case details and any accompanying images published. This study adhered to the Declaration of Helsinki.

2.3. Assessment of severity

The A-DROP system was used to evaluate pneumonia severity according to the Japanese Respiratory Society guideline[10, 11]. In brief, the A-DROP system is based on five clinical features: age (A), dehydration (D), respiration (R), orientation (O), and blood pressure (P). In this study, cases were classified as "mild" with none of the five criteria met, as "moderate" with one or two of the criteria met, as "severe" with three of the criteria met, and as "extremely severe" with four or five of the criteria met.

2.4. Statistical analysis

The Chi-squared test and the Mann-Whitney test were used to compare continuous variables between two groups. A p-value of less than 0.05 denoted a significant difference. All analyses were carried out using Stat View software (Version 5, Abacus Concepts, Cary, NC, USA).

3. Results

3.1. Patients' characteristics and treatments

A total of 285 COVID-19 and 12 influenza patients were admitted to our hospital in this period. Pneumonia was found in 46 of 285 (15.5%) COVID-19 patients and 6 of 12 (50.0%) influenza patients (Table 1). More influenza patients had pneumonia, and they were significantly younger than COVID-19 patients with pneumonia. There were more males than females with pneumonia among both influenza and COVID-19 patients.

Table 1. Patients' background characteristics by group

		COVID-19 pneumonia	Flu pneumonia	p value
Patients number		46 (46/285 =15.5%)	6 (6/12=50.0%)	0.002**
Male/Female		33/13 (Male :71.7%)	5/1 (Male:83.3%)	0.547
Age, years old		75.5 (45-93)	53.8 (19-73)	0.002**
Underlying diseases				
	Diabetes mellitus	7 (15.2%)	3 (50.0%)	0.042*
	Solid malignant tumor	6 (13.0%)	0	0.3469
	Brain stroke	6 (13.0%)	1 (1.7%)	0.806
	Dementia	5 (10.9%)	1 (1.7%)	0.676
	Heart diseases	4 (8.7%)	1 (1.7%)	0.533
	Neurological diseases	4 (8.7%)	0	0.452
	Mental disorders	2 (4.3%)	0	0.602
	Hematological diseases	2 (4.3%)	1 (1.7%)	0.543
	AIDS	1 (2.2%)	0	0.715
	Rheumatoid arthritis	1 (2.2%)	0	0.715
	Chronic lung diseases	1 (2.2%)	1 (1.7%)	0.259
	Kidney diseases	1 (2.2%)	0	0.715
Infection route				
	Clusters (Facilities)	9 (19.6%)	0	0.233
	Inpatients	5 (10.9%)	2 (33.3%)	0.129
	Nursing visit service	4 (8.7%)	0	0.452
	Home	4 (8.7%)	1 (16.7%)	0.533
	Work	2 (4.3%)	2 (33.3%)	0.012*
	Unknown	22 (47.8%)	1 (16.7%)	0.148
Vaccination				
	5 times<	4 (8.7%)	NA	
	4 times	5 (10.9%)	NA	
	3 times	6 (13.0%)	NA	
	Twice	7 (15.2%)	NA	
	Once	0	2 (33.3%)	0.304
	None	8 (17.3%)	4 (66.7%)	0.007**
	Unknown	16 (34.8%)	0	0.008

Of the underlying diseases, diabetes mellitus (DM) was significantly more common in influenza pneumonia patients than in COVID-19 pneumonia patients. Influenza pneumonia patients appeared to be infected more often in the work place and to be non-vaccinated than COVID-19 pneumonia patients.

3.2. Patients' status and bacteria isolated from sputum cultures

The rates of fever and dyspnea were similar between the influenza and COVID-19 pneumonia patients, but general malaise was more frequent in influenza pneumonia patients than in COVID-19 pneumonia patients (Table 2).

Table 2. Pneumonia conditions and findings by group

		COVID-19 pneumonia	Flu pneumonia	p value
Symptoms				
	Fever	30 (65.2%)	6 (100%)	0.082
	Dyspnea	11 (23.9%)	3 (50.0%)	0.175
	Nausea, vomitting	5 (10.9%)	0	0.396
	General malaise	3 (6.5%)	4 (66.7%)	<0.001**
	Low conciousness	2 (4.3%)	0	0.602
	Cough	2 (4.3%)	1 (2.2%)	0.223
	Palpitation	1 (2.2%)	0	0.715
	None	1 (2.2%)	0	0.715
Severity				
	Mild	9 (19.6%)	2 (33.3%)	0.474
	Moderate	31 (67.4%)	2 (33.3%)	0.103
	Severe	6 (13.4%)	2 (33.3%)	0.806
Bacteria				
	MSSA	1 (2.2%)	1 (16.7%)	0.082
	MSSA	1 (2.2%)	1 (16.7%)	0.082
	GAS	0	1 (16.7%)	0.005**
	MRCNS	1 (2.2%)	0	0.715
	E coli	1 (2.2%)	0	0.715
	Klebsiella spp	1 (2.2%)	0	0.715
Aspiration pneumonia		28 (28/46=60.9%)	1 (1/6=16.7%)	0.040*

Group A *Streptococcus* (GAS) was isolated more frequently in influenza than in COVID-19 pneumonia patients, and the other pathogenic bacteria, including methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus aureus* (MRCNS), *Escherichia coli*, and *Klebsiella* species were isolated at similar frequencies in influenza and COVID-19 pneumonia patients.

However, aspiration pneumonia was significantly more common in COVID-19 patients than in influenza pneumonia patients.

3.3. Treatments and Prognosis

Most of the COVID-19 pneumonia patients were treated by remdesivir drip infusion, and peramivir drip infusion and oral oseltamivir were frequently given to influenza pneumonia patients (Table 3).

Of the antibiotics, sulbactam/ampicillin (SBT/ABPC) was used significantly more often for COVID-19 than for influenza pneumonia patients.

Finally, 7 of 46 (15.7%) COVID-19 pneumonia patients died, and none of the 6 influenza patients died. The survival rates were not significantly different between influenza and COVID-19 pneumonia patients (p=0.304).

Table 3. Treatments and outcomes by group

		COVID-19 pneumonia	Flu pneumonia	p value
Antiviral agents				
	Remdesivir	33 (71.7%)	NA	
	Ensitrelvir	3 (7.8%)	NA	
	Molnupiravir	8 (17.4%)	NA	
	Nilmatorelvir/Ritnavir	2 (4.3%)	NA	
	Peramivir	NA	2 (33.3%)	
	Oseltamivir	NA	2 (33.3%)	
	Baloxavir marboxil	NA	1 (16.7%)	
	Laninamivir	NA	1 (16.7%)	
Antibiotics				
	SBT/ABPC	31 (67.4%)	1 (16.7%)	0.016*
	TAZ/PIPC	9 (19.6%)	1 (16.7%)	0.333
	LVFX	2 (4.3%)	1 (16.7%)	0.224
	CTRX	2 (4.3%)	1 (16.7%)	0.224
	VCM	1 (2.2%)	0	0.715
	CAZ	1 (2.2%)	0	0.715
	CEZ	1 (2.2%)	0	0.715
	CMZ	1 (2.2%)	0	0.715
	LSFX	1 (2.2%)	0	0.715
	MEPM	0	1 (16.7%)	0.005**
Death		7 (7/46=15.2%)	0	0.304

4. Discussion

Viral pneumonia is usually classified into two major types[12, 13]: pure pneumonia with pulmonary inflammation and/or edema due to viral infection alone, frequently observed in COVID-19 patients infected by the original strain before the omicron variant era[13, 14]; and secondary and/or mixed bacterial pneumonia with severe inflammation due to the combination of virus and bacteria and often exacerbated by cytokine storm[15, 16].

The latter type is well known in influenza, and it has been reported that more than 30% of influenza cases had this type of pneumonia as a fatal complication in the 2009 pandemic of influenza, although only 3% of COVID-19 patients had this latter type of pneumonia in the early days of the COVID-19 pandemic[4-6]. However, the type of pneumonia in COVID-19 patients might have changed since the omicron variant appeared[14, 17, 18].

In the present study, hospitalized influenza patients had more pneumonia and were younger than hospitalized COVID-19 patients who had pneumonia in the omicron variant era. In other words, aspiration pneumonia patients became very predominant, and SBT/ABPC was more commonly used in hospitalized COVID-19 pneumonia patients in the omicron variant era. The pathogenicity of omicron variants became weaker[18, 19], and most people, more than 80% of elderly people in Japan, had been vaccinated and/or had had COVID-19 once[20]; therefore, severe pulmonary lung complications/lung edema similar to acute lung injury might have decreased dramatically in 2022, compared with the original COVID-19 strain era around 2020.

Dee et al performed single infections and co-infections with SARS-CoV-2 combined with influenza virus or RS virus of cultures of human bronchial epithelial cells experimentally, and they found that influenza virus induced severe exfoliation of epithelial cells, but SARS-CoV-2 did not[21]. These data suggested that COVID-19 patients

did not develop severe inflammation by bacterial co-infection because the lung epithelial cells remained clean, although detached epithelial cells were found in influenza patients. In COVID-19, the patients did not die with omicron variant infection, but elderly patients became weakened and finally developed aspiration pneumonia, though SARS-CoV-2 had already disappeared 5-10 days after infection by the omicron variant.

In contrast, influenza-related pneumonia might become more severe due to bacterial co-infection and the effects of cytokine storm[16, 22], and our nationwide surveillance data also suggested that severe hospitalized influenza patients were elderly (peaked at 70 years of age), but extremely severe pneumonia patients, such as those who died, were more commonly younger, including those aged 30-50 years[23]. These data also suggested that influenza pneumonia including secondary bacterial pneumonia became predominant, and younger individuals tend to have influenza pneumonia. Greater attention to the care of younger people with influenza is needed.

This study had the limitation that it was performed in a single tertiary hospital in Japan, and small numbers of viral pneumonia patients were analyzed. A larger scale investigation and a greater number of patients will be needed to clarify the differences between COVID-19-related and influenza-related pneumonias, especially in the omicron variant era.

In conclusion, the clinical differences between COVID-19-related and influenza-related pneumonia patients in the omicron variant era were investigated. The pathogenicity of COVID-19 may now be less, and its related pneumonia has changed to the aspiration type of pneumonia in elderly people, but influenza pneumonia was more common and found in younger patients. We should take care of the aspiration pneumonia in elderly COVID-19 patients and the very frequent influenza pneumonia in younger patients in the omicron variant.

Contributions:

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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