Title

How many coinfected patients with influenza and COVID-19 are there in a single Japanese hospital during the first wave?

Running title

Coinfection with influenza and COVID-19

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Summary

Coronavirus disease 2019 (COVID-19) and influenza may infect a person simultaneously; hence, adequate measures must be prepared for the next winter in Japan. In preparation for the future, this study aimed to clarify the rate of influenza coinfection in patients with COVID-19 in previous winter. We conducted a retrospective study of the medical records of 193 patients diagnosed as having COVID-19 between January 31, 2020, and April 23, 2020, in a single hospital. We measured the rate of coinfection with COVID-19 and influenza. We found no patient was coinfected with influenza using rapid diagnostic testing. The occurrence of coinfection with influenza and COVID-19 seems to be rare in the past winter in Japan.

The ongoing pandemic caused by novel coronavirus, termed as coronavirus disease 2019 (COVID-19), has necessitated significant changes to our clinical practice in the treatment of patients with cold-like symptoms. A case of coinfection with influenza A and the novel coronavirus has been reported (1). This suggested a need to investigate the possibility of coinfection with both viruses.

On May 26, 2020, the World Health Organization (WHO) urged people to stay cautious against seasonal influenza activity, worldwide (2). Preparing for the winter, the Japan's Ministry of Health, Labour and Welfare Measures Promotion Headquarters published a guideline for novel coronavirus pathogen testing. It suggested that physicians should check patients for both seasonal influenza virus and SARS-CoV-2 infections during the seasonal influenza outbreak (3); establishing a system wherein people can be tested for both infections will help prepare for the impending third wave of COVID-19 in the winter. To determine ways on how to prepare for the next wave, we need to retrospectively observe and analyze the first wave. Hence, this retrospective study aimed to clarify the influenza virus coinfection rate in patients with COVID-19 during the first wave in Japan to prepare for overcoming the upcoming third wave.

We conducted a retrospective study using the medical records of patients diagnosed with COVID-19 between January 31, 2020, and April 23, 2020, in a single hospital (Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital). The study period began with the first COVID-19 patient's visitation and ended with the last rapid diagnostic testing for seasonal influenza virus in clinical practice, as we found that the seasonal influenza outbreak in 2019–2020 already ended on week 11 of 2020 (March 9–15) (4). All patients were diagnosed with COVID-19 at other hospitals

using reverse transcription-PCR assay for SARS-CoV-2 and were transferred to our hospital due to the availability of isolation rooms. The disease severity in this study was categorized based on the WHO guidelines (5). The following clinical factors of the patients were examined: age, sex, nationality, disease severity, diagnostic results for influenza and other pathogens, and imaging data.

We used rapid diagnostic testing to detect influenza virus (ESPLINE® Influenza A&B-N, Fujirebio) at the time of admission. The median elapsed time from the time of symptom onset to the time of influenza test result collection was 8 days (range, 0–26 days).

The study was conducted according to the Declaration of Helsinki. Regarding informed consent, the opt-out method (which provides opportunities to target patients for rejection through information disclosure via posting and publication) was employed without mandating informed consent from individuals for participation in this retrospective observational study. The institutional review board of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital approved the study protocol (IRB No: 2525).

Descriptive statistics were used to summarize the baseline characteristics of the patients. Continuous variables and non-normally distributed data are presented as median (range). For categorical variables, data are presented as n (%).

A total of 193 patients diagnosed with novel coronavirus were included in this study. The patient characteristics are summarized in Table 1. The median age of the

patients was 52 years (range 15–95). In total, 129 patients (66.8%) were male. As shown in Table 1, no major differences were noted in patient characteristics excluding nationality.

Most patients underwent rapid diagnostic testing for influenza, but none tested positive. Additionally, no patients received treatment for influenza.

The results of the present study suggest that SARS-CoV-2 and influenza virus coinfection were rare in the previous winter in Japan, consistent with a previous report that recorded a coinfection rate of only 0.08% (6).

Why are there few coinfected patients? Aren't there any coinfected patients or we just could not detect them? The reason might be that we only used rapid diagnostic testing for influenza. This test could yield an inaccurate result if it is performed at an early stage of infection, and is less sensitive as compared to PCR (7). Consequently, some patients with influenza may have been missed. However, in Japan, using rapid diagnostic testing for influenza is more reasonable than PCR because of the country's widespread system of inspection. Alternatively, were there few coinfected patients because some patients who caught both the influenza and COVID-19 did not visit the hospital? Or was it because many people who had fever in the previous winter were not tested for influenza because doctors did not want to perform the test considering the risk of splash exposure? This may be true to some extent, but we do not think that all people with coinfection did not visit the hospital or did not perform any influenza

swabs. For example, a sizable number of 567 people with influenza-like symptoms visited our hospital and underwent a rapid influenza test during the study period.

If indeed there were few coinfected patients at that time, how can we explain this result? The reason might be that influenza had not infected people across Japan at that time because of the time lag of the epidemic (8,9). Another possible explanation is that good social distancing protocols and infection prevention measures could have avoided the widespread transmission of infection (10,11). Viral interference is also a possible explanation for this result.

Viral interference is a phenomenon wherein infection by one virus is limited or delayed by other viruses. According to recent investigations, negative interactions exist between influenza and noninfluenza viruses on the scale of individual hosts (12). In addition, the influence of the second virus could change, depending on the order of infection in animal models (13). For instance, infection by influenza A (H1N1) pdm09 virus increases the proinflammatory cytokine levels in the respiratory tract, thereby inhibiting secondary infection by human respiratory syncytial virus. Patients with COVID-19 also have high proinflammatory cytokine levels (14). Thus, SARS-CoV-2 infection may inhibit infection by seasonal influenza viruses.

Previous research also indicated that the overall viral infection prevalence among patients remained broadly stable during a viral pandemic because of the simultaneous decline in the contributions of other viruses to the total infection burden (12). Seasonal influenza activity during the COVID-19 pandemic has been lower than in the previous years in Japan (9). Hence, it can also be one explanation for this result.

Several limitations of this study must be considered. First, we only used rapid

diagnostic testing for influenza. Second, this was a retrospective study that was performed at a single institution, and it featured a relatively small number of patients with COVID-19. Third, most patients with COVID-19 were diagnosed at other hospitals and then transferred to our hospital. Thus, this might have caused a selection bias. Fourth, we did not collect influenza vaccination history data in this study. Fifth, we performed the rapid influenza diagnostic test when patients were hospitalized, not at the symptom onset. The present study suggests that only few patients had coinfection in the previous winter. Which hypothesis is correct? Regarding this, we have insufficient clinical data. In this winter, high-quality, large-scale clinical research should be conducted to investigate the relationships between COVID-19 and influenza.

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Conflict of interests

None to declare

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Table 1. Patient characteristics

Characteristics (n = 193)	
Median age, years (range)	52 (15–95)
Sex, n (%)	
Male	129 (66.8%)
Male-to-female transgender	1 (0.5%)
Female	63 (32.6%)
Nationality	
Japan	173 (89.6%)
United states	4 (2.0%)
Australia	4 (2.0%)
Nepal	3 (1.6%)
China	2 (1.0%)
Philippines	2 (1.0%)
Bangladesh	2 (1.0%)
Korea	1 (0.5%)
Argentina	1 (0.5%)
Finland	1 (0.5%)
Severity n (%)	
Asymptomatic	5 (2.6%)
Mild	37 (19.2%)
Moderate	70 (36.2%)
Severe	74 (38.3%)
Critical	7 (3.6%)
Mycoplasma IgM testing, n (%)	39 (20.2%)
Detected	2 (5.1%)
Influenza testing, n (%)	179 (92.7%)
Detected	0 (0%)
Streptococcus pneumoniae urinary antigen testing, n (%)	129 (66.8%)
Detected	0 (0%)
Legionella pneumophila urinary antigen testing, n (%)	129 (66.8%)
Detected	0 (0%)