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Commentary

Detection of Various Respiratory Viruses Other than SARS-Cov-2 by Multiplex Polymerase Chain Reaction Analysis of Samples from Symptomatic Patients at a Drive-Through Style Outpatient Clinic in the End Stage of the COVID-19 Pandemic

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Abstract

There were a large number of symptomatic, but non-SARS-CoV-2 patients during the COVID-19 pandemic period. In a drive-through style clinic, diagnosis of viral pathogens including non-SARS-CoV-2 viruses was performed. At the COVID-19 pandemic end stage in the winter of 2023, virus genes were detected in 31 (56.4%) of 55 patients who had symptoms and/or a close contact history with COVID-19 patients by multiplex PCR methods. The coronavirus HKU1, OC43, human rhinovirus/enterovirus, parainfluenza virus 3, human influenza virus H3, adenovirus, and human metapneumovirus were detected, although SARS-CoV-2 genes were the most commonly detected (7/55 patients, 12.7%). Multiple virus genes were detected in 4/55 (7.2%) patients. This data suggests that respiratory non-SARS-CoV-2 viruses might also affect the prevalence of febrile patients, although COVID-19 patients were still predominant in the end stage of the pandemic.

Keywords Coronavirus; HKU1; OC43, Human rhinovirus/enterovirus; Parainfluenza virus 3; Human influenza virus; Adenovirus; Human metapneumovirus; Multiple viruses; SARS-CoV-2.

Commentary

The coronavirus disease 2019 (COVID-19) pandemic had been a critical issue in Japan and the world since February 2020, and a lot of hospitals, clinics, and facilities have started persons severe acute respiratory

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syndrome coronavirus 2 (SARS-CoV-2) surveillance by the polymerase chain reaction (PCR) and/or antigens test for febrile, symptomatic patients, and/or patients who have a close contact history with COVID-19 infected persons [1,2]. The trends of respiratory non-SAR-CoV-2 viruses, including influenza (Flu), human rhinovirus (HRV), human metapneumovirus (hMPV), and respiratory syncytial virus (RSV), may be important factors affecting the prevalence of SARS-CoV-2 in this COVID-19 pandemic era because virus-virus synergy/interference is known well [3]. Researchers previously reported that researchers found 11 HRV-infected patients among febrile and symptomatic 151 outpatients during the 2020 fall season, such as the middle of a COVID-19 pandemic [4]. However, no other viruses, including SARS-CoV-2, hMPV, RSV, and Flu were detected among the 151 outpatients in that period. Therefore, in the present study, researchers investigated the prevalence of respiratory non- SARS-CoV-2 viruses in the COVID-19 surge end period.

In researchers hospital, during January to February 2023, which was the COVID-19 pan-demic end period and omicron subvariants were dominant, respiratory virus genes in the nasal swabs from 55 patients with fever, symptoms, and/or a close con-tact history with COVID-19 patients were analyzed by the multiplex PCR method (BIOFIRE® FILMARRAY® Respiratory 2.1, bioMerieux, Lyon, France) at researchers drive-through style clinic for the diagnosis and confirmation of COVID-19 infections.

Patients average age was 29.5 years, and the ratio of male/female was 25/30 (Table 1). Seven patients had a history of close contact, and 15 patients had underlying diseases, including respiratory and cardiac diseases. Only one patient had diabetes mellitus. A total of 49 patients had symptoms-related with respiratory systems, including nasal discharge, sore throat, and cough known as the characteristic symptoms of the COVID-19 omicron subvariant [5]. No patient complained of loss of smell. 47 of 55 (85.5%) patients had finished the vaccination, including booster shots for SARS-CoV-2.

Virus genes were detected in 31 (56.4%) patients, with SARS-CoV-2 genes detected the most often (7/55, 12.7%) (Table 2). From the 31 virus-detected patients, 36 virus genes, such as the coronavirus HKU1, OC43, HRV/enterovirus, parainfluenza virus (PIV) 3, Flu H3, adenovirus, and hMPV were detected (Table 2). In addition, 4 of 55 (7.2%) patients had multiple virus genes: 3 patients had HRV/enterovirus plus PIV 3, and 1 patient had coronavirus HKU1 plus hMPV. A total of 31 virus genes were identified during this end of COVID-19 period; 7 (22.6%) were SARS-CoV-2, but the other 24 (77.4%) viruses were not, in contrast to researchers previous investigation that showed that HRV was dominant, and the other respiratory viruses were not detected, although that study period was in the middle of the COVID-19 period [4].

These differences might be dependent on the differences of not only the conditions of, the COVID-19 surge, but also the area. Researchers previously investigated the Sendai area, which is relatively urban, but far from the Tokyo metropolitan area. In the present study, in the Saitama area, which is

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relatively rural, but very close to the Tokyo metropolitan area, with large population flows, was investigated. A variety of the virus might have inflowed because the people interacted with the Tokyo metropolitan All three flu-detected patients showed high fever over 38.5 °C, although 7 of the SARS-CoV-2 patients showed mild fever but had sore throat as patients' main complaint (data not shown). Although most people were vaccinated for SARS-CoV-2, In the omicron era, the Flu and COVID-19 might be able to be distinguished. These two viruses are known to induce severe conditions, especially when co-infected [6].

Age	29.5 (1-62)
Male/Female	25/30
Close contact history	
yes	7
no	48
Underlying diseases	15
Respiratory	5
Heart	3
Obesity	2
Kidney	1
Liver	1
Neurology/Brain	1
Diabetes mellitus	1
Pregnancy	1
None	38
Fever	
Yes	19
No	36
Symptoms	49
Cough	17
Nasal discharge	17
Sore throat	14
General malaise	10
Headaches	10
Joint pain	6
Chest oppression	3
Abdominal pain	2
Vomiting	2
Diarrhea	2
None	6
Vaccination for COVID-19	85.5% (47/55)

Table 1: Clinical characteristics of the 55 patients.

Anti-viral agents for these two viruses have been developed and have become available; the pathogens should be con-firmed rapidly, and treatment and infection control started immediately. In addition, other respiratory viruses, such as the coronavirus

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HKU1, OC43, HRV, PIV3, adenovirus, and hMPV, were identified. Coronavirus HKU1 and OC43 are also known as common cold viruses, but the patients sometimes develop severe infections with pneumonia, and the differential diagnosis might be difficult [7]. HRV-infected patients were recently adult patients who had underlying diseases [4]. A variety of infectious diseases were diagnosed, and bacteria, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Escherichia coli*, were also detected in some of these HRV-infected patients. These virus-bacteria co-infected patients needed to be immediately treated by anti-biotics, in the same manner as flu-related secondary pneumonia [8,9]. PIV3 is known as one of the important respiratory pathogens, especially in pediatric patients, and it causes outbreaks in nursery schools [10]. Adenovirus infections are usually mild, but could induce life-threatening disease in the respiratory systems, especially in immunocompromised children [11,12]. Most hMPV co-infected with the other respiratory viruses, but these are pathogenic to not only children, but also elderly persons [13,14]. Patient should take care of these respiratory non-SARS-CoV-2 viruses in the COVID-19 pandemic end stage. Although the post-COVID-19 era may be coming in Japan and worldwide, early diagnosis by multiplex PCR, early treatment by anti-viral agents, and development of new vac-cines for respiratory viruses other than SARs-CoV-2 and Flu will be needed im-mediately.

	Detected number
SARS-CoV-2	7 (19.4%)
Coronavirus HKU1	7 (19.4%)
Human Rhinovirus/Enterovirus	6 (16.7%)
Coronavirus OC43	5 (13.9%)
Parainfluenza Virus 3	5 (13.9%)
Influenza A H3	3 (8.3%)
Adenovirus	2 (5.6%)
Human Metapneumovirus	1 (2.8%)
Total	36 (100%)

Table 2: Detected viruses from 55 symptomatic patients and/or patients with a contact history;4 patients co-infected two virus: 3; human rhinovirus/enterovirus + parainfluenza virus 3, and 1 patient; coronavirus HKU1+human metapneumovirus, respectively.

Ethics

This study and related analysis were ap-proved by the Institutional Review Board of Saitama Medical University International Medical Center on July 06 and December 27, 2022 as #2022-032 and #2022-146, and registered as UMIN000047691.

The patients whose specimens were analyzed provided written, informed consent to have any accompanying images and patients case details published. This study was performed according to the Declaration of Helsinki.

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