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Case Study

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TESTING RE-POSITIVE FOR SARS-COV-2 INFECTION AFTER DISCHARGE: 31 RE-POSITIVE OR RE-INFECTION CASES IN JAPAN

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ABSTRACT

Although the COVID-19 disease was expected to have been cured, there are a lot of infected individuals in the world who showed a positive response again for SARS-CoV-2 infection through PCR. The viral load detected in asymptomatic patients was similar to that in the patients demonstrating COVID-19 symptoms. In addition, PCR testing using stool samples rather than nasopharyngeal swab samples may be necessary to determine SARS-CoV-19 infection. Experts in viral infections are paying close attention to these features of SARS-CoV-2. In this Review, issues and improvements related to PCR testing for COVID-19 will be described along with new findings.

KEYWORDS: COVID-19, Positive response, Re-positive response, SARS-CoV-2, RT-PCR.

The novel coronavirus 2019, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) epidemic, which was first reported in December 2019 in Wuhan, China, has been declared a public health emergency of international concern by the World Health Organization (WHO). The coronavirus disease 2019 (COVID-19) has resulted in a pandemic associated with substantial morbidity and mortality. SARS-CoV-2 is genetically related to SARS-CoV, which caused a global epidemic with 8096 confirmed cases in more than 25 countries in 2002 and 2003.[1] The SARS-CoV epidemic was successfully contained through public health interventions, including case detection and isolation. Transmission of SARS-CoV occurred mainly after days of illness[2] and was associated with modest viral loads in the respiratory tract early during the illness, with viral loads peaking approximately 10 days after the onset of symptoms.[3]

The most frequent and reliable test used for the diagnosis of COVID-19 has been the reverse transcription-polymerase chain reaction (RT-PCR) test conducted using nasopharyngeal swabs or other upper respiratory tract specimens, including throat swabs or, more recently, saliva. A variety of SARS-CoV-2 genome RNA gene targets have been used by different manufacturers; with most tests targeting 1 or more of the envelope (*env*), nucleocapsid (*N*), spike glycoprotein (*S*), RNA-dependent RNA polymerase (*RdRp*), and open reading frame 1 (*ORF1*) genes. The test sensitivities to individual genes are comparable according to comparison studies, except the RdRp-SARSr (Charite) primer probe, which has a slightly lower sensitivity because of a likely mismatch in the reverse primer.[4]

Although the COVID-19 disease was expected to have been cured, there are at least 31 infected individuals in Japan who showed a positive response again for SARS-CoV-2 infection through PCR. Patients who were confirmed to be negative for SARS-CoV-2 infection by PCR were discharged from the hospital; however, some patients had COVID-19 symptoms recurring 1 month after discharge. The cause of this re-positive response for SARS-CoV-2 infection could be that the virus remaining in the patient's body has re-grown or that a second infection with SARS-CoV-2 in the same patient has occurred. The definitive cause of the re-positive response in patients has not been clarified. Experts in viral infections are paying close attention to these features of SARS-CoV-2.

At the end of February 2020, after the PCR test confirmed a negative result for SARS-CoV-2 infection, a positive result of infection was confirmed. The first such case was reported in Osaka Prefecture in Japan. Although this re-positive response of SARS-CoV-2 infection was confirmed as a rare case, in March 2020, the Japanese Ministry of Health, Labor and Welfare demanded that medical staff check the health status of the infected person for 4 weeks after discharge.

Such cases have now been recognized in each region of Japan. An infectious disease specialist examined the re-positive response cases of SARS-CoV-2 infection in Japan. By May 6, 2020, a re-positive response for SARS-CoV-2 infection was confirmed in a total of 31 individuals in their 20s and 90s. Twenty-eight infected individuals demonstrated COVID-19 symptoms again after discharge. No COVID-19 symptoms were observed in 3 of the infected individuals, but a re-positive response for SARS-CoV-2 infection was confirmed by repeated PCR tests. Medical staff examined the course of COVID-19 symptoms in 24 infected individuals who showed a re-positive response for SARS-CoV-2 infection. As a result, the period from discharge to the time when COVID-19 symptoms were seen again ranged from 1 to 31 days, with an average of 9.1 days.

Case 1: By the end of February 2020, a woman in her 20s in Nagoya City who had a cough and fever of 38.5°C was diagnosed with pneumonia and was confirmed to be infected with SARS-CoV-2 (Figure 1). The woman was hospitalized for approximately 10 days and discharged. However, 1 month after discharge, she presented with coughing again. A PCR test was performed and re-positive response for SARS-CoV-2 infection was obtained. In Nagoya City, a total of 4 individuals were confirmed to demonstrate COVID-19 symptoms again after discharge and were confirmed to have a re-positive response for SARS-CoV-2 infection. According to the Japanese Ministry of Health, Labor and Welfare, "SARS-CoV-2 has many undisclosed parts, so it is no wonder what happens."

Case 2: SARS-CoV-2 infection was confirmed by PCR test in a woman in her 40s. She was a nurse in Hokkaido who presented with fatigue and fever. Eight days after admission to the hospital, her COVID-19 symptoms disappeared (Figure 1). Additional PCR testing at the public health center conducted twice in succession revealed a negative response to SARS-CoV-2 infection, and the woman was discharged from the hospital. Ten days after discharge and staying at, another PCR test was performed at the hospital. Although the result of the PCR test was positive for SARS-CoV-2 infection, the woman had normal temperature and demonstrated no COVID 19 symptoms.

PCR tests were repeated in the hospital every few days. As a result, in 4 out of 5 PCR tests, the woman had a positive response for SARS-CoV-2 infection. A second PCR test at the health center revealed that the woman was positive for SARS-CoV-2 infection. One month after being discharged, the woman was readmitted to the hospital.

In Zhuhai City, Guangdong Province, China, a total of 18 patients were confirmed to show a positive response for SARS-CoV-2. Medical staff examined the correlation between COVID-19 symptoms and the viral load.[5] The staff collected 72 nasal swab and 72 pharyngeal swab samples from 1 asymptomatic patient and 17 patients demonstrating COVID-19 symptoms. The correlation between COVID-19 symptoms and the viral load was continuously monitored. In 1 patient who showed no clinical signs, a positive response for SARS-CoV-2 was confirmed using a nasal swab sample and a pharyngeal swab sample. In 17 patients demonstrating COVID-19 symptoms, a high viral load was detected immediately after onset. Furthermore, the viral load in nasal swab samples was higher than that in pharyngeal swab samples.[5] A clinical study in Zhuhai, Guangdong Province, China confirmed that the release pattern of viral nucleic acid in COVID-19 is similar to that of influenza.[1] In addition, the viral load detected in asymptomatic patients was similar to that in the patients demonstrating COVID-19 symptoms.[5]

The timeline for PCR positivity is different in specimens other than nasopharyngeal swab. PCR positivity declines more slowly in sputum samples and may remain positive even after nasopharyngeal swabs are negative.[6] In one study, PCR positivity in stool samples was observed in 55 out of 96 (57%) infected patients and remained positive beyond nasopharyngeal swab by a median of 4 to 11 days. However, this was found to be unrelated to clinical severity (Figure 2).[7] Persistence of PCR positivity in sputum and stool samples was found to be similar as assessed by Wolfel *et al*.[6] PCR testing using stool samples rather than nasopharyngeal swab samples may be necessary to determine SARS-CoV-19 infection.

In Tokyo, no notification has been approved regarding re-positive testing for SARS-CoV-2 infection. However, at a public health center in Tokyo, there is a consultation from a person infected with SARS-CoV-2, who claims to have become ill again after being discharged from the hospital. The Japanese National Institute of Infectious Diseases and the Ministry of Health, Labor and Welfare research team are analyzing such cases.

Footnote

The materials (manuscript and figures) presented here are original research, have not been published previously, and have not been submitted for publication elsewhere while under consideration.

Disclosure

The authors declare no potential conflicts of interest. The funders had no role in study design, data collection, and analysis; decision to publish; or preparation of the manuscript.

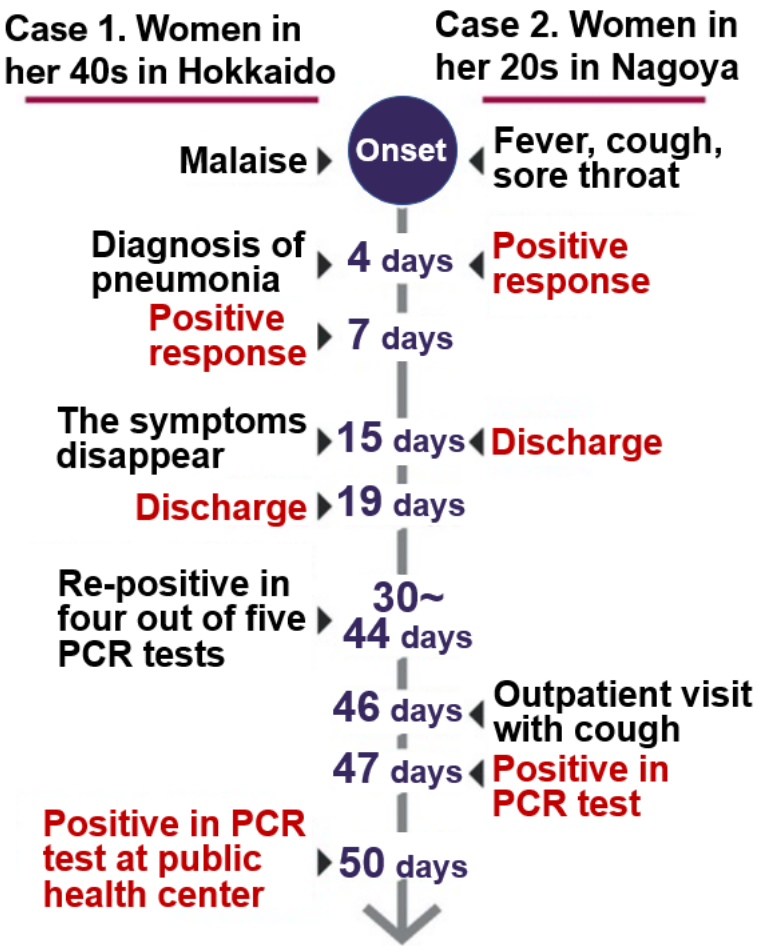

Figure 1: Cases of positive viral infection after discharge from the hospital.

Case 1: By the end of February 2020, a woman in her 20s in Nagoya City who presented with a cough and fever of 38.5°C was diagnosed with pneumonia and confirmed to be infected with SARS-CoV-2.

Case 2: SARS-CoV-2 infection was found by PCR test in a woman in her 40s, a nurse in Hokkaido, who presented with fatigue and fever. Eight days after admission to the hospital, her COVID-19 symptoms disappeared.

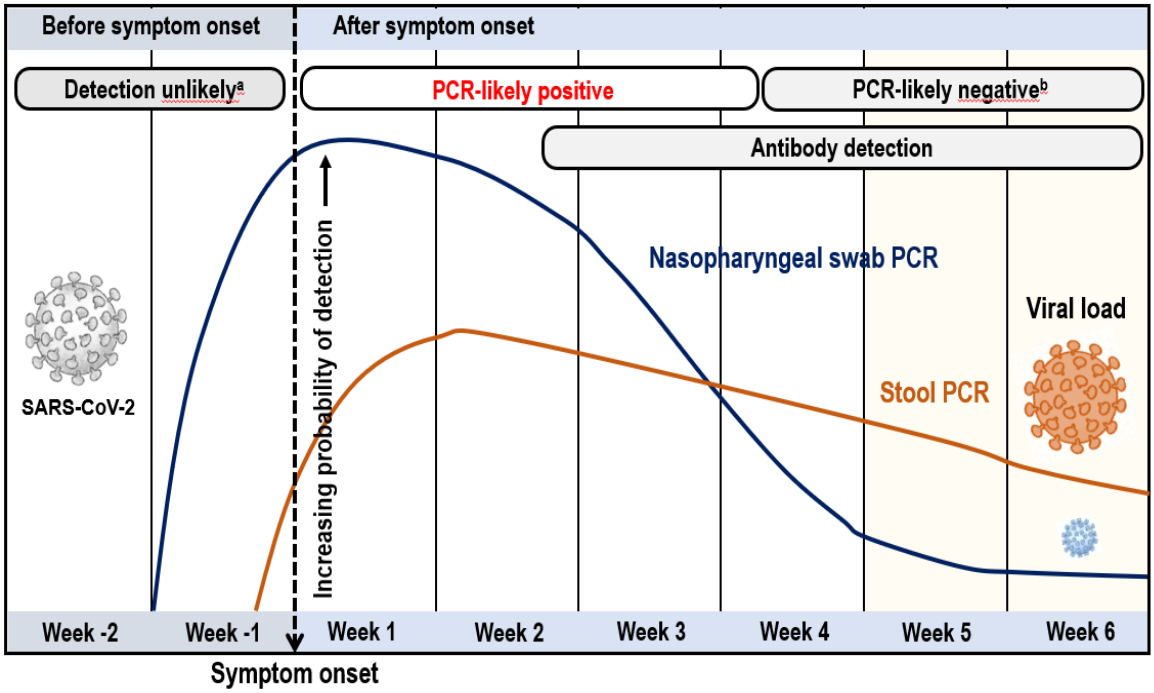

Figure 2: Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset.

Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2. Figure 2 is adapted from doi: 10.1001/jama.2020.8259.

[a]Detection occurs only if patients are followed up proactively from the time of exposure.
[b]More likely to register a negative result than a positive result by PCR of a nasopharyngeal swab.

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