

Prolonged Viral Shedding in Three Young Adult Cases of COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus-2 infection is usually self-limited, with a short duration for viral shedding within several weeks. However, prolonged viral shedding has been observed in severe or immune-compromised coronavirus disease 2019 (COVID-19) cases. Here, we reported that three young adult cases of COVID-19 patients, who were either immunosuppressed nor severe, showed prolonged viral RNA shedding from the upper respiratory tract for 58, 81, and 137 days since initial diagnosis. To our knowledge, this is the longest duration of viral shedding reported to date in young adult patients. Further studies on factors relevant to prolonged viral positivity, as well as the correlation between viral positivity and transmission risk are needed for the optimal management of COVID-19 patients with prolonged nucleic acid positive.

Keywords: COVID-19; Immune-competent; Prolonged viral shedding; SAR-CoV-2

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared as a global pandemic by WHO due to the widespread infectiousness and high contagion rate, resulting in a severe threat to public health and safety worldwide.^[1] More than 200 million confirmed cases of the COVID-19 have been reported to World Health Organization (WHO) on November 2021, with an average fatality rate of almost 2.0%.

The viral ribonucleic acid (RNA) detection by polymerase chain reaction (PCR) is widely used for determining an appropriate period of quarantine, and is important for determining control strategies to manage the disease and to reduce transmission. Most people who have COVID-19 recover within a few weeks, while a number of patients exhibit prolonged virus shedding in the body, with the longest duration for over 110 days. The median duration of viral shedding from the time of symptoms onset were 17 days (95% CI 15.5–18.6) in upper respiratory tract samples and 21.8 days (95% CI 16.4–27.1) in feces.^[2]

The factors associated with prolonged SARS-CoV-2 RNA shedding in COVID-19 patients have not been well understood. Several

risk factors including administration of immunosuppressant drugs (such as corticosteroids and B cell-depleting antibodies), delayed admission to the hospital, severe illness at admission, male sex, as well as old age have been found to be responsible for prolonged viral shedding.^[3] Moreover, recent reports suggested that impaired CD8⁺ T cells and lower NK cell count correlates the most with a longer duration of viral shedding.^[4,5] However, persistent viral positivity was rarely observed in immune-competent individuals.

Here, we reported three young adult cases of COVID-19 patients with prolonged SARS-CoV-2 RNA shedding, for 58, 81, and 137 days from initial diagnosis, and the three patients were strictly quarantined before re-admission, which excludes environment contamination or reinfection. Notably, the manifestations of these cases were mild or asymptomatic, with no relevant risk factors mentioned above. Therefore, a better understanding of the factors and impacts associated with prolonged viral shedding is warranted, which can facilitate better individual well-being and healthcare.

Case presentation

The study was approved by the Institutional Review Board of the Fourth People's Hospital of Nanning, and written informed consents were obtained from the participants.

Case 1

The patient was a 26-year-old female who was living in Wuhan and identified as a close contact with confirmed COVID-19 patients on January 2020. She was admitted to hospital on January 22, with symptoms of rhinorrhea, sore muscles, and asthenia for 3 days. She had no history of clinically significant underlying conditions, and no indications of compromised immunity. After hospitalization, the computed tomography (CT) scan revealed inflammation of the lower lobe of the left lung. She was tested positive for SARS-CoV-2 RNA on January 30. The patient received antiviral therapy including piperacillin, oseltamivir, and

Wen-Yi Dong and Ming-Ju Zhou contributed equally to this work.

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Infectious Diseases & Immunity (2022) 2:4

Received: 2 September 2021

First online publication: 6 January 2022

<http://dx.doi.org/10.1097/ID9.0000000000000041>

moxifloxacin and had remission of symptoms. Then, she was discharged from the hospital after two negative PCR results. Then she was quarantined at home, but tested positive again in the 4-week visit after discharge and showed asymptomatic. On re-admission, she was asymptomatic and received traditional Chinese medicine. SARS-CoV-2 serology was positive by chemiluminescent immunoassay (CIA) on re-admission. Moreover, the CT scan revealed a significant improvement in pulmonary infection compared to the first admission. After two negative PCR results performed 24 hours apart, she was discharged on March 21 and the timeline events for her were shown in Figure 1A. Laboratory results are shown in Table 1.

Case 2

The patient was a 25-year-old male who was working in Jakarta, Indonesia. On July 24, 2020, he complained of cough, fever, and fatigue with no medical history of immunodeficiency-related diseases. After the diagnosis of SARS-CoV-2 related pneumonia, the patient was admitted to local hospital. On August 17, he was asymptomatic and considered clinically recovered. After leaving the hospital, he was isolated in a single room arranged by the company. On September 16–18, after 55 days post initial diagnosis, three consecutive nasopharyngeal swabs (NPS) nucleic acid tests were reported negative at the local hospital, and then he returned to China but tested positive again at the customs outpatient department on September 22, 2020, but showed clinical asymptomatic. After hospitalization, the patient received antiviral treatment including arbidol tablets and Lianhuaqingwen (a Chinese herbal medicine) according to Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment. SARS-CoV-2 serology was positive by CIA. The patient was kept continuous NPS nucleic acid tests and discharged from the hospital after two negative PCR results 86 days after initial diagnosis as shown in Figure 1. Laboratory results are shown in Table 1.

Case 3

A 37-year-old male returned to China from Jakarta, Indonesia on December 29, 2020. He was tested NPS positive without clinical symptoms at entry. Then he was admitted to hospital and given interferon atomization, arbidol, Lianhuaqingwen, and traditional

Chinese medicine decoction for treatment. Two consecutive swabs of the throat and NPS were negative for PCR after treatment. The patient was discharged from hospital on February 28 and quarantined at home, but tests positive again 2 weeks later with asymptomatic. SARS-CoV-2 serology was positive by CIA on re-admission. After re-admission, antiviral treatment was continued, but the nucleic acid tests were positive for several times. He was discharged on March 21, 24 hours after two NPS negative intervals. The timeline events for him were shown in Figure 1. Laboratory results are shown in Table 1.

Discussion

The viral RNA shedding patterns in COVID-19 patients are diverse due to the heterogeneously clinical spectrum of the disease. Prolonged SARS-CoV-2 shedding in cases of immunodeficiency or older age has been reported.^[3] Recent research reports that prolonged SARS-CoV-2 shedding leads to viral evolution and reduced sensitivity to neutralizing antibodies in an immunosuppressed individual treated with convalescent plasma.^[6] In this report, we describe prolonged viral shedding duration in three young individuals without immunodeficiency-related diseases, and one of them was up to 137 days from the initial positive PCR test of COVID-19. Since these patients were strictly quarantined from the first discharge to re-admission, and cycle threshold (Ct) values for positive PCR test during rehospitalization were high [Figure 1], it is not likely they were reinfected. In addition, no new confirmed cases were reported in relation to these three cases reported here. Our data suggested that prolonged SARS-CoV-2 shedding can be found in mild or even asymptomatic cases, highlighting the need for evaluating transmission risk in COVID-19 patients with prolonged nucleic acid positive.

The RNA positivity is widely used as a marker of infectivity to guide the duration of quarantine.^[7] Currently, China applies a strict strategy for patient discharge and de-isolation. For discharge, the criteria are two consecutively negative PCR (interval ≥ 24 hours), improved respiratory symptoms, and obvious absorption of inflammation in pulmonary imaging. For de-isolation, the criteria are RNA negative 2 weeks after discharge. However, it remains unclear whether the prolonged viral shedding is associated with lasting infectivity. Prolonged hospital stays and quarantine can be a

Table 1: Clinical characteristics of patients

	Case 1	Case 2	Case 3
Age (years)	26	25	37
Sex	Female	Male	Male
BMI (kg/m ²)	19.0	26.2	20.3
Symptoms	Rhinobyon, fatigue sore muscles	Cough, fever, fatigue	Asymptomatic
Onset to admission (days)	3	3	N/A
Disease severity	Mild	Mild	Asymptomatic
Re-admission			
CRP (mg/L)	<0.5	4	1
CD4+ T cells (cells/mL)	426	773	847
CD8+ T cells (cells/mL)	558	891	560
IgG	Positive	Positive	Positive
IgM	Negative	Positive	Negative
Ct values	N/A	27.35	31.65
Treatment	Traditional Chinese medicine	Arbidol, Lianhuaqingwen	Arbidol, Lianhuaqingwen

BMI: body mass index; CRP: C-reactive protein; Ct: Cycle threshold; IgG: Immunoglobulin G; IgM: Immunoglobulin M; N/A: Not available.

significant challenge to healthcare resources, as well as to patients' mental health outcomes, such as fears, frustration, boredom, inadequate information, financial loss, anxiety, and stigmatization.

The confirmation of SARS-CoV-2 infection mainly depends on PCR, which can only detect part of viral genome, and cannot distinguish infective virus from inactive virus.^[8] Virus culture assays,

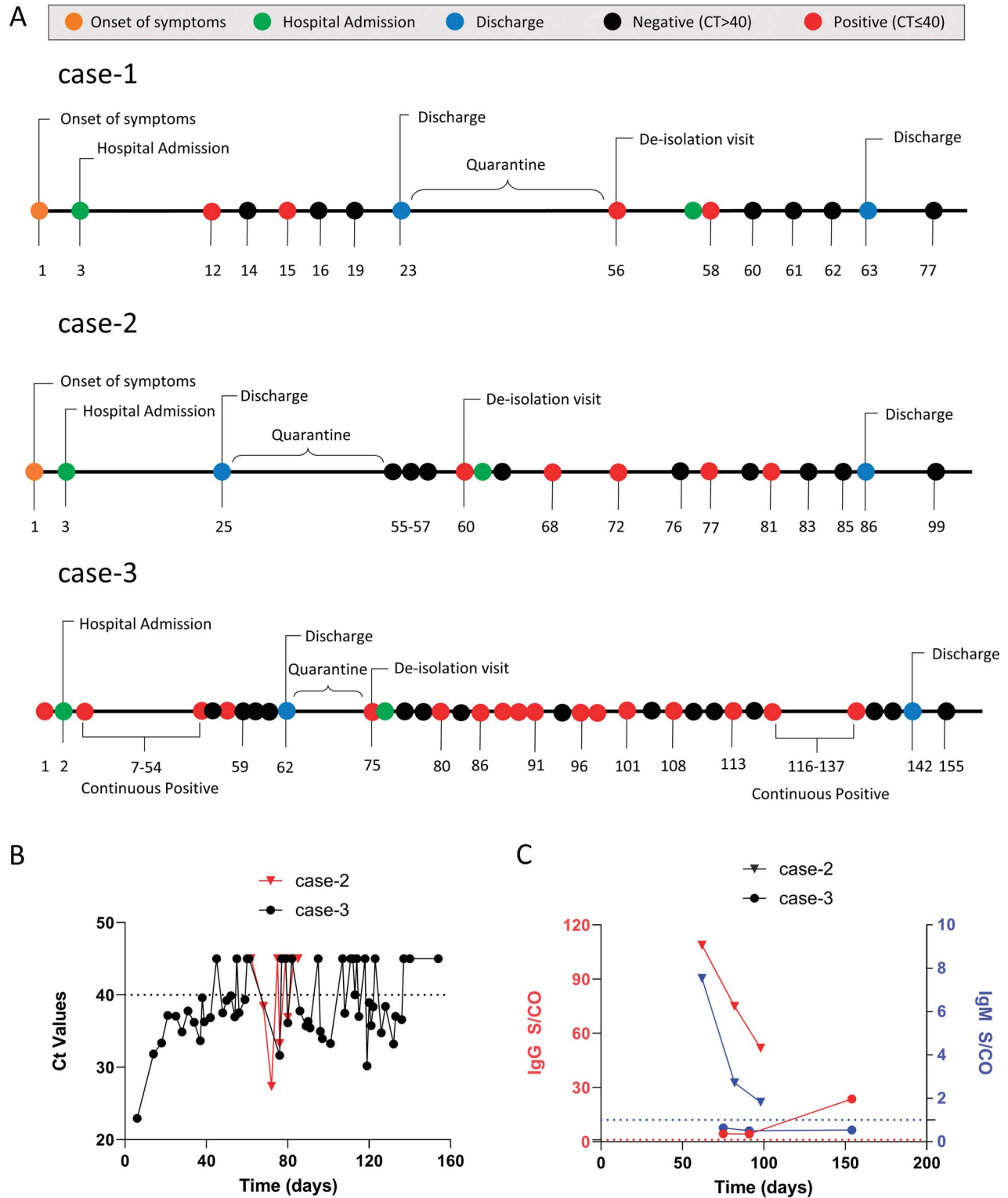


Figure 1: (A) Timeline of events for the three cases with prolonged viral shedding in this study. (B) The dynamic information of PCR Ct values and (C) IgG or IgM antibody titers of re-admission for case-2 and case-3. Ct: cycle threshold.

which are the gold standard for verification of infectivity, but live virus culture is time-consuming, require high stringent biosafety measures, and there is also the problem of potentially low detection rates. Therefore, it is urgent to develop new strategies for infectious assessment to manage patients with prolonged viral shedding. For example, it was recommended to detect subgenomic SARS-CoV-2 RNA to monitor the shedding of infectious virus.^[9] In addition, studies have shown that infectious virus particles mainly exist in the early stage of infection, although nucleic acid is positive in the later stage, but the possibility of infectivity is low.^[10] Moreover, the Ct values of PCR can be used as quantitative measure for predicting the infectivity of shedding virus.

In conclusion, in this study, we presented three non-severe cases of COVID-19 with prolonged viral shedding. Although lack of insight for exact mechanism, our observations called for developing strategies to evaluate viral infectivity in persistently SARS-CoV-2 positive individuals, which might have significant implications on current isolation/quarantine and work restriction policies.

Funding

This study was supported by the Key Research and Development Program of Guangxi (AB20059001).

Author Contributions

Zhou-Hua Xie conceived and designed the study. Wen-Yi Dong and Zhou-Hua Xie took care of patients and provided the clinical information. Ming-Ju Zhou and Chao Zhang drafted the manuscript. Lei Huang and Fu-Sheng Wang provided comments on the study. All authors revised the manuscript and approved the final manuscript.

Conflicts of Interest

None.

Editor note: Chao Zhang and Fu-Sheng Wang are the editors of Infectious Diseases & Immunity. The article was subject to the journal's standard procedures, with peer review handled independently by these editors and their research groups.

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Edited By Haijuan Wang

How to cite this article: Dong WY, Zhou MJ, Huang L, et al. Prolonged viral shedding in three young adult cases of COVID-19. *Infect Dis Immun* 2022;2(4):289–292. doi: 10.1097/ID9.0000000000000041