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LETTER TO THE EDITOR

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Recurrence of positive SARS-CoV-2 in patients recovered from COVID-19

Dear Editor,

In December 2019, an outbreak of respiratory infectious disease (COVID-19) due to a novel coronavirus (at the time officially named SARS-CoV-2) emerged in the city of Wuhan in the Chinese province of Hubei. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 12 March 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). As of 20 May 2020, this pandemic has affected 213 countries and territories around the world with 4 989 546 confirmed cases and 324 974 deaths (https://www.worldometers.info/coronavirus/).

The currently recommended medical observation period or containment period for COVID-19 patients is 14 days. According to the WHO's guidelines on clinical management, a patient can be discharged from hospital after two consecutive negative polymerase chain reaction (PCR) results at least 24 hours apart in a clinically recovered patient (https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation). However, prolonged SARS-CoV-2 RNA shedding with a median duration of 53 days and a maximum of 83 days has been reported recently in 36 patients by Li et al[1] in the *Journal of Medical Virology*. In another study, a median viral shedding duration of 20 days was observed with a maximum of 37 days.[2] In addition to prolonged carriage, the recurrence of SARS-CoV-2 in patients who had recovered from COVID-19 has been described.[3-5] Yuan et al[4] showed that 14.5% (25/172) of discharged COVID-19 Chinese patients with negative PCR, had a later positive RT-PCR test for SARS-CoV-2. This proportion was 21.4% (15/70) and 9.1% (5/55) in other studies.[3,4] These patients had experienced an average of 15.36 ± 3.81 days in hospital and the average period between the previous discharge and the positive test was ranged from 4 to 17 days.[4,5]

Currently, there is a certain possibility of reverse-transcription PCR (RT-PCR) rendering false negative results, including due to the sampling procedure, sources of samples and the sensitivity/specificity of the nucleic acid test kit.[6] It is, therefore, possible that recurrences should be actually persistent infections in which the PCR resulted falsely negative at discharge. Indeed, a high false-negative rate (48/384, 12.5%) of RT-PCR results for SARS-CoV-2 detection was observed.[7] Patients with two consecutive false negative RT-PCR results had a significant longer nucleic acid conversion time (period from the date of symptom onset to the first negative RT-PCR result), 36 days vs 21 days, $P < .001$, compared with the control group.[3] Nasal swab sampling rather than throat swabs and anal swabs for SARS-Cov-2 testing could reduce the false negative rate of nucleic acid tests.[3] Currently, due to the underestimated proportion of patients with prolonged SARS-CoV-2 RNA conversion and high false negative rate of viral test results, recurrence of positive SARS-CoV-2 may occur from false negative RT-PCR results. A longer observation period should be considered for certain groups of recovered COVID-19 patients.

Alternatively, it cannot be excluded that truly negative discharged patients suffered reactivation or were re-infected with another SARS-CoV-2 strain. SARS-CoV-2 reactivation or reinfection will be a persistent and vexing problem. It is a major public health concern in terms of global morbidity and possibly mortality. We suggest conducting a genetic characterization of viruses to distinguish between reactivation and reinfection with SARS-CoV-2 in the context of confirmed recurrence during patient convalescence.

Little is known about prolonged SARS-CoV-2 RNA shedding and recurrence of viral RNA shedding in asymptomatic patients. The asymptomatic rate in SARS-CoV positive patients may be high and documented transmission by asymptomatic carriers has been described.[8] In addition, SARS-CoV-2 RNA detection was found positive in anal swabs but negative in nasopharyngeal swabs for 42 days in an asymptomatic carrier, raising the question of a possible transmission via fecal-oral route.[9] Serological tests could be used to facilitate identification of asymptomatic COVID-19 patients in the community.[10]

To our knowledge, no other study has thus far been conducted that investigates the contagiousness of patients with prolonged or recurrence of viral RNA shedding. If such patients actually carry living viruses and are therefore contagious when they are released from quarantine, they might be a potential and mobile infectious source to others. The living/dead status of SARS-CoV-2 should be taken into consideration for infection control. When possible, viral cultures are recommended to more accurately assess the contagiousness of these patients.

Considering the significance of this ongoing global public health emergency, it is necessary to carry out large studies to better understand the issue of potential SARS-CoV-2 recurrence in COVID-19 patients.

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