LETTER TO THE EDITOR

Recurrent positive SARS-CoV-2: Immune certificate may not be valid

To the Editor,

Currently, coronavirus disease in 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] has become a global pandemic. The presence of SARS-CoV-2 in patients with COVID-19 is usually confirmed using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) method.[2] Our hospital previously reported four cases of recurrent positive RT-PCR test results in healthcare providers recovered from COVID-19.[3] It is still unknown to what extend this problem occurs and why it happens. Many also believe that people who have had COVID-19 and been tested positive for immunoglobulin G (IgG) antibodies for SARS-CoV-2 may show that as an immune certificate and return to normal life. We assessed the rate of recurrent positive RT-PCR test results for SARS-CoV-2 in patients who were recovering from COVID-19 and the results of their immunoglobulin M (IgM)/IgG tests[4] for SARS-CoV-2.

We used data from 150 patients who were recovering from COVID-19 and received RT-PCR tests and IgM/IgG rapid tests for SARS-CoV-2 in Zhongnan Hospital of Wuhan University in Wuhan, China from 1 March 2020 to 13 March 2020. Patients who were recovering from COVID-19 had two consecutively negative RT-PCR test results separated by at least 24 hours. Methods for RT-PCR test for SARS-CoV-2 in throat swabs and serum IgM/IgG rapid test were previously described.[3,5] Serum IgM and IgG antibodies to SARS-CoV-2 were measured with COVID-19 IgM/IgG chemiluminescence test kit on a fully-automated chemiluminescence immunoassay analyzer. The test kit contained recombinant SARS-CoV-2 antigen (spike protein and nucleocapsid protein) labeled with magnetic beads, anti-human IgM monoclonal antibody, and anti-human IgG monoclonal antibody. Data were collected from electronic medical records. The study was approved by the institutional ethics board at Zhongnan Hospital. Requirement for written informed consent was waived.

Age and days from symptom onset to test were reported as median and interquartile range and differences were compared using Mann-Whitney test. Categorical variables were described as frequency rates and percentages. The χ^2 test was used for the comparison of categorical variables and Fisher's exact test was used when frequency was too low. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute; Carey, NC). A two-sided $P < .05$ was considered statistically significant.

Among 150 patients who were recovering from COVID-19, 11 (7.3%, 95% confidence interval: 3.1%-11.6%) tested positive again for SARS-CoV-2 in throat swabs. Positive rates for SARS-CoV-2 did not differ by sex or age. Characteristics were similar between those positive and those not (Table 1). There were no differences in the prevalence of IgM or IgG to SARS-CoV-2 (Figure S1) or serum levels of these antibodies (Table 1) between those positive and those not. All those with recurrent positive SARS-CoV-2 were tested positive for IgG to this virus.

Recurrent positive RT-PCR tests for SARS-CoV-2 were found in 7.3% of patients who were recovering from COVID-19, indicating that this is a quite common problem. Presence of IgM to SARS-CoV-2 was similar between those with recurrent positive RT-PCR test results and those without, which strongly suggest that it is unlikely due to reinfections with SARS-CoV-2 viruses. Those patients with recurrent positive SARS-CoV-2 most likely never fully cleared the virus from their systems. Whether they will eventually eradicate the virus is to be studied. The possibility of chronic infection with SARS-CoV-2 could not be ruled out and should be closely monitored. Actually, it reported that over 30 cases of patients infected with SARS-CoV-2 were never able to clear the virus and were still positive for the virus 2 to 3 months after initial infection, according to the National Health Commission, China. SARS-CoV-2 virus was detected in the throat swabs, which strongly suggests that those patients can still shed SARS-CoV-2 virus[6] and are infectious. Additionally, those patients all had IgG antibodies to SARS-CoV-2, which casts doubts on the protective role of IgG antibodies against this virus and the validity of using positive IgG test results as an immune certificate for COVID-19. Our findings suggest that some of those with positive IgG test results may be tested positive again for SARS-CoV-2 in their throat swabs and thus infectious after two consecutive negative tests for SARS-CoV-2. These findings have important implications for public health and management of recovered patients with COVID-19 around the world.

TABLE 1 Characteristics of patients who were recovering from COVID-19 with recurrent positive RT-PCR test results for SARS-CoV-2 and those without (N = 150)

	Median (interquartile range) or n (%)	
	Recurrent positive[a] (n = 11)	Not positive[b] (n = 139)
Median age, y	49 (37-62)	54 (40-63)
Sex		
Female	5 (45.5)	71 (51.1)
Male	6 (54.5)	68 (48.9)
Presence of IgM/IgG to SARS-CoV-2[c]		
IgM	5 (45.5)	66 (47.5)
IgG	11 (100.0)	126 (90.6)
Serum levels of IgM/IgG to SARS-CoV-2, AU/mL		
IgM	9.6 (4.1-24.9)	8.9 (4.3-21.9)
IgG	243.0 (164.9-353.1)	185.1 (76.0-331.8)
Days from symptom onset to RT-PCR test	38 (35-44)	39 (34-45)
Days from symptom onset to IgM/IgG test	39 (37-46)	39 (34-45)

Note: P values for differences in characteristics between those with recurrent RT-PCR test results for SARS-CoV-2 and those without were all >.05.

Abbreviations: COVID-19, coronavirus disease-2019; IgG, immunoglobulin G; IgM, immunoglobulin M; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Patients recovered from COVID-19 with recurrent positive RT-PCR test results for SARS-CoV-2 in throat swabs.

[b]Patients recovered from COVID-19 without recurrent positive RT-PCR test results for SARS-CoV-2 in throat swabs.

[c]Serum IgM and IgG antibodies to SARS-CoV-2 were measured with COVID-19 IgM/IgG chemiluminescence test kit on a fully-automated chemiluminescence immunoassay analyzer.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

XW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. TL, SW, and GZ contributed equally to the study. XW, FG, and YL contributed equally as senior authors. Concept and design: TL, SW, and GZ. Acquisition, analysis, or interpretation of data: TL, SW, GZ, and FZ. Drafting of the manuscript: TL, SW, FG, and XW. Critical revision of the manuscript for important intellectual content: SW and XW. Statistical analysis: TL and FG.

Tao Liu MD[1]
Sanyun Wu MD, PhD[2]
Guang Zeng MD[1]
Fuling Zhou MD[2]
Yirong Li MD, PhD[3]
Fangjian Guo MD, PhD[4,5]
Xinghuan Wang MD[1]

[1]Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China
[2]Department of Hematology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China
[3]Department of Laboratory Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China
[4]Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, Galveston, Texas
[5]Center for Interdisciplinary Research in Women's Health, The University of Texas Medical Branch at Galveston, Galveston, Texas

Correspondence

Fangjian Guo, MD, PhD, Department of Obstetrics and Gynecology, Center for Interdisciplinary Research in Women's Health, The University of Texas Medical Branch at Galveston, 301 University Blvd, Galveston, TX 77555-0587.
Email: faguo@utmb.edu

Xinghuan Wang, MD, Department of Urology, Zhongnan Hospital of Wuhan University, No. 169 Donghu Rd, Wuchang, Wuhan, 430071 Hubei, China.
Email: wangxinghuan@whu.edu.cn

Tao Liu, Sanyun Wu, and Guang Zeng contributed equally as first authors to this work. Yirong Li, Fangjian Guo, and Xinghuan Wang contributed equally as senior authors to this work.

ORCID

Fangjian Guo http://orcid.org/0000-0003-3729-2724
Xinghuan Wang https://orcid.org/0000-0003-3497-0024

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.