

## RESEARCH ARTICLE

# The clinical characteristic of eight patients of COVID-19 with positive RT-PCR test after discharge

Hong Cao | Lei Ruan | Jian Liu | Wenhui Liao 

Department of Gerontology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

**Correspondence**

Wenhui Liao, Department of Gerontology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Rd, 430030 Wuhan, China.

Email: doctormit@126.com

**Abstract**

Corona virus disease 2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The phenomenon of positive real time reverse transcription polymerase chain reaction (RT-PCR) result of SARS-CoV-2 in recovered patients had occurred and the research about these patients was rare. In our study, we did a retrospective review of medical records from COVID-19 patients admitted to one ward of Tongji Hospital of Hua Zhong University of Science and Technology from 10 February to 13 April 2020. From 10 February to 13 April 2020, there were 108 patients of COVID-19 admitted in the one ward of Tongji Hospital. Among them, eight cases were readmission patients because the RT-PCR result of SARS-CoV-2 was positive again after discharge. On the second admission, they had no symptoms and their chest computed tomography was almost normal. Data from laboratory tests of the readmission patients showed that all eight patients had normal white blood cell count, lymphocyte count. The inflammatory factors like procalcitonin and interleukin 6 were normal. After treatment, two patients met the standard and were discharged. The other six patients were still in the hospital because their RT-PCR of SARS-CoV-2 did not get three consecutive negative results and the course of two patients had persisted more than 90 days. We still needed to be alert that these patients could infect other people as a source of infection, and we also needed to be alert that these patients become chronic virus carriers. It also aroused our concern about the discharge standard of COVID-19.

**KEYWORDS**

corona virus disease 2019, discharge standard, positive RT-PCR, readmission, severe acute respiratory syndrome coronavirus-2

## 1 | INTRODUCTION

Corona virus disease 2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and spread all over the world.<sup>1,2</sup> It was a highly infectious disease and was announced by World Health Organization (WHO) as a global public health emergency. The main clinical manifestation was fever, cough and fatigue.<sup>2</sup> By 15 April 2020, COVID-19 cases raised over 1 million 870 thousand in the world and more than 110 thousand cases were fatal. With the effort of the whole world, the

number of cured patients was also increasing. There were also new problems in the follow-up and reexamination of cured patients. The phenomenon of positive real time reverse transcription polymerase chain reaction (RT-PCR) result of SARS-CoV-2 in recovered patients had occurred recently.<sup>3,4</sup> And the research about the readmission patients due to positive RT-PCR after discharge was rare. In this study, we retrospectively analyzed the clinical data and laboratory characteristics of eight readmission patients of positive test for SARS-CoV-2 to provide reference for the management and follow-up of COVID-19.

## 2 | METHOD

### 2.1 | Study design and patients

We did a retrospective review of medical records from COVID-19 patients admitted to one ward of Tongji Hospital of Hua Zhong University of Science and Technology from 10 February to 13 April 2020. The diagnosis and clinical classification (mild, moderate, severe, and critically ill) of COVID-19 pneumonia was based on the new coronavirus pneumonia prevention and control program published by the National Health Commission of China.<sup>5</sup> The discharge standards was following: (a) the body temperature returned to normal for more than 3 days, (b) respiratory symptoms improved significantly, (c) inflammation of the lungs showed obvious signs of resolution, and (d) respiratory nucleic acid was negative for two consecutive times (24 hours sampling time interval at least), which was from the guideline proposed by the National Health Commission of China.<sup>5</sup> The positive SARS-CoV-2 results of the eight patients were tested by RT-PCR after discharge.

Ethical approval: this study was approved by the Medical Ethical Committee of Tongji Hospital.

### 2.2 | Data collection

The clinical data (age, sex, symptoms, comorbidities, laboratory characteristics, treatments, and outcomes) of patients during hospitalization were collected from electronic medical records by two investigators (CH and RL). All data of the patients were independently checked and typed into the database by two analysts (LJ and LW). The clinical outcomes were observed up to 17 April 2020, the final date of follow-up.

Deep nasal cavity swab samples or throat swab samples were collected, extracted SARS-CoV-2 RNA and tested for SARS-CoV-2 by RT-PCR assay using a SARS-CoV-2 nucleic acid detection kit according to the protocol of manufacture (Shanghai Huirui Biotechnology CO Ltd).<sup>6</sup> All samples were tested at the Department of Clinical Laboratory of Tongji Hospital.

### 2.3 | Statistical analysis

Statistical analysis was done with SPSS (version 22.0). Continuous variables were expressed as the range. Categorical variables were expressed as number (%).

## 3 | RESULTS

From 10 February to 13 April 2020, there were 108 patients of COVID-19 admitted in the one ward of Tongji Hospital. Among them, eight cases were readmission patients because the RT-PCR result of SARS-CoV-2 was positive again after discharge. The age range of these

eight patients was 26 to 72 years. There were five females and three males. One patient had hypothyroidism and another one had obsolete pulmonary tuberculosis. None of them had common chronic disease like hypertension, cardiovascular disease or diabetes (Table 1).

Of these eight cases, six were moderate patients and two were severe patients at the first admission. The symptom onset time was from 7 January to 8 February 2020. Two patients could not remember clearly the exact symptom onset time. One said the onset time was mid-January and another one was early-February. The eighth patient was asymptomatic infection and his RT-PCR of SARS-CoV-2 tested positive on 5 February 2020 because he had contacted the confirmed patients before. Of the eight patients on the first admission, fever (5 [75%]) and cough (5 [75%]) was the most common clinical manifestation. Other symptoms were also observed as following: one patient (12.5%) had sputum, two patients (25%) had dyspnea, three patients (37.5%) had fatigue, one (12.5%) had myalgia, three (37.5%) had anorexia, and one (12.5) had nausea (Table 1). All of them had typical signs of viral infection by chest computed tomography (CT).

After the standard treatment according to the China, and according to the discharge standards, they were discharged from 8 February to 8 March 2020. For safety reason, the discharged patients were told to isolate at home for another 2 weeks. And as the order of the government, from the time of 22 February 2020, all discharged patients needed to go to the hotel for better isolation and observation for 2 weeks. And they were tested again during the isolation period. And RT-PCR of SARS-CoV-2 of these eight patients tested positive between 24 February to 14 March 2020 and they were admitted to hospital again because the positive nucleic acid (Table 1).

On the second admission, they had no symptoms and their chest CT was almost normal with no signs of viral infection. Data from laboratory tests of the readmission patients showed that all eight patients had normal white blood cell count, neutrophil count, lymphocyte count, hemoglobin, blood platelet count, albumin, total bilirubin, urea nitrogen, creatinine, and D dimer. One patient had anemia, one patient had elevated concentration of alanine aminotransferase and aspartate aminotransferase, and three patients had increased concentration of lactic dehydrogenase. The inflammatory factors like procalcitonin and interleukin six were normal except the C-reactive protein of some patients were slightly high. After they were admitted to the hospital again, SARS-CoV-2 RT-PCR was tested positive at least one time. They were detected of serum SARS-CoV-2 specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, two patients had positive SARS-CoV-2 IgM antibodies, and all eight patients had positive SARS-CoV-2 IgG antibodies (Table 2).

After the second admission, antiviral treatment, Chinese herbs were used to treat these patients and the thymopeptides also used to improve the immunity of the patients. No antibiotic was used. For the consideration of safety and caution, our hospital decided the discharge condition of these patients should be the three consecutive negative results of RT-PCR of SARS-CoV-2 instead of two besides other discharge standard. Two patients met the standard and were discharged. The other six patients were still in the hospital because

**TABLE 1** Details of clinical data of readmission patients

Items	No.1	No.2	No.3	No.4	No.5	No.6	No.7	No.8	n (%)
Sex	Female	Female	Female	Female	Male	Male	Female	Male	
Age	54	72	60	65	58	64	36	26	
Comorbidity	N	N	N	Hypothyroid-ism	Tuberculosis	N	N	N	
Severity on first admission	Severe	Moderate	Moderate	Moderate	Moderate	Severe	Moderate	Moderate	
Symptom onset time	Mid-Jan	Jan 23	Jan 29	Jan 22	Jan 7	Early Feb	Feb 8	Feb 5 <sup>a</sup>	
Discharge time	Feb 21	Feb 20	Feb 28	Feb 28	Feb 8	Feb 6	Mar 8	Feb 24	
Turn positive time	Mar 5	Mar 4	Mar 9	Mar 12	Feb 24	Mar 5	Mar 14	Mar 2	
First admission symptoms									
Fever	No	Yes	Yes	Yes	Yes	No	Yes	No	5 (62.5)
Cough	Yes	Yes	Yes	Yes	Yes	No	No	No	5 (62.5)
Sputum	No	No	Yes	No	No	No	No	No	1 (12.5)
Dyspnea	No	Yes	Yes	No	No	No	No	No	2 (25)
Fatigue	No	Yes	Yes	No	No	Yes	No	No	3 (37.5)
Myalgia	No	Yes	No	No	No	No	No	No	1 (12.5)
Anorexia	No	No	No	No	Yes	Yes	Yes	No	3 (37.5)
Nausea	No	No	No	No	No	No	Yes	No	1 (12.5)
Second admission symptoms									
Fever	No	No	No	No	No	No	No	No	0
Cough	No	No	No	No	No	No	No	No	0
Sputum	No	No	No	No	No	No	No	No	0
Dyspnea	No	No	No	No	No	No	No	No	0
Fatigue	No	No	No	No	No	No	No	No	0
Myalgia	No	No	No	No	No	No	No	No	0
Anorexia	No	No	No	No	No	No	No	No	0
Nausea	No	No	No	No	No	No	No	No	0

Note: N means none.

<sup>a</sup>Asymptomatic infection: February 5 was the time of positive result of SARS-CoV-2.

their RT-PCR of SARS-CoV-2 did not get three consecutive negative results, the course of two patients (patient one and patient five) had persisted more than 90 days from the first symptoms onset up to 17 April 2020, the final date of follow-up (Table 3).

## 4 | DISCUSSION

The outbreak of COVID-19 threatened a lot of people in the world and WHO had announced it as a pandemic disease and the grade of the global risk assessment was very high.<sup>7</sup> It was believed that the outbreaks of COVID-19 might be connected to the quick transmission from person to person.<sup>8</sup> Since there was no particular valid medicine or vaccine for COVID-19 at present, the isolation was important to prevent the spread of the disease.<sup>9,10</sup> With the effort of all over the world, more patients were recovered from COVID-19 and got discharged. But after they were discharged from the hospital, are they all totally cured?

From our study and a few reports before,<sup>3,4</sup> we could not answer yes definitely. Zhang et al<sup>3</sup> reported the SARS-CoV-2 of a patient

turned positive after discharge. Lan et al<sup>4</sup> reported four recovered patients of COVID-19 had positive RT-PCR test. In our study, from Feb 10th to Apr 13th, there were 108 patients of COVID-19 admitted in the one ward of Tongji Hospital. Among them, eight cases were readmission patients because the RT-PCR of SARS-CoV-2 was positive again after discharge. These eight patients including six Moderate and two severity cases were treated according to the guideline and discharged when they met the discharge standard at first admission. They were all isolated at home or at hotel, with no contact to other patients. So they were not likely infected by others. But why their RT-PCR of SARS-CoV-2 turned positive after discharge? We think the possible reason of positive nucleic acid after discharge might be the following:

(a) The recovery of COVID-19 might take a long period of time and in the process of inflammation resolution, intermittent virus excretion could happen, which resulted in the positive nucleic acid. In our study, up to the last following day, the course of some patients had persisted more than 90 days from the first symptoms onset. During this course, it was possible that the viral had been cleaned transitorily, so the test of the viral was negative. We still

**TABLE 2** Laboratory characteristics of readmission patients

Items	No.1	No.2	No.3	No.4	No.5	No.6	No.7	No.8
White blood cell count, 10 <sup>9</sup> /L	5.57	5.69	5.83	6.5	5.53	5.71	5.97	4.97
Neutrophil count, 10 <sup>9</sup> /L	2.94	3.16	4.18	3.82	1.94	59.2	4.24	2.89
Lymphocyte count, 10 <sup>9</sup> /L	2.37	1.61	1.19	1.99	2.82	1.59	1.35	1.44
Lymphopenia, <10 <sup>9</sup> /L	No	No	No	No	No	No	No	No
Hemoglobin, g/L	134	120	135	128	140	152	107	149
Blood platelet count, 10 <sup>9</sup> /L	268	225	345	159	189	166	216	174
Alanine aminotransferase, U/L	25	17	32	11	21	19	13	103
Aspartate aminotransferase, U/L	27	26	38	13	18	20	15	48
Albumin, g/L	43.3	46.9	46.5	38.4	41	42.6	40.5	45.3
Total bilirubin, μmol/L	10	6.6	7.7	5.6	7	7.3	8	15.9
Lactic dehydrogenase, U/L	238	340	320	125	195	219	141	180
Urea nitrogen, mmol/L	4.4	6.9	4.1	7.1	5.7	7.9	4.2	3.6
Creatinine, μmol/L	47	66	72	63	74	63	61	82
D dimer, μg/mL	0.53	0.41	0.62	0.25	<0.22	<0.22	NA	<0.22
C-reactive protein, mg/L	5	2.7	0.4	3.9	2	1.6	NA	NA
Procalcitonin, ng/L	<0.02	<0.02	0.05	0.04	NA	NA	<0.02	0.04
Interleukin 6, pg/mL	1.78	2.03	<1.5	3.27	6.84	3.83	NA	1.5
SARS-CoV-2 IgM antibody	-	+	-	-	-	-	-	+
SARS-CoV-2 IgG antibody	+	+	+	+	+	+	+	+
Positive SARS-CoV-2 RT-PCR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CT evidence of pneumonia								
Typical signs of viral infection	No	No	No	No	No	No	No	No

Note: NA = not applicable, - means negative, + means positive.

Abbreviations: CT, computerized tomography; IgG, immunoglobulin G; IgM, immunoglobulin M; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

did not know clearly about the viral clearance feature after being infected by SARS-CoV-2. It was likely virus excretion might happen again subsequently. In the recent research by Francesca et al<sup>11</sup>, SARS-CoV-2 RNA was found in ocular swabs days after it was undetectable in nasal swabs. And 5 days after the SARS-CoV-2 RNA became undetectable at day 21, it turned positive again in the ocular swab sample collected at day 27. In their research, they showed the viral detected in the ocular swabs was infections by inoculating RNA-positive ocular sample in Vero E6 cells and cytopathic effect was observed.<sup>11</sup>

(b) Drug treatment course was not enough and virus removal was not complete. It was possible that during hospitalization, virus

replication was inhibited due to drug treatment, resulting in insufficient load or below the lower detection limit during detection, and then the negative results were produced. However, the actual virus had not been completely eliminated. With the lack of treatment course and drug reduction after discharge, the proliferation of the virus would increase, resulting in the positive test of nucleic acid. Just like the mention above in the research of Francesca et al<sup>11</sup>, SARS-CoV-2 RNA was found in ocular swabs days after it was undetectable in nasal swabs. During the time when it was undetectable in nasal swabs, was the virus totally cleaned in the respiratory tract or just the virus load not enough? In a patient in the USA, the virus was found positive in the stool sample.<sup>12</sup> It had been recognized that SARS-CoV-2 invaded the

**TABLE 3** Outcome of readmission patients

	No.1	No.2	No.3	No.4	No.5	No.6	No.7	No.8	n (%)
Discharge	No	No	No	Yes	No	No	No	Yes	2 (25%)
Still in the hospital	Yes	Yes	Yes	No	Yes	Yes	Yes	No	6 (75%)

cells of human via the receptor angiotensin converting enzyme II (ACE2), so except respiratory system, other system which had ACE2 expression such as digestive, cardiovascular, and urinary systems et al<sup>13</sup> were also vulnerable to SARS-CoV-2 infection. So it was also possible the virus in the respiratory tract was cleaned temporarily, but the virus in other system was not totally cleaned.

(c) False-negative RT-PCR test results might be happened due to the following reasons: the source of samples collected, the method of samples collected, antiviral drugs or hormone taken, sample transportation, test operation, the sensitivity of nucleic acid test kit.<sup>14,15</sup> Because the main invasion site of SARS-CoV-2 was the lower respiratory tract, the best sample was the alveolar lavage fluid or the respiratory tract sample taken under the tracheoscope. But most of the patients with COVID-19 had no sputum, and the bronchoscope lavage was an invasive operation, so the lower respiratory tract sample was not easy to obtain. Currently, most of the nucleic acids used for RT-PCR were nasal cavity swab samples or throat swab. The samples were taken by experience and it was possible that the location of the samples was not accurate. Even if the operation was correct, the target virus might not be collected. The other factors like sample transportation, test operation, the test kit could also affect the test result. A high proportion of false-negative of RT-PCR results was reported by Li et al<sup>15</sup>, which included 610 patients with infected by SARS-CoV-2. Xiao et al<sup>16</sup> reported that in a study of 70 COVID-19 patients, 21.4% patients had a positive RT-PCR test of SARS-CoV-2 after two consecutive negative results. And they concluded that might be connected to the false negative of RT-PCR detection. In our study, these eight patients not only got two consecutive negative results, but their symptom and chest signs of viral infection had relieved when they were discharged at the first time. On the second admission, they also had no symptoms and their chest CT was almost normal, plus the data from laboratory tests of the readmission patients showed that they had normal white blood cell count, lymphocyte count and inflammatory factors. So the reason of their RT-PCR of SARS-CoV-2 turned positive could not all count to the false-negative result. But the situation of false negative did happen in the diagnosis of the COVID-19. So it was necessary to test SARS-CoV-2 specific IgM and IgG antibodies when screening for COVID-19. In our study, in the second admission, all patients had IgG antibody, and two patients had IgM. After being infected by SARS-CoV-2, the human body would produce antibodies. The IgM antibody would be produced about 1 week after infection, lasting for about half a month. IgG antibody was produced about half a month after infection and lasted for a long time.<sup>17,18</sup> But in our study, the course of the 2nd patient had been more than 30 days from the onset of the symptom when he was tested serum IgM. So in some patients, IgM antibody could last longer. The detection of IgG and IgM immunoglobulin antibody could combine with the detection of nucleic acid, which was helpful to eliminate the suspected cases in case of the false negative result of RT-PCR alone.

Traces of SARS-CoV-2 detected by RT-PCR were not necessarily correlated with the ability of transmission. It was not known whether the detected virus was active or not. Detection of virus specific gene

fragments by RT-PCR alone did not prove that the virus had pathogenic activity. Other method like culturing virus should be used to determine whether the detected virus was active or not. According to the current data in China, the discharge patients of SARS-CoV-2 retested positive by RT-PCR did not infect others. However, when we did not know the virus activity at this moment, these patients should be managed according to the principle of prevention and treatment of infectious diseases.

Although at present, these eight patients of SARS-CoV-2 RT-PCR turned positive after discharge were asymptomatic and had no signs of viral infection in lung CT changes, we still needed to be alert that these patients could infect other people as a source of infection, and we also needed to be alert that these patients become chronic virus carriers. It also aroused our concern about the discharge standard of COVID-19. The study was limited to a small number of patients. Further studies should follow up more patients and the follow up time should be longer to understand better the progression and prognosis of the disease.

#### ACKNOWLEDGMENTS

We would like to acknowledge all the medical worker from other province to support Wuhan.

#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### AUTHOR CONTRIBUTIONS

CH and LW were involved in the concept and design. CH and RL collected electronic medical records. LJ and LW helped in data checking and typing. CH, RL, LJ, and LW were involved in drafting and revising the manuscript. The corresponding authors had final responsibility for the decision to submit for publication.

#### ORCID

Wenhui Liao  <http://orcid.org/0000-0001-8015-6918>

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**How to cite this article:** Cao H, Ruan L, Liu J, Liao W. The clinical characteristic of eight patients of COVID-19 with positive RT-PCR test after discharge. *J Med Virol*. 2020;92:2159-2164. <https://doi.org/10.1002/jmv.26017>