Journal of Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

Positive rectal swabs in young patients recovered from coronavirus disease 2019 (COVID-19)

Introduction

As of 27 March, 2020, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for 530,000 infection cases with 23,552 deaths globally and the number is still increasing rapidly.[1] A total of 197 counties have been involved in this emerging infectious disease. On March 11, 2020, Dr Tedros, the World Health Organization Director-General, said that COVID-19 can be characterized as a pandemic for the alarming levels of spread, severity, and inaction.

In China, diagnostic test by real-time reverse transcription polymerase chain reaction (RT-PCR) assay is the main means of confirmation, and throat swab samples are collected for convenience and noninvasiveness.[2] However, this technique has a certain rate of false-negative results which might render convalescent COVID-19 patients to meet the current criteria of current discharge or discontinuation of quarantine, resulting in spread of virus.[3] In clinical settings, at least two repeat RT-PCR assays are performed to reduce the false-negative rate. A recent study reported that four medical professionals, aged from 30 to 36 years, still had positive RT-PCR results 5-13 days after recovery,[4] which caused widespread concern. However, this phenomenon was not explained by authors. We could not determine whether it was disease relapse or not. In this study, we followed up seven patients who had positive RT-PCR results after recovery from COVID-19 pneumonia and tried to find the possible explanation.

Methods

This study was approved by the institutional review boards of the First Affiliated Hospital of Jinan University and Dongguan Ninth People's Hospital, and informed consent was waived. The seven hospitalized COVID-19 patients were treated at Dongguan Ninth People's Hospital from January 30 to February 5, 2020. Laboratory confirmation of SARS-CoV-2 infection was performed by RT-PCR assays of throat or rectal swabs according to the standard protocol.[5] SARS-CoV-2 infection was defined by at least two positive RT-PCR test results. Epidemiological characteristics, demographic information, laboratory findings, and radiological features were collected from electronic medical records. The criteria for discharge were according to the seventh trial version of the COVID-19 pneumonia guidelines released by China[6]: 1) normal temperature lasting longer than three days, 2) significantly relieved respiratory symptoms, 3) substantially improved acute exudative lesions on chest computed tomography, and 4) a series of two repetitive negative RT-PCR test results with at least one day interval. After hospital discharge, all the patients were quarantined in designated hospitals and followed up by RT-PCR tests.

Results

Among the seven patients, four had a recent travel to Wuhan, one had visited their relatives in Wuhan, and one had contacted family member who had been to Wuhan. Three children (patient 1-3) had at least one infected family member. The seven patients included one female infant (10 months), two male adolescents (13 and 14 year-old), and four young adult males (26, 33, 35, and 35 year-old). All the patients had no underlying diseases except for the patient 7 had hepatitis B. Four patients (patient 1, 2, 5, 6) were initially asymptomatic, and three (patient 3, 4, 7) had fever, dry cough, malaise or combinations occurred at onset. Table 1 showed laboratory tests of the seven patients, only patient 4, 6 had lymphopenia. Six patients had normal chest CT on admission except for the infant had bilateral pneumonia. All the seven patients had positive RT-PCR test results of throat swabs. The severity of COVID-19 was mild in six patients and moderate in only one patient.

The infant patient received oseltamivir (15 mg twice daily). The four adult patients received arbidol (200mg three times daily, orally), lopinavir and ritonavir (400 mg twice daily) and interferon alpha 1b (50 μg twice daily). One adolescent received oseltamivir (15 mg twice daily), arbidol (100 mg three times daily) and lopinavir and ritonavir (400 mg every 12 hours), and the other adolescent received arbidol (100 mg three times daily), and lopinavir and ritonavir (400 mg every 12 hours). Six patients were supplemented with oxygen via nasal cannula. After treatment, three patients' respiratory symptoms were significantly relieved. The infant's pneumonia was obviously absorbed, while the chest CT images of remaining patients were unchanged. Six patients had at least two consecutive negative RT-PCR results of throat swabs and one adult had two consecutive negative RT-PCR results of both throat and rectal swabs. The time from admission to recovery ranged from 11 to 23 days.

After hospital discharge, the patients were asked to continue the quarantine in designated hospitals for 14 days. During the quarantine, four patients had positive RT-PCR assays of rectal swabs only, two had positive RT-PCR results of throat swabs, and one had positive RT-PCR results of both throat and rectal swabs (Fig. 1). The time from hospital discharge to positive RT-PCR results after recovery was 7–11 days. The patients were asymptomatic and chest CT images showed no change from the last scan before discharge. They did not report contact with any suspected or confirmed person. All the patients were admitted to hospital again because positive rectal swabs in six patients or positive throat swabs in one patient. They were treated with Chinese medicine toujiequwenkeli (11g twice daily, orally). The median length of second hospital stay was 10 days (interquartile,

https://doi.org/10.1016/j.jinf.2020.04.023

Table 1
The laboratory features and treatments of the seven COVID-19 patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Laboratory features							
Leucocytes ($\times 10^9$ per L; normal range 3.5–9.5)	4.07	9.49	11.2	4.47	6.05	5.31	5.60
Neutrophils ($\times 10^9$ per L; normal range 1.8–6.3)	1.96	5.56	2.43	3.34	4.37	4.39	4.01
Lymphocytes ($\times 10^9$ per L; normal range 1.1–3.2)	1.72	2.79	7.73	0.34	1.02	0.65	1.13
Platelets ($\times 10^9$ per L; normal range 125•0–350•0)	260	216	352	261	211	240	215
Hemoglobin (g/L; normal range 130.0–175.0)	142	162	116	117	168	166	144
Activated partial thromboplastin time (s; normal range 28.0–44.0)	39.2	40.1	32.2	41.3	40.3	29.4	38.2
Prothrombin time (s; normal range 11.0–15.0)	13.8	14.2	12.1	12.1	12.7	14.0	13.2
D-dimer (μg/ml; normal range 0.0–0.5)	0.12	normal	normal	0.20	0.19	0.08	0.16
Albumin (g/L; normal range 35.0–52.0)	43.8	44.2	48.5	44.2	67.4	41.2	69.3
Alanine aminotransferase (U/L; normal range 9.0–50.0)	9.1	29.4	27.3	22.6	38.7	16.6	117.5
Aspartate aminotransferase (U/L; normal range 15.0–40.0)	16.2	18.7	49.1	19.6	21.5	10.7	46.0
Total bilirubin (μmol/L; normal range 0.0–21.0)	9.7	11.6	5.8	3.7	24.3	9.8	18.6
Serum creatinine (μmol/L; normal range 57.0–97.0)	81	75	18	96	88	76	65
Cystatin C (mg/L, 0.63-1.25)	0.92	1.0	0.86	1.17	1.15	1.14	1.28
Creatine kinase (U/L; normal range 50.0–310.0)	85	68	159	62	62	27	47
Lactate dehydrogenase (U/L; normal range 120.0–250.0)	174	184	263	168	162	106	130
Myoglobin (ug/L; normal range 23.0–112.0)	normal	39	25	61	26.7	normal	17.6
Procalcitonin (ng/mL; normal range 0.0–0.5)	normal	0.16	0.01	0.25	0.28	0.08	0.57
C-reactive protein (mg/L; normal range 0.0–5.0)	0.98	0.91	<0.50	0.77	1.51	<0.50	0.79
Partial pressure of oxygen (mmHg, 83-168)	90.9	114	-	167	not available	179	92.9
Oxygen saturation (%, 93-100)	97.1	98.7	-	99.9	not available	99.8	97.7
Partial pressure of carbon dioxide (mmHg, 35-45)	40.8	40.5	-	38.3	not available	40.9	46.6
Antiviral treatment							
Oseltamivir		√	√				
Lopinavir and ritonavir	√	√		√	√	√	√
Arbidol	√	√		√	√	√	√
Interferon alpha 1b				√	√	√	√
Oxygen Inhalation	√	√	-	√	√	√	√
Oxygen concentration (%)	21	21	-	29	21	21	21
Flow-rate	low and high	low and high	-	low	low	low	low

6-10 days). Several days before the second discharge, most patients had at least two repetitive negative RT-PCR tests of both throat and rectal swabs, but the patients 3, 6, and 7 continued the quarantine in designated hospitals because of negative throat swabs but positive rectal swabs. After 2, 14, and 2 days respectively, rectal swabs of the three patients turned negative. The time from initial positive to negative rectal swabs ranged from 5 to 23 days. Given that the first discharge criteria of patients were based on throat swabs instead of rectal swabs, the longest rectal virus shedding might be more than 23 days.

Discussion

In this case series, we reported seven young patients who met the current criteria for discharge in China but still had positive RT-PCR test results 7-11 days after discharge. These findings suggested that some recovered patients may still be virus carriers, which questioned the current discharge criteria that two repetitive negative RT-PCR tests (with a one-day gap between the two tests) of throat swabs are necessary. In this study, most patients had two consecutive negative RT-PCR test results of throat swabs before discharge but positive RT-PCR test results of rectal swabs after discharge, indicating the necessity of adding RT-PCR testing of rectal swab specimens to the criteria for discharge or discontinuation of quarantine. The current discharge criteria can be more stringent if current testing load and medical resource allowed. Previous findings showed rectal swab-testing might be more useful than throat swab-testing in determining the effect of treatment and the timing of termination of quarantine.[7] A recent study showed persistent rectal swab positives even after nasopharyngeal swab testing turned negative in eight children.[8] It was speculated that different sampling tissues may have different levels of viral nucleic acid and lasting time of virus shedding. The detection rate of specimens is limited by the level of viral nucleic acid. Viral shedding from the digestive system might be more severe and lasting longer than that from the respiratory tract. More rectal swab positives were found in a later stage of infection as compared with oral swab positives, suggesting viral shedding and transmitting through oral-fecal route.[9] In addition, intermittent virus shedding might occur in recovered patients. One patient had both negative throat and rectal swabs before hospital discharge but had positive throat swab during quarantine. Therefore, positive RT-PCR results occurred in most patients recovered from COVID-19 might not be caused by virus recurrence or second virus infection. All the patients continued to be asymptomatic and chest CT showed no changes from previous images might also support this viewpoint.

Although positive RT-PCR test results were found for convalescent patients, antiviral therapy might not be needed because most patients' RT-PCR results would turn negative in several days. Antibodies IgM and IgG against SARS-CoV-2 infection may be produced in these patients, therefore, the transmission risk is low even if the patients have positive RT-PCR test results after recovery. Antibody IgG can persist a very long time.[10] Although there is no firm evidence indicating these patients would transmit the virus to others, we should be aware the potential way of transmission through the oral-faecal route.[11,12] Patients should continue the quarantine in designated hospitals for at least 14 days and be followed up by RT-PCR assays of both throat and rectal swabs to avoid false-negative. In addition, psychological intervention is necessary for patients recovered from COVID-19 but have positive RT-PCR results again, because they may experience psychological problems including anxiety, depression, sleeplessness, and stress. The study

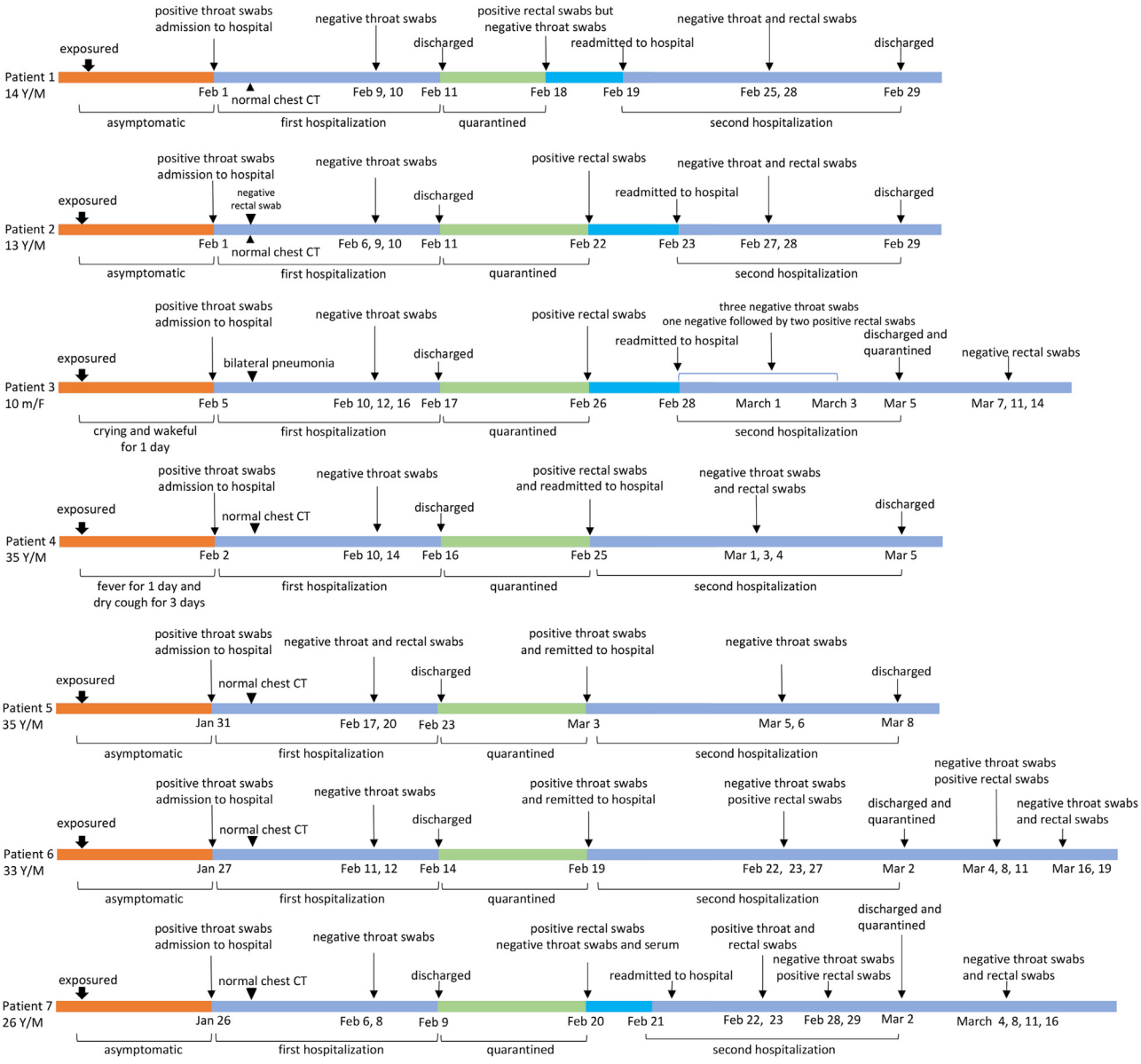

Fig. 1. Timeline of epidemiological history, first hospitalization, first discharge, quarantine, second hospitalization, second discharge and RT-PCR testing in the seven patients with COVID-19. RT-PCR testing was performed on admission, during hospitalization and quarantine. Abbreviation: RT-PCR, real-time reverse transcription polymerase chain reaction.

was limited to a small number of patients with mild or moderate SARS-CoV-2 infection. Patients with severe or critically ill diseases should be included for further study. Large cohort study may be needed to confirm these findings.

Declaration of Competing Interest

The authors declare no competing interests.

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Bin Zhang[†], Shuyi Liu[†]
The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, China

Yuhao Dong
Guangdong Provincial People's Hospital/Guangdong academy of medical sciences, Guangzhou, Guangdong, China

Lu Zhang
The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, China

Qingyang Zhong
Dongguan Ninth People's Hospital, Dongguan, Guangdong, China

Yujian Zou[**]
Dongguan People's Hospital, Dongguan, Dongguan, Guangdong, China

Shuixing Zhang[*]
The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, China

[*]Corresponding authors: Shuixing Zhang, M.D., Ph.D., No. 613 Huangpu West Road, Tianhe District, Guangzhou, Guangdong, 510627, China.
[**]Yujian Zou, MD, No. 3 Xinguyongwandao South Road, Wanjiang District, Dongguan, Guangdong, 523000, China, Tel: (0769) 2863 6606.
E-mail addresses: zouyujian@sohu.com (Y. Zou), shui7515@126.com (S. Zhang)
[†] Bin Zhang and Shuyi Liu contributed equally to this work.