



Clinical characteristics of re-hospitalized COVID-19 patients with recurrent positive SARS-CoV-2 RNA: a retrospective study

Lei Pan¹ · Runsheng Wang² · Na Yu³ · Chao Hu² · Junhong Yan⁴ · Xiaomin Zhang⁵ · Tao Wang¹ · Jungui Hao⁶ · Fuquan Gao¹ · Tonggang Liu⁷ · Jing Wang¹ · Xiaojing Liu¹ · Mi Mu⁸ · Wei Huang⁹ · Yongzhong Guo¹⁰ · Changjun Lv¹ · Xiaozhi Wang¹ · Lei Tu¹¹ · Kun Wan¹² · Guogang Xu¹³

Received: 9 October 2020 / Accepted: 30 December 2020 / Published online: 15 January 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH, DE part of Springer Nature 2021

Abstract

At present, it has been noticed that some patients recovered from COVID-19 present a recurrent positive RNA test of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) after being discharged from hospitals. The purpose of the current study was to characterize the clinical features of re-hospitalized patients with recurrent SARS-CoV-2 positive results. From January 12 to April 1 of 2020, our retrospective study was conducted in China. The exposure history, baseline data, laboratory findings, therapeutic schedule, and clinical endpoints of the patients were collected. All the patients were followed until April 10, 2020. Among all COVID-19 patients included in the current study, there were 14 re-hospitalized patients due to recurrent positive tests of SARS-CoV-2 RNA. Fever (11 [78.6%]), cough (10 [71.4%]), and fatigue (7 [50.0%]) were the most common symptoms on the patient's first admission, and less symptoms were found on their second admission. The average duration from the onset of symptoms to admission to hospital was found to be 8.4 days for the first admission and 2.6 days for the second admission ($P = 0.002$). The average time from the detection of RNA (+) to hospitalization was 1.9 days for the first admission and 2.6 days for the second admission ($P = 0.479$), and the average time from RNA (+) to RNA (–) was 11.1 days for the first admission and 6.3 days for the second admission ($P = 0.030$). Moreover, the total time in hospital was 18.6 days for the first admission and 8.0 days for the second admission ($P = 0.000$). It may be necessary to increase the isolation observation time and RT-PCR tests should be timely performed on multiple samples as soon as possible.

Keywords SARS-CoV-2 · COVID-19 · Re-hospitalization · Management · Outcome

Introduction

On Mar 14, 2020, the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared by

the World Health Organization (WHO) that induced coronavirus disease 2019 (COVID-19), which resulted in the present worldwide pandemic. COVID-19 is spreading around the world and threatening global health [5, 8]. Tillett et al. used genome sequencing to show that one patient could be infected by SARS-CoV-2 in two different occasions and found that the second infection of this patient had more severe symptoms than that in the first infection [15], which shows that reinfection with SARS-CoV-2 may challenge the efficacy of vaccines [6]. However, Cento et al. believed that a recurrent positive test of SARS-CoV-2 RNA did not mean of a transmissible virus in vivo [1]. The symptomatic patients with COVID-19 are supposed to be the main source of outbreak, but asymptomatic infections may be a potential troubling occurrence in the near future [10, 12, 20].

Asymptomatic infections were announced in the seventh edition of the guidelines from National Health Commission of China. In clinical practice, very few cured patients were detected

Lei Pan, Runsheng Wang, Na Yu, Chao Hu contributed equally to this work. They are listed as co-first authors. Xiaozhi Wang, Lei Tu, Kun Wan and Guogang Xu are listed as co-corresponding authors.

✉ Xiaozhi Wang
bzyxy3013@163.com

✉ Lei Tu
tulei_1985@126.com

✉ Kun Wan
301wk@sina.com

✉ Guogang Xu
guogang_xu@163.com

Extended author information available on the last page of the article

with positive SARS-CoV-2 RNA even after discharging [7, 9, 18, 19]. A meta-analysis of 17 studies with 5182 COVID-19 patients reported a recurrence positive SARS-CoV-2 RNA rate of 12%. They believed that the respiratory tract samples should be repeated nucleic acid tests in both the first and second months after recovery from COVID-19 [13]. Follow-up observation of the baseline characteristics of these patients and whether family members are infected with SARS-CoV-2 may help to develop management strategies in targeting these groups. Here, we reported 14 re-hospitalized patients due to a recurrent positive result of SARS-CoV-2 RNA. Further investigations of the clinical characteristics of such patients may contribute to the improvement of current criteria for release and reduction of recurrence rate.

Materials and methods

Study design

The study was performed in China from January 12 to April 1, 2020 and had been approved by the Ethics Committees of Huanggang Central Hospital (No. HGY-2020-005) and Wuhan Union Hospital (No. 2020-0077-1). In total, 1350 patients with COVID-19 from the general wards and intensive care units (ICU) were initially enrolled in the current study.

The inclusion criteria were (1) diagnosis of COVID-19 was all confirmed by positive test of SARS-CoV-2 RNA from the throat swab or sputum samples according to WHO interim guidance; (2) criteria for all COVID-19 patients discharging from hospitals were based on the guidelines by National Health Commission of China: (i) normal temperature for at least 3 days, (ii) no obvious respiratory symptoms, (iii) significant absorption of lesions in chest computerized tomography (CT) scans, (iv) double check of negative SARS-CoV-2 RNA tests (sampling interval over 24h); (3) the patients were hospitalized no less than 2 times due to re-detectable positive SARS-CoV-2 RNA; (4) chest CT scans and blood tests were performed. Those patients who did not meet all of the criteria listed above were excluded from the current study.

Data collection

Each COVID-19 case report was carefully reviewed from electronic medical records. All the data were collected by two different co-authors independently. The exposure history, demographic data, baseline characteristics, laboratory data, therapeutic programs, and clinical endpoints, especially the RNA test of SARS-CoV-2, were extracted. The results of viral RNA were based on the first positive and the first valid negative data (i.e., the first negative result before reaching the discharge standard). In the present study, samples by throat swabs were obtained from the patients at the time of admission, and during the time of home or

hotel quarantine were tested by real-time reverse transcription PCR [4].

Statistical analysis

Continuous data were shown as means (\pm standard deviation [SD]) or medians with interquartile range (IQR). Categorical data were described as percentages. All laboratory results were assessed if the measurements exceeded the normal level. A paired *t* test was used for continuous data and chi-squared test was applied to compare count data. A two-tailed *P* value less than 0.05 was selected as the cutoff value for statistical significance. SPSS version 20 (SPSS, Chicago, IL, USA) was used to conduct statistical analyses in the current study.

Results

Baseline characteristics

A total of 1350 COVID-19 patients were selected as the initial study population from January 12 to April 1, 2020. Only 20 cases of COVID-19 were re-detected with positive SARS-CoV-2 RNA. Six patients who lack complete data were excluded. Finally, 14 cases met the inclusion criteria. The final follow-up was April 10, 2020.

Baseline characteristics of 14 patients on two admissions are summarized in Tables 1, 2, and Fig. 1. The average age of the patients was 44.4 years old ($SD \pm 15.0$), with 10 males and 4 females. According to the epidemiological history, 7 (50.0%) patients remembered clearly about their history of exposure in the first admission and 14 (100.0%) patients in the second admission. Fever (11 [78.6%]), cough (10 [71.4%]), and fatigue (7 [50.0%]) were the most common symptoms, and digestive symptoms such as lack of appetite (4 [28.6%]) and diarrhea (1 [7.1%]) were reported on the first admission. However, except for one patient who had a cough, the remaining 13 patients had no symptoms on the second admission. Additionally, new lesions were not found in all patients undergoing chest CT on second admission. Meanwhile, most patients rarely had underlying comorbidities. On the first admission, there were 14 (100.0%) patients receiving antiviral drugs including lopinavir/ritonavir or arbidol, 11 (78.57%) receiving Lianhua Qingwen, and 8 (57.1%) receiving nebulized α -interferon treatment. Similarly, 10 (71.43%) patients on second hospitalization received antiviral treatment.

RNA test outcomes of SARS-CoV-2

The results of SARS-CoV-2 RNA are shown in Table 2 and Fig. 1. In detail, the average time from detection of RNA (+) to hospital admission was 1.9 days ($SD \pm 1.6$) for the first admission and 2.6 days ($SD \pm 2.2$) for the second admission (*P* =

Table 1 Baseline characteristics and clinical outcomes of 14 re-hospitalized COVID-19 patients after recurrent positive test of SARS-CoV-2 RNA

Characteristics	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8		Case 9		Case 10		Case 11		Case 12		Case 13		Case 14									
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd								
Age, years	50	30	61	53	31	56	40	57	30	20	39	70	56	29	70	56	29	70	56	29	70	56	29	70	56	29	70	56	29	70						
Sex (M/F)	Female	Male	Male	Female	Male	Male	Male	Male	Female	Male	Male	Male	Male	Female	Male	Male	Male	Female	Male	Male	Male	Male	Male	Male	Male	Male	Female	Female	Female	Female						
Disease condition	S	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo	Mo						
Respiratory rate	21	18	20	18	20	18	20	22	20	22	20	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	20					
Time from onset of symptoms to admission	8	2	5	2	18	2	10	4	3	1	4	3	1	4	3	1	4	3	1	4	3	1	4	3	1	4	3	1	4	3	1	4				
Time from onset of RNA (+) to admission	1	2	1	2	6	2	1	4	1	4	1	4	1	3	2	1	3	2	1	3	2	1	3	2	1	3	2	1	3	2	1	3				
Time from onset of RNA (+) to RNA (-)	9	3	17	2	10	4	6	8	9	6	33	15	5	4	5	4	5	4	5	4	5	4	5	4	5	4	5	4	5	4	5	4				
Time from onset of RNA (-) to RNA (+)	29	12	19	40	26	22	7	17	22	7	17	22	7	17	22	7	17	22	7	17	22	7	17	22	7	17	22	7	17	22	7	17	22			
Time from discharge to RNA (+)	11	8	14	14	21	15	1	12	10	13	6	13	6	13	6	13	6	13	6	13	6	13	6	13	6	13	6	13	6	13	6	13	6			
Total days in hospital	27	4	19	4	18	5	30	4	9	5	13	7	16	11	38	18	15	8	15	8	15	8	15	8	15	8	15	8	15	8	15	8				
Common symptoms																																				
Fever	✓	x	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x			
Cough	✓	x	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x	✓	x			
Short of breath	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Diarrhea	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Lack of appetite	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x			
Weakness	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x			
Muscle pain	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Exposure history																																				
Clear exposure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Unclear exposure																																				
Comorbidities																																				
Respiratory disease	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Gastrointestinal diseases	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiovascular system disease	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	
Nervous system disease	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Endocrine system disease	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Malignant tumor	x	x	x	x	x	✓	x	x	x	✓	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood system diseases	x	x	x	✓	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Treatments																																				
Antibiotic treatment	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	
Antifungal treatment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Antiviral treatment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glucocorticoids	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	
Nebulized IFN-α	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	x	✓	x	
Immunoglobulin	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Lianhua Qingwen	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

S severe, Mo moderate, Mi mild, IFN-α α-interferon

Table 2 Clinical outcomes of COVID-19 patients between two admissions

Characteristics	All patients (<i>n</i> = 14)		<i>P</i> value
	First admission (<i>n</i> = 14)	Second admission (<i>n</i> = 14)	
Age, years [mean (SD)]	44.4 ± 15.0		/
Sex (M/F)	(10/4)		
Respiratory rate	20.9 ± 1.4	20.4 ± 2.1	0.530
Days from onset of symptoms to admission	8.4 ± 5.5	2.6 ± 2.2	0.002
Days from onset of RNA (+) to admission	1.9 ± 1.6	2.6 ± 2.2	0.479
Days from onset of RNA (+) to RNA (-)	11.1 ± 7.7	6.3 ± 4.0	0.030
Days from onset of RNA (-) to RNA (+)	20.8 ± 8.7		/
Days from discharge to RNA (+)	12.2 ± 4.9		/
Total days in hospital	18.6 ± 8.3	8.0 ± 4.9	0.000
Common symptoms			
Fever	11 (78.6%)	0 (0.0%)	0.003
Cough	10 (71.4%)	1 (7.1%)	0.008
Short of breath	1 (7.1%)	0 (0.0%)	0.999
Diarrhea	1 (7.1%)	0 (0.0%)	0.999
Lack of appetite	4 (28.6%)	0 (0.0%)	0.134
Fatigue	7 (50.0%)	0 (0.0%)	0.023
Muscle pain	3 (21.4%)	0 (0.0%)	0.249
Epidemiological history			
Clear contact history	7 (50.0%)	14 (100.0%)	0.023
Unclear contact history	7 (50.0%)	0 (0.0%)	0.023
Medical treatment after admission			
Antibiotic treatment	5 (35.7%)	1 (7.1%)	0.221
Antifungal treatment	0 (0.0%)	0 (0.0%)	
Antiviral treatment	14 (100.0%)	10 (71.4%)	0.134
Glucocorticoids	4 (28.6%)	0 (0.0%)	0.134
Nebulized α -interferon treatment	8 (57.1%)	4 (28.6%)	0.134
Intravenous immunoglobulin therapy	2 (14.3%)	0 (0.0%)	0.480
Lianhua Qingwen	11 (78.6%)	3 (21.4%)	0.013

0.479). The average time from RNA (+) to RNA (-) was 11.1 days (SD ± 7.7) for the first admission and 6.3 days (SD ± 4.0) for the second admission (*P* = 0.030). The average time from onset of RNA (-) to RNA (+) was 20.8 days (SD ± 8.7) and the range of days from onset of RNA (-) to RNA (+) were 7 to 40 days for these patients. The average time from discharge to RNA (+) was 12.2 days (SD ± 4.9) and the days ranged from 1 to 21 days. Of the 14 cases, 4 (28.6%) patients had more than 14 days from discharge until recurrent positive SARS-CoV-2 RNA. Moreover, the average time from onset of symptoms to admission was 8.4 days (SD ± 5.5) for the first admission and 2.6 days (SD ± 2.2) for the second admission (*P* = 0.002). Additionally, the total time in hospital was 18.6 days (SD ± 8.3) for the first admission and 8.0 days (SD ± 4.9) for the second admission (*P* = 0.000).

Laboratory findings

Table 3 shows the details of laboratory data for two admitted in patients with COVID-19. White blood cell counts were $4.4 \times 10^9/L$ (SD ± 1.8) on the first admission and $5.8 \times 10^9/L$ (SD ± 1.4) on the second admission (*P* = 0.013), which may be a result of the increased lymphocyte and monocyte on the second admission (*P* = 0.000, 0.014). Platelet counts were $175.4 \times 10^9/L$ (SD ± 42.6) on the first admission and $207.6 \times 10^9/L$ (SD ± 46.7) on the second admission (*P* = 0.016). Moreover,

several endpoints including prothrombin time, activated partial thromboplastin time, aspartate aminotransferase, and creatinine were significantly lower on the second admission than on the first admission (all *P* < 0.05). However, the significance of these changes is still unclear. There were no significant differences in other lab data for the second admissions.

Discussion

Fourteen COVID-19 patients with recurrent positive test of viral RNA after hospital discharging or termination of quarantine in Hubei, China (without clinical symptoms and radiological abnormalities and with two consecutive negative viral RNA test results over 24 h interval), were characterized in the present study. All these patients had positive test in 7–40 days since RNA (-), without any aggravation on symptoms and chest CT. Despite the fact that the incidence of recurrent SARS-CoV-2 positive results in recovered patients is low, this group of patients should be tested timely for many times.

Till now, the asymptomatic patients with SARS-CoV-2 infection could be a new source of transmission, which would bring some new infectious disease prevention and control issues [11, 14]. In general, these recurrent cases are characterized as asymptomatic viral carriers, but they are different from the “true” first diagnostic asymptomatic patient. These

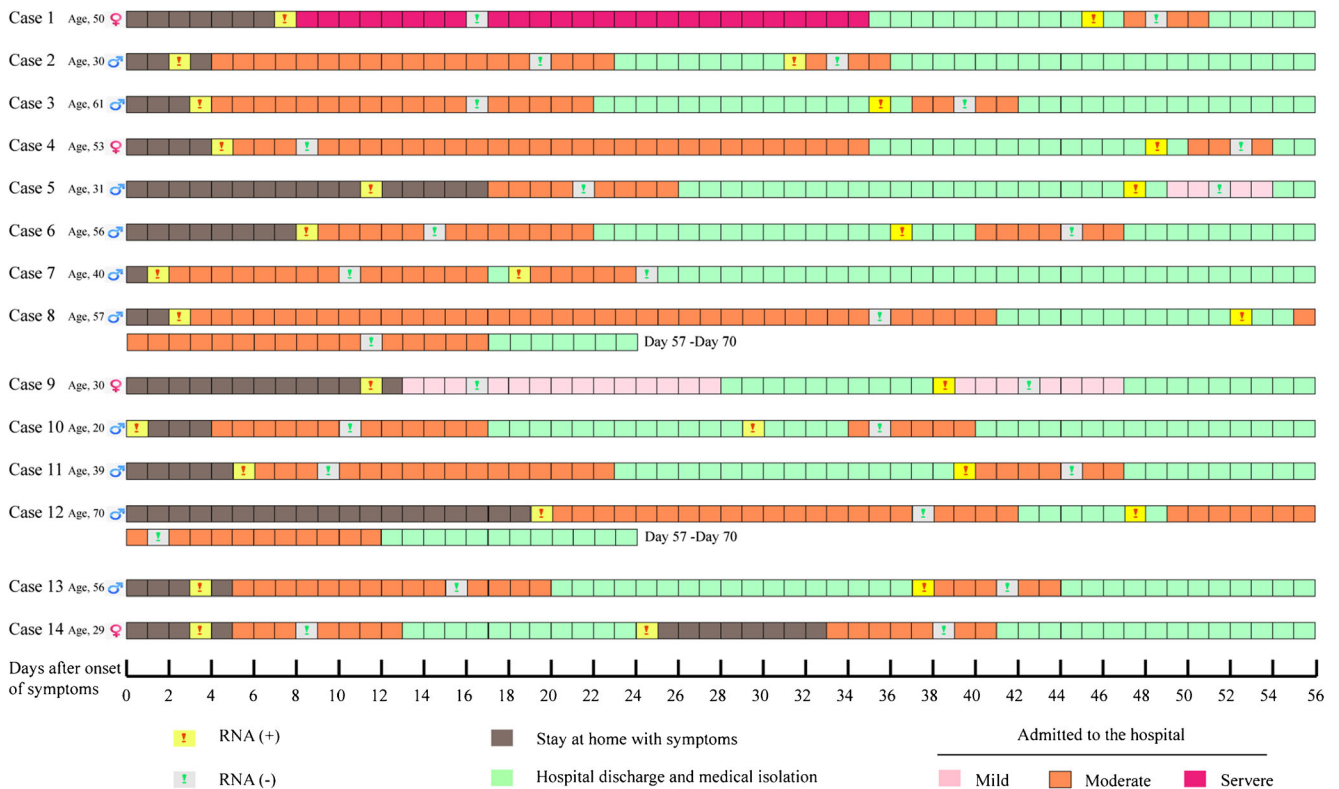


Fig. 1 The admission and discharge history of 14 re-hospitalized COVID-19 patients after recurrent positive SARS-CoV-2 RNA

Table 3 Laboratory findings of patients with COVID-19 between two admissions

Characteristics	All patients (n = 14)		P value
	First admission (n = 14)	Second admission (n = 14)	
White blood cell count, × 10 ⁹ /L	4.4 ± 1.8	5.8 ± 1.4	0.013
Neutrophil count, × 10 ⁹ /L	2.9 ± 1.3	3.6 ± 1.0	0.119
Red blood cell count, × 10 ⁹ /L	4.6 ± 0.5	4.3 ± 0.7	0.103
Hemoglobin, g/L	137.9 ± 16.1	134.1 ± 22.3	0.318
Neutrophil ratio, %	65.1 ± 9.8	61.2 ± 6.0	0.214
Lymphocyte count, × 10 ⁹ /L	1.1 ± 0.5	1.6 ± 0.4	0.000
Lymphocyte ratio, %	26.3 ± 8.3	28.5 ± 5.1	0.353
Monocyte count, × 10 ⁹ /L	0.3 ± 0.1	0.4 ± 0.2	0.014
Platelet count, × 10 ⁹ /L	175.4 ± 42.6	207.6 ± 46.7	0.016
Prothrombin time, s	12.1 ± 1.0	11.2 ± 1.2	0.003
Prothrombin activity, %	109.3 ± 22.2	109.4 ± 18.1	0.653
Activated partial thromboplastin time, s	32.8 ± 4.7	31.0 ± 2.8	0.049
Fibrinogen, g/L	4.1 ± 1.3	3.5 ± 0.8	0.098
Alanine aminotransferase, U/L	25.8 ± 22.7	33.79 ± 25.6	0.162
Aspartate aminotransferase, U/L	25.7 ± 9.7	21.8 ± 9.6	0.029
Total bilirubin, mmol/L	14.3 ± 9.1	16.2 ± 9.4	0.352
Albumin, g/L	41.1 ± 5.7	41.4 ± 3.8	0.930
Blood nitrogen, mmol/L	4.4 ± 1.6	4.6 ± 0.9	0.626
Creatinine, μmol/L	83.2 ± 19.8	68.6 ± 13.3	0.014
Fasting blood glucose, mmol/L	5.2 ± 0.9	5.2 ± 0.6	0.946

patients were previously diagnosed with COVID-19 and were discharged after standard treatment to meet the criteria for discharging. Moreover, it is important to note that people who had close contact with these recurrent cases were not found to have signs of COVID-19 infection. From this point of view, the management strategy for these recurrence cases is mainly isolation and observation. Our results suggested that antiviral therapy may not be a necessary treatment and that personalized treatment should be adopted for COVID-19 patients with recurrent positive SARS-CoV-2 RNA.

The underlying mechanisms of fluctuated SARS-CoV-2 RNA results are worth investigating. According to our results, all the 14 COVID-19 patients reported here with recurrent positive test of SARS-CoV-2 RNA had very clear history of a known exposure before their second admission and were related to the re-infection [21], which may explain the recurrence. Besides, real time-PCR assays with respiratory samples are considered as the reference standard for the diagnosis of COVID-19 [2]. As angiotensin converting enzyme-2 (ACE-2) is the host cell receptor for SARS-CoV-2 and is more easily spread in the lungs, the SARS-CoV-2 results may be false negative in nose or throat swab samples [3, 17], due to the lower viral load in these sites. Therefore, point-of-care technologies and serologic immunoassays may be a useful detection method [2]. Moreover, the proficiency of the operators and the accuracy of the kits are also important factors affecting the SARS-CoV-2 RNA results and can result in a false-negative RT-PCR result for detection of the virus [16]. What is more, the interval between two negative RT-PCR tests may not be sufficient to evaluate the degree of virus clearance. Before the second infection, further investigation is necessary to clarify pre-existing immune responses and viral load [6]. Viral load should be given more consideration as it is the most reliable method in determining whether it is safe for the patient to return to society [1].

In view of the possibility that the RT-PCR test results of the patients under the current criteria for hospital release from quarantine may convert to positive, some measures can be put in place to improve the current criteria and reduce the recurrence rate. Firstly, all the discharged patients are currently suggested to self-quarantine in their houses for 14 days according to China's National Health Commission. However, our results indicated that the range of days from discharge to RNA (+) were 1 to 21 days, and 4 (28.6%) patients had more than 14 days from discharge to recurrent positive SARS-CoV-2 RNA. Mao et al. found that after a 14-day isolation, asymptomatic COVID-19 patients could be a source of viral transmission and proposes a challenge to self-quarantine [12]. Therefore, we believe that it may be more appropriate to recommend 3 weeks of self-quarantine for COVID-19 patients after discharge, who were performed RT-PCR test as soon as possible. Secondly, a longer interval, such as 48 h, between two consecutive negative results in the

criteria for discharging from hospitals or the termination of the quarantine may be feasible to ensure that the patients to be discharged are not contagious and are less likely to have a recurrent positive SARS-CoV-2 RNA. Additionally, some laboratory examinations such as the absolute white blood cell as well as lymphocyte counts could be combined with the RT-PCR results as the criteria for hospital discharge to assure that the patients have completely recovered. Moreover, as SARS-CoV-2 RNA could be detected from sputum, throat swab, blood, or stool swab samples, multiple tests of different samples can be helpful in improving sensitivity. The test from bronchoalveolar lavage fluid specimen could be more reliable; however, a higher risk of exposure might occur. Finally, there is still no strong evidence of the contagious period of SARS-CoV-2 and the sample size was limited, and further studies will be needed to reduce the recurrence rate.

Limitations in the current study should be noted. Firstly, several missing data or even failure to follow-up can affect the accuracy of a patient's identification. Therefore, selection bias is hard to avoid and might occur for the retrospective study, and further prospective studies are needed. Second, our results were mainly based on two hospitals, and a large-scale multi-center study will be needed to pay more attention to the interesting topic in future. Last but not least, because of the lack of genome sequencing, we are unable to confirm that the positive test results in the re-hospitalized patients were due to the relapse of the same viral strain or reinfection with a new strain. In future research, we will try genome sequencing to help us identify whether the disease is due to reinfection or a relapse.

Conclusion

In conclusion, the incidence of recurrent positive SARS-CoV-2 RNA test in the patients with COVID-19 after discharge is relatively low and these patients have virtually no symptoms. However, considering the possible potential infectivity, we believe that the current national guidelines may need to be further revised, especially those with recurrent positive results of SARS-CoV-2 RNA test. Furthermore, it could be particularly necessary to increase the isolation observation time and RT-PCR tests should be timely performed on multiple samples as soon as possible. Additionally, we should pay more attention to genome sequencing in order to identify whether the patient is reinfected or relapsed. Considering the patients' underlying disease, personalized treatment should be taken to treat recurrent positive patients with COVID-19.

Acknowledgments We thank all the patients included in the current study. All co-authors sincerely appreciate all the medical staffs who assisted Hubei and fought in the front line. We also thank Troy Gharibani (University of Maryland, USA) for improving the manuscript.

Authors' contributions LP, LT, GX, KW, and XW conceptualized the manuscript and edited subsequent versions. LP, RW, NY, and CH wrote the first draft. JY, XZ, TW, JH, FG, TL, JW, XL, MM, and WH collected and analyzed data. YG and CL contributed ideas on the texts. All authors approved the final manuscript.

Funding This work was supported by Technology Plan Project of Binzhou Medical University (CN, BY2017KJ30), Health and Family Planning Commission of Shandong Province (CN, 2017WS366), and National Natural Science Foundation of China (CN, 81700490).

Data availability All data generated or analyzed during this study are included in this published article [and its tables and figures].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study had been approved by the Ethics Committees of Huanggang Central Hospital (No. HGGY-2020-005) and Wuhan Union Hospital (No. 2020-0077-1).

Consent to participate Exemption.

Consent for publication The participant has consented to the submission of this article to the journal. We confirm that the manuscript, or part of it, has neither been published nor is currently under consideration for publication. This work and the manuscript were approved by all co-authors.

Code availability SPSS version 20 (SPSS, Chicago, IL, USA).

References

- Cento V, Colagrossi L, Nava A, Lamberti A, Senatore S, Travi G et al (2020) Persistent positivity and fluctuations of SARS-CoV-2 RNA in clinically-recovered COVID-19 patients. *J Infect* 81:e90–e92. <https://doi.org/10.1016/j.jinf.2020.06.024>
- Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M et al (2020) Diagnostic testing for severe acute respiratory syndrome-related coronavirus-2: a narrative review. *Ann Intern Med*. <https://doi.org/10.7326/M20-1301>
- Feng H, Liu Y, Lv M, Zhong J (2020) A case report of COVID-19 with false negative RT-PCR test: necessity of chest CT. *Jpn J Radiol*. <https://doi.org/10.1007/s11604-020-00967-9>
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395:497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Hui DS, E, I. A., Madani, T. A., Ntoumi, F., Kock, R., Dar, O., et al. (2020) The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 91:264–266. <https://doi.org/10.1016/j.ijid.2020.01.009>
- Iwasaki A (2020) What reinfections mean for COVID-19. *Lancet Infect Dis*. [https://doi.org/10.1016/S1473-3099\(20\)30783-0](https://doi.org/10.1016/S1473-3099(20)30783-0)
- Jiang DM (2020) Recurrent PCR positivity after hospital discharge of people with coronavirus disease 2019 (COVID-19). *J Infect*. <https://doi.org/10.1016/j.jinf.2020.03.024>
- Khot WY, Nadkar MY (2020) The 2019 novel coronavirus outbreak - a global threat. *J Assoc Physicians India* 68:67–71
- Lan L, Xu D, Ye G, Xia C, Wang S, Li Y et al (2020) Positive RT-PCR test results in patients recovered from COVID-19. *JAMA*. <https://doi.org/10.1001/jama.2020.2783>
- Li C, Ji F, Wang L, Wang L, Hao J, Dai M et al (2020) Asymptomatic and human-to-human transmission of SARS-CoV-2 in a 2-family cluster, Xuzhou, China. *Emerg Infect Dis* 26. <https://doi.org/10.3201/eid2607.200718>
- Ling Z, Xu X, Gan Q, Zhang L, Luo L, Tang X et al (2020) Asymptomatic SARS-CoV-2 infected patients with persistent negative CT findings. *Eur J Radiol* 126:108956. <https://doi.org/10.1016/j.ejrad.2020.108956>
- Mao ZQ, Wan R, He LY, Hu YC, Chen W (2020) The enlightenment from two cases of asymptomatic infection with SARS-CoV-2: is it safe after 14 days of isolation? *Int J Infect Dis*. <https://doi.org/10.1016/j.ijid.2020.03.041>
- Mattuzzi C, Henry BM, Sanchis-Gomar F, Lippi G (2020) SARS-CoV-2 recurrent RNA positivity after recovering from coronavirus disease 2019 (COVID-19): a meta-analysis. *Acta Biomed* 91: e2020014. <https://doi.org/10.23750/abm.v91i3.10303>
- Qian G, Yang N, Ma AHY, Wang L, Li G, Chen X et al (2020) A COVID-19 Transmission within a family cluster by presymptomatic infectors in China. *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciaa316>
- Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A et al (2020) Genomic evidence for reinfection with SARS-CoV-2: a case study. *Lancet Infect Dis*. [https://doi.org/10.1016/S1473-3099\(20\)30764-7](https://doi.org/10.1016/S1473-3099(20)30764-7)
- Xiao AT, Tong YX, Zhang S (2020) False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: rather than recurrence. *J Med Virol*. <https://doi.org/10.1002/jmv.25855>
- Xie C, Lu J, Wu D, Zhang L, Zhao H, Rao B et al (2020) False negative rate of COVID-19 is eliminated by using nasal swab test. *Travel Med Infect Dis* 101668. <https://doi.org/10.1016/j.tmaid.2020.101668>
- Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y et al (2020) Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* 26:502–505. <https://doi.org/10.1038/s41591-020-0817-4>
- Yuan J, Kou S, Liang Y, Zeng J, Pan Y, Liu L (2020) PCR assays turned positive in 25 discharged COVID-19 patients. *Clin Infect Dis*. <https://doi.org/10.1093/cid/ciaa398>
- Zhang J, Tian S, Lou J, Chen Y (2020) Familial cluster of COVID-19 infection from an asymptomatic. *Crit Care* 24:119. <https://doi.org/10.1186/s13054-020-2817-7>
- Zhou L, Liu K, Liu HG (2020) Cause analysis and treatment strategies of "recurrence" with novel coronavirus pneumonia (covid-19) patients after discharge from hospital. *Zhonghua Jie He He Hu Xi Za Zhi* 43:E028. <https://doi.org/10.3760/cma.j.cn112147-20200229-00219>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Affiliations

Lei Pan¹ · Runsheng Wang² · Na Yu³ · Chao Hu² · Junhong Yan⁴ · Xiaomin Zhang⁵ · Tao Wang¹ · Jungui Hao⁶ · Fuquan Gao¹ · Tonggang Liu⁷ · Jing Wang¹ · Xiaojing Liu¹ · Mi Mu⁸ · Wei Huang⁹ · Yongzhong Guo¹⁰ · Changjun Lv¹ · Xiaozhi Wang¹ · Lei Tu¹¹ · Kun Wan¹² · Guogang Xu¹³

¹ Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital, Binzhou, China

² Department of Respiratory Medicine, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Medical College of PLA, Chinese PLA General Hospital, Beijing, China

³ Department of Gynecology, Shandong Provincial Third Hospital, Jinan, China

⁴ Department of Ultrasound, Binzhou Medical University Hospital, Binzhou, China

⁵ Department of Nephrology, Binzhou Medical University Hospital, Binzhou, China

⁶ Department of Infection Diseases, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

⁷ Department of Infectious Diseases, Binzhou Medical University Hospital, Binzhou, China

⁸ Department of Disease Prevention and Control, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing, China

⁹ Department of Infection Diseases, Huanggang Central Hospital, Huanggang, China

¹⁰ Department of Respiratory Medicine, Xuzhou Central Hospital, The Xuzhou School of Clinical Medicine of Nanjing Medical University, Xuzhou Clinical School of Xuzhou Medical University, Xuzhou, China

¹¹ Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

¹² Medical Supplies Center, Chinese PLA General Hospital, Beijing, China

¹³ The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing, China