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RESEARCH ARTICLE

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Clinical characteristics of rehospitalized patients with COVID-19 in China

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Abstract

This study aims to observe the clinical characteristics of recovered patients from Coronavirus Disease 2019 (COVID-19) with positive in reverse transcription-polymerase chain reaction (RT-PCR) or serum antibody. The profile, clinical symptoms, laboratory outcomes, and radiologic assessments were extracted on 11 patients, who tested positive for COVID-19 with RT-PCR or serum antibody after discharged and was admitted to Hubei No. 3 People's Hospital of Jianghan University for a second treatment in March 2020. The average interval time between the first discharge and the second admission measured 16.00 ± 7.14 days, ranging from 6 to 27 days. In the second hospitalization, one patient was positive for RT-PCR and serum antibody immunoglobulin M (IgM)-immunoglobulin G (IgG), five patients were positive for both IgM and IgG but negative for RT-PCR. Three patients were positive for both RT-PCR and IgG but negative for IgM. The main symptoms were cough (54.55%), fever (27.27%), and feeble (27.27%) in the second hospitalization. Compared with the first hospitalization, there were significant decreases in gastrointestinal symptoms (5 vs 0, $P = .035$), elevated levels of both white blood cell count ($P = .036$) and lymphocyte count ($P = .002$), remarkedly decreases in C-reactive protein and serum amyloid A ($P < .05$) in the second hospitalization. Additionally, six patients' chest computed tomography (CT) exhibited notable improvements in acute exudative lesions. There could be positive results for RT-PCR analysis or serum IgM-IgG in discharged patients, even with mild clinical symptoms, however, their laboratory outcomes and chest CT images would not indicate the on-going development in those patients.

KEYWORDS

clinical characteristics, convalescent patient, COVID-19

1 | INTRODUCTION

In December 2019, pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, Hubei Province, China. As of 7 March 2020, a total of 80 695 COVID-19 cases have been confirmed in China. Nevertheless, the number has experienced an obvious decline as the disease has been brought under reasonable control. Till 17 March 2020, there were no new confirmed cases reported for 13 consecutive days in Hubei Province except Wuhan city. By contrast, a total of 69 725 cases were cured

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and discharged. At present, the disease has quickened its spread in many countries and regions across the world, sparking wide concerns among governments and scientists. This epidemic is a major health risk and sends ripples through national economy, which has infected more than 100 000 worldwide.[1,2] In previous studies, epidemiological, clinical, and radiological features of COVID-19 patients have been intensively reported.[3,4] However, there was less attention on the follow-up of discharged patients. Therefore, this study further investigated the 11 cases of rehospitalized patients with COVID-19 in Hubei No. 3 People's Hospital of Jianghan University since March 2020 with positive outcomes for reverse transcription-polymerase chain reaction (RT-PCR) or serum antibody.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

We performed a retrospective review of 11 rehospitalized patients with COVID-19 in Hubei No. 3 People's Hospital of Jianghan University from 1 March to 7 March 2020, whose RT-PCR or serum antibody tests were positive from 4 to 27 days after discharge. This study was reviewed and approved by the Medical Ethical Committee of the Hubei No. 3 People's Hospital of Jianghan University (202004). All of the patients with COVID-19 included in this study were diagnosed in accordance to the World Health Organization interim guidance and were diagnosed by a multidisciplinary diagnosis and treatment team composed of infectious disease experts, respiratory medicine staff and intensive care unit staff.[5]

2.2 | Data collection

The clinical symptoms, laboratory outcomes, and chest computed tomography (CT) were extracted from electronic medical records. Data were entered into a computerized database and cross-checked. Laboratory assessments consisted of complete blood count, blood chemistry, liver and renal function, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase, and D-Dimer. The RT-PCR results of SARS-CoV-2 were collected and analyzed from patients' oropharyngeal swab samples. These diagnostic criteria were based on the recommendation by the National Institute for Viral Disease Control and Prevention (China) (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html). Primers and probes targeting are recommended from an open reading frame (ORF) 1ab gene and nucleoprotein (N) gene regions of SARS-CoV-2. Target 1 (ORF1ab): forward primer, CCCTGTGGGTTTTACACTTAA; reverse primer, ACGATTGTGCATCAGCTGA; and the probe, 5′-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3′. Target 2 (N): forward primer, GGGGAACTTCTCCTGCTAGAAT; reverse primer, CAGACATTTTGCTCTCAAGCTG; and the probe, 5′-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3′. Serum antibody was detected by colloidal gold immunochromatography.

2.3 | Statistical analysis

Statistical analysis was performed with SPSS, version 26.0. Continuous variables were directly expressed as mean, median, and interquartile range values. Comparisons between the groups were performed using the Mann-Whitney *U* test. Categorical variables were expressed as numbers (%) and compared by χ^2 test or Fisher's exact test between the different groups. All tests were two-sided tests, and $P < .05$ has a statistical significance.

3 | RESULTS

3.1 | Baseline characteristics of rehospitalized patients

As of 11 rehospitalized patients, there were three males and eight females, at the mean age of 48.45 ± 14.12 years, ranging from 33 to 72 years. The first hospital stay was significantly longer than the second ([22.27 ± 4.85] days vs [7.00 ± 2.56] days; $P < .001$). The average interval time between the first discharge and the second admission measured 16.00 ± 7.14 days, ranging from 6 to 27 days. The average count of negative results by RT-PCR before discharge was 2.63 ± 0.92 times, in the range of 2 to 5 times. During the second hospitalization, one patient displayed positive outcomes both for RT-PCR analysis and immunoglobulin M (IgM)-immunoglobulin G (IgG), five patients were double-positive for IgG-IgM but negative for RT-PCR, three patients were positive both for RT-PCR and serum antibody IgG but negative for IgM. The quantitation of IgM and IgG was not available in all patients before April. Three patients had common chronic illness, with two cases of diabetes and one case of hypertension (Table 1).

3.2 | Clinical symptoms of rehospitalized patients

The main symptoms of the 11 patients' second admission were cough (6, 54.55%), fever (3, 27.27%), and feeble (3, 27.27%), respectively. There was no expectoration, pant and muscular soreness during the second hospitalization, and the rate of gastrointestinal symptoms were statistically different between the two hospitalizations (5 vs 0, $P = .035$; Table 2).

3.3 | Laboratory results of rehospitalized patients

The routine blood test, CRP, ESR, serum amyloid A (SAA), and PCT were used to reflect changes of an inflammatory response in COVID-19. Compared with the first hospitalization, there was an increase in both white blood cell count and lymphocyte count, a significant fall in CRP and SAA in the second hospitalization, and the difference was statistically significant ($P < .05$). There was no difference in biochemical criteria between the two hospitalizations ($P > .05$; Table 3).

TABLE 1 Baseline characteristics of rehospitalized patients

	Patient											
ID	1	2	3	4	5	6	7	8	9	10	11	Mean ± SD
Gender	M	M	M	M	M	M	F	F	M	M	F	–
Age	35	36	42	66	53	33	49	38	72	42	67	48.45 ± 14.12
Hospital stay												
The first hospitalization	16	21	22	28	23	19	28	30	24	17	17	22.27 ± 4.85
The second hospitalization	3	4	8	7	8	8	7	6	6	7	13	7.00 ± 2.56
Interval time	27	11	21	24	15	15	8	8	19	22	6	16.00 ± 7.14
Total	46	36	51	59	46	42	43	44	49	46	36	45.27 ± 6.65
Count of RT-PCR (−) in the first hospitalization	2	3	3	2	3	2	2	5	2	2	3	2.63 ± 0.92
Second hospitalization												
RT-PCR	−	+	+	+	+	−	+	+	−	−	−	
IgG antibody	+	N/A	+	+	+	+	N/A	+	+	+	+	
IgM antibody	+	N/A	−	−	+	+	N/A	−	+	+	+	
Chronic illness	N	Diabetes	N	N	Hypertension	N	N	N	N	N	Diabetes	

Note: N/A, not available; "+" positive, "−" negative.
Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin; RT-PCR, reverse transcription-polymerase chain reaction; SD, standard deviation.

3.4 | Changes of chest CT

The patients' chest CT imaging showed ground-glass opacification or mixed ground-glass opacification and consolidation at the onset. In the second hospitalization, chest CT images of the six patients showed a substantial improvement of the acute, discharged from the Hubei No. 3 People's Hospital of Jianghan University for the first time. In addition, the chest CT of patient 1, patient 2, and patient 6 showed that the lesions were completely absorbed in the second hospitalization (Figure1).

4 | DISCUSSION

For hospital discharge or suspension of quarantine, patients had to meet the following five criteria including (a) normal temperature without fever for over 3 days, (b) improved respiratory symptoms, (c) substantially improved acute exudative lesions on chest CT images, and (d) two consecutively negative results of RT-PCR analysis with 1-day interval at least.[6] However, since March 2020, there were 11 discharged patients exhibiting positive results in RT-PCR analysis or serum antibody when rechecking in Hubei No. 3 People's Hospital

TABLE 2 Clinical symptoms of rehospitalized patients

	First hospitalization (n = 11)		Second hospitalization (n = 11)			
Clinical symptoms	No.	(%)	No.	(%)	χ^2	*P* value
Fever	7	63.64	3	27.27	0.087	.198
<37.3	4	36.36	8	72.73	…	…
37.3-38	2	18.18	0	0	…	…
38-39	4	36.36	3	27.27	…	…
>39	1	9.9	0	0	…	…
Cough	7	63.64	6	54.55	0.665	1.000
Expectoration	3	27.27	0	0	3.474	.214
Pant	1	9.9	0	0	1.048	1.000
Gastrointestinal symptoms	5	45.45	0	0	6.471	.035
Diarrhea	2	18.18	0	0	2.200	.476
Nausea	3	27.27	0	0	3.474	.214
Headache	2	18.18	1	9.9	0.386	1.000
Muscular soreness	1	9.9	0	0	1.048	1.000
Feeble	4	36.36	3	27.27	0.210	1.000

Note: The data is expressed as n (%).

TABLE 3 Laboratory results of rehospitalized patients

		First hospitalization (n = 11)	Second hospitalization (n = 11)	*Z*	*P* value
Routine blood	**Normal range**				
WBC (cells•L^{-1})	3.5-9.5	4.10 ± 1.60	5.83 ± 1.71	−2.102	.036
NEU (cells•L^{-1})	1.8-6.3	2.77 ± 1.43	3.72 ± 1.36	−1.609	.108
N%	40-75	66.43 ± 15.80	62.74 ± 10.47	−1.084	.278
LYM (cells•L^{-1})	1.1-3.2	0.86 ± 0.40	1.54 ± 0.66	−3.122	.002
RBC (cells•L^{-1})	3.8-5.1	3.98 ± 0.27	4.03 ± 0.51	−0.427	.669
Hb, g•L^{-1}	1115-150	126.09 ± 11.87	126.36 ± 13.69	−0.033	.974
PLT (cells•L^{-1})	125-350	190.18 ± 84.07	194.54 ± 58.17	−0.460	.646
Inflammatory markers					
CRP, mg•L^{-1}	0-5	36.32 ± 35.75	2.79 ± 2.49	−3.217	.001
ESR, mm•h^{-1}	0-20	31.21 ± 26.58	28.60 ± 25.98	−0.066	.948
SAA, mg•L^{-1}	0.1-10	375.31 ± 501.65	7.43 ± 12.7	−3.710	<.001
PCT, ng•mL^{-1}	0.04-0.25	0.36 ± 0.78	0.01 ± 0.02	−1.710	.087
Biochemical criterion					
ALT, U•L^{-1}	5-35	21.81 ± 19.93	23.51 ± 18.82	−0.033	.974
AST, U•L^{-1}	8-40	34.07 ± 13.86	30.32 ± 12.23	−0.985	.324
GGT, U•L^{-1}	0-50	27.92 ± 31.02	26.34 ± 25.35	−0.361	.718
Cr, μmol•L^{-1}	44-120	58.18 ± 31.24	55.45 ± 11.22	−0.297	.767
BUN, mmol•L^{-1}	2.5-6.7	5.59 ± 4.89	4.52 ± 1.28	−0.756	.450
LDH, U•L^{-1}	109-245	237.36 ± 108.02	167.18 ± 34.25	−1.741	.082
D-dimer, μg•L^{-1}	0-1	0.69 ± 0.80	0.33 ± 0.26	−0.891	.373

Abbreviations: ALT, alanine transaminase; AST, glutamic oxalacetic transaminase; BUM, urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transpeptidase; GLU, glucose; Gr, creatinine; Hb, hemoglobin; IL-6, interleukin-6; LDH, lactic dehydrogenase; LYM, lymphocytes; N%, neutrophil ratio; N/A, not available; NEU, neutrophils; PCT, procalcitonin; PLT, blood platelet; RBC, red blood cells; SAA, serum amyloid A; WBC, white blood cells.

of Jianghan University. Eight rehospitalized patients were female, at the average age of below 50. The longest interval between the first discharge and the second admission was 27 days whereas 13 days reported by LanLan.[7] One patient was negative in RT-PCR tests for five times before the first discharge but positive on 8th day after discharge. These findings suggest that at least a proportion of recovered patients were potential virus carriers. Previous study suggested that false-negative RT-PCR test results could have occurred.[8] The nucleic acid testing may be influenced by the different samples. Previous studies suggested the possibility of extended duration of viral shedding in faeces, for nearly 5 weeks after the patients' respiratory samples tested negative for SARS-CoV-2 RNA, maybe the delayed clearance of viral RNA in patients' stools.[9-10]

In addition, the results of RT-PCR or serum antibody test of 11 patients were different in the second hospitalization. One patient was positive for both RT-PCR and serum antibody IgM-IgG. To some extent, this patient was still in active phase of infection and had acquired some immunity to SARS-CoV-2 (persistent antibody IgG has been produced). By contrast, five patients were double-positive in serum antibody IgG-IgM but negative for RT-PCR. These outcomes suggested that those patients were in course of recovery and virus has not been fully eliminated or the RT-PCR results were false negative and the patient was still in the active period of infection. As for the false negatives, there was one possibility that SARS-CoV-2 infection is prone to starts at the lungs, not in the upper respiratory tract, therefore, sampling during the early infection stage using throat swab or sputum may not detect the virus.[11] Three patients were positive in RT-PCR and serum antibody IgG but negative in IgM. These results showed that the patients could be in the middle or late phage of the SARS-CoV-2 infection or in the reactive infection. In some cases, the IgM level might well be below its peak and not detectable by test. A study encouraged more research and development of the COVID-19 IgG-IgM combined antibody test kit to improve the diagnostic sensitivity and specificity for patients.[12] Patients can be diagnosed as recurrent infection when the IgG antibody is increased to four times or more in the convalescent compared with the acute phase. Unfortunately, the quantification of the IgG titer was not available in March. Therefore, this study suggested that the patients should take a prolonged quarantine and more reexaminations from varying samples after discharge with COVID-19. The latest diagnosis and treatment of COVID-19 pneumonia in China (7th edition) issued by the National Health Commission, PRC recommends that patients shall continue to undergo an intensive isolation for 14 days after discharge, and followed by reexamination at 2 and 4 weeks after discharge.[13]

In this study, the main clinical symptoms were cough, fever, and feeblein the second hospitalization. More of them were mild and relieved. The gastroinstestinal symptoms with diarrhea or nausea of five patients

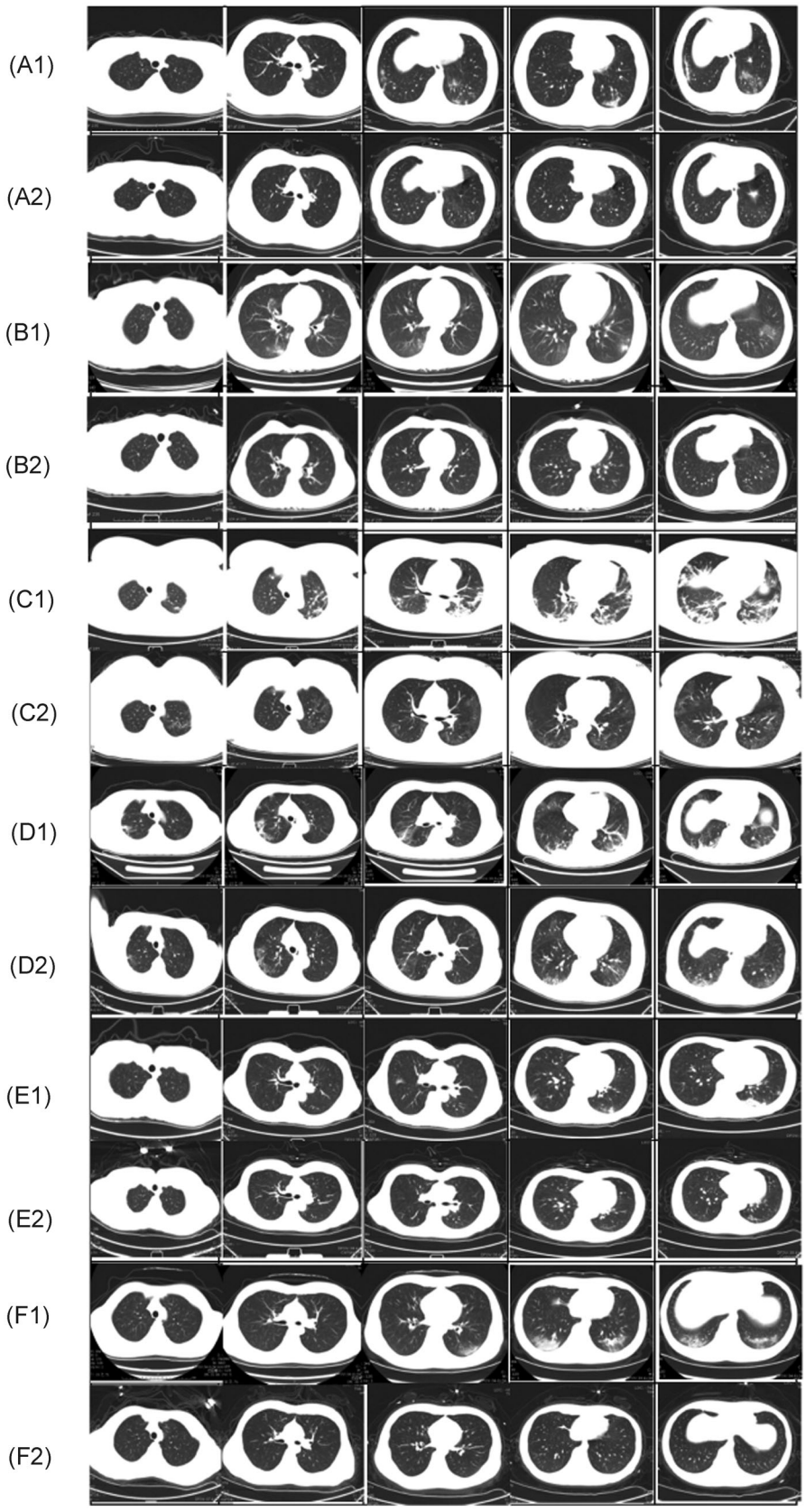

FIGURE 1 Changes of chest CT of six patients (A, B, C, D, E, F). A1: chest CT in the first hospitalization of patient 1; A2: chest CT in the second hospitalization of patient 1; B1: chest CT in the first hospitalization of patient 2; B2: chest CT in the second hospitalization of patient 2; C1: chest CT in the first hospitalization of patient 3; C2: chest CT in the second hospitalization of patient 3; D1: chest CT in the first hospitalization of patient 4; D2: chest CT in the second hospitalization of patient 4; E1: chest CT in the first hospitalization of patient 5; E2: chest CT in the second hospitalization of patient 5; F1: chest CT in the first hospitalization of patient 6; F2: chest CT in the second hospitalization of patient 6. CT, computed tomography

in the second hospitalization were obviously improved. Recent studies have suggested that there was no direct relationship between gastrointestinal symptoms and virus in faecal.[9] Therefore, this results discharged that patients need reexamination of virus RNA although asymptomatic. A study showed that in patients recovering from COVID-19 infection, four stages of evolution on chest CT were identified: early-stage (0-4 days); progressive stage (5-8 days); peak stage (10-13 days) and absorption stage (≥14 days).[14] In this study, the chest CT indicated that the patients were all in the absorptive stage after first discharge.

5 | CONCLUSION

Together, there were still positive outcomes in RT-PCR analysis or serum IgM-IgG in rehospitalized COVID-19 patients, though they met the discharge criteria at the end of the first hospitalization. However, in the second hospitalization, there was a shortened hospital stay, relieved clinical symptoms improved laboratory outcomes, and ameliorated CT manifestations on the second admission, which suggest that these rehospitalized patients were more likely to be in a status of recovery.

This study was a single-center, small-sample, retrospective study. A larger cohort of longitudinal studies will help to understand the prognosis of the disease.

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AUTHOR CONTRIBUTIONS

Min Chen, Wei An, and Fei Xia had the idea for and designed the study and had full access to all data in the study. Mingwei Zhang, Jialin Liu, and Yafang Zhang take responsibility for the integrity of the data and the accuracy of the data analysis. Ping Yang, Kuangyu Li, Qin Zhou, Shasha Fang, Yaling Liao, Xin Xu, Shiguo Liu, and Tao Qin contributed to the writing of the report. Min Chen, Guowei Zhang, and Fei Xia contributed to the revision of the manuscript. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

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

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