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Reactivation of SARS-CoV-2 infection following recovery from COVID-19

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ABSTRACT

Introduction: Many individuals test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA after recovering from the coronavirus disease (COVID-19), but the incidence of reactivation is unknown. We, therefore, estimated the incidence of reactivation among individuals who had recovered from COVID-19 and determined its predictors.
Methods: In this retrospective cohort study, patients with COVID-19 were followed up for at least 14 days after two consecutive negative SARS-CoV-2 polymerase chain reaction test results obtained ≥24 h apart, and the frequency of SARS-CoV-2 reactivation was assessed.
Results: Of the 109 patients, 29 (27%) experienced reactivation, and seven (24%) of these were symptomatic. The mean period for the real-time PCR tests for SARS-CoV-2 from negative to positive results was 17 days. Compared with patients without reactivation, those with reactivation were significantly younger and more likely to have a lymphocyte count of <1500/μL (odds ratio [OR]: 0.34, 95% confidence interval [CI]: 0.12–0.94) and two or fewer symptoms (OR: 0.20, 95% CI: 0.07–0.55) during the initial episode.
Conclusion: Risk-stratified surveillance should be conducted among patients who have recovered from COVID-19.

Plain language summary

The possibility of recurrent infection with SARS-CoV-2 or COVID-19 relapse is largely unknown. We followed patients after their recovery from COVID-19 and investigated the predictors for the relapse. Among 109 patients who we studied, 27% of them had the virus reactivation defined by the positive real-time PCR test results from their sputum specimens, and 7% of them were symptomatic reactivation (disease relapse) for an average of 29 days after discharge from the hospital. We also found that several clinical features during the early onset of the disease had a higher probability to predict the reactivation or recurrent infection with symptoms, which included low lymphocyte cell count in the blood test (<1500/μL) and having two or fewer symptoms at the onset of COVID-19. Patients with these features were more likely to have the virus reactivation during the recovery. Our data suggest that risk-stratified surveillance is needed among patients who have recovered from COVID-19, particularly healthcare providers and other essential workers during the pandemic.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently identified virus belonging to the human coronavirus family [1]. Coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, typically manifests as an acute respiratory infection and progresses to respiratory failure in approximately 17% of patients [2]. Owing to high levels of urbanization and international travel, SARS-CoV-2 spread globally following its emergence in Wuhan, China, and rapidly became pandemic. This has raised

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serious concerns about its adverse impact on healthcare resources and economic growth [3]. Currently, there is no effective preventive vaccine. Therefore, the promotion of social distancing, hand washing, and quarantine of infected individuals are the major methods for preventing transmission.

Recent guidelines on the management of patients with COVID-19, published by the United States Centers for Disease Control and Prevention (CDC), recommend that even healthcare workers with confirmed COVID-19 can return to work if at least 3 days (72 h) have passed since recovery (defined as the resolution of fever without the use of antipyretic medications and improvement in respiratory symptoms, e.g., cough and shortness of breath) and at least 10 days have passed since symptom initiation [4]. Alternatively, a test-based strategy can be used including (1) resolution of fever without the use of antipyretic medications and improvement in respiratory symptoms (e.g., cough and shortness of breath); and (2) negative results on a Food and Drug Administration (FDA) Emergency Use Authorized COVID-19 molecular assay for the detection of SARS-CoV-2 RNA of at least two consecutive respiratory specimens collected ≥24 h apart (a total of two specimens with negative results) [4]. These recommendations were made on the assumption of no disease recurrence or relapse after the first episode of SARS-CoV-2 infection.

Although the possibility of recurrent infection with SARS-CoV-2 or COVID-19 relapse is largely unknown, a few recurrent cases have been reported in several recent publications. Chen D et al. [5], published a case report of a patient with COVID-19 whose oropharyngeal swab test for SARS-CoV-2 RNA yielded positive results in three days after two consecutive negative test results on specimens collected ≥24 h apart. However, the short duration of follow-up – It is unclear whether the patient had been asymptomatic for at least 72 h – raised questions about the accuracy of the real-time polymerase chain reaction (RT-PCR) assay which had not been FDA approved [6]. Ye et al. [7], reported a case series of five patients with recurrent positive results on RT-PCR for SARS-CoV-2 (using throat swabs) after an asymptomatic period of 4–17 days. Four of these five patients had a recurrent fever, cough, sore throat, and fatigue during the period of recurrence.

As some cases in the study reported by Ye et al. had met the United States CDC criteria of passing at least 3 days (72 h) after the resolution of symptoms and a period of at least 10 days since the symptoms first appeared, this demonstrated the need for further investigation of recurrent SARS-COV-2 infection and COVID-19 relapse. However, these previous studies included very few patients, with a short duration of follow-up, and the reports were preliminary, which limits the generalizability of the findings. Given these uncertainties, we designed a retrospective cohort study to investigate the frequency of recurrent infection of SARS-COV-2 and COVID-19 relapse. In addition, we analyzed the data to identify possible predictors of recurrent SARS-COV-2 infection. Our study aimed to provide evidence for clinicians, health authorities, and policymakers to inform their management of patients who have recovered from COVID-19 and to assess the need for continued surveillance of SARS-COV-2 infection.

Material and methods

Study design and patient recruitment

This retrospective cohort study recruited patients at the Beijing Ditan Hospital, which is affiliated with Capital Medical University, an academic tertiary care center in Beijing, China. The hospital is also a designated center in Beijing for the diagnosis and treatment of COVID-19. Eligible patients were those who had been hospitalized with confirmed COVID-19, with at least one follow-up visit, more than 14 days after discharge. Patients who did not have a SARS-CoV-2 RT-PCR test during the post-discharge visit were excluded from the study. A confirmed case was defined as a patient with clinical features of COVID-19 and a positive SARS-CoV-2 RT-PCR test result for at least one of the respiratory specimens collected. Patients who met any of the following criteria were considered as having severe COVID-19: (1) dyspnea with a respiratory rate >30/min; (2) hypoxemia with oxygen saturation <93%; (3) PaO_2/FiO_2 <300 mmHg; or (4) complications, such as sepsis, metabolic acidosis, organ failure, and acute respiratory distress syndrome.

We collected epidemiological and clinical data, which included data of chronology of symptom onset; the history of the first presentation and disease progression; past medical history; physical findings; laboratory testing and imaging results, treatment, and clinical course; post-discharge quarantine information with possible contact or exposure to SARS-CoV-2 after discharge; and other clinical data with laboratory reports on follow-up visits as outpatients. Data were collected from medical records and self-reported data from a questionnaire that patients completed during their hospital stay and visits to the clinic. Individual data were grouped according to whether patients developed a recurrent infection.

Study measures

The primary measures included aggregated case counts on the recurrence of SARS-CoV-2 infection, which was defined as recurrent positive RT-PCR test results for SARS-CoV-2 RNA in two consecutive respiratory specimens collected ≥24 h after at least 14 days had passed since recovery from COVID-19 or the date of discharge from hospital, whichever occurred first. At our center, recovery (discharge criteria) referred to the resolution of fever without the use of antipyretic medications and improvement in respiratory symptoms (e.g., cough and shortness of breath) and the passage of at least 14 days since symptom onset. In addition, patients were required to have tested negative for SARS-CoV-2 using an RT-PCR assay on at least two consecutive respiratory specimens collected ≥24 h apart.

Secondary measures assessed included: (1) the proportion of patients with disease relapse, which was defined as the recurrence of SARS-CoV-2 infection based on the definition given above; (2) predictors of recurrent SARS-CoV-2 infection assessed by comparing individuals with and without recurrence of positive RT-PCR assay results for SARS-CoV-2 after recovery from COVID-19; and (3) predictors of COVID-19 relapse assessed by comparing individuals with recurrent symptoms after 14-day recovery and those without recurrence of positive RT-PCR assay results for SARS-CoV-2 after recovery from COVID-19.

Laboratory testing for SARS-CoV-2

Laboratory investigations of SARS-CoV-2 were performed by the China CDC using an oropharyngeal swab, nasopharyngeal swab, or sputum specimens obtained from patients during their stay in hospital and post-discharge follow-up visits, which had been the standard of care at our hospital. The specimens were maintained in a viral transport medium and kept at −70 °C before testing. RT-PCR assays were performed using the same protocol as described by Huang et al. [8]. The detection reagents were based on the RT-PCR, specifically designed primers, a TaqMan probe (ThermoFisher Scientific, Waltham, MA, USA) for the *ORF1ab/N* gene of SARS-CoV-2, and a fluorescence PCR detector to achieve specific detection of SARS-CoV-2. The detailed procedure and protocol for the laboratory testing are presented in the supplementary material (online publication). The RT-PCR (Duplex PCR) kits were provided by Shanghai BioGerm Medical Technology Co. Ltd (Shanghai, China).

Table 1
Clinical features of patients with or without recurrent positive RT-PCR assay results for SARS-CoV-2 on consecutive respiratory specimens.

Variables n (%), or as specified	All patients (n = 109)	Comparison of patients with and without recurrent positive SARS-CoV-2 RT-PCR test results[a]		
		Recurrent group (n = 29)	Non-recurrent group (n = 80)	*P* value
Age (years), mean ± SD	43˙69 ± 19·77	36·22 ± 22·38	46·40 ± 18·14	·02
Male sex	61/109 (56·0)	15/29 (51·7)	46/80 (57·5)	·59
Smoking history	6/109 (5·5)	0/29 (0)	6/80 (7·5)	·34
Chronic conditions	41/109 (37·6)	9/29 (31·0)	32/80 (40·0)	·39
Hospitalization at the onset of illness	2/109 (1·8)	2/29 (6·9)	0/80 (0)	·07
Headache	18/109 (16·5)	4/29 (13·8)	14/80 (17·5)	·87
Fever	92/109 (84·4)	21/29 (72·4)	71/80 (88·8)	·08
Temperature ≥38 °C	54/109 (49·5)	15/29 (51·7)	39/80 (48·8)	·78
Fatigue	39/109 (35·8)	9/29 (31·0)	30/80 (37·5)	·53
Cough	60/109 (55·0)	16/29 (55·2)	44/80 (55·0)	·99
Sore throat	15/109 (13·8)	3/29 (10·3)	12/80 (15·0)	·76
Shortness of breath	5/109 (4·6)	1/29 (3·4)	4/80 (5·0)	>·99
Nausea/vomiting	5/109 (4·6)	0/29 (0·0)	5/80 (6·3)	·32
Diarrhea	8/109 (7·3)	1/29 (3·4)	7/80 (8·8)	·60
Myalgia/arthralgia	26/109 (23·9)	6/29 (20·7)	20/80 (25·0)	·64
O_2 saturation <93%	11/109(10·1)	2/29(6·9)	9/80(11·3)	·76
Chest pain	1/109 (0·9)	0/29 (0)	1/80 (1·3)	>·99
≥2 signs or symptoms	75/109 (68·8)	12/29 (41·4)	63/80 (78·8)	<·001
PaO_2/FiO_2, mean (±SD)	395·02 ± 147·71	377·88 ± 104·37	398·54 ± 155·98	·77
Leukocyte (count/L), mean ± SD	5·10 ± 1·87	5·71 ± 2·05	4·87 ± 1·76	·03
Hemoglobin (g/L), mean ± SD	137·33 ± 17·30	138·06 ± 15·10	137·06 ± 18·13	·79
Lymphopenia[b]	72/108 (66·7)	12/29 (41·4)	60/79 (75·9)	·001
Thrombocytopenia[c]	24/108 (22·2)	5/29 (17·2)	19/79 (24·1)	·45
Sodium (mmol/L), median (IQR)	139·0 (137·0–140·0)	139·4 (138·3–140·3)	139·00 (136·9–140·0)	·29
Potassium (mmol/L), mean ± SD	3·85 ± 0·43	3·93 ± 0·48	3·73 ± 0·44	·04
Chloride (mmol/L), median (IQR)	103·0(100·7-105·1)	103·5(102·0-105··2)	102·8(100·2-105·0)	·31
Creatinine ≥133 μmol/L, n (%)	1/104 (1·0)	0/29 (0)	1/75 (1·3)	>·99
Aspartate aminotransferase >40 U/L, n (%)	10/59 (16·9)	0/17 (0)	10/42 (23·8)	·07
Alanine aminotransferase >40 U/L, n (%)	19/103 (18·4)	3/29 (10·3)	16/74 (21·6)	·18
Total bilirubin ≥17·1 μmol/L, n (%)	2/57 (3·5)	0/17 (0)	2/40 (5·0)	>·99
Creatinine kinase ≥200 U/L, n (%)	11/100 (11·0)	4/25 (16·0)	7/75 (9·3)	·58
C-reactive protein level ≥10 mg/L, n (%)	44/98 (44·9)	12/26 (46·2)	32/72 (44·4)	·88
Elevated erythrocyte sedimentation rate, median (IQR)	21·0(8·5-48·0)	20·5(4·0-32·8)	21·0(9·5-52·0)	·25
Lactose dehydrogenase ≥250 U/L, n (%)	23/56 (41·1)	4/14 (28·6)	19/42 (45·2)	·27
D-dimer ≥0·5 mg/L, n (%)	21/58 (36·2)	5/16 (4·6)	16/42 (38·1)	·63
Activated partial thromboplastin time (seconds), median (IQR)	34·2 (31·2–39·7)	33·8 (30·6–39·2)	34·4 (31·4–41·3)	·83
Prothrombin time (seconds), median (IQR)	12·1 (11·6–13·0)	11·9 (11·2–12·3)	12·2 (11·6–13·1)	·08
Myoglobin (ng/mL), median (IQR)	12·0(9·5-18·5)	9·5(8·8-13·3)	15·0(10·0-19·0)	·06
Local patchy shadowing, n (%)	22/107 (20·6)	5/28 (17·9)	17/79 (21·5)	·68
CT bilateral patchy shadowing, n (%)	75/107 (70·1)	16/28 (57·1)	59/79 (74·7)	·08
CT Interstitial abnormalities	4/109(3·6)	1/29(3·4)	3/80(3·8)	>0·99
CT ground-glass opacities, n (%)	87/107 (81·3)	21/28 (75·0)	66/79 (83·5)	·32
ARDS, n (%)	5/109 (4·6)	1/29 (3·4)	4/80 (5·0)	>·99
Acute renal injury, n (%)	1/109 (0·9)	0/29 (0)	1/80 (1·3)	>·99
Septic shock, n (%)	1/109 (0·9)	0/29 (0)	1/80 (1·3)	>·99
Secondary infections, n (%)	35/109 (32·1)	5/29 (17·2)	30/80 (37·5)	·05
More than one complication, n (%)	4/109 (3·7)	0/29 (0)	4/80 (5·0)	·57
Clinical recovery, n (%)	109/109 (100·0)	29/29 (100·0)	80/80 (100·0)	>·99
Length of stay for patients discharged (days), median (IQR)	21·0 (15·0–30·0)	21·0 (15·5–30·0)	20·5 (15·0–30·8)	·83

Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; IQR, interquartile range; PaO2/FiO2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

[a] Data represent clinical characteristics of patients at the first medical evaluation during the initial hospitalization.

[b] Lymphopenia: lymphocyte count <1,500/μL.

[c] Thrombocytopenia: platelet count <150,000/μL.

Ethical considerations

The study protocol was approved by the Institutional Review Board of Beijing Ditan Hospital, Capital Medical University in Beijing (approval number: JDLY2020-015-01). The need for informed consent was waived because the study was retrospective and posed minimal risk to enrollees. All data were de-identified before analysis.

Statistical analysis

Continuous variables were presented as medians with ranges or mean with standard deviations. Categorical variables are presented as frequencies and proportions. Between-group comparisons to identify risk factors for recurrent SARS-CoV-2 infection or COVID-19 relapse were performed using the chi-square or Fisher's exact test, as appropriate. Variables with $P < 0.05$ in the univariate analyses were further investigated using multivariate logistic regression. All statistical analyses were performed using SPSS version 24·0 (IBM Corp., Armonk, NY, USA). All tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance.

Results

All available clinical data of patients with COVID-19 managed at our center before the study conclusion date (April 23, 2020)

Table 2
Initial presentation of patients with persistently positive RT-PCR assay results with or without relapse of COVID-19.

Variables[a] n (%), or as specified	Asymptomatic individuals (n = 22)	Relapsed patients (n = 7)	*P* values
Age (years), mean ± SD	37·32 ± 24·60	32·79 ± 14·22	·65
Male sex, n (%)	11/22 (50·0)	4/7 (57·1)	>·99
Smoking history, n (%)	0/22 (0)	0/7 (0)	>·99
Chronic conditions, n (%)	7/22 (31·8)	2/7 (28·6)	>·99
Hospitalization at the onset of illness, n (%)	2/22 (9·1)	0/7 (0)	>·99
Headache, n (%)	3/22 (13·6)	1/7 (14·3)	>·99
Fever, n (%)	15/22 (68·2)	6/7 (85·7)	·64
Temperature ≥38 °C, n (%)	11/22 (50·0)	4/7 (57·1)	>·99
Fatigue, n (%)	8/22 (36·4)	1/7 (14·3)	·38
Cough, n (%)	14/22 (63·6)	2/7 (28·6)	·19
Sore throat, n (%)	3/22 (13·6)	0/7 (0)	·56
Shortness of breath, n (%)	1/22 (4·5)	0/7 (0)	>·99
Nausea/vomiting, n (%)	0/22 (0)	0/7 (0)	>·99
Diarrhea, n (%)	1/22 (4·5)	0/7 (0)	>·99
Myalgia/arthralgia, n (%)	5/22 (22·7)	1/7 (14·3)	>·99
O_2 saturation <93%	2/22(9·1)	0/7(0)	>·99
Chest pain, n (%)	0/22 (0)	0/7 (0)	>·99
≥2 signs or symptoms, n (%)	11/22 (50·5)	1/7 (14·3)	·19
Leukocyte (count/L), mean ± SD	5·98 ± 2·27	4·96 ± 0·87	·26
Hemoglobin (g/L), mean ± SD	136·14 ± 13·8	144·14 ± 18·45	·29
Lymphopenia[b], n (%)	9/22 (40·9)	3/7 (42·9)	>·99
Thrombocytopenia[c], n (%)	4/22 (18·2)	1/7 (14·3)	>·99
Sodium (mmol/L), mean ± SD	138·85 ± 2·70	140·06 ± 1·46	·27
Potassium (mmol/L), mean ± SD	3·95 ± 0·53	3·88 ± 0·26	·75
Chloride (mmol/L), mean (±SD)	103·40 ± 2·91	102·66 ± 3·16	·57
Creatinine ≥133 μmol/L, n (%)	0/22 (0)	0/7 (0)	>·99
Aspartate aminotransferase >40 U/L, n (%)	0/13 (0)	0/4 (0)	>·99
Alanine aminotransferase >40 U/L, n (%)	1/22 (4·5)	2/7 (28·6)	·14
Total bilirubin ≥17·1 μmol/L, n (%)	0/13 (0)	0/4 (0)	>·99
Creatinine kinase ≥200 U/L, n (%)	2/19 (10·5)	2/6 (33·3)	·23
C-reactive protein level ≥10 mg/L, n (%)	9/19 (47·4)	3/7 (42·9)	>·99
Lactose dehydrogenase ≥250 U/L, n (%)	3/11 (27·3)	1/3 (33·3)	>·99
D-dimer ≥0·5 mg/L, n (%)	4/12 (33·3)	1/4 (25·0)	>·99
Activated partial thromboplastin time (seconds), median (IQR)	34·8 (30·0–40·4)	33·1 (30·6–37·3)	>·99
Prothrombin time (seconds), median (IQR)	11·6 (10·9–12·4)	12·0 (11·8–12·3)	·39
CT local patchy shadowing, n (%)	3/21 (14·3)	2/7 (28·6)	·57
CT bilateral patchy shadowing, n (%)	12/21 (57·1)	4/7 (57·1)	>·99
CT interstitial abnormalities	1/22(4·5)	0/7(0)	>0·99
Ground-glass opacities, n (%)	15/21 (71·4)	6/7 (85·7)	·64
ARDS, n (%)	1/22 (4·5)	0/7 (0)	>·99
Acute renal injury, n (%)	0/22 (0)	0/7 (0)	>·99
Septic shock, n (%)	0/22 (0)	0/7 (0)	>·99
Coinfection, n (%)	5/22 (22·7)	0/7 (0)	·30
More than one complication, n (%)	0/22 (0)	0/7 (0)	>·99
Clinical recovery, n (%)	22/22 (100·0)	7/7 (100·0)	>·99
Length of stay for patients discharged, days, median (IQR)	20·0 (15·0–28·5)	21·0 (17·0–36·0)	>·99

Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; IQR, interquartile range; RT-PCR, real-time polymerase chain reaction; SD, standard deviation.

[a] Data represent clinical characteristics of patients at the first medical evaluation during the initial hospitalization.
[b] Lymphopenia: lymphocyte count <1,500/μL.
[c] Thrombocytopenia: platelet count <150,000/μL.

were reviewed. Among 208 consecutive patients with confirmed COVID-19 who were admitted to the hospital for quarantine or treatment, 109 met the eligibility criteria and were enrolled in the study. Among the 99 patients who did not meet the enrollment criteria, 17 were still hospitalized, three died during hospitalization, 25 were lost to follow-up after discharge, and 54 had incomplete data or no follow-up SARS-CoV-2 RNA test results. Among the participants, the first and last cases of SARS-CoV-2 infection during the first admission were diagnosed on January 18, 2020, and March 19, 2020, respectively. Their mean age was 43·69 ± 19·77 years, and 37·6% (41/109) had pre-existing chronic diseases. The initial clinical features of study participants at COVID-19 onset are shown in Table 1. The median length of hospital stay was 21 days (interquartile range [IQR]: 15–30 days). As per the standard of care, all patients met the following criteria before discharge: (1) 14 days had passed since the onset of COVID-19; (2) normal body temperature without antipyretic medication and other symptoms had improved; and (3) negative RT-PCR assay results for SARS-CoV-2 RNA in two consecutive respiratory specimens collected ≥24 h apart. The local disease control regulations required that all patients with COVID-19 stay at home for at least 14 days in self-quarantine after discharge from the hospital. The epidemiological records and self-reported data were reviewed for all study participants, to check whether they had any record of contact with other patients with COVID-19 or individuals with suspected SARS-CoV-2 infection.

The study patients were followed-up for a median of 29 days (IQR, 27–42 days) following discharge. During this period, 29/109 (26.6%) patients had recurrent positive SARS-CoV-2 RT-PCR assay results. The median length of follow-up after discharge from the hospital was significantly shorter in patients without reinfection than in patients with recurrent positive SARS-CoV-2 RT-PCR assay results (28 days [IQR: 27–34 days] vs 44 days [IQR: 38–53 days], $P < 0.001$). To better understand the clinical features of patients with recurrent infection and disease relapse, the study

Table 3
Clinical characteristics of patients without SARS-CoV-2 reactivation compared to those of patients with relapse of COVID-19.

Variables[a] n (%), or as specified	Patients who recovered completely (n = 80)	Relapse patients (n = 7)	*P* values
Age (years), mean ± SD	46·40 ± 18·14	32·79 ± 14·22	·06
Male sex, n (%)	46/80 (57·5)	4/7 (57·1)	>·99
Smoking history, n (%)	6/80 (7·5)	0/7 (0)	>·99
Chronic conditions, n (%)	32/80 (40·0)	2/7 (28·6)	·70
Hospitalization at the onset of illness, n (%)	0/80 (0)	0/7 (0)	>·99
Headache, n (%)	14/80 (17·5)	1/7 (14·3)	>·99
Fever, n (%)	71/80 (88·8)	6/7 (85·7)	·59
Temperature ≥38 °C, n (%)	39/80 (48·8)	4/7 (57·1)	·71
Fatigue, n (%)	30/80 (37·5)	1/7 (14·3)	·41
Cough, n (%)	44/80 (55·0)	2/7 (28·6)	·25
Sore throat, n (%)	12/80 (15·0)	0/7 (0)	·59
Shortness of breath, n (%)	4/80 (5·0)	0/7 (0)	>·99
Nausea/vomiting, n (%)	5/80 (6·3)	0/7 (0)	>·99
Diarrhea, n (%)	7/80 (8·8)	0/7 (0)	>·99
Myalgia/arthralgia, n (%)	20/80 (25·0)	1/7 (14·3)	·86
O_2 saturation <93%	9/80(11·3)	0/7(0)	>·99
Chest pain, n (%)	1/80 (1·3)	0/7 (0)	>·99
≥2 signs or symptoms, n (%)	63/80 (78·8)	1/7 (14·3)	·001
Leukocyte (count /L), mean ± SD	4·87 ± 1·76	4·96 ± 0·87	·90
Hemoglobin (g/L), mean ± SD	137·06 ± 18·13	144·14 ± 18·45	·33
Lymphopenia[b], n (%)	60/79 (75·9)	3/7 (42·9)	·15
Thrombocytopenia[c], n (%)	19/79 (24·1)	1/7 (14·3)	·91
Sodium (mmol/L), median (IQR)	139·0 (136·9–140·0)	140·0 (139·0–141·0)	·31
Potassium (mmol/L), mean ± SD	3·73 ± 0·44	3·88 ± 0·26	·38
Chloride (mmol/L), mean (±SD)	102·71 ± 3·69	102·66 ± 3·16	·97
Creatinine ≥133 μmol/L, n (%)	1/ 75 (1·3)	0/7 (0)	>·99
Aspartate aminotransferase >40 U/L, n (%)	10/42 (23·8)	0/4 (0)	·56
Alanine aminotransferase >40 U/L, n (%)	16/74 (21·6)	2/7 (28·6)	>·99
Total bilirubin ≥17·1 μmol/L, n (%)	2/40 (5·0)	0/4 (0)	>·99
Creatinine kinase ≥200 U/L, n (%)	7/75 (9·3)	2/6 (33·3)	·13
C-reactive protein level ≥10 mg/L, n (%)	32/72 (44·4)	3/7 (42·9)	>·99
Lactose dehydrogenase ≥250 U/L, n (%)	19/42 (45·2)	1/3 (33·3)	>·99
D-dimer ≥0·5 mg/L, n (%)	16/42 (38·1)	1/4 (25·0)	>·99
Activated partial thromboplastin time (seconds), median (IQR)	34·4 (31·4–41·3)	33·1 (30·6–37·3)	>·99
Prothrombin time (seconds), median (IQR)	12·2 (11·6–13·1)	12·0 (11·8–12·3)	·58
CT local patchy shadowing, n (%)	17/79 (21·5)	2/7 (28·6)	>·99
CT bilateral patchy shadowing, n (%)	59/79 (75·7)	4/7 (57·1)	·58
CT interstitial abnormalities	3/80(3·8)	0/7(0)	>0·99
CT ground-glass opacities, n (%)	66/79 (83·5)	6/7 (85·7)	>·99
ARDS, n (%)	4/80 (5·0)	0/7 (0)	>·99
Acute renal injury, n (%)	1/80 (1·3)	0/7 (0)	>·99
Septic shock, n (%)	1/80 (1·3)	0/7 (0)	>·99
Coinfection, n (%)	30/80 (37·5)	0/7 (0)	·09
More than one complication, n (%)	4/80 (5·0)	0/7 (0)	>·99
Clinical recovery, n (%)	80/80 (100·0)	7/7 (100·0)	>·99
Length of stay for patients discharged, days, median (IQR)	20·5 (15·0–30·8)	21·0 (17·0–36·0)	·87

Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

[a] Data represent clinical characteristics of patients at the first medical evaluation during the initial hospitalization.

[b] Lymphopenia: lymphocyte count <1,500/μL.

[c] Thrombocytopenia: platelet count <150,000/μL.

patients were assigned to three groups for further comparison: patients without recurrent infection, patients with recurrent SARS-CoV-2 infection, and those with COVID-19 relapse (symptomatic patients).

Patients with reactivation of SARS-CoV-2 infection

Among the 29 patients who had a reactivation of SARS-CoV-2 infection after discharge from the first admission to the hospital, 7 (6.4%) had overt COVID-19 and 22 (75.9%) had an asymptomatic reactivation of infection. Compared to patients without reactivation, patients with reactivation were significantly younger, and were significantly more likely to have been afebrile, experienced two symptoms or less, or have developed a secondary infection, leukocytosis, lymphopenia, and hyperkinemia during their first hospitalization (Table 1). However, their lymphocyte count, lactose dehydrogenase level, and D-dimer levels were often normal. In the multivariate analysis, the initial presentation of lymphocyte count <1500/μL (odds ratio [OR]: 0.34, 95% confidence interval [CI]: 0.12–0.94) and having two symptoms or fewer (OR: 0.20, 95% CI: 0.07–0.55) were independent predictors of SARS-CoV-2 reactivation after recovery from COVID-19. A subgroup analysis comparing the initial presentations of patients with COVID-19 relapse (N = 7) to those of patients with asymptomatic reactivation of SARS-CoV-2 (N = 22) (Table 2) did not reveal any significant differences in any of the clinical and laboratory parameters between the two groups at during their first hospitalization.

Clinical features of patients with COVID-19 relapse

In our cohort, 7/109 (6.4%) patients had disease reactivation and experienced recurrence of COVID-19 with symptoms after discharge from the hospital. Their initial clinical presentations were similar to those of patients without recurrent infection with SARS-

Table 4
Clinical presentation at the time of COVID-19 relapse.

	Patients with both recurrent SARS-CoV-2 infection and symptom relapse[a]						
Clinical Features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age	45	33	4·5	48	37	29	33
Sex	Male	Male	Female	Female	Female	Male	Male
SARS-CoV-2 negative to positive (days)	11	9	23	22	22	21	8
Date of first admission	2020/1/22	2020/1/25	2020/1/27	2020/2/27	2020/2/3	2020/2/7	2020/2/27
Date of first discharge	2020/2/27	2020/2/26	2020/2/11	2020/3/18	2020/2/20	2020/3/16	2020/3/19
Date of second admission	2020/3/7	2020/3/2	2020/2/26	2020/4/2	2020/3/8	2020/3/31	2020/4/2
Date of second discharge	2020/3/12	2020/3/30	2020/3/4	2020/4/12	2020/3/22	2020/4/8	2020/4/6
Temperature ≥38 °C	No	No	No	No	No	No	No
Fatigue	No	Yes	No	No	No	No	No
Cough	No	Yes	No	Yes	Yes	No	No
Sore throat	Yes	Yes	No	No	No	No	No
Shortness of breath	Yes	Yes	No	No	No	No	No
Nausea/vomiting	No	No	No	No	No	No	No
diarrhea	No	No	No	No	No	No	No
Myalgia/arthralgia	No	Yes	No	No	No	No	No
Chest pain	No	No	No	No	No	No	No
≥2 signs or symptoms	Yes	Yes	No	Yes	No	No	No
Leukocyte ($\times 10^9$ count /L)	6·89	12·51	3·65	6·85	4·74	5·49	5·75
Hemoglobin (g/L)	143	155	122	124	142	162	161
Lymphopenia[b]	Yes	Yes	No	No	No	No	No
Thrombocytopenia[c]	No	No	No	No	No	No	No
Sodium (mmol/L)	140·7	141·4	140·6	137·7	138	140·6	137·1
Potassium (mmol/L)	3·90	3·93	3·68	3·71	3·90	3·76	4·52
Creatinine ≥133 μmol/L	No	No	No	No	No	No	No
Aspartate aminotransferase >40 U/L	No	No	No	No	No	Yes	No
Alanine aminotransferase >40 U/L	No	No	No	No	No	Yes	No
Total bilirubin ≥17.1 μmol/L	No	Yes	No	No	No	No	No
Creatinine kinase ≥200 U/L	No	No	No	No	No	Yes	No
C-reactive protein level ≥10 mg/L	Yes	Yes	No	No	No	No	No
Lactose dehydrogenase ≥250 U/L	No	No	No	No	No	No	No
D-dimer ≥0·5 mg/L	No	No	Yes	NA	NA	NA	NA
Activated partial thromboplastin time (seconds)	34·3	37·1	36·5	NA	NA	NA	NA
Prothrombin time (seconds)	11·3	15·8	11·9	12·3	NA	NA	11·9
Local patchy shadowing	No	No	NA	No	Yes	No	Yes
Bilateral patchy shadowing	No	Yes	NA	Yes	No	Yes	No
Ground-glass opacities	No	Yes	NA	No	No	Yes	Yes
ARDS	No	No	No	No	No	No	No
Acute renal injury	No	No	No	No	No	No	No
Septic shock	No	No	No	No	No	No	No
Co-infections	No	Yes	No	No	No	No	No
More than one complication	No	No	No	No	No	No	No
Received antibiotic therapy	No	Yes	No	No	No	No	No
Received antiviral therapy	No	Yes	Yes	No	Yes	No	Yes
Use of corticosteroid	No	No	No	No	No	No	No
Clinical recovery	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cases remained at the hospital	No	No	No	No	No	No	Yes
Discharged	Yes	Yes	Yes	Yes	Yes	Yes	No
Length of stay for the second admission (days)	5	28	7	10	14	8	4

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease; CT, computed tomography; NA, test results not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Data represent clinical characteristics of patients at second hospitalization on account of recurrent symptomatic infection with SARS-CoV-2.

[b] Lymphopenia: lymphocyte count <1,500/μL.

[c] Thrombocytopenia: platelet count <150,000/μL.

CoV-2 in most respects (Table 3), but patients who relapsed were significantly more likely to have had two or fewer than two symptoms, or severe disease required hospitalization. In the multivariate analysis, having two symptoms or less at the initial presentation independently predicted COVID-19 relapse after the first discharge (OR: 0.05; 95% CI: 0.01–0.40). The mean period for seroconversion for SARS-CoV-2 from negative to positive results was 17 days (range: 8–23 days). The median interval between the date of discharge and the date of relapse of symptoms was 6 days (IQR: 5–14 days). All seven patients who experienced a relapse of COVID-19 were re-admitted to the hospital for further management and quarantine. The mean duration of their second stay in hospital was 11 days (range: 4–28 days). The clinical presentations and treatments of patients during disease relapse are shown in Table 4. All seven patients recovered from COVID-19 without complications or the need for mechanical ventilation during the relapse.

Discussion

We assessed a cohort of 109 patients with confirmed COVID-19 and SARS-CoV-2 reactivation. During a median follow-up duration of 29 days, reactivation occurred in 27% of patients and 6% of patients had a recurrence of symptomatic COVID-19. Having a lymphocyte count <1500 cells/μL or having two symptoms or less at the first presentation were independent predictors of reactivation. These findings have important implications for public health policy regarding the prevention of the spread of SARS-CoV-2 and the management of patients with COVID-19 during their convalescence.

SARS-CoV-2 spreads mainly from person to person in close contact environments (within approximately 6 feet/2 m) [4]. Recent studies indicate that asymptomatic patients can transmit SARS-CoV-2 [9–12]. The United States CDC recommends the following

preventive methods [4]: maintenance of social distancing outside of the household, frequent hand hygiene practices, and self-quarantine for 10–14 days at home when experiencing a mild disease. Additionally, the CDC recommends that healthcare workers with COVID-19 can return to work if they have been afebrile for at least 3 days without the use of antipyretic medications and at least 10 days have passed since the symptoms first appeared. Alternatively, patients are required to have negative SARS-CoV-2 RNA results on testing using an FDA-approved molecular test on at least two consecutive respiratory specimens collected ≥24 h apart. However, these recommendations were made based on the assumption that no SARS-CoV-2 reactivation occurred after recovery. In our study, although all patients had met the aforementioned criteria for returning to work, 27% of them were tested positive for SARS-CoV-2 and 6% experienced a COVID-19 relapse.

To the best of our knowledge, the present study is the largest cohort study of recurrence of SARS-CoV-2 infection following recovery from COVID-19 to date. Our study confirmed the preliminary findings reported by Ye et al. [7] and estimated the reactivation rate. The relatively high reactivation rate should be considered when implementing surveillance and prevention measures. We identified a lymphocyte count of <1500/μL and having two symptoms or less were independent predictors of reactivation. There are several key points we learned from the current study: COVID-19 patients could have the disease recurrence after recovery from the first episode of infection; patients who had fewer symptoms, or low lymphocyte count during the first infection of COVID-19 were likely to have the disease reactivation to the overt COVID-19 infection again even after recovery. Recently, a case reported by He et al. on a COVID-19 patient with systemic lupus erythematosus also suggested that long-term immune-suppressive patients could be susceptible to relapse of COVID-19: [9] The other case reports or case series indicated that the relapse of COVID-19 was often among older patients in France [10]. The aforementioned reports, together with our current study, highlighted the fact that COVID-19 relapse could occur in different countries with different supertype/superclade (predominantly, "B" in China, versus "A or C" in France) [11,12]. Our findings provide important evidence on the need for surveillance among patients at risk after recovery from COVID-19, particularly among individuals who experience difficulties with practicing social distancing. These individuals include healthcare providers, nursing home workers, homeless people, and individuals living in close quarters or shared housing. Without surveillance, they may transmit the infection to others when reactivation occurs. The risk factors suggested by our data and other studies could be used when selecting patients for risk-stratified surveillance.

However, our study had several limitations. The reactivation rate may have been underestimated due to the relatively short follow-up period. A majority of patients in East Asia are infected with SARS-CoV-2 type B, while most patients in Europe and the Americas are infected with SARS-CoV-2 types A and C [12]. The risk factors for reactivation in sub-population of patients could be different, although the reactivation occurs in both Europeans and Asians. Finally, our study had limitations inherent to its retrospective design, such as the potential misclassification of subjects or missing measurements of some key variables. Despite these limitations, our findings provide important insights regarding the frequency and clinical features of SARS-CoV-2 reactivation, as well as risk factors for reactivation. Considering the recent rapid increase in access to SARS-CoV-2 testing in most countries affected by COVID-19, our findings provide timely evidence to inform policies regarding surveillance of individuals who have recovered from SARS-CoV-2 infection.

Conclusion

We observed a 27% incidence of SARS-CoV-2 reactivation in a cohort of patients with confirmed COVID-19 during a median follow-up of 29 days. A lymphocyte count of <1500 cells/μL and having two or fewer symptoms at the onset of COVID-19 independently predicted SARS-CoV-2 reactivation among convalescent patients. Our findings suggest that patients with risk factors for SARS-CoV-2 reactivation or convalescent individuals who have difficulty with practicing social distancing should undergo active surveillance to detect disease reactivation. Future studies should investigate the association between the viral load during the first illness and disease reactivation. Besides, therapeutic interventions for prophylaxis against reactivation should be explored.

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Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request. Participant data without names and identifiers may be shared with other researchers after approval from the corresponding author and the authorities including the Institutional Review Board and the National Health Commission. The proposal with a detailed description of study objectives and a statistical analysis plan will be needed for evaluation of the reasonability to request for our data. The corresponding author will decide based on these materials.

Author Contributions

CQP and ZC conceived the study; CQP designed the study and database for data collection; ZC supervised the data collection; ZC and WX played roles in clinical management, patient recruitment, and formulated the treatment regimens; ZG, YW, HZ, JW, YX, WZ, MS, SC, and XW contributed to data collection and data entry; CQP and ZG performed the statistical analyses; CQP interpreted the data and wrote the manuscript. All authors reviewed and approved the final version of the manuscript. CQP is the guarantor. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Disclosures

All authors declare that they have no conflict of interest.

Compliance with ethics guidelines

The study protocol was approved by the Institutional Review Board of Beijing Ditan Hospital, Capital Medical University in Beijing (approval number: JDLY2020-015-01). The need for informed consent was waived because the study was retrospective and posed minimal risk to enrollees. All data were de-identified before analysis.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2021.02.002.

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