



RESEARCH ARTICLE

Positive result of Sars-Cov-2 in faeces and sputum from discharged patients with COVID-19 in Yiwu, China

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Abstract

Background: With the effective prevention and control of COVID-19 in China, the number of cured cases has increased significantly. Further monitoring of the disease prognosis and effective control of the “relapse” of the epidemic has become the next focus of work. This study analysed the clinical prognosis of discharged COVID-19 patients by monitoring their SAR-CoV-2 nucleic acid status, which provided a theoretical basis for medical institutions to formulate discharge standards and follow-up management for COVID-19 patients.

Methods: We included 13 discharged COVID-19 patients who were quarantined for 4 weeks at home. The patient's daily clinical signs were recorded and sputum and faecal specimens were regularly sent for detection of SARS-CoV-2 nucleic acid.

Results: The time between initial symptoms and meeting discharge criteria was 18 to 44 days with an average of 25 ± 6 days. The faecal samples of two patients still tested positive after meeting the discharge criteria and the sputum samples of four patients returned positive 5 to 14 days after discharge. The rate of the recurring positive test result in samples from the respiratory system was 31% (4/13).

Conclusion: Under the present discharge criteria, the high presence of SARS-CoV-2 nucleic acid in faecal and respiratory samples of discharged COVID-19 patients indicates potential infectivity. Therefore, we suggest that faecal virus nucleic acid should be tested as a routine monitoring index for COVID-19 and a negative result be added to the criteria. Simultaneously, we should strengthen the regular follow-up of discharged patients with continuous monitoring of the recurrence of viral nucleic acid.

KEYWORDS

COVID-19, discharge criteria, SARS-CoV-2, virus nucleic acid test

Youjiang Li and Yingying Hu are co-first author.

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1 | INTRODUCTION

In December 2019, a novel coronavirus caused an outbreak in Wuhan, China.^{1,2} The World Health Organization (WHO) declared the novel coronavirus pneumonia (COVID-19) outbreak to be a Public Health Emergency of International Concern (PHEIC) on January 30, 2020 and a global pandemic on March 11, 2020.³ By March 28, 2020, SARS-CoV-2 had spread to more than 150 countries worldwide with 81 439 infections and 75 448 discharged in China alone.⁴

SARS-CoV-2 belongs to a genus of coronaviruses that are enveloped with round or oval particles 60 to 140 nm in diameter and are often polymorphic. COVID-19 is genetically different from SARS-CoV and MERS-CoV.⁵ Current studies show that the homology of coronavirus with bat SARS is more than 85%. At present, researchers focus on the epidemiological history, clinical characteristics, treatment plan, and virus detection methods of confirmed cases and less attention has been given to the clinical outcome, follow-up visits, and management of discharged patients. Recently, it was reported in many places in China that the nucleic acid test results of discharged patients returned positive during their follow-up visits. However, there are no available studies on the causes, clinical symptoms, secondary infection, and timeline of viral nucleic acid re-emergence in these patients. With effective prevention and control of COVID-19 in China, the number of cured cases has increased significantly. Further monitoring of the disease prognosis and effective control of the "relapse" of the epidemic has become the next focus of work. As one of the designated hospitals for the diagnosis and treatment of COVID-19, all patients in our hospital met the discharge criteria after treatment as described in "Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia (trial version 5)".⁶ The aim of this study is to analyse the causes of viral nucleic acid re-emergence by investigating the follow-up data of COVID-19 patients who met the discharge criteria. This may provide evidence that medical institutions should strengthen the follow-up management of discharged COVID-19 patients.

2 | MATERIALS AND METHODS

2.1 | Study population

We recruited 13 patients who were diagnosed as COVID-19 at the Fourth Affiliated Hospital of Zhejiang University from January 26, 2020 to February 6, 2020. All patients with COVID-19 tested positively for SARS-CoV-2 by the use of quantitative reverse-transcription polymerase chain reaction (RT-PCR) on samples from the respiratory tract. All cases met the latest discharge criteria or COVID-19 patients from February 9, 2020 to February 28, 2020. Discharge criteria of COVID-19 were based on the Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia: (a) normal body temperature more than or equal to 3 days, (b) resolved respiratory symptoms, (c) substantially improved acute exudative lesions on chest computed tomography (CT) images, and (d) two consecutively negative viral nucleic acid test results at least 1 day apart in specimens from the respiratory tract. This study was reviewed and approved by the Medical Ethical Committee of the Fourth Affiliated

Hospital, Zhejiang University School of Medicine (approval number K20200025). Written informed consent was obtained from each enrolled patient.

2.2 | Follow-up observation and monitoring indicators

Oral swabs, nasal swabs, sputum, blood, faeces, urine, vaginal secretions, and milk of COVID-19 patients were collected for viral nucleic acid test upon hospitalisation. After COVID-19-confirmed patients meet the discharge criteria, they should: (a) Be quarantined for 4 weeks at home (b) wear medical masks when leaving home and keep distance with others to reduce contact (c) attend a follow-up visit in the first, second, and fourth week after discharge with sputum and faecal viral nucleic acid tests, routine blood examination, biochemistry tests including C-reactive protein, and lung CT scan. (d) Monitor body temperature and other symptoms daily during isolation. If any symptoms such as fever, cough, sore throat, fatigue, and muscle soreness are found, patients should immediately return to the hospital to determine the respiratory and faecal virus nucleic acid status.

2.3 | Viral nucleic acid test

SARS-CoV-2 nucleic acid was detected by real-time RT-PCR. The nucleic acid RT-PCR test kit we employed was recommended by the Chinese Center for Disease Control and Prevention (China CDC) and produced by Shanghai Zhijiang Biotechnology, China. Nucleic acid was extracted from the samples using an EX2400 Automatic Nucleic Acid Extractor (Shanghai Zhijiang Biotechnology). RT-PCR was performed in a LightCycler 480 Instrument II (Roche, Germany). We quantified the RdRP, E, and N gene in the SARS-CoV-2 genome and used the criteria described by the manufacturer to determine positivity. Specimen collection, treatment, and laboratory procedures were in strict accordance with the operating procedures recommended by WHO for RT-PCR, and we performed clinical resampling if results were unclear.

2.4 | Data acquisition

Baseline information, laboratory and imaging examinations, diagnosis, and treatment process of the included cases were obtained from the electronic medical record system. All information was obtained and curated with a standardised data collection form. Two researchers independently reviewed the data collection forms.

2.5 | Statistical analysis

Statistical analysis was performed using SPSS 20.0. Continuous variables were summarised as means and standard deviations or medians and interquartile ranges as appropriate. Categorical

TABLE 1 Clinical and laboratory characteristics of patients with COVID-19

| Clinical characteristics | Patient 1 | Patient 2 ^b | Patient 3 ^b | Patient 4 | Patient 5 ^a | Patient 6 | Patient 7 | Patient 8 ^b | Patient 9 ^b | Patient 10 | Patient 11 | Patient 12 | Patient 13 ^a |
|--|-----------|------------------------|------------------------|----------------------|------------------------|-----------|------------|------------------------|------------------------|------------|------------|------------|-------------------------|
| Sex | Female | Female | Female | Female | Female | Female | Female | Male | Male | Male | Male | Male | Male |
| Age, y | 24 | 72 | 71 | 56 | 33 | 37 | 33 | 37 | 73 | 47 | 1 | 70 | 22 |
| Other family members infected | No | Yes | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Date of first symptom | Jan. 23 | Jan. 23 | Jan. 20 | Jan. 22 | Jan. 12 | Jan. 23 | Jan. 30 | Jan. 23 | Jan. 15 | Jan. 11 | Jan. 30 | Jan. 31 | Jan. 22 |
| Date of admission | Feb. 3 | Jan. 30 | Feb. 6 | Jan. 28 | Feb. 28 | Jan. 26 | Feb. 2 | Jan. 26 | Jan. 28 | Jan. 30 | Feb. 1 | Feb. 1 | Jan. 29 |
| Date of meeting discharge criterion | Feb. 17 | Feb. 19 | Feb. 12 | Feb. 11 | Feb. 9 | Feb. 11 | Feb. 17 | Feb. 14 | Feb. 9 | Feb. 24 | Feb. 28 | Feb. 28 | Feb. 10 |
| Days between initial symptoms and meeting discharge criteria | 23 | 27 | 23 | 20 | 27 | 19 | 18 | 22 | 25 | 44 | 30 | 28 | 19 |
| Inpatient days | 14 | 19 | 6 | 14 | 11 | 16 | 15 | 19 | 12 | 25 | 27 | 27 | 12 |
| Sputum SARS-CoV-2 negative to positive (days) | NA | 14 | 7 | NA | NA | NA | NA | 5 | 6 | NA | NA | NA | NA |
| Days of faecal SARS-CoV-2 positive after sputum turning negative | NA | NA | NA | NA | 14 | NA | NA | NA | NA | NA | NA | NA | 15 |
| Complications | None | Chronic hypertension | Chronic hypertension | Chronic hypertension | None | None | Depression | None | Chronic hypertension | None | None | None | None |
| Signs and symptoms | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | Yes |
| Fever | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | Yes | Yes |
| Cough | No | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | Yes | Yes |
| Myalgia | No | No | No | No | No | No | Yes | Yes | No | Yes | No | No | No |
| Fatigue | No | No | Yes | No | No | No | Yes | Yes | No | No | No | No | No |
| White blood cell count (×10 ⁹ /L) | 3.5 | 30.9 | 4.2 | 5.7 | 5.7 | 4.3 | 4.6 | 5.8 | 5.5 | 4.4 | 7 | 4.8 | 5.6 |

TABLE 1 (Continued)

| Clinical characteristics | Patient 1 | Patient 2 ^b | Patient 3 ^b | Patient 4 | Patient 5 ^a | Patient 6 | Patient 7 | Patient 8 ^b | Patient 9 ^b | Patient 10 | Patient 11 | Patient 12 | Patient 13 ^a |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Low or normal leukocyte count (<9.5 × 10 ⁹ /L) | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Lymphocyte count (<10 ⁹ /L) | 0.8 | 26.9 | 0.7 | 1.7 | 1.7 | 1.1 | 1.1 | 0.54 | 1.6 | 1.9 | 3.5 | 1.8 | 1.9 |
| Lymphopenia (<1.5 × 10 ⁹ /L) | Yes | No | Yes | No | No | Yes | Yes | Yes | No | No | No | No | No |
| Elevated ALT (>45 U/L) or AST (>35 U/L) | No | No | No | No | No | No | No | No | No | No | No | No | No |
| ALT (U/L) | 23 | 19 | 18 | 9 | 18 | 17 | 18 | 21 | 8 | 15 | 8 | 21 | 18 |
| AST (U/L) | 34 | 25 | 19 | 30 | 23 | 17 | 23 | 23 | 15 | 17 | 111 | 19 | 18 |
| C-reactive protein (Normal: <6 mg/L) | 2.3 | 3.6 | 50.2 | 19.5 | 0.1 | 0.7 | 0.1 | 2.4 | 1.2 | 4.7 | 0.6 | 0.5 | 0.4 |
| CT evidence of pneumonia | | | | | | | | | | | | | |
| Typical signs of viral infection | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Lung CT scans (discharged) | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption | Inflammation ab-sorption |
| Diagnosis (Clinical type) | Common type | Common type | Common type | Common type | Common type | Common type | Common type | Common type | Common type | Common type | Common type | Common type | Common type |
| Oxygen support (nasal catheter) | No | Yes | Yes | No | No | Yes | No | No | Yes | No | No | No | No |
| Antiviral therapy | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Antibiotic therapy | No | Yes | No | Yes | No | Yes | No | Yes | No | No | No | No | Yes |
| Use of corticosteroid | No | No | No | No | No | No | No | No | No | No | No | No | No |

Note: Diagnosis and discharge criteria of COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program (5th edition) published by the National Health Commission of China.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; COVID-19, 2019 novel coronavirus disease; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aPatient that had continued positivity of SARS-CoV-2 nucleic acid in faeces after negative results from respiratory samples.

^bPatient that had recurrence of SARS-CoV-2 nucleic acid in sputum after discharge.

variables were expressed as counts and percentages in each category. For laboratory results, we also assessed whether the measurements were outside the normal range.

3 | RESULTS

3.1 | Demographics and baseline characteristics of COVID-19 patients

We included 13 patients confirmed with COVID-19, six males and seven females with an average age of 52.8 ± 20.2 years. The time from onset of symptoms to the diagnosis of the COVID-19 patients was 1 to 19 days and discharge criteria were met between 9 and 28 February 2020. The time from the initial onset of symptoms to meeting the discharge criteria was 18 to 44 days with a median time of 25 ± 6 days. According to the epidemiological history of the patients, four were long-term residents of Wuhan returning to Yiwu, nine had direct contact with people who had returned from Wuhan. All patients presented with common main symptoms of fever, cough, fatigue, muscle soreness, and sore throat. The laboratory parameters showed that 10 cases had a low to normal white blood cell count, five cases had lymphocytopenia, and only two cases presented with elevated C-reactive protein while all 13 cases had normal transaminase levels. The CT examination indicated the typical features of viral pneumonia such as patchy ground-glass opacity. The main therapies were antiviral, antibiotic, and oxygen inhalation without additional glucocorticoid treatment (Table 1).

3.2 | Viral nucleic acid test results before discharge

We tested each type of specimen more than 3 times for SARS-CoV-2 nucleic acid upon hospitalisation. Test results showed that the positive rate in sputum was 100% (13/13), oral swab was 40% (4/10), nose swab was 75% (9/12), and faeces was 38% (5/13). Concurrently, the urine and blood viral nucleic acid of all 13 patients tested negative. Similarly, the vaginal secretions of the six female patients tested negative and the milk of one lactating patient was also negative (Table 2 and Figure 1).

3.2.1 | Follow-up results of patients after meeting discharge criteria

In subsequent monitoring of the viral nucleic acid status of discharged patient, faeces from two patients (patient 5 and 13) continuously tested positive for SARS-CoV-2 even though the sputum was negative. The faeces from patient 5 tested positive for 14 days and patient 5 for 15 days after sputum was negative (Figure 2).

By March 28, 2020, all discharged patients were followed-up for 4 weeks. Four discharged patients (Patient 2, 3, 8, 9) presented a positive sputum viral nucleic acid test during a later follow-up between 5 and 14 days after discharge. In particular, patient 8 who had a recurrence of viral nucleic acid 5 days after discharge was able to meet discharge criteria again, after which the patient once more tested positive 7 days after the second discharge (Figure 3). And patient 2 had a complication of chronic lymphocytic leukemia (Table 1). Although we detected SARS-CoV-2 nucleic acid in these

TABLE 2 Results of SARS-CoV-2 nucleic acid test in different types of specimens of COVID-19 patients

| Patients | Sex | Age | Specimen | | | | | | | |
|-------------------------|--------|-----|------------|----------|----------|---------|----------|---------|--------|--------|
| | | | Sputum | OS | NS | Blood | Faeces | Urine | VS | BM |
| 1 | Female | 24 | + | - | + | - | - | - | - | NT |
| 2 | Female | 72 | + | - | + | - | - | - | - | NT |
| 3 | Female | 71 | + | NT | + | - | + | - | - | NT |
| 4 | Female | 56 | + | - | - | - | - | - | NT | NT |
| 5 | Female | 33 | + | - | + | - | + | - | - | NT |
| 6 | Female | 37 | + | - | - | - | - | - | - | NT |
| 7 | Female | 33 | + | + | + | - | - | - | - | - |
| 8 | Male | 37 | + | + | + | - | - | - | NT | NT |
| 9 | Male | 73 | + | NT | - | - | - | - | NT | NT |
| 10 | Male | 47 | + | - | + | - | - | - | NT | NT |
| 11 | Male | 1 | + | NT | NT | - | + | - | NT | NT |
| 12 | Male | 70 | + | + | + | - | + | - | NT | NT |
| 13 | Male | 22 | + | + | + | - | + | - | NT | NT |
| Total-no./total no. (%) | | | 13/13(100) | 4/10(40) | 9/12(75) | 0/13(0) | 5/13(38) | 0/13(0) | 0/6(0) | 0/1(0) |

Abbreviations: +, positive; -, negative; BM, breast milk; NT, Do not detect; NS, nasal swab; OS, oral swab; VS, vaginal secretion.

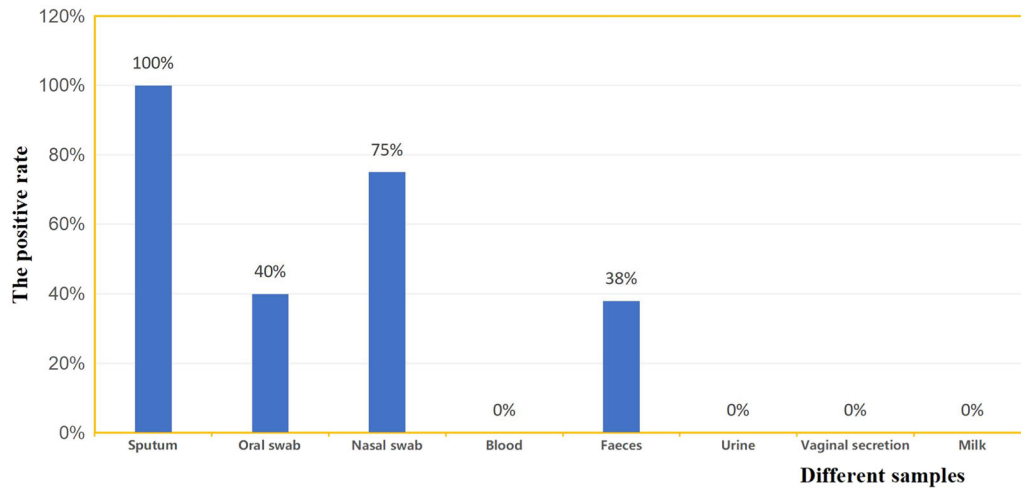


FIGURE 1 Positive rate of SARS-CoV-2 nucleic acid test in different types of specimens

patients after discharge, the blood examination, C-reactive protein levels, biochemistry, and lung CT showed no obvious abnormalities and no clinical symptoms were observed (Figures 4 and 5). The sputum and faecal samples of the other seven patients remained negative in absence of clinical symptoms. Similarly, the laboratory and imaging results showed no abnormalities.

4 | DISCUSSION

Currently, the recognised transmission route of COVID-19 is mainly through respiratory droplets and close contact. The patient's infectivity is determined by the presence of the virus in different body fluids, secretions, and excrements. It has been confirmed that viral nucleic acid can be detected in samples of oral swabs, sputum, faeces, urine, and tears of COVID-19 patients.^{7,8} In this study, 5 of the 13 patients (38%) tested positive for faecal nucleic acid, which was higher than previously reported.^{9,10} Blood and urine samples of all patients were negative for SARS-CoV-2 nucleic acid, possibly because we included relatively few

cases in this study and all of them were mild cases with common symptoms. The results of viral nucleic acid tests in the vaginal secretions of six female patients and the milk of one lactating patient were negative, consistent with previous studies.¹¹ Similar to other reports, we found that the positive rate of viral nucleic acid test in respiratory tract specimens was the highest in the sputum, followed by nasal swab and oral swab.¹² It is suggested that sputum collection should be given priority when collecting respiratory tract specimens of COVID-19 patients for viral nucleic acid testing. In the absence of sputum, the nasal swab may be more sensitive than the oral swab for detection of SARS-CoV-2 nucleic acid.

In our study, two patients continued to test positive for SARS-CoV-2 nucleic acid in the faeces for up to 15 days after the negative results from respiratory tissues. Zhang et al¹³ reported that three children with COVID-19 were discharged from the hospital with negative respiratory virus, and were re-examined with positive nucleic acid from faeces within 10 days. Although the first symptoms of COVID-19 are mainly respiratory symptoms, gastrointestinal symptoms were still found in many patients in clinical practice. Wang et al¹⁴ analysed 138 confirmed

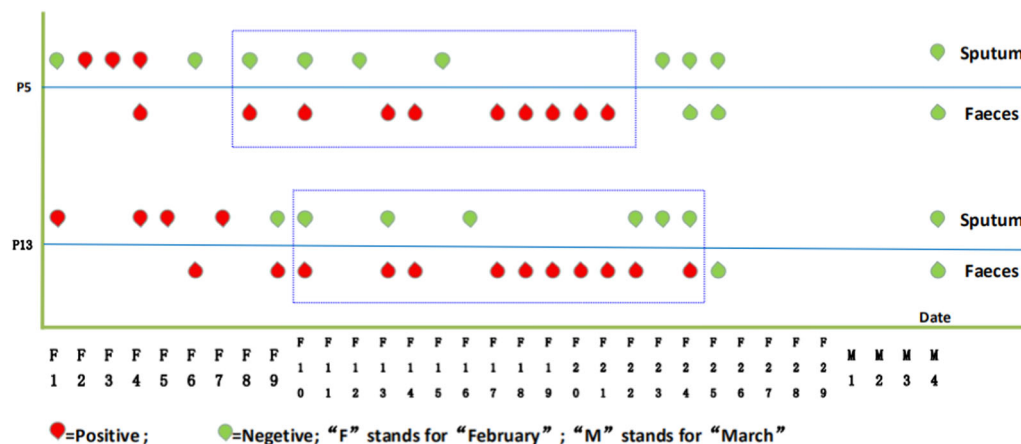


FIGURE 2 Continued positivity of SARS-CoV-2 nucleic acid in faeces of two patients after negative results from respiratory samples

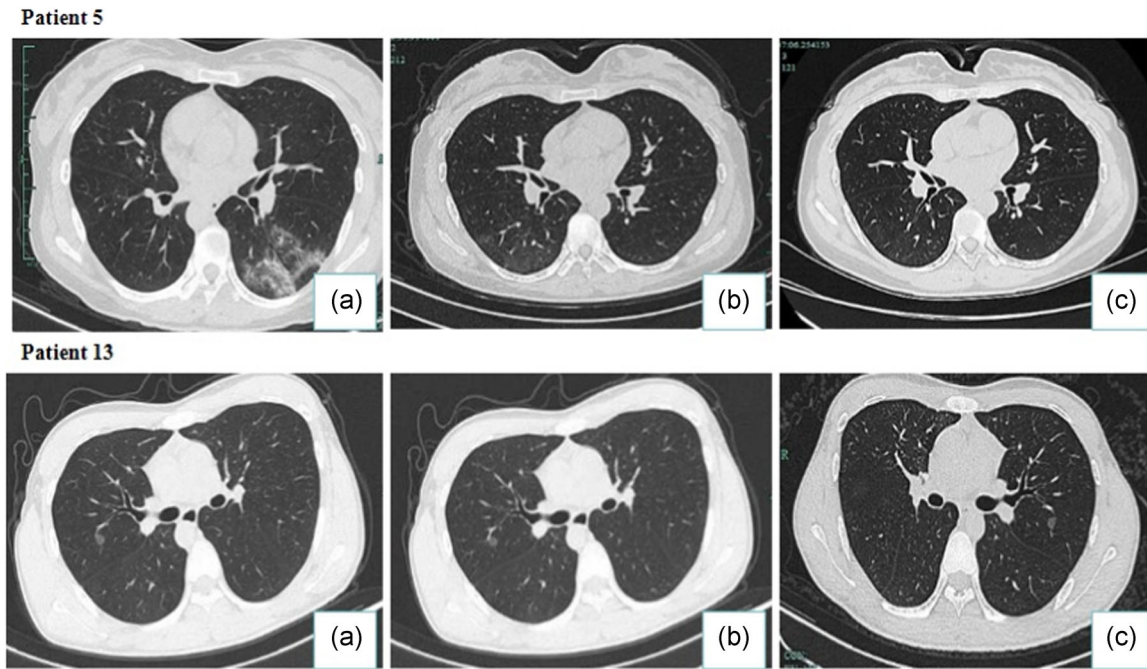


FIGURE 4 Transverse chest CT images from COVID-19 patients with faecal SARS-CoV-2 nucleic acid positivity. A, During hospitalization, CT scans typical signs of COVID-19: density-increased patchy consolidation and ground-glass shadow. B, Lung CT scan of patients meeting discharge criteria: strip high-density shadows have been mostly absorbed. C, Lung CT scans at the time of faecal SARS-CoV-2 nucleic acid positivity after sputum turned negative: similar to (B). CT, computed tomography

above the detection limit. Finally, cured patients may have developed a secondary infection with SARS-CoV-2 due to re-exposure to the virus.

In our study, all four discharged patients had negative sputum (not pharyngeal swab) results in 4 to 5 consecutive viral nucleic acid tests with at least 1 day between each test before recurrence of the virus. This indicates that the results were unlikely to be false negative due to improper sampling. In an earlier study of COVID-19, virus-specific IgM and IgG antibody was detected in 50% (8/16) and 81% (13/16) of the patients' serum, respectively, after 10 days of treatment. On day 15 after treatment, the presence of virus-specific IgM and IgG was as high as 81% (13/16) and 100% (16/16), respectively, indicating that patients with COVID-19 generally produce protective antibodies in the early stage of disease.⁸ A SARS-CoV study showed that in SARS patients, specific IgG antibodies can persist for 12 years.²² These studies suggest that patients infected with SARS-CoV-2 carry protective antibodies after recovery and may be able to maintain immunity for a long time. And the four patients were kept in strict isolation at home after discharge, with no history of re-epidemiological exposure. Therefore, the possibility of reinfection in a short time is very small. Simultaneously, we did not observe any clinical symptoms related to viral pneumonia during the follow-up in the four patients with recurring viral nucleic acid and no progression of the disease was found in CT scans of the lungs, which indicated that the patients were not cases of recurrence of the disease but rather an asymptomatic virus carrier.

SARS-CoV-2 has a strong transmission capability and a fast infection rate. The elderly and those with chronic underlying diseases have a poor prognosis.²³ At present, the sources of infection are COVID-19 patients and asymptomatic virus carriers may also spread the virus. The results of this study indicated that under the current discharge criteria, there may be a large proportion of discharged patients who are still virus carriers. To determine whether these viral nucleic acid relapsing patients are infectious, we need to consider two factors. One is to clarify the relationship between the chance of viral transmission and viral load in patients. We can then determine the viral load in relapsing patients to assess their infectiousness. Second, it is necessary to distinguish whether the viral nucleic acid positivity of discharged patients is due to residual virus or active replication. Currently, these factors remain to be elucidated. Therefore, without clear evidence that discharged patients are not infectious, the patients themselves and others will be at great risk if they are not adequately followed-up and strictly isolated after discharge.

5 | CONCLUSION

In view of the current discharge criteria, the presence of viral nucleic acid in the faeces and the rate of recurrence in the sputum of discharged patients have led us to propose the following suggestions. First, it may be necessary to reassess the suitability of the current

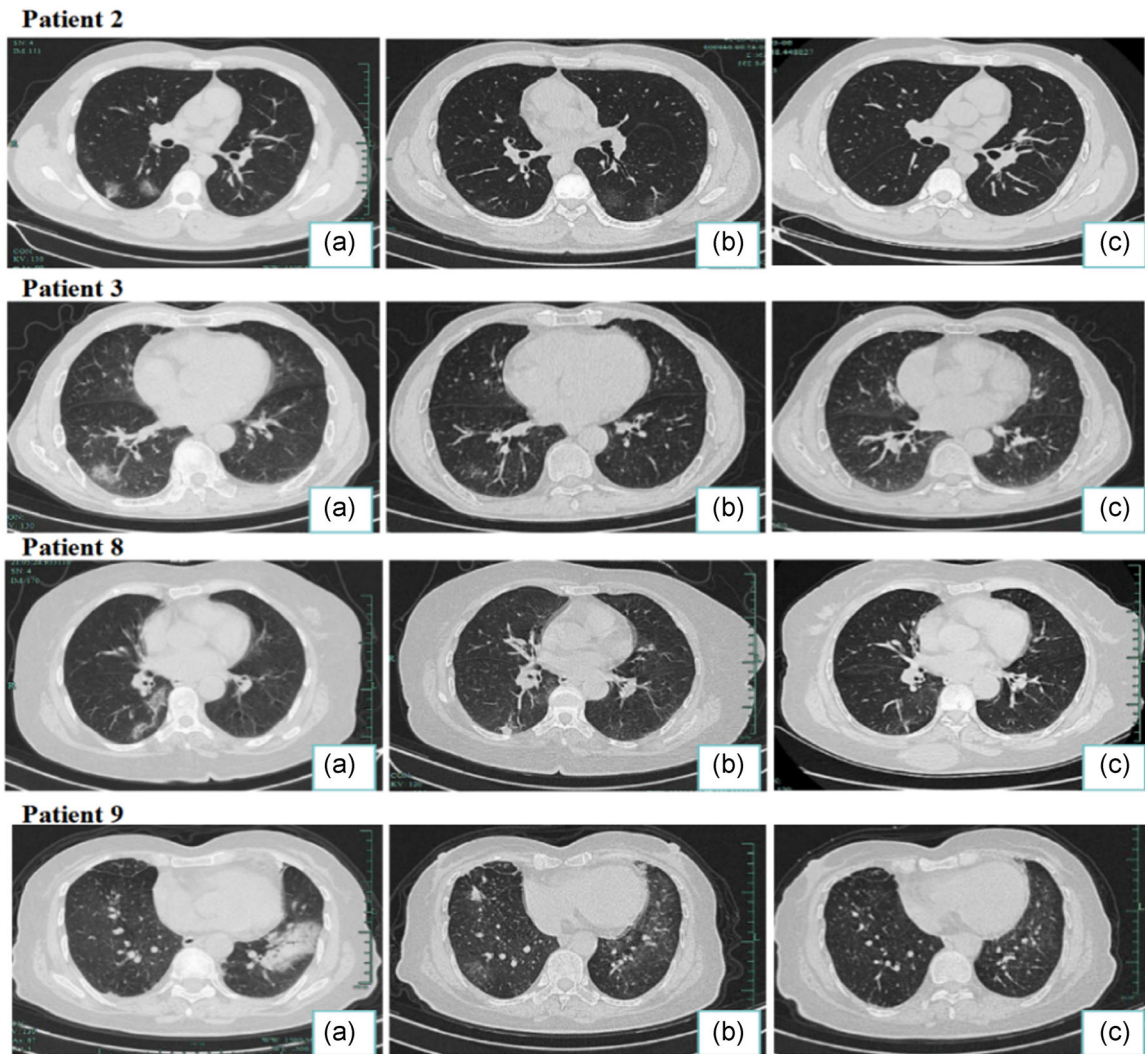


FIGURE 5 Transverse chest CT images from COVID-19 patients with recurrence of SARS-CoV-2. A, During hospitalization, CT scans typical signs of COVID-19: density-increased patchy consolidation and ground-glass shadow. B, CT scans while patient had met the current discharge standards: strip high-density shadows of the lung with largely absorbed. C, Lung CT scans at the time of nucleic acid recurrence: similar to (B). CT, computed tomography

discharge criteria, which requires two consecutive days of negative viral nucleic acid testing in respiratory samples at least 1 day apart. Faecal virus nucleic acid should be tested as a routine monitoring index for COVID-19, and it may be necessary to add a negative faecal result to the criteria. Second, medical institutions should strengthen the regular follow-up and re-examination of discharged patients and continuously monitor changes in viral nucleic acid in discharged patients. Considering the significance of this ongoing global public health emergency, although our conclusions are limited by the small sample size, we believe that the findings are important to understand SARS-CoV-2 relapse potential in COVID-19 patients. In the next step, we will collect more data and evaluate the outcome of the disease in a larger population of discharged patients during a longer and more complete follow-up period, providing a basis for optimizing discharge criteria and follow-up management of discharged patients with COVID-19.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All the authors participated in generating the idea. B.L. and G.H. took part in sample collection. Y.L., Y.W., and X.Z. tested all samples by RT-PCR assay. Y.Y. took part in data collection and interpretation. Y.L. and Y.H. analysed and interpreted the data and wrote the manuscript. J.X. critically reviewed and edited it with his comments.

DATA AVAILABILITY STATEMENT

With the permission of the corresponding authors, we can provide participant data without names and identifiers, but not the study protocol, statistical analysis plan, or informed consent form. Data can be provided after the article is published. Once the data can be made public, the research team will provide an email address for communication. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided.

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