Risk factors associated with PCR repositivity in patients with COVID-19 after recovery in Guangzhou, China: a retrospective cohort study

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Abstract

Some patients retested positive for SARS-CoV-2 following negative testing results and discharge. However, the potential risk factors associated with redetectable positive test results in a large sample of patients who recovered from COVID-19 have not been well estimated. A total of 745 discharged COVID-19 patients were enrolled between January 30, 2020, and September 9, 2020, in Guangzhou, China. Data on the clinical characteristics, comorbidities, drug therapy, RT-PCR testing, and contact modes to close contacts were collected. Patients who tested positive for SARS-CoV-2 after discharge (positive retest patients) were confirmed by guidelines issued by China. The repositive rate in different settings was calculated. Among 745 discharged patients, 157 (21.1%; 95% CI, 18.2% to 24.0%) retested positive, of which 55 (35.0%) were asymptomatic, 15 (9.6%) had mild symptoms, 83 (52.9%) had moderate symptoms and 4 (2.6%) had severe symptoms at the first admission. The median time from discharge to repositivity was 8.0 days (IQR, 8.0 to 14.0 days). Most positive retest patients were without clinical symptoms, and lymphocyte cell counts were higher than before being discharged. The likelihood of repositive testing for SARS-CoV-2 RNA was significantly higher among patients who were younger age (OR, 3.88; 95% CI, 1.74 to 8.66, 0 to 17 years old), had asymptomatic severity (OR, 4.36; 95% CI, 1.47 to 12.95) and did not have clinical symptoms (OR, 1.89; 95% CI, 1.32 to 2.70, without fever). We found that the positive retest rate of COVID-19 was relatively high, and these patients tested positive again with a median of 8.0 to 14.0 days after discharge. Positive retest results were mainly observed in young patients without severe clinical symptoms. These findings suggest that a significant proportion of patients could carry viral fragments for a long time, and effective management, such as a prolonged quarantine phase for discharged patients, is necessary.

Introduction

Since the outbreak in December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has given rise to a worldwide pandemic(Li et al., 2020). As of December 13, 2020, 70 million COVID-19 cases and 1.6 million deaths have been reported globally(WHO, 2020). At the same time, tens of millions of patients with COVID-19 have recovered and been discharged from the hospital. However, some patients affected by COVID-19 who fully met the criteria for discontinuation of quarantine had another positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) result at a follow-up visit(An et al., 2020; F. Hu et al., 2020; Lan et al., 2020; Mei et al., 2020; Su et al., 2020; Zheng et al., 2020), which increases the complexity of disease control and has attracted widespread concern.

Several studies, mainly case reports, have been performed to investigate the clinical characteristics and virologic course of discharged patients(An et al., 2020; F. Hu et al., 2020; Lan et al., 2020; Mei et al.,

2020; Su et al., 2020; Zheng et al., 2020). However, to date, many questions about patients who tested positive for SARS-CoV-2 again (hereafter, positive retest patients) have not been answered; these questions include the overall prognosis of patients with COVID-19 after meeting the criteria for hospital discharge, the potential risk factors associated with redetectable positive test results, and whether the persistent presence of virus fragments means that the discharged patient is still contagious. As the number of discharged patients increases, effective management becomes critical to successfully reducing the spread of SARS-CoV-2. To promote the comprehensive rehabilitation of COVID-19 patients, China has implemented a series of measures for discharged COVID-19 patients, including management of quarantine, regular follow-up, health monitoring, and rehabilitation therapy, which provide empirical information and evidence support for the management of patients with COVID-19(National_Health_Commission_of_China, 2020).

In this retrospective cohort study, we examined the potential risk factors associated with redetectable positive test results among 745 patients affected by COVID-19 after meeting the criteria for hospital discharge in Guangzhou, China.

Material and methods

Patients and study design

Only COVID-19 patients who met all the following criteria(National_Health_Commission_of_China, 2020) could be discharged from the hospital and admitted to the follow-up study project: (1) body temperature returned to normal for more than 3 consecutive days, (2) had significant improvement in any symptom, such as fever, dry cough and expectoration, (3) had substantial improvement in acute exudative lesions on chest computed tomography (CT) images, and (4) had negative RT-PCR test results for SARS-CoV-2 RNA from a nasopharyngeal swab, an anal swab or other respiratory specimens two consecutive times (at least 24 hours apart).

Between January 30, 2020, and September 9, 2020, a total of 745 patients who officially recovered from COVID-19 were discharged from the hospital and enrolled in this study in Guangzhou, China. All discharged patients were required to undergo 14 days of quarantine in designated health care facilities and 28 days of community follow-up to observe their clinical symptoms and RT-PCR results. The positive retest patients were re-admitted to the hospital for therapy, and close contacts were traced and followed-up. The remaining discharged patients who continued to have negative RT-PCR test results were closely followed-up in their communities. **Fig. 1** shows the flowchart of the management of discharged patients.

This study was reviewed and approved by the Ethics Committee of the Guangzhou CDC (GZCDC). As required by the National Health Commission of China, CDCs were responsible for the work for an ongoing public health response to COVID-19, and our cohort study was based on the data from the GZCDC. Patients were informed about the surveillance before providing written consent, and data were collected and anonymized for analysis. All analyses of personally identifiable data took place onsite at the GZCDC.

Definition and Confirmation of Positive Retest Patients

This study refers to discharged patients who tested positive for SARS-CoV-2 again using RT-PCR as positive retest patients. Based on open reading frame 1ab (ORF 1ab) and nucleocapsid (N) protein genes in the SARS-CoV-2 genome, RT-PCR was performed to assess the results(Corman et al., 2020; Luo, Liu, Zhang, et al., 2020). If the cycle threshold (Ct) value of RT-PCR is less than 37, the sample is positive; if the Ct value ranges between 37 and 40, and if the amplification curve has an obvious peak, then the sample is considered positive. Otherwise, the sample is considered as negative.

The following three conditions are considered positive. First, the two targets, ORF 1ab and N protein, are both positive. Second, in case of the result showing positivity for one target, samples shall be recollected for another test. If it is still positive for a single target, the result should be considered positive. Third, if two types of specimens show one single target as positive at the same time or if one target is positive in two samples of the same type, then the result should be considered positive.

Measures

Quarantine for discharged patients

After discharge from the hospital, patients were put under centralized quarantine and health monitoring for 14 days at designated health care facilities. During the quarantine period, the discharged patients lived in a well-ventilated single room, dined separately, practiced hand hygiene, and minimized close contacts. Nasopharyngeal and anal specimens collected on the 1^{st}, 7^{th}, and 14^{th}days or more frequently were sent to the laboratory for RT-PCR testing. The discharged patients were monitored for body temperature, and medical staff recorded whether they had respiratory symptoms (such as fever and dry cough) or digestive tract symptoms (such as diarrhea) every day. If the RT-PCR test result was consecutively negative and no symptoms or CT images progressed, these patients could return to normal life and be regularly followed up by the community after the discontinuation of quarantine. If they were symptomatic (had clinical manifestations and had a positive RT-PCR test result) or asymptomatic (had no clinical manifestations but had a positive RT-PCR test result) patients, diagnosis and treatment should be conducted strictly in accordance with Chinese clinical guidance for COVID-19(National_Health_Commission_of_China, 2020). When the positive retest patients met the hospital discharge criteria, they were quarantined for another 14 days.

Follow-up for discharged patients

After discharged patients completed 14 days of quarantine, it is recommended for these patients to be followed up in their communities for at least 28 days. GZCDC follows the health management plan for discharged COVID-19 patients released by the National Health Commission of China(National_Health_-Commission_of_China, 2020), and RT-PCR testing was performed on the 14^{th} and 28^{th} days after quarantine or more frequently. During the follow-up period, if a person tested positive by RT-PCR, he or she should go to the hospital for a comprehensive evaluation as soon as possible, and treatment should be conducted according to the latest national clinical guidance. If a person tested negative by RT-PCR but CT images showed abnormalities or symptoms occurred, symptomatic treatment could be given according to the related disease(s).

Close contact tracing and management

If the discharged patient was diagnosed as a positive retest patient, close contacts should be traced and followed up. Close contacts are to be put under centralized quarantine and medical observation. If this is not feasible, home quarantine and health monitoring can be used instead. At home, they were recommended to wear a mask, live in a well-ventilated single room, reduce close contact with family members, wash hands frequently and avoid going out(Chinese_CDC, 2020). The quarantine period should last until 14 days after the last contact without effective protection with a positive retest patient. Samples including nasopharyngeal and anal swabs were all collected for RT-PCR diagnosis in an attempt to reduce the chance of false negatives caused by differences in primer specificity and sensitivity. Monitoring and evaluating close contacts were documented in a previous study(Luo, Liu, Liao, et al., 2020).

Data collection

The information collected for COVID-19 patients included demographic characteristics (age, sex and continent), comorbidities (hypertension, diabetes, etc.), drug therapy, severity, clinical symptoms (fever, dry cough, expectoration, myalgia, diarrhea, shortness of breath, fatigue, etc.), radiological examinations (CT), and blood examinations (white blood cell count, lymphocyte cell count and lymphocyte cell percentage) at the first admission. The second admission information of positive retest patients was also collected. The information collected for close contacts included demographic characteristics, quarantine site (health care facilities and home), frequency of contact (often, moderate, and occasional), and contact modes (household, public transportation, health care settings, workplaces, and entertainment places).

Statistical analysis

The repositive rate of SARS-CoV-2 was estimated by dividing the number of positive retest patients by the

number of COVID-19 patients. Categorical variables are described as absolute numbers and percentages (%). Skewed and normally distributed continuous variables are described as the median (interquartile range [IQR] or range) and mean (standard deviation [SD]), respectively. Chi-square tests and t-tests were used to compare characteristics between positive retest patients and negative retest patients.

Univariate and multivariable logistic regression models(Tripepi, Jager, Dekker, & Zoccali, 2008) were performed to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations of potential risk factors with retested positivity. Age (0-17, 18-44, 45-59, or [?]60 years), sex (male or female), continent (Asia, Africa or others), severity (asymptomatic, mild, moderate, or severe) and clinical symptoms (fever, dry cough, expectoration, myalgia, diarrhea or shortness of breath) at the first admission were included in the multivariable model.

Analyses were all performed with SAS software (version 9.4 for Windows, SAS Institute, Inc., Cary, NC, USA). Statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

Results

Clinical characteristics of 745 patients with COVID-19

A total of 745 patients who officially recovered from COVID-19 were enrolled in this study, and they were all tested for SARS-CoV-2 by RT-PCR after discharge. Up to September 21, 2020, 157 patients (21.1%; 95% CI, 18.2 to 24.0) retested positive by RT-PCR and were transferred to the designated hospital. **Fig. S1** shows the distribution of COVID-19 patients by date of the first admission, and the characteristics at the first admission of the 157 positive retest patients are shown in **Table 1** . Positive retest results were observed in patients in all age groups (age ranging from 3 months to 82.0 years, with a median age of 33.0 years), which was significantly younger than that of negative retest patients (median age of 38.0 years). The days from the first admission to discharge of positive retest patients were significantly shorter than those of negative retest patients (11.2 [5.5, 16.4] vs. 13.0 [8.0, 20.0] days). During their first admission, all patients were updated by the progression of their illness, and the most severe condition was their final severity designation. One in three positive retest patients was asymptomatic compared with one in six negative retest patients (P <0.001). The positive retest patients had fewer comorbidities (such as cardiovascular disease, 1 [0.6%] vs. 29 [4.9%]), were less likely to be treated with anti-infective drugs (58 [36.9%] vs. 308 [52.4%]) and were likely to be in the ICU (4 [2.6%] vs. 37 [6.3%]). After discharge from the hospital, RT-PCR testing was performed regularly, and the median number of tests was 4.0 times (IQR, 3.0 to 6.0 times) for positive retest patients, which was significantly greater than that of negative retest patients (P <0.001). The median time for discharged patients retested as being viral RNA-positive was 8.0 days (IQR, 8.0 to 14.0 days) after discharge (**Table 1 and Fig. 2**). After discharge, 4 (2.6%) patients had symptoms of dry cough, 10 (6.4%) patients had expectoration, 2 (1.3%) patients had sore throat and 2 (1.3%) had fatigue, which was lower than that of the first admission. Among the 127 patients who underwent CT examination, 104 (81.3%) patients had abnormal but obvious absorption. Lymphocyte cell counts and lymphocyte cell percentages were increased compared with those before (**Table 2**).

Risk factors associated with repositivity among COVID-19 patients

Table 3 presents the association between various potential risk factors and repositivity among COVID-19 patients before and after adjustment. A higher repositivity rate of males than females (23.4% [95% CI, 19.3 to 27.4] vs 18.1% [13.9 to 22.3]) was observed, but this difference was not statistically significant. The repositivity rate decreased with age, with 42.9% (27.9 to 57.8) for 0-17 years, 22.0% (18.1 to 25.9) for 18-44 years, 16.3% (10.7 to 21.9) for 45-59 years and 16.2% (9.1 to 23.2) for 60 or over years (P for trend = 0.0023), and decreased with severity, with 34.6% (27.2 to 42.0) for asymptomatic, 18.5% (10.1 to 27.0) for mild symptoms, 17.7% (14.3 to 21.2) for moderate symptoms and 10.8% (0.8 to 20.8) for severe symptoms (P for trend < 0.001). Manifestation of some symptoms at the first admission, such as fever (26.7% [22.1 to 31.4] vs 16.2% [12.6 to 19.8]), was associated with an increased risk of repositivity. In addition, comorbidities, CT lung abnormalities, and some clinical symptoms (such as fatigue, chills, and sore throat) were not separately

assessed due to multicollinearity with age, severity and other clinical symptoms, and the repositivity rate of COVID-19 by these variables is shown in **Table S1** .

Management and infection of close contacts

Because all the discharged patients were put under centralized quarantine for 14 days at health care facilities, only 26 positive retest patients had close contacts, and 148 close contacts were traced.**Table 4** presents the characteristics of positive retest patients and close contacts. The demographic characteristics of the 148 close contacts were as follows: sex distribution was more male (89, 60.1%) than female (59, 39.9%); all age groups were included, and 18 to 44 years old accounted for most of the close contact (92, 62.2%). A total of 137 (92.6%) close contacts were quarantined at health care facilities, and 11 (7.4%) close contacts quarantined at home. Among all close contacts, 41.2% (61/148) were public transportation contacts, 28.4% (42/148) were household contacts, 21.0% (31/148) were entertainment place contacts, 8.1% (12/148) were workplace contacts and 1.4% (2/148) were healthcare setting contacts. Positive retest patients with moderate severity had the closest contacts (96, 64.9%), followed by asymptomatic patients (40, 27.0%). After quarantine for 12.0 days (IQR, 6.0 to 14.0 days) at a health care facility or at home and 4.5 times (IQR, 3.0 to 10.0 times) of RT-PCR testing, 148 close contacts tested negative for SARS-CoV-2 RNA, and no suspicious clinical symptoms were reported.

Discussion

We found that the repositive rate of SARS-CoV-2 was over 20% (157/745, 21.1%) among discharged patients affected by COVID-19 at a follow-up visit after at least 6 weeks. They reported positive RT-PCR testing results with median days 8.0 to 14.0 after discharge. Over 4 in 10 children and adolescents were found to be positive again; in contrast, the repositivity rate of SARS-CoV-2 in middle-aged and elderly individuals was 16%. Moreover, patients with more clinically severe disease were less likely to have redetectable positive test results than those with mild severity; asymptomatic patients were most likely to have redetectable positive test results. Manifestation of certain symptoms at first admission, such as fever, was also associated with a lower risk for repositivity. Based on the Chinese guidelines for discharged patients (National_Health_-Commission_of_China, 2020), positive retest patients were required to quarantine for a second time. No other positive patients emerged within their families and close contacts.

Several studies, mainly case reports, have been performed to investigate the percentage of retested positivity and the clinical characteristics of discharged patients(Habibzadeh et al., 2020; Lan et al., 2020; Tao et al., 2020). Previous studies reported that the repositivity rate ranged from 6.9% to 69.0% for discharged patients(Habibzadeh et al., 2020; Landi et al., 2020; Tao et al., 2020). However, the studies were limited to a small number of patients with mild or moderate infection. In our study, we evaluated the overall prognosis of patients with COVID-19 after meeting the criteria for discharge in Guangzhou, China. After screening 745 discharged patients, up to September 21, 2020, the repositivity rate was over 20% (157/745), which was higher than that in other cities of China (20/182, 11.0%)(Yuan et al., 2020) and Italy (16.7%)(Landi et al., 2020), and this may be due to the longer follow-up time, more stringent monitoring and higher frequency of RT-PCR testing in Guangzhou. Our study has lasted more than 7 months since the start of the outbreak, which was far longer than other study (most lasted for one or two months)(Lu et al., 2020; Tao et al., 2020; Yuan et al., 2020; Zheng et al., 2020) and to some extent represented the overall prognosis of the disease.

According to the Chinese clinical guidance for COVID-19(National_Health_Commission_of_China, 2020), all positive retest patients should test negative for nasopharyngeal and anal swabs for two successive tests before discharge. Then, all discharged patients were continuously quarantined in designated health care facilities with strict interventions on disease transmission. Thus, the identification of another positive SARS-CoV-2 test during the quarantine period likely excludes the possibility that positive retest patients are caused by secondary viral infection. A recent study also experimentally confirmed that the virus was involved in the initial infection instead of a secondary infection(F. Hu et al., 2020). Abnormal CT and lymphopenia are common and correlate with poor clinical outcomes in patients with COVID-19(Cheng et al., 2020). Most positive retest patients at the second admission showed increased lymphocyte cell counts, and CT

examination showed abnormal but obvious improvements (**Table 2**), suggesting that positive retest patients have no obvious disease progression but are still asymptomatic carriers of the virus.

Our results showed that the observation of positive retest patients was not random and was mainly observed in young patients without severe clinical symptoms, which was consistent with previous studies(F. Hu et al., 2020; Lu et al., 2020). At present, it has been reported that negative conversion of viral RNA generally takes 2 to 3 weeks or longer(X. Hu et al., 2020; Hung et al., 2020; To et al., 2020; L. Zou et al., 2020), and one study showed that SARS-CoV-2 nucleic acid existed in fecal samples for 47 days after the first symptom onset(Wu et al., 2020). In our study, the days of first hospitalization were shorter in positive retest patients than in negative retest patients (**Table 1**), suggesting that the SARS-CoV-2 virus may not be completely eliminated due to the lighter symptoms and the faster attainment of the discharge standard. In addition, one study reported that recurrently positive RT-PCR testing results in patients with three consecutive negative results were significantly decreased compared with those in patients with two consecutive negative results(Y. Zou et al., 2020), suggesting that a prolonged quarantine phase is necessary.

Among positive retest patients in our study, no families or close contacts of positive retest patients tested positive, which was consistent with current studies(Chandrashekar et al., 2020; Lu et al., 2020). All positive retest patients had observed social distancing measures and worn face masks. Regarding these observations, it is very difficult to affirm whether these patients were truly contagious. RT-PCR testing does not discriminate between an infectious virus and noninfectious RNA(Atkinson & Petersen, 2020; Quick et al., 2017). Therefore, positive testing may not necessarily imply an active infection or ability to transmit infection. However, whether discharged patients have infectivity is an issue of concern around the world at present. One recent study reported that no infectious strain could be obtained by culture, and no full-length viral genomes could be sequenced using samples of positive retest patients(Lu et al., 2020). However, other studies found that active SARS-CoV-2 viral replication was observed(Gousseff et al., 2020) and managed to obtain a nearly full-length viral genome sequence in positive retest patients by detecting intracellular SARS-CoV-2 subgenomic messenger RNA (sgmRNA)(F. Hu et al., 2020), and the presence of SARS-CoV-2 sgmRNA was widely accepted as direct evidence of active viral replication and production(Kim et al., 2020; Wölfel et al., 2020). Furthermore, a recent study found that SARS-CoV-2 viral particles remained in the lungs of patients in the hospital whose nasopharyngeal swab sample testing results were negative at three consecutive times(Yao et al., 2020). Therefore, careful consideration should be given to the potential for patients who are positive retest patients to become chronic virus carriers.

Our study has some limitations. First, as our data were based on the public health response to COVID-19, sample collection did not follow a stringent study design. Therefore, some of the patients, especially in the early stage, had missing fecal samples. Second, nasopharyngeal swab samples cannot differentiate whether the virus comes from the nasopharynx or from secretions from the lower respiratory tract; thus, virus elimination in the lower respiratory tract cannot be confirmed. In contrast, the positive rate of RT-PCR testing through alveolar lavage fluid may be higher. However, this method is invasive and cannot be widely performed in clinical practice. In our opinion, both qualities of respiratory samples and the variability of technique sensitivity can be attributed to the influencing factors of repositivity. Third, as the discharge patients were usually placed under centralized quarantine and medical observation, the infectivity of the positive retest patients might be underestimated.

In summary, we found that the repositivity rate of discharged patients was relatively high (21.1%), and they tested positive with a median of 8.0 to 14.0 days after discharge. The observation of positive retest patients was not random and was mainly observed in young patients without severe clinical symptoms. We suspected that SARS-CoV-2 may not be completely eliminated in positive retest patients due to the lighter symptoms and the faster attainment of the discharge standard. Meanwhile, as the discharge patients were usually put under centralized quarantine, it is difficult to affirm whether these patients were truly contagious. These findings suggest that a significant proportion of patients could carry viral fragments for a long time, and effective management, such as a prolonged quarantine phase for discharged patients, is necessary.

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Data Availability Statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures legend:

Fig. 1. Study flow diagram.

Fig. 2. Distribution of days from discharge to re-positivity among re-positive cases according to the severity at first hospitalization.

Tables:

Table 1. Characteristic of 157 re-positive and 588 non-re-positive cases with COVID-19.

Table 2. Characteristic of 157 re-positive cases at first and second admission.

Table 3. Risk factors associated with re-positivity among COVID-19 cases (n=745).

Table 4. Characteristic of re-positive cases and the close contacts.

Table S1. Prevalence rate of Re-positivity among 745 COVID-19 cases.

Fig. S1. Distribution of date of first admission in cases with and without re-positivity.

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