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The characteristics of 527 discharged COVID-19 patients undergoing long-term follow-up in China

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\textbf{A B S T R A C T}

\textbf{Background:} Almost a year after the outbreak of coronavirus disease 2019 (COVID-19), many hospitalized COVID-19 patients have recovered. However, little is known about the long-term follow-up (> 2 months) of discharged patients.

\textbf{Methods:} This study enrolled 527 discharged COVID-19 patients from 05 February to 11 March 2020. Basic characteristics, imaging features, nucleic acid detection results, and antibody levels of these patients were retrospectively reviewed.

\textbf{Results:} Of the 527 discharged patients, 32 (6.1%) had re-detectable positive (RP) nucleic acid results for SARS-CoV-2 during follow-up examinations, with 11 and four detections entailing stool samples and anal swabs, respectively, rather than respiratory samples. Juveniles were more susceptible to “infection recurrence” than other age groups, with shorter time spans for re-detectable positive (RP) RNA tests (an average of 8.8 days [6.0–9.0 days]), while the reverse was true for the middle-aged group (17.5 days on average [14.0–17.5 days]). Similar improvements in the imaging features of both RP and no RP (NRP) groups were observed. Negative antibody detections in patients at 3 and 6 months after discharge were 14.2% and 25.0%, respectively. Cases evidencing negative antibodies were more common among juvenile patients (40% vs. 15.6%, \( P = 0.03 \)) 6 months post-discharge.

\textbf{Conclusions:} A total of 6.1% of 527 discharged patients showed RP status, which may be easier to be identified from stool samples than from other samples. Given the dropping rate of SARS-CoV-2 antibodies, reinfection may happen, especially in juvenile patients (aged < 18 years). These findings have implications for the long-term management of recovered COVID-19 patients.

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\textbf{Introduction}

Among existing viruses, coronaviruses, which have the largest RNA genome, have attracted considerable attention in light of the recent emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhou et al., 2020b). Coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2, has created a pandemic, posing global health challenges. As of 11 September 2020, 280,418,42 COVID-19 cases had been diagnosed globally, resulting in 906,094 deaths. In China, 90,643 cases had been diagnosed, of whom 85,505 had been cured and discharged from the hospitals where they were treated (Chinese Center for Disease Control and Prevention, 2019). In recent months, multiple studies have described the clinical characteristics of COVID-19 (Chen et al., 2020b; Huang et al., 2020; Zhou et al., 2020a). With the rising numbers of clinically cured patients, there has been increased research on individuals discharged from hospitals (Bowles et al., 2020; Lan et al., 2020). In compliance with the criteria for hospital discharge in China, these “recovered” patients generally had no
clinical symptoms and tested negative in two reverse transcription polymerase chain reaction (RT-PCR) tests performed 24 h apart. However, given uncertainty regarding the infectivity and health status of discharged COVID-19 patients, appropriate epidemic prevention and control measures remain unclear.

A recent postmortem pathological study conducted on a COVID-19 patient whose throat swabs produced negative results for the SARS-CoV-2 nucleic acid test on three consecutive occasions revealed residual virus in the pneumocytes (Yao et al., 2020). Moreover, several studies have reported re-detectable positive (RP) SARS-CoV-2 nucleic acid test results for some discharged patients (An et al., 2020; Lan et al., 2020). Until now, it was unclear whether RP patients could transmit the virus and infect others. Therefore, studies that determine the prognostic status of discharged patients and identify factors affecting RP would contribute to preventing the pandemic’s spread. The discovery of RP patients has also raised concerns about hospital discharge standards relating to COVID-19. Up to now, few studies have focused on recovered patients, especially those discharged with a long follow-up duration (>2 months), which limits a comprehensive understanding of the disease. More such studies would contribute to refining clinical guidelines for containing and managing COVID-19.

In Shandong, where follow-up of discharged COVID-19 patients is mandatory for a 6-month period, some cured COVID-19 patients had RP RT-PCR test results along with certain significant traits. While reviewing these patients’ long-term follow-up data, their post-recovery conditions were also examined, including imaging features and antibody levels. These findings will provide valuable input into the management of convalescing COVID-19 patients.

Materials and methods

Study design and patients

The data of 527 discharged patients (294 male, 233 female) from COVID-19 designated hospitals in Shandong, China, were examined. The patients were admitted to hospitals with confirmed SARS-CoV-2 infections between 21 January and 16 February 2020 during the early phase of this pandemic. The discharge criteria for recovered patients (Zhou et al., 2020a), were as follows: (1) a normal body temperature for more than 3 days; (2) significantly improved respiratory symptoms; (3) significant improvement of acute exudative lung lesions confirmed through CT imaging; and (4) negative results for nucleic acid tests using respiratory tract samples on two consecutive occasions (with a sampling interval of at least 24 h). The RP patients were defined as discharged patients with re-detectable positive nucleic acid test results using any sampling means. The severity of the disease was categorized according to the Guideline on the management of COVID-19 published by the National Health Commission of the People’s Republic of China. Mild cases evidenced mild symptoms and no imaging observations of pneumonia. Severe cases displayed one of the following characteristics: dyspnea with a respiratory rate ≥ 30 breaths per minute, oxygen saturation ≤ 93%, or arterial blood oxygen partial pressure (PaO2)/oxygen concentration (FiO2) ≤ 40 kPa.

Data collection

All of the patients’ medical records and radiological report results stored in the electronic medical system were reviewed. The baseline data and information collected from patients included sex, age, residential location, hospitals of initial attendance and discharge, date of disease onset, and admission and discharge times.

Specimen collection and testing

The collection of samples for the SARS-CoV-2 test from the patients’ sputum, throat and anal swabs, and stool samples complied with the Technical guidelines for COVID-19 laboratory testing, version 2. Pathogen testing was performed using an ORFlab/N Gene Nucleic acid detection kit (BioGerm, China), following the manufacturer’s instructions. The assay targeted the SARS-CoV-2N gene and the ORF1ab gene. A total of 12 μL of nucleic acid amplification reactant, 4 μL of enzyme mixture, 4 μL of ORF1ab/N reactant (including the primer and probe), and 5 μL of RNA extracted from the sample were mixed together in a suitable centrifuge tube, making up the total fluid volume (25 μL) in the tube. Reactions for the amplifications and detection were incubated at 50 °C for 10 min and at 95 °C for 5 min, followed by 40 cycles of 10 s at 95 °C and 40 s at 55 °C. Subsequently, melting curve analyses were performed to enable the exclusion of nonspecific applications. The results were interpreted according to the kit instructions: a cycle threshold value of 38 was considered a positive test result; otherwise, test results were negative.

Statistical analysis

Continuous results were expressed as average and interquartile ranges (IQRs), and dichotomous variables were presented as n (percentages). Parameter differences were calculated using the Mann–Whitney U test, 2 test, or Fisher’s exact test, as appropriate. A two-sided α < 0.05 was considered statistically significant.

Table 1
Clinical characteristics of patients who recovered from COVID-19.

|                         | RP patients (n = 32) | NRP patients (n = 495) | All patients (n = 527) | P-value |
|-------------------------|----------------------|------------------------|------------------------|--------|
| Sex                     |                      |                        |                        |        |
| Male                    | 16 (50.0%)           | 278 (56.2%)            | 294 (55.8%)            | 0.50   |
| Female                  | 16 (50.0%)           | 217 (43.8%)            | 233 (44.2%)            | 0.003  |
| Age (years)             | 32.5 (13.3–42.5)     | 43.1 (31.0–54.0)       | 42.5 (32.0–54.0)       |        |
| Age range (years)       |                      |                        |                        |        |
| 0–17 (juvenile)         | 9 (28.1%)            | 26 (5.3%)              | 35 (6.6%)              | <0.001 |
| 1–44 (youth)            | 15 (46.9%)           | 236 (47.7%)            | 251 (47.6%)            | 0.93   |
| 45–59 (middle-aged)     | 4 (12.5%)            | 155 (31.3%)            | 159 (30.2%)            | 0.03   |
| ≥60 (elderly)           | 4 (12.5%)            | 78 (15.8%)             | 82 (15.6%)             | 0.62   |
| Number of severe or critical patients | 0 (0%) | 46 (9.3%) | 46 (8.7%) | 0.07   |
| Days from illness onset to admission | 4.1 (1.8–6.0) | 4.4 (1.0–6.0) | 4.4 (1.0–6.0) | 0.85   |
| Days from admission to discharge | 20.4 (15.0–25.0) | 20.0 (14.0–25.0) | 20.1 (14.0–25.0) | 0.51   |

Data are presented as averages (IQR) or n (n/N), where N is the total number of corresponding patients. P-values for comparing re-detectable positive (RP) and no re-detectable positive NRP patients were obtained from a Chi-square test, Mann–Whitney U test, or Fisher’s exact test, as appropriate.
Results

Baseline data for the discharged patients

Data for 527 discharged patients from COVID-19 designated hospitals in Shandong were obtained. The number of male patients was slightly higher than that of female patients (294 [55.8%] vs 233 [44.2%]). The patients’ ages ranged from 9 months to 91 years, with an average age of 42.5 years (IQR 32.0–54.0 years) (Table 1). According to the nucleic acid test results, 32 (6.1%) of the recovered patients had “infection recurrence” post-discharge. A total of 93.9% of the patients had no re-detected positive (NRP) test results (juveniles, 4.9%; youth, 44.8%; middle-aged, 29.4%; elderly, 15.8%) (Figure 1A).

The RP patients were, on average, younger than the NRP patients (32.5 [IQR 13.3–42.5] years vs 43.1 [IQR 33.0–54.0] years). Infection recurrence was more common among juvenile patients than among other age groups, while the reverse was true for middle-aged patients (Table 1). None of the RP patients experienced severe or critical COVID-related symptoms during their previous hospitalization (Table 1). The average duration from the onset of symptoms to admission was 4.4 days (1.0–6.0 days) for all patients, while that from admission to discharge was 20.1 days (14.0–25.0 days). There were no significant differences between the RP and NRP groups for the durations from illness onset to admission and from admission to discharge.

Characteristics of patients with infection recurrence

The majority of the RP patients (20, 62.5%) were positively re-detected via nucleic acid tests within 7–14 days post-discharge (Figure 1B). Infection recurrence within 14–28 days post-discharge was observed among a few patients (5, 15.6%) and no RP patients were identified 28 days post-discharge. A comparison of the different age groups revealed that compared with youth (13.7 [IQR 11.5–14.0] days) and middle-aged individuals (17.5 [IQR 14.0–17.5] days), children (8.8 [IQR 6.0–9.0] days) showed the shortest RP time (Figure 1C).

Sampling methods for RP

Rapid and accurate diagnostic tests are essential for controlling the ongoing COVID-19 pandemic. In this study, throat swabs were obtained from all 32 RP patients, and 16 patients tested positive for the nucleic acid test. In addition to positive test results obtained from throat swabs, 14, three, and four patients, respectively, tested positive in the nucleic acid test for their stool samples, sputum samples, and anal swabs (Figure 2A–H). Notably, 16 RP patients were independently identified of throat swab: 11 through stool samples, one though a sputum sample, and four through anal swabs.

Strikingly, after patients were grouped according to the time of their RP diagnosis, it was found that the positive rate of nucleic acid detection from the stool samples of patients who recovered within 14 days was much higher than that for throat swabs (Figure 2B–C). To ascertain the reason, the GTEX and FANTOM5 datasets were searched and it was found that ACE2 and TMPRSS2, which are two essential proteins used by SARS-CoV-2 to penetrate cells, have the highest expression levels in the digestive organs (i.e., small intestine, stomach and colon) (Figure 2D–G). This may partially explain why the nucleic acid of the virus was more likely to be detected in the RP patients’ feces, which is a digestive tract secretion. In other words, the virus may not have been totally cleared from the systems of patients who met the hospital discharge standard at the time of their discharge, and it may continue to hide in their digestive organs.
Levels of antibodies in the discharged patients

Among the RP patients, 18 and 16, respectively, underwent antibody detection tests 28 days and 3 months post-discharge, whereas 25 and 111 NRP patients underwent tests at the same time (Figure 3). By the sixth month post-discharge, the numbers of examined patients dropped to three RP patients and 61 NRP patients. In the interim, the rate of specific negative antibodies was observed in 16.2% of all examined cases 3 months post-discharge, with this proportion rising to 24.6% by 6 months post-discharge. In other words, 6 months after recovery, SARS-CoV-2 antibody was still positive in 46 of the 61 patients in the sera. However, none of the RP patients in the sample tested negative for SARS-CoV-2 antibodies, possibly because of the limited sample sizes (n = 16 3 months post-discharge, and n = 3 6 months post-discharge). To identify key characteristics of patients lacking antibodies, their basic characteristics were compared with those of other patients. As shown in Table 2, the antibody test was administered to 127 patients (69 males and 58 females) and 64 patients (30 males and 34 females) 3 months and 6 months, respectively, after discharge. Evidently, the negative rate of SARS-CoV-2 antibodies occurred more in juvenile patients (40.0%); however, as Table 2 shows, there was no difference in these rates for male and female patients.

Imaging results for the discharged patients

Chest computed tomography (CT) scans have proven valuable for detecting virus-induced pulmonary injury and viral pneumonia. In total, 420, 396, 245, and 93 NRP patients, respectively, underwent CT examinations at different time points (at 2 and 4 weeks and at 3 and 6 months post-discharge), whereas all of the RP patients underwent CT examinations within a month of being discharged. The scans revealed that among 465 recovered patients with COVID-19, 286 (63.3%) were found to have inflammation absorption in image diagnostic reports 14 days post-discharge. The reports for RP and NRP patients revealed the following features: no obvious abnormality (21.9% vs 20.2%), nodular shadowing (9.4% vs 12.1%) and pleural incassation (9.4% vs 7.4%) were also noted in RP or NRP patients’ imaging diagnostic reports at 14 days after discharge (Table 3). However, 28 days after discharge, “no obvious abnormality” appeared more frequently in the imaging diagnostic reports for all patients compared with their reports 14 days post-discharge (25.8% vs 20.2%). Three and 6 months after discharge, 245 and 93 patients underwent imaging examinations, with 27.3% and 26.9% of these patients, respectively, reported to have “no obvious abnormality”. Because many patients without symptoms refused to undergo CT examinations after their discharge, the
number of patients, and especially NRP patients, with “no obvious abnormality” may have been underestimated.

Discussion

There is currently a lack of research about discharged COVID-19 patients. It is believed that this is the first study to investigate the recovered COVID-19 patients undergoing long-term follow-up. This study comprehensively analyzed clinical and follow-up data compiled for 527 discharged patients. The findings can provide valuable input into policies on infection prevention and prognosis management post-discharge.

A growing body of evidence has revealed that varying disease intensities and patients’ immune responses to the disease, drug utilization, sampling sites, and processing methods may all affect virus detection results and lead to RP test results for discharged COVID-19 patients (Mei et al., 2020; Yan et al., 2020). It is widely acknowledged that the clinical manifestations of COVID-19 are associated with age and that patients manifesting severe COVID-19 symptoms are almost all either elderly or already suffering from chronic diseases (Chen et al., 2020a, 2020b). None of the 46 (8.7%) patients with severe symptoms in the current study were RP, although there were no statistical differences in the proportions of RP and NRP patients with severe symptoms, possibly because of the limited sample size.

According to the date from early outbreaks in China, the SARS-CoV-2 infection rate among children was lower than that of adults (Dong et al., 2020). Previous studies have also reported milder
symptoms and faster clinical remission among juveniles with SARS-CoV-2 infections compared with adults (Pierce et al., 2020; Xu et al., 2020). The current finding that juvenile patients displayed several distinct features—like a higher incidence rate of RP and a shorter time before a re-detectable positive diagnosis—was consistent with that of previous reports (An et al., 2020). After digging deeper into this issue, it was found that hospital stay of juvenile RP patients (16.3 [IQR 14.0–16.0] days) was significantly shorter than those of adult RP patients (24.8 [IQR 18.0–28.0] days; not shown in a table or figure). These results indicate that children recover quickly and their prognoses are favorable; a finding that may be linked to their balanced immune responses rather than to their ability to rapidly clear viruses and having strong adaptive immune responses (Pierce et al., 2020; Xu et al., 2020). In other words, possibly because of the early discharge of juvenile patients, the virus in their bodies is not completely cleared, which may induce the high RP rate. The current results suggest that caution is required in the treatment of discharged patients, especially juveniles, who do not display any symptoms but in whom residual virus may still be present.

Another important factor influencing RP pertains to long-term virus residual levels in the gut and other tissues, given their high ACE2 and TMPRSS2 content. Samples from the upper respiratory tract are commonly used and are the current standard samples used for nucleic acid testing to detect SARS-CoV-2 infections (Wang et al., 2020). Prolonged shedding of SARS-CoV-2 in stool specimens of infected individual raises the possibility that the virus might be detected from many sources besides throat swabs after discharge. In this study, 15 patients, whose RNA extracted from throat swabs tested negative, were diagnosed as RP according to the results obtained for their fecal samples and anal swabs. One study conducted on 41 COVID-19 patients showed that the continuous duration of stool samples that tested positive was 11.2 days longer than the duration of respiratory samples that tested positive (Wu et al., 2020). They also found that SARS-CoV-2 nucleic acid can even persist in the digestive tract and feces for nearly 50 days (Wu et al., 2020). Consequently, the rate of positive results for fecal samples exceeded that for throat swabs obtained from discharged patients, which partially accounted for the RP phenomenon. Because the virus may remain in the digestive organs for a longer time than in the respiratory organs, positive results are more likely to occur for stool samples or anal swabs collected from discharged patients compared with other detection means. Other studies have also suggested that virus detection targeting the gastrointestinal tract may provide a more accurate assessment of therapeutic efficacy and recovery (Xu et al., 2020). Accordingly, future studies should focus on applying more precise and sensitive detection methods for different patients of different ages and at varying stages of illness to reduce the incidence of RP and the risk of the virus re-spreading.

It has been shown that individuals infected with SARS-CoV-2 will have a strong immune response and produce a large quantity of neutralizing antibodies (Juno et al., 2020). As shown in the pie charts (Figure 3), RP and NRP patients seemed to display different plasma IgG and IgM levels after discharge. A recent study reported durable production of antibodies against SARS-CoV-2 lasting at least 2–3 months after illness onset (Ripperger et al., 2020). In compliance with previous research, SARS-CoV-2 antibodies in 14.7% of patients in the current study returned to baseline levels within 3 months after discharge. Edridge et al. reported that reinfections of the four coronaviruses that cause the common cold occur after an average of 12 months (Edridge et al., 2020). Over time, a significant decline in antibody levels in all of the discharged patients was noticed. Given the continually decreasing antibody levels in COVID-19 patients post-discharge, more studies reporting on individuals who are infected twice with COVID-19 may emerge (Goldman et al., 2020). Therefore, the potential for SARS-CoV-2 reinfection and continued transmission to occur after hospital discharge requires attention. Notably, the current study also found that the rate of disappearance of antibodies at 6 months after discharge was highest in juvenile patients (aged <18 years) compared with other age groups. As mentioned, under SARS-CoV-2 infection, the intensity of immune response, especially adaptive immune response, of children may not be as high as adults (Pierce et al., 2020). Existing research had shown that the types of antibodies induced by SARS-CoV-2 differ in children and adults (Weisberg et al., 2021). The IgG antibody, which can recognize the spike protein, is produced in children. By contrast, adult patients produce more varieties of antibodies, with a stronger ability to defend against not only spike proteins but also many other viral proteins (Weisberg et al., 2021). These findings
may partly explain the reason why the antibodies of the juvenile group in the current study disappeared in advance. However, given quantitative data gaps, more research is needed to provide convincing evidence.

Combining assessments of CT findings with clinical and laboratory findings could assist in the diagnosis and management of patients with COVID-19 (Lee et al., 2020, Shi et al., 2020). In the current study, continuous observations over time revealed improvements in imaging features among all patients. The lung imaging reports for RP and NRP patients showed no significant differences, indicating that sustained remission or no lesions in the lungs occurred among both groups. A previous study showed that abnormal chest radiographs were seen in 30% of SARS patients 6 months after infection (Hui et al., 2005). Interestingly, high-resolution CT scans showed no significant difference between mechanically ventilated and non-mechanically ventilated SARS patients (Joynt et al., 2004). Relatively high rates of persistent radiological abnormalities at 6 months were also observed in the current study. Due to the limitations of this study, the reasons for this phenomenon need to be validated in the future.

Currently, no study has been able to provide an accurate estimate of the infection period for this novel coronavirus. None of the discharged patients in this 6-month study, including RP patients, passed the infection on to others. Some studies have suggested that SARS-CoV-2 loses its infectivity by the tenth day post-symptom onset or after the first positive PCR result in most cases (Sze et al., 2021). The literature does not contain any reports on RP relating to other highly pathogenic coronaviruses—such as SARS-CoV and the Middle East Respiratory Syndrome (MERS)-CoV—possibly because of high associated mortality rates and the small numbers of infected people (Peeri et al., 2020). Compared with other highly pathogenic coronaviruses, COVID-19 not only spreads faster and more widely but may also have a more complex infection course (Peeri et al., 2020).

This study had several limitations. First, there were missing rates for some key indexes, given that this was a retrospective study entailing a long follow-up duration. The number of cases examined in this study may not have been sufficient to fully reveal all of the key factors for specific data, which therefore may have been underestimated. Moreover, it also lacked data about clinical status of patients during follow-up. More compact designs and scientific clinical trials are required to evaluate the potential risk of SARS-CoV-2 RP test results. Another limitation was that dynamic changes of serum-specific antibody levels in RP patients were not quantifiable. Differences between RP and relapsed patients in which distinct prevention and control strategies are adopted should also be compared.

In conclusion, this study screened discharged patients undergoing 6 months of follow-up, including their basic characteristics, nucleic acid test results obtained using different sampling methods, imaging features, and antibody detection results. Therefore, this study provides a foundation for studying hospital policies for SARS-CoV-2 and their discharge standards. This study also provided input that can facilitate treatment planning and the study of changing conditions of patients who have been infected with SARS-CoV-2. With the progressive emergence of novel coronaviruses, it is essential to ascertain the complete mechanisms in infected and recovered subjects to enable people to protect themselves. Currently, discharge criteria for hospitalized COVID-19 patients exhibit considerable heterogeneity across different countries (Sze et al., 2021). In the current context of a global pandemic, more in-depth studies focusing on recovered COVID-19 patients are urgently needed to explore the possibility of standardizing discharge criteria, containing the spread of the disease, and even improving prognosis.

Competing interests

The authors declare no conflicts of interest.

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Availability of data and materials

The data used and analyzed during this research are available from the corresponding author on reasonable request.

Ethical approval

This was a retrospective study and all accessed patient data complied with relevant data protection and privacy regulations.

Authors’ contribution

LD conceived and designed the study, had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. JTW drafted the paper and performed the analysis. JWX, SYZ, CTW, XMW, WZ, KN, YP, TL, and JJP collected the key data and critically reviewed the article before submitting it. All authors made substantial contributions to this manuscript and agree to be accountable for all aspects of the work.

Consent for publication

Not applicable.

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