

PRIORITY PAPER

Positive SARS-CoV-2 RNA recurs repeatedly in a case recovered from COVID-19: dynamic results from 108 days of follow-up

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One sentence summary: The evidence of long-term clinical dynamic on SARS-CoV-2 re-positive case are less and awareness of atypical presentations such as this one is important to prompt the improvement of the management of COVID-19.

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ABSTRACT

The evidence of long-term clinical dynamic on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA re-positive case are less. We performed a 108 days follow-up on dynamic clinical presentations in a case, who hospitalized three times due to the positive recurrence of SARS-CoV-2 RNA after discharge, to understand the prognosis of the 2019-Coronavirus disease (COVID-19). In this case, positive SARS-CoV-2 recurred even after apparent recovery (normal CT imaging, no clinical symptoms, negative SARS-CoV-2 on stool sample and negative serum IgM test) from COVID-19, viral shedding duration lasted for 65 days, the time from symptom onset to disappearance was up to 95 days.

Erythrocyte-associated indicators, liver function and serum lipid metabolism presented abnormal throughout during the observation period. Awareness of atypical presentations such as this one is important to prompt the improvement of the management of COVID-19.

Keywords: coronavirus disease 2019; SARS-CoV-2 re-positive; recovered patients; long-term follow-up; erythrocyte

INTRODUCTION

Potential infectivity of the recovered patients has been aroused great concern in many countries as the recurrence of positive SARS-CoV-2 during post-discharge surveillance (China Daily Website 2020; Lan et al. 2020; Yao et al. 2020). Nowadays, the virus is spreading rapidly around the world. There will be more and more discharged patients in the future with medical rescuing. However, the infectivity of such cases remains unknown, and the evidence of long-term clinical dynamic on SARS-CoV-2 RNA re-positive cases are less. The present report describes

3.5-months presentations of the virus, clinical symptom, laboratory finding and CT image in a case who was admitted to hospital three times due to SARS-CoV-2 RNA recurred positive after discharge.

METHODS

At our institution, Xixi Hospital (a designated infectious disease hospital of Zhejiang province, China), the negative pressure isolation ward was reserved for confirmed cases of COVID-19.

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Individual with respiratory symptoms but without suspicious exposure or travel history was placed solely in surveillance ward. The other general wards were all ceased operating. All patients were advised to avoid mingling and to wear a surgical mask at all times; visitors were not allowed. Each of healthcare workers used full personal protective equipment including face shields, N95 masks, gloves and isolation gowns; hands disinfecting before and after contact with patients. All of the hospital staff, who contacted with confirmed patients, were isolated in a designated hotel. The re-positive patient, who readmitted to the hospital, was treated as a confirmed case. Breathing apparatus, catheter, patient monitoring and other equipment for confirmed patients were all discarded and disposed of as biohazard waste after discharge. Air disinfection (twice a day) was performed by air-sterilizing machines in each ward for the prevention of COVID-19 transmission.

The case in this study was diagnosed as COVID-19 by the positive detection of SARS-CoV-2 RNA in nasopharyngeal swabs according to the manufacturer's instructions (Liferiver, Shanghai, China), which recommended by Zhejiang Center for Disease Control and Prevention. In brief, the target genes of reverse transcription-polymerase chain reaction (RT-PCR) were E gene (first line screen assay), RdRP gene (confirmatory assay) and N gene (additional confirmatory assay). The reaction condition started with 45°C for 10 min and 95°C for 3 min, followed by 45 cycles of amplification at 95°C for 15 s and 58°C for 30 s. The test results of SARS-CoV-2 were reported as positive (Cycle threshold; $Ct \leq 43$) and negative ($Ct > 43$). A total of two consecutively RT-PCR tests were conducted on each respiratory sample during the period of discharge surveillance. Laboratory results were collected and standardized as a uniform table, and checked by two researchers of this study.

Fitness for discharge were improvement of chest radiographic evidence, SARS-CoV-2 negative in respiratory samples for two consecutive detections at least one day apart and abatement of fever for at least three days (National Health Commission of the People's Republic of China 2020). The patient was isolated in a single-occupancy room of the community hospital for the next 2 weeks, and evaluated with the results of SARS-CoV-2 RNA on days 7 and 14 after discharge, to determine whether he could be released from quarantine.

All Healthcare workers in our hospital and the community hospital underwent two nasopharyngeal swabs for the RT-PCR of SARS CoV-2 RNA, which were performed seven days apart. Each healthcare worker will be released from isolation after fulfilled the criteria of both SARS CoV-2 RNA detection presented negative. This study was approved by the Institutional Review Board of Xixi Hospital.

RESULTS

No hospital staff was infected during the observation period. The case was a 35-years-old man with an exposure history of Hubei province in China. He presented high fever (39°C), cough, sore throat and fatigue, and was admitted to hospital as positive detection of SARS-CoV-2 RNA on 30 January 2020. He denied other underlining diseases. The severity of disease was mild.

Time kinetics of CT presentation, clinical symptom (cough or sputum) and virus are described in Fig. 1. The day of symptom onset was defined as day 1. On day 2, CT images showed patchy ground-glass opacities and patchy hyperdense areas in the lower lunge zone.

During the first hospitalized period, lopinavir (LPV) combined with interferon $\alpha 2b$ atomization inhalation (IAI) and arbidol

hydrochloride granules (AHG) was used for more than fourteen days, methylprednisolone (MPD) was added to the combined therapy for four days after the radiographic lesions progressed (days 3 and 5), the nasopharyngeal swab tests of SARS-CoV-2 RNA were positive on the days 2, 10 and 13 and were negative on days 14 and 15. Improvement of radiographic lesions and clinical symptoms (productive cough) occurred on days 9 and 13, respectively. Temperature decreased to normal (under 37.4°C) after five days of treatment (data not shown). He discharged on day 16 and quarantined under surveillance for 2 weeks. On day 25, the results of SARS-CoV-2 RNA from nasopharyngeal swab and stool sample were both negative; the opacities on radiography almost shrunk completely and maintained normal until the end of the observation period. However, the nasopharyngeal swab test of SARS-CoV-2 RNA revealed positive and clinical symptoms deteriorated on day 30; then, he was admitted to hospital again on day 31.

In the period of the second hospitalization, LPV and AHG were used throughout; the nasopharyngeal swab performed with a positive result for SARS-CoV-2 on days 36 and 37, a negative result on days 35, 40, 41 and 42. The clinical symptoms improved on day 34, after which there was a continuous improvement until the end of the second hospitalization. However, on day 50 that of under post-discharge surveillance, the SARS-CoV-2 RNA of nasopharyngeal swab revealed positive again, but negative on stool sample. The results of IgM for SARS-CoV-2 presented negative, and IgG showed positive.

During the third hospitalization, the case was treated on admission with combined therapy (IAI + AHG) throughout, had a mild symptom of white productive cough which improved continuously since the day 53 and completely disappeared on day 56. But, there was a sore throat following with fever on day 53, which receded significantly after antibiotics using. The test of respiratory tract samples revealed negative on days 54 (nasopharyngeal swab) and 56 (sputum), respectively. Chest radiography was repeated on day 54 and showed no abnormalities. He was discharged and isolated under surveillance for the next 2 weeks as before. On day 65, the test of RT-PCR for SARS-CoV-2 on sputum showed positive again, the virus test of stool specimen still presented negative, clinical symptoms that had disappeared before re-emerged, but just presented slight cough. Then, the cough disappeared on day 95 after two consecutively negative virus detections of sputum (on days 81 and 95). The serum test of IgM presented negative on days 56, 65 and 108. At the end of the observation, the detection of SARS-CoV-2 on sputum revealed negative.

Figure 2 showed the changes over time in eighteen laboratory indicators during the observation period. As can be seen from the figure, most values of triglyceride, red cell distribution width (RDW), red blood cell count (RBC) were above the upper bound of normal range. The levels of high-density lipoprotein cholesterol (HDL-C), mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) were mainly under the lower threshold of normal range. About half of the levels of blood hemoglobin were under the lower threshold of normal range. Part of the values of gamma-glutamyltransferase (GGT) were greater than the upper bound of normal range. At the early stage of COVID-19, aspartate transaminase (AST), alanine transaminase (ALT) and rapid c-reactive protein (CRP) levels were high, the values of lymphocyte count and glomerular filtration rate (GFR) were low, but all returned to normal within 15 days after the symptom onset. Nearly all the values of $\beta 2$ -macroglobulin ($\beta 2$ -MG), respiratory rate (RR), creatine kinase isoenzyme (CKMB) and lactate dehydrogenase (LDH) were normal during the observation period.

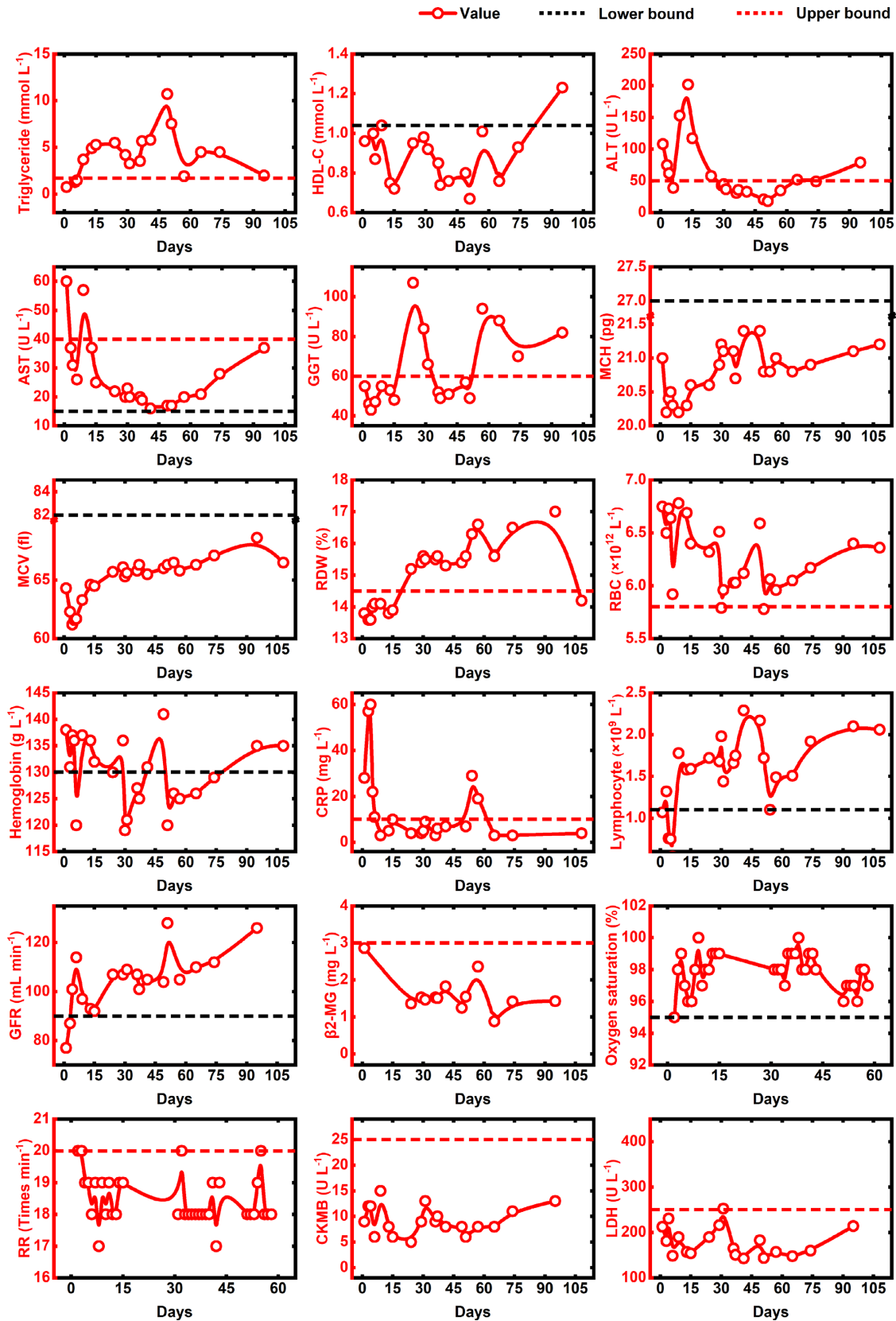


Figure 2. The temporal changes of laboratory indicators in a patient recovered from COVID-19. HDL-C: high-density lipoprotein cholesterol; ALT: alanine transaminase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; RDW: red cell distribution width; RBC: red blood cell count; CRP: rapid c-reactive protein; GFR: glomerular filtration rate; β 2-MG: β 2-microglobulin; RR: respiratory rate; CKMB: creatine kinase isoenzyme; LDH: lactate dehydrogenase.

of chest CT, it could be one of the underlining causes of the lingering characteristic of COVID-19. How different underlying liver conditions influence the relapse of COVID-19 needs to be meticulously evaluated in large-scale clinical trials.

Of this case, the time from symptom onset to disappearance was at least 95 days and the duration of viral shedding after COVID-19 onset lasted for 65 days which is longer than that of 37 days (Zhou et al. 2020). These issues present great difficulties and challenges for the screen of COVID-19 and for the prevention and control of this epidemic.

Our study has limitations; the inherent shortcomings due to a retrospective observational case study, the absence of RT-PCR detection of SARS-CoV-2 RNA on broncho-alveolar lavage fluid and the lack of pathological examination on liver and lung tissues make it difficult to reach a firm conclusion. All above limitations require further study; nonetheless, our primary results provided new and important insights for this topic.

In this study, no hospital staff was infected. Control measures including isolation, effective protection and social distancing, play pivotal roles for the prevention of SARS-CoV-2 infection. Nowadays, the epidemic is under control in China; most COVID-19 patients were discharged from the hospital. We believed that the implementation of isolation and surveillance for at least 14 days effectively prevents the second spread of COVID-19. However, how much time will be needed for isolation for recovered cases and the infectivity of them still require more clinical evidence to confirm. Awareness of atypical presentations such as this one is important to prompt the management of patient isolation and prevent inter-human transmission in the world.

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We express our greatest respect and sincere wishes to the front-line workers in the struggle against COVID-19.

AUTHOR CONTRIBUTIONS

LF, CZB and HJS conceived, designed and organized the study, interpreted the results and drafted the manuscript. XAF helped supervise the study. The other authors contributed to collect the data on site.

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Conflicts of interest. The authors declare that they have no competing interests.

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