Clinical Characteristics Analysis of the “Re-positive” Discharged COVID-19 Pneumonia Patients in Wuhan, China

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Research Article

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Abstract

Background: To analyze the clinical characteristics of the re-positive discharged COVID-19 patients and find markers to distinguish them.

Methods: The demographic features, clinical symptoms, laboratory results, comorbidities, co-infections, treatments, illness severities and chest CT scan results of 267 patients were collected during 1st January and 15th February 2020. COVID-19 was diagnosed by RT-PCR. The subsequent clinical symptoms and nucleic acid test results was obtained during the 14 days post-hospitalization quarantine.

Results: 30 out of 267 COVID-19 patients were detected re-positive during the post-hospitalization quarantine. Re-positive patients couldn't be distinguished by demographic features, clinical symptoms, laboratory results, comorbidities, co-infections, treatments, chest CT scan results or subsequent clinical symptoms. However, the re-positive rate were found illness severity correlated, along with APACHE II and CURB-65.

Conclusion: Common clinical characteristics arn't able to distinguish re-positive patients. However, severe and critical cases with high APACHE II and CURB-65 scores are more likely to turn re-positive after discharge.

Authors Shengyang He, Wenwu Sun, Kefu Zhou contributed equally to this work.

Introduction

The Corona Virus Disease 2019 (COVID−19), caused by the severe acute respiratory syndrome coronavirus−2 (SARS-CoV−2), has affected most countries all over the world since its first case in 2019. The genomic characteristics of SARS-CoV−2 was initially reported by Lu and colleagues, suggesting this coronavirus had enveloped RNA, resembling severe acute respiratory syndrome coronavirus (SARS-CoV) in both structural and homological ways [1]. Up to now, nearly 2 million people have been diagnosed with COVID−19, with more than 100 thousand deaths globally. Specifically, China had more than 80 thousands confirmed cases with more than 3 thousands deaths, according to the World Health Organization (WHO) daily COVID−19 report (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200414-sitrep−85-covi d−19.pdf?sfvrsn = 7b8629bb_4), but other countries including Italy, Korea, the United States, have also shown to have many confirmed cases, and COVID has been officially declared a pandemic.

Previous studies have reported that some patients, after 'recovering' from the virus, could be tested nucleic acid positive again by RT-PCR [2, 3]. However, the mechanisms behind this positive test result remain unclear. It is unknown whether these recovered patients may still be virus carriers. Considering the lack of detailed info regarding these patients and the lack longitudinal studies, the management of discharged COVID−19 patients is crucial.

In the present study, the clinical data of 267 confirmed COVID–19 patients who had been discharged from the Central Hospital of Wuhan, China has been retrospectively analysed. Data showed that, 30 of 267 patients were shown to be SARS-CoV–2 nucleic acid positive again following the 14 days quarantine. A further comparative analysis to explore the characteristics of those “re-positive” discharged patients was further performed. After reviewing their demographic characteristics, main symptoms, laboratory and radiology results, treatments and disease progression, no differences were found in those ‘re-positive’ patients, suggesting this ‘special’ group of COVID–19 patients could be quite hard to detect by simply using common clinical data. However, we did noticed that people with severer illness tend to be more possible turning re-positive.

To formulate a more efficient and effective COVID–19 patients management strategy, in this investigation a novel method to asses and distinguish ‘re-positive patients’ infectivity from common COVID–9 patients is presented.

Methods

Study design and participants

Patients’ admission time ranges from January 1st to February 15th. COVID–19 diagnoses were made according to the diagnostic criteria from the *7th version of the guidelines on the Diagnosis and Treatment of COVID–19* by the National Health Commission of China. All the raw clinical and laboratory results were collected from the electronic medical records system of the Central Hospital of Wuhan, followed by a follow up visit up to 14 days (also known as the discharge quarantine) to check for a re-positive nucleic acid result. All participants signed the informed consent. The study was approved by the ethics committee of the Central Hospital of Wuhan and was performed in accordance with the principles of the Helsinki Declaration II.

Data collection

All 267 patients enrolled in the study were from different COVID–19 units of the Central Hospital of Wuhan. All COVID–19 tests were performed by different departments of the Central Hospital of Wuhan. Computer Tomography (CT) scan evaluations were made by at least 2 specialists from the radiology department. The SARS-CoV–2 nucleic acid RT-PCR test quality control was performed by specialists from the clinical laboratory department. The clinical data included: the demographic descriptions, main symptoms, comorbidities, changes of laboratory results, main treatments, etc. For privacy reasons, the raw data of these patients are not presented. However,

Clinical definition

COVID–19 diagnosis was made by detecting SARS-CoV–2 RNA in nasopharyngeal swabs after each patient's attendance to hospital. The RNA detection kits were provided by Sansure Biotech (Changsha, China) and ZJ Bio-Tech (Shanghai, China), manipulated by specialized clinical laboratory technicians according to the manufacturer's protocol.

The severity of COVID–19 patients was defined according to the 7th version of the *Guidelines on the Diagnosis and Treatment of COVID–19* by the National Health Commission of China. Briefly,

(1) mild type: mild clinical symptoms without any radiology findings; (2) general type: limited clinical symptoms, like fever, cough and other common pneumonia related symptoms with radiological abnormality; (3) severe type: patients have any of the following items: (a) respiratory distress, respiratory rate ≥ 30 per min; (b) oxygen saturation on room air at rest ≤ 93%; (c) partial pressure of oxygen in arterial blood / fraction of inspired oxygen ≤ 300 mmHg; (4) critical type: patients have any of the following items: (a) respiratory failure occurs and mechanical ventilation is required; (b) shock occurs; (c) patients with other organ dysfunction needing intensive care unit monitoring treatment.

COVID–19 patients could be considered discharged when they meet all the criteria from the 7th version of the *Guidelines on the Diagnosis and Treatment of COVID–19* by the National Health Commission of China. Briefly, (1) normal body temperature for more than 3 days; (2) significantly recovered respiratory symptoms; (3) lung imaging shows obvious absorption and recovery of acute exudative lesion; (4) negative results of the nucleic acid tests of respiratory pathogens for consecutive two times (sampling interval at least 1 day).

Definition of "re-positive": when a confirmed CPVID–19 patient is detected SARS-CoV–2 RNA positive during the 14 days post-discharge quarantine (random test timing).

Laboratory confirmation and treatment

All the laboratory results were double checked by at least 2 specialists from the clinical laboratory medicine department. The hospitalized patients were tested for SARS-CoV–2 RNA every 24–72 hours before discharge. The brief indications for corticosteroid utility(intravenous injection) are described as follow: (1) respiratory distress, respiratory rate ≥ 30 per min; (2) deteriorations on radiology results after initial treatments; (3) oxygen saturation on room air at rest ≤ 93%.

Statistics analysis

Continuous variables are presented as median (interquartile range, IQR) and categorical variables as n (%). Differences in clinical characteristics and laboratory findings between groups were compared by using the Mann–Whitney U test (continuous variables) and the chi-squared test or Fisher's exact test (categorical variables). All analyses were performed by using R software (The R Foundation, http://www.r-

project.org, version 3.6.1). A two-sided significance level of 0.05 was used to evaluate statistical significance.

Results

Demographic features and clinical symptoms

267 COVID–19 patients of the Central Hospital of Wuhan from January 2 to February 15, 2020 were enrolled in the present study. 30 out of 267 COVID–19 patients (Table 1) were detected 're-positive' during the post-discharge quarantine. The demographic characteristics were found not associated with 're-positive' rate. Common symptoms of hospitalized COVID–19 patients, including fever, muscle ache, fatigue, headache, cough, chest tightness, chest pain, and diarrhea were taken into consideration and none of these clinical symptoms could account for the 're-positive' outcome.

Comorbidities and co-infections

Most of the patients (Table 2) had comorbidities such as hypertension (33%), diabetes (17%), chronic kidney disease (2%), lung diseases (7%) and tumor-related diseases (2%). Still, none of these co-morbidities were found to correlate with 're-positive' patients. Furthermore, common co-infections (i.e. mycoplasma, chlamydia and other respiratory virus- Table 2) detected at admission or during hospitalization, were also found to have no correlation with 're-positive' outcomes (Table 2).

Treatments and severities

According disease severity, different treatment plans were adopted, such as antibiotics including quinolone and cephalosporins; antivirus including ribavirin, oseltamivir, abidor and lopinavir/ritonavir. Methylprednisolone, intravenous gamma globulin (IVIG), ventilation were selectively utilized. No significance differences in treatments modalities, comparing with the re-positive patients (Table 3) were observed. However, severity of illness (as per classification described above) showed that the 're-positive' patients tend to be severe, along with APACHE II score and CURB–65 score which are all indicators of severities. Similarly, the hospitalization time and whole medical care costs results were consistent (Table 3).

CT scan outcomes

To simplify the CT scan evaluation, all the enrolled patients were divided into three group. 1: lesions present in 0%–30% of the bilateral lung field; 2: 31%–60%; 3: more than 61%, respectively. CT scan outcomes were found statistically insignificant (Table 4). The representative CT scan developments of both re-positive and non-re-positive patients are shown in Figure 1.

Laboratory results

Routine blood tests, other blood biochemistry and blood gas analysis results at day 1, day 3, day 7 and day14, are presented in Table 5. No statistically differences were identified in ‘re-positive’ patients.

Follow-up survey

To further evaluate the recovery of COVID–19 patients, a phone follow-up visit was set up with each patient, focusing on the incidence of clinical symptoms (Table 6). Results showed that many patients still had subsequent symptoms, including coughing (21%), phlegm (13%), palpitate (34%), chest tightness (25%), paracenesthesia (12%) and fatigue (48%). Moreover, 9 out of 30 >‘re-positive’ patients spent their quarantine in home with family, and no infected case by them have been reported so far.

Discussion

Since the outbreak of the COVID–19 crisis in late 2019, millions of people have been diagnosed all over the world. Fortunately, the majority of hospitalized COVID–19 patients have been successfully discharged. However, many studies have reported that those discharged from hospital could be tested viral nucleic acid positive again [2–5], arising the possibility of a potential re-infection.

Results in this study showed that ‘re-positive’ patients do not show any distinguishing clinical markers, except the illness severity, casting a shadow on the existence of such a special group of patients.

What was accepted by all researchers was that the sensitivity of many viral RNA detection kit currently in use could be relatively low and was affected by many factors (e.g. quality control of the kits, quality and delivery method of the samples, etc) [6]. Xiao and colleagues found this re-positive phenomenon could possibly be resulted from the false-negative of RT-PCR, and they did observe that a certain number of patients had a prolonged viral RNA conversion time [7]. Their results were consistent with ours in that the re-positive patients might not exist as a special group but appeared due to some technical reasons. Moreover, Yuan and colleagues retrospectively studied 25 re-positive COVID–19 patients in Shenzhen, China and suggested the results of viral nucleic acid by RT-PCR were fluctuated and unstable, even if the patients could have negative results of the nucleic acid tests of respiratory pathogens for consecutive two times before discharge [8]. This study also suggested that the re-positive phenomenon could be a technical bias rather than an existing patient group.

Besides the possibility of false-negative results from RT-PCR, sample selection and collection could also lead to the ‘re-positive’ samples detection. For instance, the sample (nasopharyngeal swab) that is collected might have less virus load compared to other lower respiratory tract samples (e.g. alveolar lavage fluid), leading to an unreliable RT-PCR result. Efficient virus load could be key to have positive RT-PCR results, however, SARS-CoV–2 binds to ACE2 receptor which are mainly located in lower respiratory tract rather than upper [9]. Furthermore, even though samples are collected properly resulting in positive

results, it could potentially not prove that patients are infective, as only those who can transmit live virus are supposed to be defined as infective patients [10].

Some researchers argued that the use of corticosteroid may have potential risks, as it could suppress our immune functions, decreasing the ability of viral clearance [11]. Theoretically, this could be a reasonable hypothesis, accounting for the occurrence of re-positive cases, however, in the present study, the use of corticosteroid did not give rise to 're-positive' patients, consistent with previous work by Lan [2].

Lan and colleagues found those 're-positive' patients to be younger with a shorter hospitalization time and shorter seroconversion. However, in the present study, the opposite was found. Specifically, 're-positive' patients tend to be severe cases, with higher APACHE II score, CURB–65 score and longer hospitalization time.

Some limitations of the present study merit consideration. Firstly, no mild case were enrolled in this study due to different local medical care policies. Specifically, Wuhan was the first city in China with the COVID–19 outbreak, and had largest cases patients in the country. To increase the medical care efficiency, many Fangcang shelter hospitals were created for mild COVID–19 cases [12]. Therefore, the Central Hospital of Wuhan, as a large general hospital, mainly dealt with patients ranging from moderate to critical level. Additionally, at the beginning of COVID–9 outbreak in Wuhan, every large general hospital was overloaded, which may have resulted in an imperfect quality control of sample collection and delivery. Consequently, patients enrolled in this study are different to previous published result by Lan, which may lead to bias. Moreover, in Lan's study, the severity type of their enrolled patients are different from ours as most of the COVID–19 patient in their study are general cases which may also cause bias. Additionally, a novel pathogen as SARS-CoV–2 is, it currently not certain that what, the virus itself or the excessive immune reaction, account for the severity of patients. Therefore, it remains possible those severe and critical patients have higher viral loads and longer clearance time. More researches regarding this problem are necessary. Furthermore, this study is a single-center, retrospective study with limited participants, therefore, more prospective clinical researches are needed.

Some researchers hypothesized that the re-positive cases could be a virus re-infection[13]. Immunologically speaking, after the acute infection of the SARS-CoV–2, the human body could generate specific neutralizing antibodies against this virus for at least 7 days [14]; furthermore a recent animal experiment in rhesus macaque indicated re-infection phenomenon would not happen [15]. These result are in line with other studies on severe acute respiratory syndrome (SARS)[16] and middle east respiratory syndrome (MERS)[17], as these three different viruses are all members of corona virus family, sharing many common features.

In conclusion, in the present study, 30 're-positive' COVID–19 patients were compared to 237 non-'re-positive' patients, showing no significant differences between these two groups based on clinical characteristics, but correlated to illness severity. Up to now, no evidence indicates 're-positive' patients are still infective, and those who have close contacts with 're-positive' patients are currently safe, but follow up studies are in progress.

Still, since understanding of the mechanisms of SARS-CoV–2 is lacking, a careful discharge protocol should be applied (e.g. negative results of the nucleic acid tests of respiratory pathogens for 3 consecutive times), and the post-discharge quarantine should be strictly observed, especially those COVID–19 patients in severe and critical groups.

Declarations

Acknowledgement

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Notes

To fight against this viral crisis together, emails for more details of our data with reasonable requests to corresponding authors are welcomed, and we will make responses accordingly.

Disclosure

The authors report no conflicts of interest in this work.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

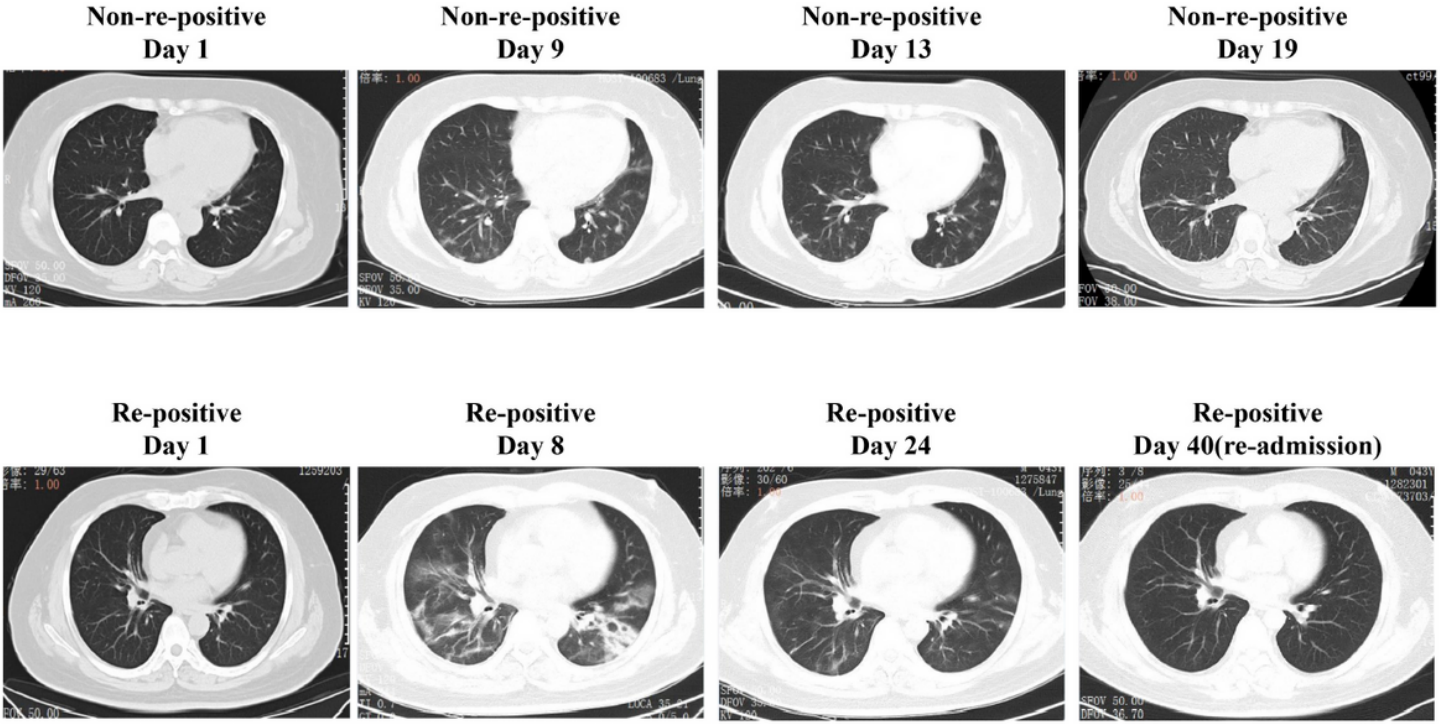

Figure 1

CT scan of representative patients in both non-re-positive patients and re-positive patients. Non-re-positive patients: Female, 61yo, few ground-glass opacity in bilateral lung field at day 1. Deterioration occurred subsequently(day9), and those lesions were absorbed in the following week(day 13 and day 19), accompanied by symptoms relief. Re-positive patient: male, 42yo, few ground-glass opacity in bilateral lung field at day 1. Deterioration occurred subsequently(day 8), and those lesions were absorbed in the following week(day 24), accompanied by symptoms relief. The lung lesions in CT scan were almost absorbed when found re-positive(day 40), without any recurrence of clinical symptoms.

Supplementary Files

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- Tables.pdf