Epidemiological and clinical characteristics of 26 asymptomatic SARS-CoV-2 carriers

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Brief

The asymptomatic SARS-CoV-2 carriers are important potential infection sources of COVID-19 and may have a long carrying period of SARS-CoV-2. Patients with normal chest CTs had a shorter period from diagnosis to being SARS-CoV-2-negative than those with typical CT changes.

Abstract

Background We retrospectively analysed 26 persistently asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carriers. **Methods** Epidemiological and clinical characteristics from the 26 asymptomatic patients with positive results for SARS-CoV-2 RNA testing were obtained. **Results** Twenty-two patients (84.6%) correlated with clustering occurrence. The median period from contact to diagnosis and the last positive nucleic acid test was 19 (8–24 days) and 21.5 days (10–36 days), respectively. The median period from diagnosis to negative nucleic acid test was significantly different between patients with normal or atypical chest computed tomography (CT) findings (n=16, 61.5%; 7.5 days [2–20 days]) and patients with typical ground-glass or patchy opacities on CT(n=10, 38.5%; 12.5 days[8–22 days]; P<0.01). Seven patients (70.0%) with initial positive nucleic acid test results had a negative result simultaneously with improved CT findings. Obvious improvement in CT findings was observed in three patients (30.0%) despite positive nucleic acid test results. **Conclusion:** In asymptomatic patients, changes in biochemical and inflammatory variables are small and changes on chest CT can occur. It is worth noting the long existence of SARS-CoV-2 in some asymptomatic patients and false-negative results need to be considered in SARS-CoV-2nucleic acid test.

Key words: Coronavirus Disease 2019; Severe Acute Respiratory Syndrome Coronavirus 2;

asymptomatic; clinical characteristics

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causation agent of a novel respiratory infectious coronavirus disease (termed COVID-2019), which has disseminated quickly among people. Since its initial outbreak in Wuhan, China was reported in December 2019, there have been 1279722 cases worldwide up to April 7, 2020[1, 2]. COVID-19 is highly contagious with rapid transmission, and people are general susceptible to this new coronavirus.

Patients with SARS-CoV-2 infection may show COVID-19-related symptoms. Asymptomatic carriers have also been found[3]. For instance, there are reports documenting a substantial fraction of truly asymptomatic individuals with COVID-19 from the Diamond Princess Cruise ship (approximately 18%) and Japanese evacuees out of Wuhan[4, 5]. There are a few other case reports in various journals in Table 1[3, 6-10]. These reports mainly focus on the estimated asymptomatic proportion, mode of transmission, some radiological findings, and solutions to identify and isolate asymptomatic patients. Emerging evidence suggests that patients with clinical manifestations are contagious, with analysis of their clinical characteristics[11, 12]. However, there are few studies reported the epidemiological and clinical characteristics of asymptomatic patients. A few studies have described the clinical characteristics of asymptomatic patients, but some of the asymptomatic patients in these studies were asymptomatic at the time of diagnosis but later developed symptoms, so they cannot truly represent the clinical characteristics of asymptomatic patients[13, 14]. Here, we identified a total of 26 persistently asymptomatic patients with positive test results for SARS-CoV-2 nucleic acid to determine the clinical characteristics and asymptomatic carrier transmission of COVID-19 infection.

Methods

Study design

A total of 26 hospitalized patients with a SARS-CoV-2 epidemiological history and positive SARS-CoV-2 nucleic acid test results were identified to analyze the epidemiological and clinical characteristics of COVID-19-infected asymptomatic carriers. These patients' sputum and throat swab were sampled for SARS-CoV-2 confirmation and tested using reverse transcription polymerase chain reaction (RT-PCR). An epidemiological history was defined as a close contact with a diagnosed or possible case of COVID-19 or had a history of residence in or travel to Wuhan. Informed consent was obtained from each registered patient and this study was reviewed and approved by the Medical Ethics Committee of Zhengzhou University.

Data collection

Detailed information regarding the epidemiological history and information of other family members of each patient was obtained. We also collected information regarding patient age, sex, previous medical history, clinical manifestations, laboratory tests, chest computed tomography (CT) scans, treatment measures, and prognosis.

Statistical analysis

Normally distributed continuous variables are presented as mean ± standard deviation (SD) and were compared using the t-test. Non-normally distributed data are described as the median and were analyzed using the rank sum test of two groups. Categorical variables are show as percentages. All statistical analysis was performed using the SPSS software version 22.0.

Results

Basic information

A total of 26 patients with asymptomatic SARS-CoV-2 infection were collected in this study, of whom 16 (61.5%) were men and 10 (38.5%) were women. The median age was 29.5 years (2 to 80 years) and the age of 18 patients (69.2%) ranged from 20 to 60 years. Two patients had a history of smoking (both for over 20 years), with an average of 20 cigarettes per day. Two patients had a history of hypertension and one had coronary heart disease.

Epidemiological history

Regarding the source of the infection, six patients (23.0%) has a history of travel to Wuhan, with no clear contact with a source of infection. Exact contacts with confirmed or possible patients were found in eighteen cases (69.2%), and the contact history was unknown in two patients (7.8%). Among patients with a clear source of infection, 10 cases (55.6%) had previously talked to or had a meal with a confirmed COVID-19 patient, and eight cases (44.4%) lived with a confirmed patient. The sources of infection in these cases included confirmed patients with clinical symptoms (n=16, 88.8%), a possible COVID-19 patient with clinical symptoms (n=1, 5.6%), and a confirmed patient without clinical symptoms (n=1, 5.6%). In addition, 22 cases (84.6%) were

found to be correlated with a local cluster. The close contacts of these 26 enrolled patients were traced, and only two SARS-CoV-2-infected patients were identified.

In the six patients with a recent history of travel to Wuhan, the median period from leaving Wuhan to a COVID-19 diagnosis was 15 days (14-19 days). In 18 patients with a clear source of infection, the median period from contact with a confirmed or possible case to the confirmed to diagnosis was 19 days (8–24 days). This period was longer than 14 days in 14 cases (77.8%) and over 20 days in four cases (22.2%) (Figure 1).

Laboratory examinations

The initial leukocyte counts were slightly lower than the normal value in two patients, slightly higher in one patient, and normal in the other patients. The lymphocyte count was normal in 26 patients. Regarding coagulation function, there was an elevated platelet count in four patients, higher prothrombin time in one patient, and increased D-dimer in four patients. Procalcitonin was slightly elevated in three cases, all of which were less than 1 ng/ml, and C-reactive protein was normal in 26 patients. Additionally, investigations revealed three patients with reduced albumin, four patients with mildly abnormal transaminase, and two patients with slightly elevated creatinine levels. Five patients had slightly lower serum sodium concentration and one patient had higher serum potassium concentration. Lactate dehydrogenase and creatine kinase levels were slightly elevated in three patients and one patient, respectively. There was no statistical significance between the initial and following results for all the above indicators ($P>0.05$).

Nucleic acid result change

Being SARS-CoV-2-free was defined as two consecutive negative nucleic acid results with an interval of at least 24 hours. The period from diagnosis to being confirmed SARS-CoV-2-free was 10 days in 15 patients, 20 days in 23 patients, and more than 20 days in three patients (20 days, 20 days, and 22 days, respectively). The exact time of contact with a confirmed or possible COVID-19 case was clear in 18 patients. The median period from contact to the last positive COVID-19 nucleic acid test was 21.5 days (10 to 36 days) and in four patients this was over 30 days. In a case originating from Wuhan, the period from leaving Wuhan to the last positive COVID-19 nucleic acid test was 35 days (Figure 1). There were positive test results for SARS-CoV-2 following a negative result in two patients. In particular, in one patient, the SARS-CoV-2 nucleic acid tests repeatedly had positive and negative results (Figure 1).

Chest CT characteristics

Chest CT scans were performed an average of 3–4 days after the initial CT examination and each patient had at least two CT scans. The results of the first CT scan of the 26 patients were as follows: nine patients (34.6%) with normal CT scans, 10 patients (38.5%) with typical manifestations (patch-like, ground-glass opacities distributed in the extrapulmonary zone), seven patients with changes in a unilateral lung, and three patients with changes in bilateral lungs. In seven patients (26.9%), CT scans showed atypical CT manifestations (chronic inflammation and small cord shadows), including a small strip shadows in three patients (11.5%), small nodular shadows in one patient, thickened bronchial vascular bundles in two patients, and a small manifestation of chronic inflammation in one patient.

In patients with normal CT scans on admission, the chest CT manifestations did not significantly change during hospitalization and seven patients with atypical CT manifestations also showed no significant changes on chest CT scans. For patients with typical chest CT manifestations, improved chest CTs were observed in seven patients and three patients showed improvement after an initial progression of lesions (Figure 2).

Correlations between SARS-CoV-2 nucleic acid changes and chest CT changes

Patients with normal or atypical chest CT findings had a relatively short period from diagnosis to continuous negative COVID-19 nucleic acid results, with a median period of 7.5 days (2–20 days). In patients with typical patchy or ground-glass opacities, the median period was 12.5 days (8–22 days). This difference was statistically significant ($P < 0.01$). Of the 10 patients with typical chest CT manifestations, seven patients showed improved chest CT results that synchronized with the negative SARS-CoV-2 nucleic acid test result, while three patients had a marked improvement in CT results without a negative SARS-CoV-2 nucleic acid test result.

Evidence of dissemination from SARS-CoV-2 carriers

Evidence 1: Case 1 was a 30-years-old man who lived in Wuhan, Hubei for a long time. After returning home from Wuhan on January 23, 2020, he lived with his wife, children and father. His nucleic acid test was positive on February 11, 2020, but there were no clinical symptoms. His chest CT scan showed a few chronic inflammatory changes that were not correlated with COVID-19 infection. His wife, child, and father were examined. Both the wife and child had negative nucleic acid test results. However, his father (case 2) had a positive nucleic acid test result, with no symptoms and no abnormalities in chest CT. Except for case 1, case 2

had no history of contact with any other confirmed or possible COVID-19 patients over the previous 14 days (Figure 3).

Evidence 2: Case 3 was a 25-years-old man who lived in Hubei for a long time. He returned home on January 20, 2020, and then lived with his father and mother. The patients had no history of contact with any confirmed or possible COVID-19 patients in the 14 days before diagnosis. On January 25, his mother began to have fever, cough, and chest tightness. Three days later, on January 28, his father began to have fever, cough, sputum, and sore throat. The patients had positive nucleic acid test results on February 3. After the parents were diagnosed, Case 3 was hospitalized and isolated for inspection. Case 3 experienced no clinical symptoms throughout this period, while his nucleic acid test result was positive on February 4 and his chest CT showed a slightly increased density in the basal segment of the lower left lung (Figure 4).

Treatment strategy

All patients were isolated and treated with one or more antiviral drugs. Recombinant human alpha-1b interferon nebulized inhalation (5 million U bid for adults and 3 million U bid for children) was administered in 25 cases. Twenty-two patients received oral lopinavir/ritonavir (400 mg/ 100 mg bid for adults, 200 mg/ 50 mg qd for children). Five adult patients were treated with oral arbidol (200 mg tid) and one patient developed purulent tonsillitis during hospitalization and was treated with antibiotics.

Prognosis of asymptomatic COVID-19 patients

One patient developed nausea during hospitalization, which may have been caused by lopinavir/ritonavir. Another case developed a transient fever, which was related to suppurative tonsillitis. This patient felt better after antibiotic treatment. Neither of the two symptoms was associated with SARS-CoV-2 infection. The remaining cases were asymptomatic during hospitalization. Discharge criteria for COVID-19 were as follows: 1) normal body temperature for more than 3 days; 2) significantly improved respiratory symptoms; 3) significantly improved chest radiography; and 4) two consecutive negative SARS-CoV-2 nucleic acid test results (sampling interval at least 1 day). All 26 patients were discharged from the hospital. The period from admission to discharge was ranged from 10 to 24 days, with a median of 13 days.

Discussion

SARS-CoV-2, a new coronavirus that recently appeared, has rapidly spread across many countries and regions around the world. This new coronavirus is reported to be more contagious than atypical pneumonia (SARS) and Middle Eastern respiratory syndrome coronavirus (MERS) [15-17]. COVID-19 is mainly seen a mild to moderate conditions, with a mortality rate of 3.2%[11]. Isolating sources of infection is an important measure to control this current epidemic[2, 18]. Infected individuals with clinical symptoms can be tracked according to their clinical symptoms, while those who are asymptomatic, especially those without an epidemiological history, are difficult to track. These asymptomatic cases may also capable of transmitting SARS-CoV-2, which could cause difficulties in COVID-19 prevention and control. At present, there are few studies of asymptomatic disease, most of which focus on the proportion of asymptomatic patients and the evidence of asymptomatic transmission. The description of clinical features of asymptomatic patients is technically a description of asymptomatic disease at the time of diagnosis, with some patients going on to develop symptoms. There is also little research on asymptomatic epidemiology. The infectiousness and effect of the asymptomatic epidemiological characteristics and disease clinical characteristics of dynamic change are not clear. Therefore, this study focused on persistently asymptomatic cases of COVID-19.

By tracing and isolating the contacts of people who were diagnosed or possible COVID-19 patients, this study identified a total of 26 asymptomatic patients. Asymptomatic carriers were found to be of any age, mainly concentrated in the 20–60 years age range and are characterized by local clusters. Disease transmission from two asymptomatic patients was included in this study. Infected patients may have clinical symptoms or may be asymptomatic. The study found that asymptomatic cases were mostly infected by symptomatic patients and a few were infected by asymptomatic patients. Only two asymptomatic of the 26 enrolled asymptomatic patients infected others. Therefore, we speculate that asymptomatic carriers may be less infectious than symptomatic patients.

In asymptomatic carriers, there was a long period between contact with the infection source to diagnosis, with a median of 19 days. These asymptomatic carriers were identified only when they contacted diagnosed or possible COVID-19 patients, suggesting the difficulty in detecting these asymptomatic carriers. The period from diagnosis to negative nucleic acid test tests was within 20 days for 23 (88.5%) patients (Figure 1). The duration of SARS-CoV-2 infection in asymptomatic patients is unclear. The median period from contact with diagnosed or possible cases to the last positive nucleic acid test was 21.5 days (10–36 days). Most patients will miss the

real last positive assays since nucleic acid tests for SARS-CoV-2 were not performed every day, so this time might be shorter than the actual time. The period was longer than 30 days in four patients, of whom one patient talked with a COVID-19 patient for 1 hour, without contact with any other confirmed or possible patients contacted, 35 days previously (Figure 1). In addition, this period of 35 days was for a patient with a Wuhan-related history (Figure 1). Therefore, asymptomatic patients may carry SARS-CoV-2 for more than one month, suggesting that this virus is carried in asymptomatic patients for a long period.

In two patients, there was a positive nucleic acid test after an initial negative result and one patient had recurrent alternation of positive and negative results. This phenomenon may be caused by false-negative results of assays and detection can be affected by factors including the specimens, reagents, and operations. Thus, positive nucleic acid tests cannot be used as the only criterion for COVID-19 diagnosis. Standardized operation and repeated verifications are required to improve the positive rate. Patients with normal chest CTs had a shorter period from diagnosis to being SARS-CoV-2-negative than those with typical CT changes. In some patients, conversion of nucleic acid test results from positive to negative was synchronized with an improvement in chest CT findings, but this change may also occur later than the improvement on CT. Therefore, CT improvement cannot be used to indicate that a patient is not infectious.

Indices of blood cell counts, liver and renal function, and inflammation in asymptomatic patients did not change significantly during the disease. Reduced lymphocyte and leukocyte counts are characteristics of clinically symptomatic COVID-19, but these changes were not common in the asymptomatic patients in this study. Chest CT in asymptomatic patients can be normal or present with typical ground-glass opacities, usually limited to a unilateral lung but sometimes occurring in bilateral lungs. Three patients with asymptomatic infections developed lung infections during treatment and then improved. Although these asymptomatic patients appear normal, some relatively light damage may have already been produced.

This study also has some limitation. For example, only 26 patients were included in this study. In addition, this retrospective analysis did not include daily nucleic acid tests for SARS-CoV-2. Large-scale prospective studies are needed to validate our findings.

In summary, asymptomatic infections can occur at any age and appear to be correlated with local clusters of diseases. Asymptomatic transmission may be less contagious but should still be recognized as an infection source for COVID-19 transmission. There were no significant changes in the biochemical and inflammatory variables in these patients. However, changes on chest CT may occur in these patients. It is necessary to note

that SARS-CoV-2 can be present for a long time in some asymptomatic patients; the change in nucleic acid test results from positive to negative in some patients may not occur synchronously with the CT improvement; and false negatives of the nucleic acid test for SARS-CoV-2 may occur.

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Table 1. Asymptomatic cases reports in various journals

Journal	Research Focus	Location	Reference
N Engl J Med	Transmission of 2019-nCoV Infection From an Asymptomatic Contact	Germany	Camilla Rothe, et.al[3]
BMJ	Identifying and Isolating Asymptomatic People	Italian Village	Michael Day[6]
Lancet Infect Dis	Radiological Findings in Both Symptomatic and Asymptomatic patients	Wuhan, China	Heshui Shi, et.al[7]
J Nucl Med	Nuclear Medicine Services in Asymptomatic Patients	Brescia, Italy	Domenico Albano, et.al[8]
Lancet Infect Dis	Asymptomatic cases in a family cluster with SARS-CoV-2 infection	Guangdong, China	Pan X,et al[9]
Int J Infect Dis	Delivery of infection from asymptomatic carriers of COVID-19 in a familial cluster	Chengdu, China	Ye F,et al[10]

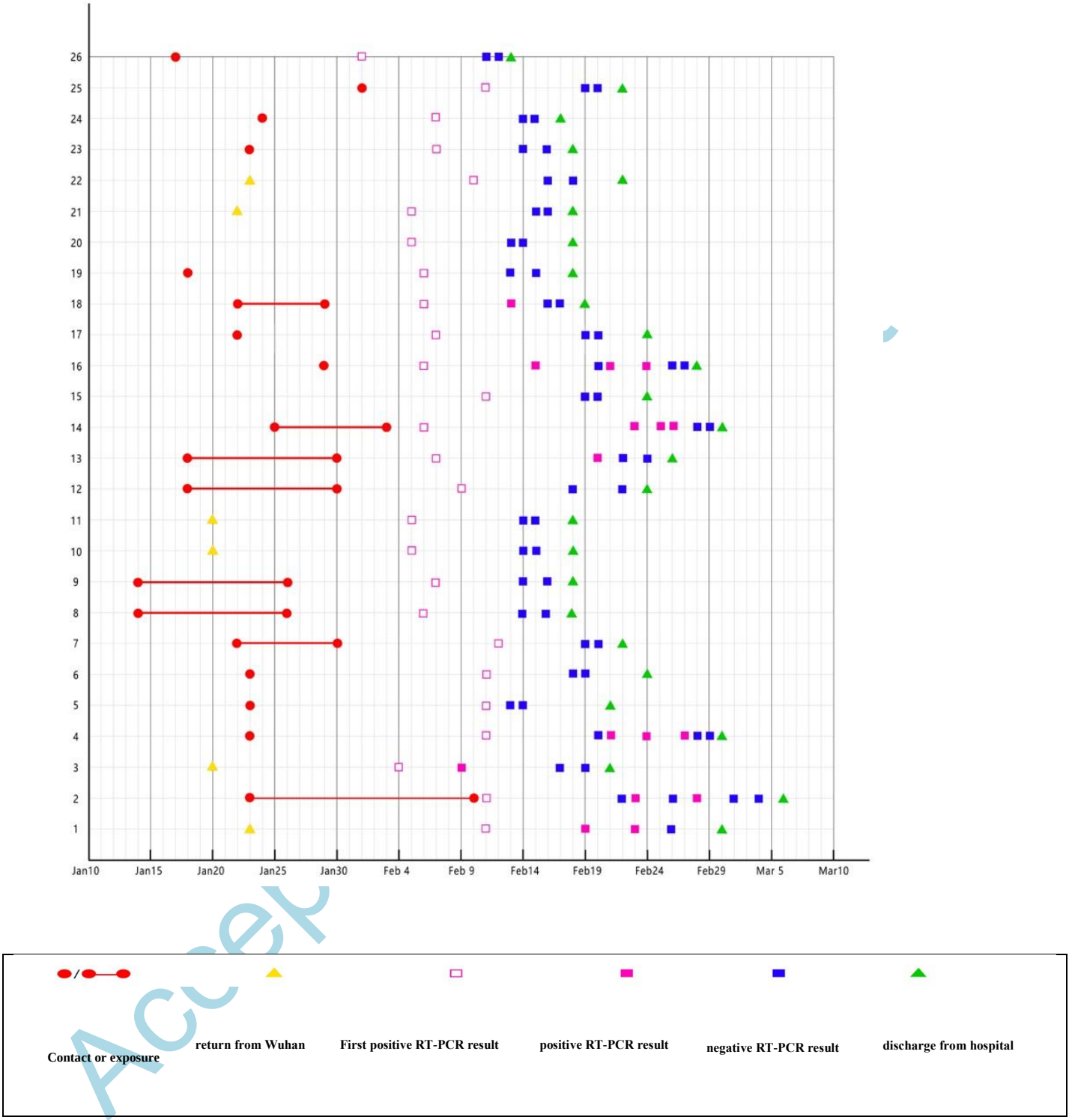

Figure.1 Timeline of 26 asymptomatic SARS-CoV-2 carriers (from contact with or exposure to the infection source/ return home from Wuhan to discharge from hospital)

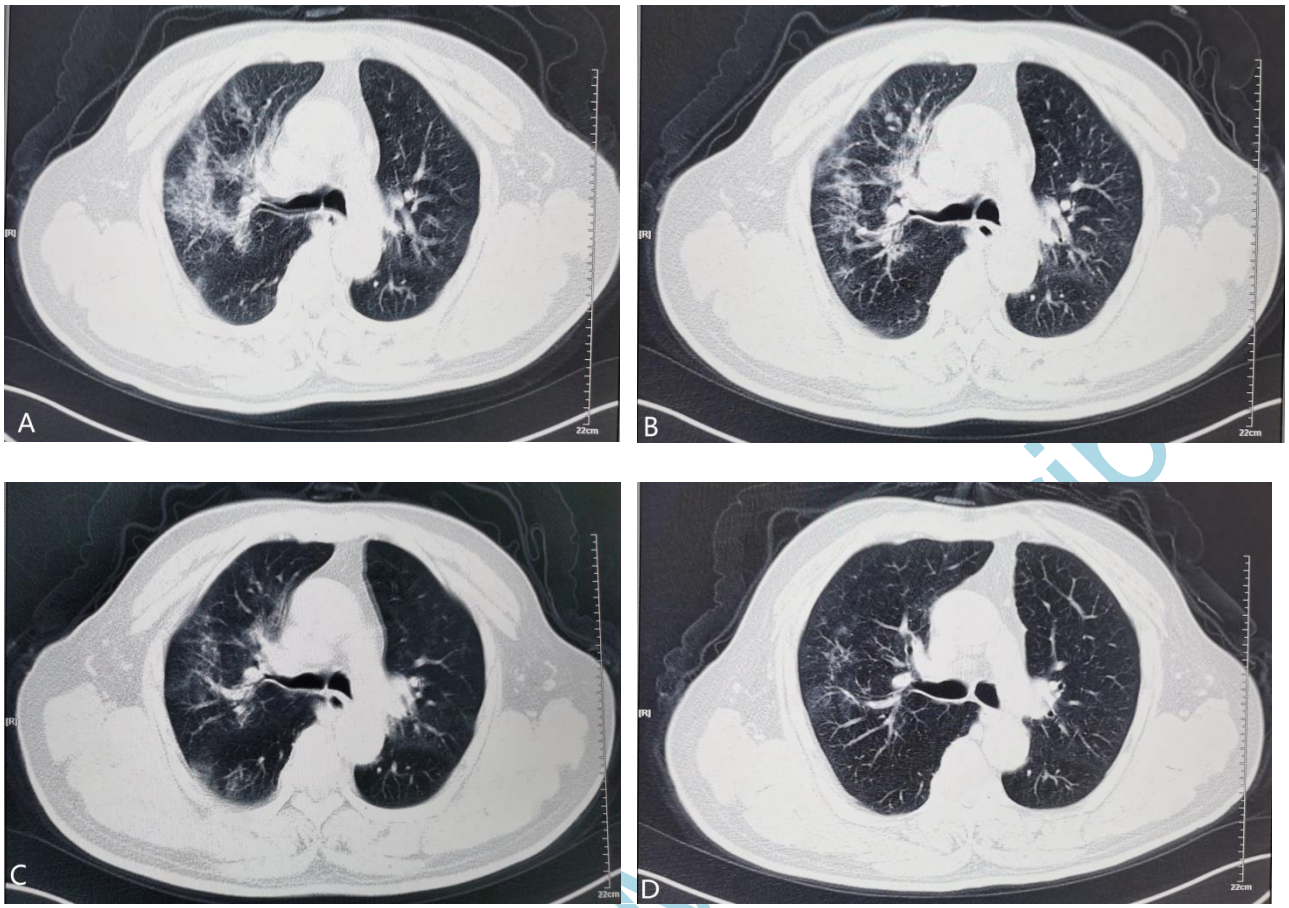

Figure.2 Chest CT changes from admission to discharge in case 14

Multiple patchy ground glass opacities can be seen in the right lung on February 6. The infection progressed more than before on February 11. On February 16, the signs of viral pneumonia in the right lung improved slightly, and on February 26, the chest CT improved.

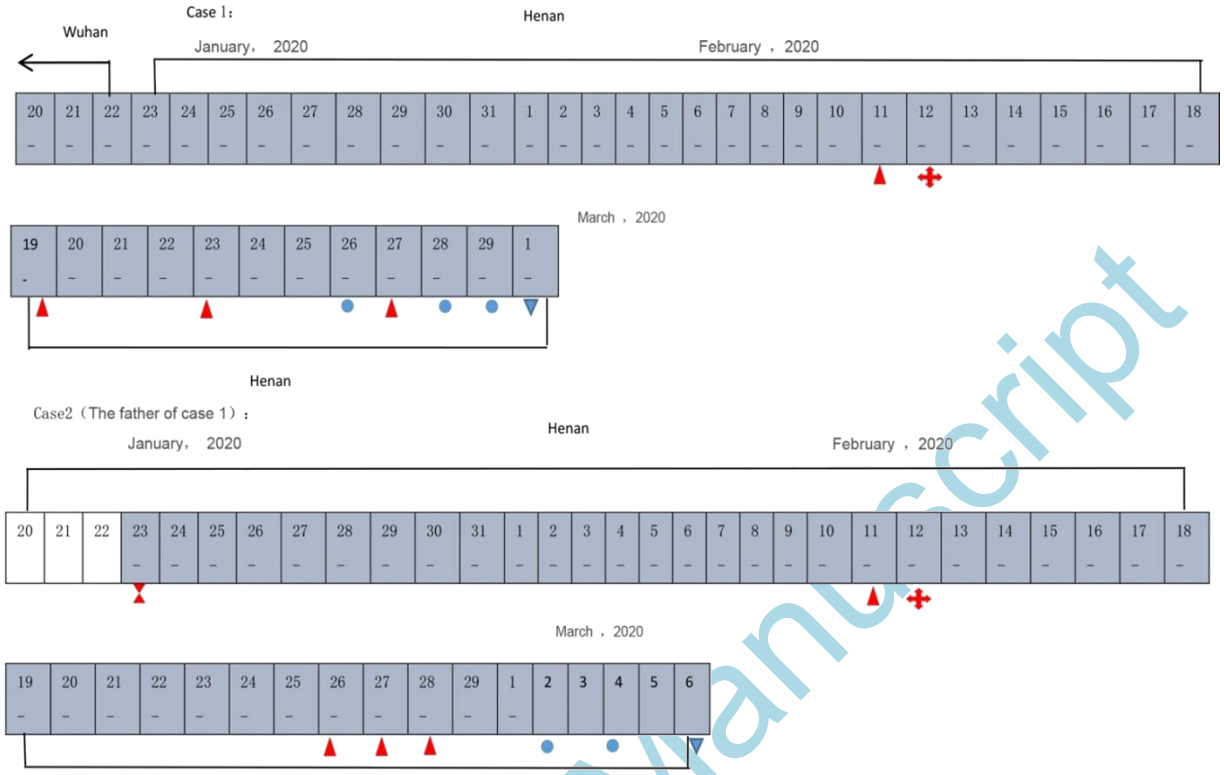

Figure.3 Transmission evidence of SARS-CoV-2 carriers 1

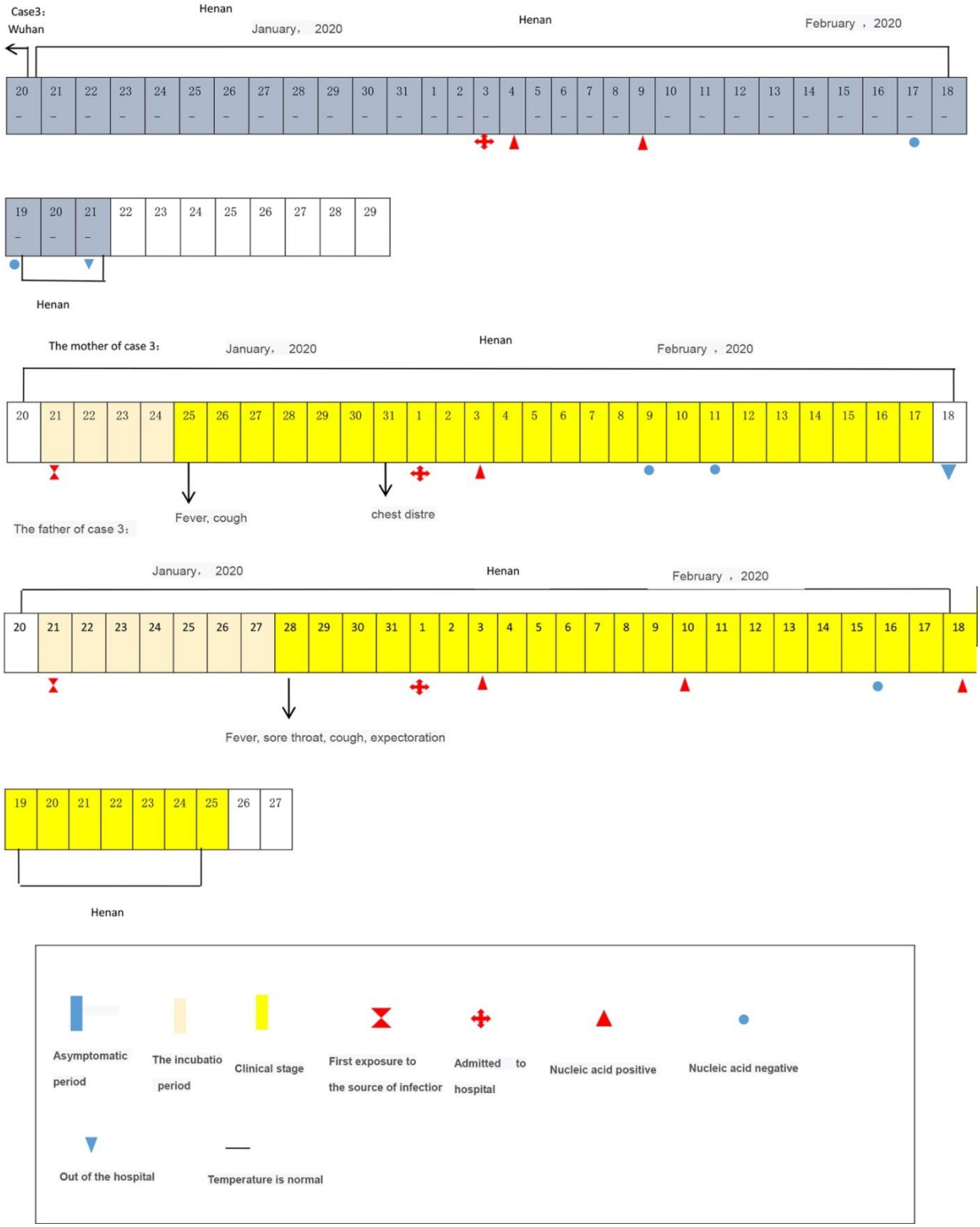

Figure.4 Transmission evidence of SARS-CoV-2 carriers 2