Clinical Characteristics, Serological and Radiological Longitudinal Changes of Patients With COVID-19

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Research article

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Abstract

Background Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) that began in Wuhan and rapidly spread globally. The speed and scope of spread of COVID-19 makes urgent of the defining clinical characteristics, serological and radiological changes of the affected patients. Method 7 patients with laboratory-confirmed COVID-19 who admitted to the Third affiliated hospital of Sun Yat-sen university Yuedong hospital from January 2020 to March 2020 were retrospectively enrolled and their clinical features, serological and radiological longitudinal changes were analyzed. Results Among the 7 patients, all (100%) had a clear epidemiological history. The most common symptoms were respiratory symptoms 6 (85.7%), and only 2 (28.6%) of the patients had fever at their first visit. The cohort included 4 (57.1%) common types and 3 (42.9%) severe types. Two (28.6%) common types patients developed to severe type in a short time. All of the 7 patients (100%) had abnormal liver function, normal renal function and normal procalcitonin. The detection time of specific antibody in 7 patients was 5~13d after symptoms. Before the specific antibody could be detected, the absolute value of lymphocytes decreased in 2 (28.6%) common type cases transferred to severe type cases accompanied with obvious progress in pulmonary imaging, and the phenomenon of decreased albumin and elevated globulin occurred in 6 patients (85.7%). The predominant pattern of lung lesions observed was bilateral (71.4%) and mainly near the pleura at the first diagnosis. Bilateral pulmonary involvement occurred in 6 cases (85.7%) during the course of disease. In 4 cases (57.1%) with obvious pulmonary lesions, the absolute value of lymphocytes decreased, albumin decreased and globulin increased during the course of the disease. Conclusion Serum specific antibodies can be detected within 2 weeks of onset. Close observation of the dynamic changes of absolute value of blood lymphocytes, serum albumin and globulin which were related to pulmonary imaging changes in patients will contribute to assessment of COVID-19.

Background

An outbreak of coronavirus disease 2019 (COVID-19) that began in Wuhan, China, has spread rapidly, with cases now confirmed in multiple countries. At present, the COVID-19 epidemic has caused infections in more than 80,000 people across the country, with over 3,000 deaths, suggesting strong human-to-human transmission[1–4]. The World Health Organization (WHO) had declared COVID-19 a public health emergency of international concern[5]. A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV), was identified as the causative organism. SARS-CoV-2 is a β-coronavirus, which belongs to the subgenus Sarbecovirus like severe acute respiratory syndrome (SARS) virus[6]. Both of them enter the human cell through S protein binding to host angiotensin-converting enzyme 2 (ACE2) receptor[7, 8], and the former has stronger binding ability to human ACE2 receptor[9]. COVID-19 epidemic has caused more harm than SARS. The speed and scope of spread of COVID-19 makes urgent of the defining clinical characteristics and severity of the disease. Here, we describe the results of clinical features, serological and radiological longitudinal changes of patients with COVID-19 in Meizhou, China.

Methods

Study design and participants

This was a retrospective analysis study of 7 patients with COVID-19 in the Third affiliated hospital of Sun Yat-sen university Yuedong hospital from January 2020 to March 2020. Covid-19 patients were diagnosed and defined the degree of severity on the basis of the Diagnosis and Treatment of COVID-19 pneumonia (Trial Edition 7)[10] and all cases were later confirmed by real-time RT-PCR analysis. This study was approved by the Third Affiliated Hospital of Sun Yat-sen University Yuedong Hospital (No.2020-01). Written informed consent was waived by the Ethics Commission for emerging infectious diseases. These patients have been included in another study, which has been submitted to medRxiv by us[11]. But the data of this study has not been demonstrated before.

Data source

We extracted the recent exposure history, clinical symptoms or signs, radiological results and laboratory findings. Radiologic assessments included chest radiography or computed tomography (CT), and all laboratory testing was performed according to the clinical care needs of the patient. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, assessment of liver and renal function, and measures of electrolytes, procalcitonin, and serum specific antibody. COVID-19 specific total antibody detection kits (LOT NO: 20200201) were provided by Beijing Hotgen Biotech Co.Ltd, and were used to detect IgM and IgG antibody in serum by colloidal gold immunochromatography according to instruction.

Study Definitions

The incubation period was defined as the interval between the potential earliest date of contact of the transmission source. In our study, the incubation period for patients from the epidemic area was calculated from the day they left Wuhan, China. Fever was defined as an axillary temperature of 37.3℃ or higher. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells per cubic millimeter. The positive time of specific antibody test was the time from the onset of symptoms to the first positive of multiple dynamic serum.

Statistical Analysis

Analyses were performed with SPSS software version 22.0. Normally distributed data were presented as mean (SD), non-normally distributed data as median (IQR), and categorical variables as frequency (%). We used Prism, version 8.3, to plot the absolute value change graph of albumin, globulin and lymphocyte.

Results

Epidemiologic feature

Of the seven patients, 5 (71.4%) were from the epidemic area of Wuhan, 1 (14.3%) had been to Guangzhou, Guangdong Province for the annual meeting who had admitted to contact with the fever patients from Wuhan, and 1 (14.3%) was local resident who had contact with the visit relatives from Wuhan. There were 2 familial clusters of infections. All patients had a clear epidemiological history, and the possible incubation period was 3-14 days (Table 1).The incubation period for patients from the epidemic area was calculated from the day they left Wuhan. Case 1 has developed into COVID-19 during Wuhan, the incubation period was unknown.

Demographic and Clinical characteristics

The patients included 3 males (42.9%) and 4 females (57.1%). The age of patients ranged from 25 to 62 years old and the median age was 41.3 years (SD 14.1). Among the overall population, 3 patients (42.9%) had coexisting illness, one patient (14.3%) with diabetes, one patient (14.3%) with sequelae of cerebral infarction, and one patient (14.3%) with sequelae of infantile paralysis. Of the seven diagnosed patients, 6 (85.7%) had a positive nucleic acid test for the first time and 1 (14.3%) had a positive nucleic acid test for the second time.

Moreover, six of the patients (85.7%) had symptoms of upper or lower respiratory tract, such as cough, sore throat, rhinobyon, sneezing. Two patients (28.6%) had fever, with a body temperature of 37.8°C to 38.4°C. Two (28.6%) patients were accompanied with fatigue. The time from onset of symptoms to hospitalization was 1-8 days. Four cases (57.1%) were common types and three cases (42.9%) were severe types. All of the three severe patients had underlying diseases and the median age was 54.0 years (SD 6.9). Two patients (28.6%) who had mild symptoms, showing only trachyphonia, cough, and discomfort in the pharynx at the first visit were considered as common cases at first. However, after 4 days, they started to have shortness of breath and fever with the lung lesions progressing obviously and the lymphocytes obviously decreasing , which developed into severe cases.

Laboratory findings

The absolute value of lymphocytes was lower than the reference value in 1 case (14.3%) at the first time of hospital visit and in all of 3 severe cases (42.9%) , the absolute value of lymphocytes decreased. All 7 patients (100.0%) had abnormal bilirubin or aminotransferase but normal renal function. PCT increased in none of cases (0%). In 4 patients (57.1%) with obvious pulmonary lesions, a decrease in the absolute value of lymphocytes and an inversion of the albumin and globulin were observed. After reaching its peak, globulin gradually decreased, and lymphocytes gradually increased. The changes of absolute lymphocyte values, serum albumin, serum globulin in the 4 patients were shown in figure 1b, figure 1d, figure 1e, figure 1f. The other detailed were shown in figure 1a-g, the yellow arrow showed the detectable time points for the specific antibody. Seven patients with specific antibody could be detected on 5~13d after onset of symptoms or 2~9d after hospitalization. In 6 cases (85.7%) the decrease of albumin and the increase of globulin were detected before specific antibody could be detected. In our study, the positive time of antibody test was the first positive time of symptom to multiple dynamic serum. Actually, the first positive antibody test of single serum sample in case 2 was the 7th day of hospitalization.

Radiologic findings

All patients had abnormal CT imaging features. At the first diagnosis, 2 cases (28.6%) had unilateral and 5 cases (71.4%) had bilateral lesions. The lesions were single or multiple and mainly near the pleura. A total of 6 cases (85.7%) had bilateral lung involvement and 1 case (14.3%) of unilateral lesion absorption improved. The range of lung lesions was small in case 5 and 6 at first but the progress was obvious within 4 days. CT imaging changes were shown in Fig.2 and 3. When the lung lesions progressed, the decrease of the absolute value of leukomonocyte and serum albumin were accompanied by the increase of serum globulin. The CT scans of case 5 were representative. The right lower lobe lesion consisted of a small, slightly high-density sheet with surrounding blurring, which developed into a large sheet of exudation after 4 days. Later, the exudation gradually absorbed and became high-density of strip shadow, with the surrounding ground-glass opacity appearance.

Treatment and outcomes

The treatment plan was decided by the expert panel every morning after listening to the report from the doctor in the isolation ward combined with laboratory and radiological results. Lopinavi/Rinovir (500 mg, twice daily, orally) combined with Oseltamivir (75 mg, twice daily, orally) were the basic antiviral treatment. If the treatment effect was not satisfied, Oseltamivir was replaced with Abidol (0.2g, three times daily, orally) or Chloroquine Phosphate tablets (0.5g, twice daily, orally). For both common and severe type patients whose imaging showed obvious lung lesions, intravenous injection of human immunoglobulin (20g, once daily), Methylprednisolone (40mg, once daily) and Moxifloxacin (0.4g, once daily) were used to prevent infection. For those with hypoproteinemia were continued to receive nutritional supportive therapy and were given human serum albumin (10 g, once daily) if necessary.

After treatment, in all cases (100%), the clinical symptoms disappeared, the lesions were obviously absorbed, and the pharyngeal swab and fecal nucleic acid were negative for 2 consecutive times (not the same day). These 7 patients were discharged and continued isolation management and health monitoring for 14 days.

Discussion

In this study, the epidemiology, early clinical features, serological and radiologic changes of 7 confirmed patients were summarized, and the clinical evolution of the disease was obtained by analyzing the dynamic changes of laboratory and imaging. Our 7 patients were composed of common and severe type. During the treatment of common type patients, we observed the process of transformation to severe type accompanying serological and imaging changes. Through timely treatment, 3 severe patients were successfully treated. We had observed the complete progress from the normal type to the severe type, and the recovery process of severe type.

All seven patients had a clear history of epidemiology, either from or in contact with people from epidemic areas including 2 family cluster cases. The outbreak was approaching the Spring Festival, the movement

of people accelerated the spread of the epidemic. Timely measures such as "close-off cities" in time, isolating people came back from epidemic areas and reducing the number of residents going out for parties had played an important role in preventing the spread of the epidemic during the Spring Festival.

In terms of clinical features, the main clinical manifestations of 6 patients were respiratory symptoms, most of which were mild. Only 2 cases came to see a doctor because of fever, and monitoring body temperature alone may not be able to discover potential infected patients. Notably, in one case the first nucleic acid test was negative, but positive for the second time. For high-risk groups, re-examination of throat swabs is necessary. The symptoms of two patients were mild and the progression of pulmonary imaging in a short time was obviously, who classified as severe type later. It is necessary to closely observe the common type patients whose clinical symptoms and pulmonary imaging changes are not serious, especially those age older than 50 years with underlying diseases.

Serologically, 7 patients showed no elevation of PCT, whether normal or severe type, mild or severe pulmonary lesions.This finding might be due to COVID-19 as viral infections and the use of antibiotics during treatment to prevent secondary infections

There was no significant change in the absolute count of blood lymphocytes in the common type patients, but the absolute count of lymphocytes in the severe type patients decreased suddenly during the course of the disease, and gradually increased after the improvement of the disease, which was consistent with the report of Liu et al.[12]. Bilirubin or aminotransferase abnormalities were observed in all patients during the course of the disease, which may be caused by drugs or associated with systemic inflammatory responses[13]. The renal function tests of all patients were normal, which was consistent with the report of Wang et al.[14]. In common type and severe type patients, abnormal liver function was common, renal function abnormality was rare, and PCT was normal when without secondary infection. There were individual differences in the absolute count of blood lymphocytes and the changes of serum albumin and globulin. The changes in patients with severe pulmonary lesions (Fig. 1b, 1d, 1e, 1f) were more obvious than those in common type patients (Fig. 1a, Fig. 1c, Fig. 1g). In severe type patients, the absolute count of lymphocytes decreased in the course of treatment, accompanied by the increase of serum globulin and the decrease of serum albumin, and finally serum globulin level exceeded serum albumin, resulting in the phenomenon of A/G inversion. After the serum globulin level reached its peak, serum albumin began to rise and the absolute count of lymphocytes began to rise too. The change of serum albumin and globulin was less likely to be caused by exogenous transfusion of blood products, and this phenomenon was not observed in the treatment of other diseases with high-dose immune globulin[15, 16]. The decrease of serum albumin and the increase of serum globulin were found in 6 cases before the specific antibody could be detected, which may be related to the activated host immune system, resulting in an increased antibody production by B cell and above changes in serology. According to the exclusion criteria of suspected cases in the seventh edition of the national diagnosis and treatment plan, the diagnosis of suspected cases can be excluded if SARS-CoV-2 specific antibodies IgM and IgG are still negative 7 days after onset[10]. In data of our confirmed patients, the time period of the specific

antibody could be detected was 5–13 days after the onset of symptoms, which suggested that the time setting for excluding suspected cases should be different when using different detection kits.

The imaging changes of the lungs in severe patients were dynamic process. The acute exudation of the lungs were associated with the decrease of the absolute count of blood lymphocytes, and the lesions were gradually absorbed and striped after effective treatment. Significantly, acute exudative changes in lung lesions in common type patients developing to severe type were accompanied by a decrease in the absolute count of lymphocytes, which occurs before specific antibodies could be detected. The appearance of specific antibodies may be related to the decrease of the absolute count of peripheral blood lymphocytes and the progress of pulmonary imaging in severe patients. It is necessary to pay attention to whether the antibody dependence enhancement (ADE) effect was exist just as SARS virus. The study of SARS virus found that it could not directly infect lymphocytes which lacking ACE2 receptors, and lymphopenia during the disease process was likely caused by lymphocytes apoptosis or necrosis through indirect mechanisms[17]. In vitro experiments showed that SARS virus could infect lymphocytes by ADE effect through FcγRII[18, 19]. Excessive activation of T lymphocyte function due to pulmonary immune response may be responsible for the decrease in absolute lymphocyte values in severe and critical patients. Previous studies have shown that SARS specific antibodies were associated with lung immune damage. Acute lung injury occurred in Chinese rhesus macaques vaccinated with the SARS-CoV two days after intravenous injection of anti-spike IgG (S-IgG), which was similar to that of SARS-CoV infection of human[20]. This effect is related to viral load, antibody level and FcγRII polymorphism[21]. Autopsy of the patients with COVID-19 showed that the changes of lungs were similar to those of SARS and middle east respiratory syndrome (MERS), which mainly showed severe immune injury. At the same time, it was accompanied by excessive activation of T lymphocytes and decrease of peripheral blood lymphocytes[22]. The pulmonary imaging changes CT shown were associated with inflammation caused by immune response. In our patients, 2 cases of common type converted to severe type were accompanied with lymphocytopenia and obviously pulmonary imaging progressed, acute pulmonary exudation was absorbed and the absolute count of lymphocytes increased after treatment with glucocorticoid and high-dose human immune globulin in time. The effectiveness of the treatment also suggested that the changes of serology and imaging were related to immune factors.

Combined with the above clinical data and literature, we speculated that in the process of immunological clearance of SARS-CoV-2 virus, the virus proliferating in the incubation period and the specific antibodies secreted by host immune cells produce antigen-antibody immune reaction in the lungs. There are individual differences in this response, and patients with high viral load and severe immune response have decreased absolute count of lymphocytes and obvious progress of pulmonary imaging, which are severe type and critical type patients. In the treatment of COVID-19, antiviral therapy to inhibit viral replication is the basis. Close observation of the changes of the patient's condition and timely use of appropriate amount of glucocorticoid and human immune hemoglobin or other drugs regulating immune response at the stage of severe development of the disease would help to control the disease. During the treatment, the dynamic changes of absolute count of blood lymphocytes, serum albumin and serum globulin can be used as a reference for judging the disease progress. The decrease of absolute count of

lymphocytes, the decrease of serum albumin and the rise of serum globulin form the first cross to indicate the progress of the disease, suggesting that it is possible to be severe type. We have observed that the appearance of SARS-CoV-2 specific antibodies may be related to the progression of lung disease, and whether SARS-CoV-2 virus has the ADE effect similar to SARS virus remains to be studied in the future.

COVID-19 patients with individual differences in the development of the disease are often at different stages of the disease on admission. At the same time, some clinical indicators of the patients change significantly. The present research about the evolution of the disease through cross-sectional analysis were not accurate enough, and there is no dynamic analysis of serological and imaging changes. In clinical work, the clinical, serological and imaging changes of patients are not isolated, but synchronously developed and related to each other. Understanding the rules is helpful to the clinical treatment and the study of the pathophysiology of the disease. Through the analysis of the progression from common type, common type to severe type and severe type patients, we spliced out the dynamic evolution of COVID-19 and described the disease development more accurately. This will help us to understand the nature of the disease and guide clinical treatment.

Conclusion

We conducted a longitudinal analysis of serological and imaging changes in patients with COVID-19 for the first time. Close observation of the dynamic changes in absolute value of lymphocyte, serum albumin and globulin will contribute to assessment of disease. Our study had some limitations. Because of the short time for case collection, light and critical types were not available in this study. Findings requires more clinical data for further study.

Abbrevations

ACE2 : angiotensin-converting enzyme 2

A/G: albumin/globulin

ADE: antibody dependence enhancement

COVID-19: coronavirus disease 2019

MERS : middle east respiratory syndrome

SARS: severe acute respiratory syndrome

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Declarations

Ethics approval and consent to participate

This study was approved by the Third Affiliated Hospital of Sun Yat-sen University Yuedong Hospital (No.2020-01). Written informed consent was waived by the Ethics Commission for emerging infectious diseases.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YZW and YMX conceptualized the study and wrote the original draft. LGW, LGR, XJJ and ZH were responsible for resources, supervision, validation and visualization. LG and JYS interpreted the data and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1 Epidemiology and clinical characteristics of 7 patients

Patient ID	Comorbidities	Epidemiology	Family cluster	Incubation	Course of disease at first visit	Symptoms	Case type	Positive time of specific antibody
1	No	From Wuhan	No	Unknown	7d	Cough, Sputum, Chest tightness	Common	13d
2	No	Contact with patients from Wuhan	No	9d	4d	Fever(Maximum temperature 38.4°C), Sneeze, Weakness	Common	10d
3	No	From Wuhan	No	14d	2d	Weakness	Common	6d
4	Diabetes	From Wuhan	No	3d	8d	Pharyngalgia, Fever(Maximum temperature 37.8°C)	Severe	13d
5	Sequelae of Cerebral Infarction	Contact with patients from Wuhan	Yes	13d	2d	Trachyphonia, Cough	Severe	9d
6	Sequelae of infantile paralysis	From Wuhan	Yes	8d	4d	Pharynx discomfort, Rhinobyon	Severe	10d
7	No	From Wuhan	Yes	12d	1d	Pharyngalgia	Common	14d

Figures

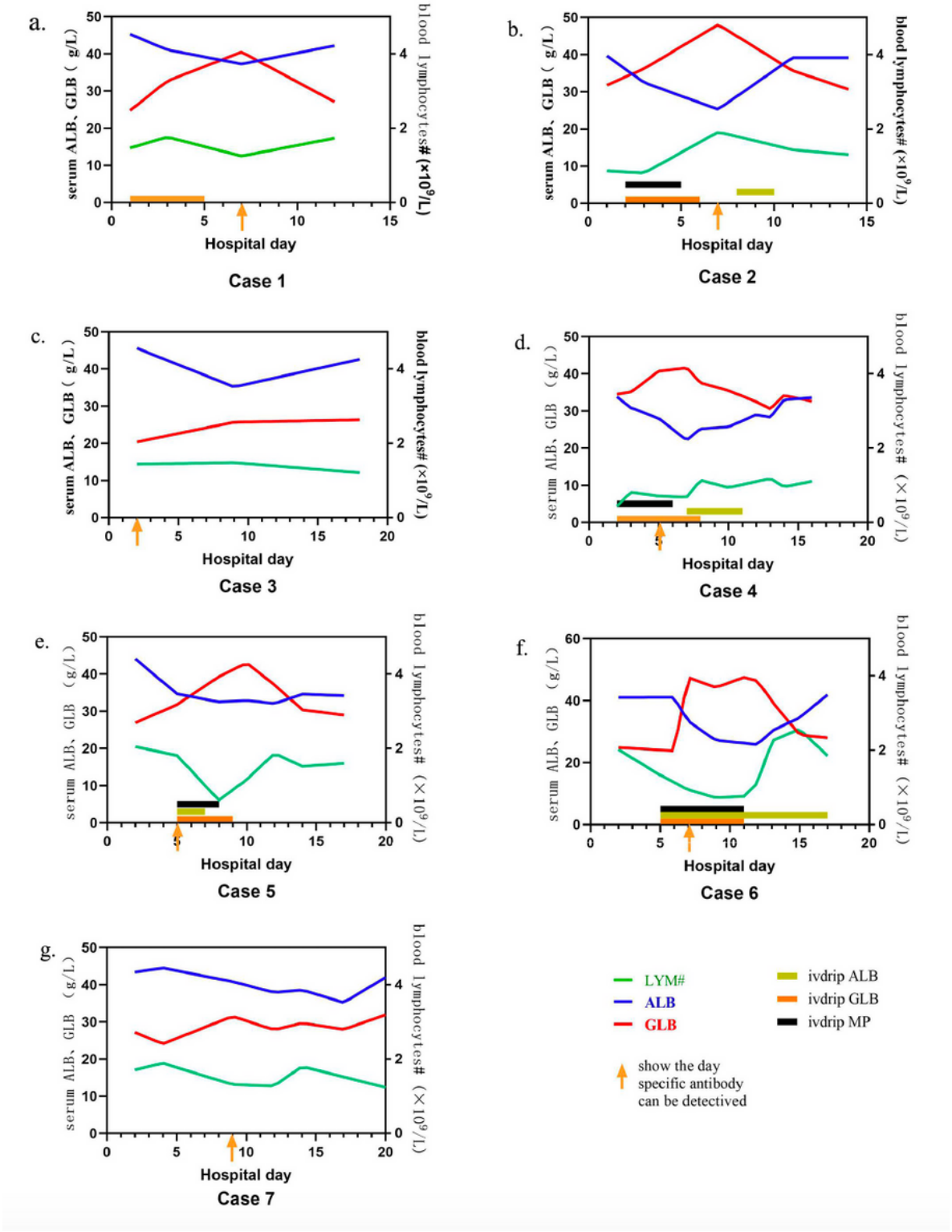

Figure 1

Changes of serum albumin, globulin, lymphocyte absolute value and specific antibody in 7 patients. (a)-(g):case 1-case 7. The yellow arrow showed the detectable time points for the specific antibody.

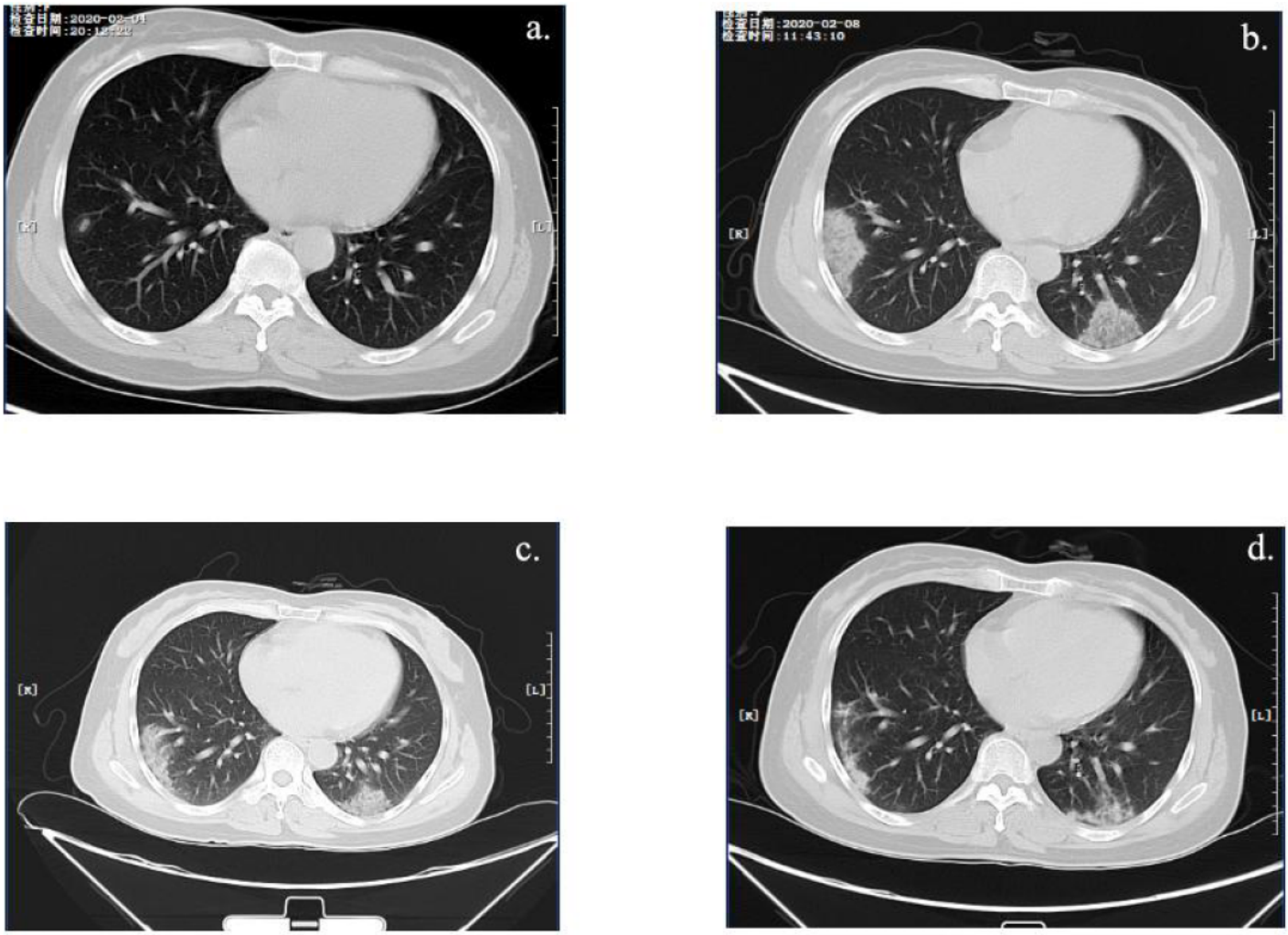

Figure 2

Dynamic change image of chest CT in case 5 (a) Day 1 of hospitalization. (b) Day 5 of hospitalization. (c) Day 8 of hospitalization. (d) Day 14 of hospitalization.

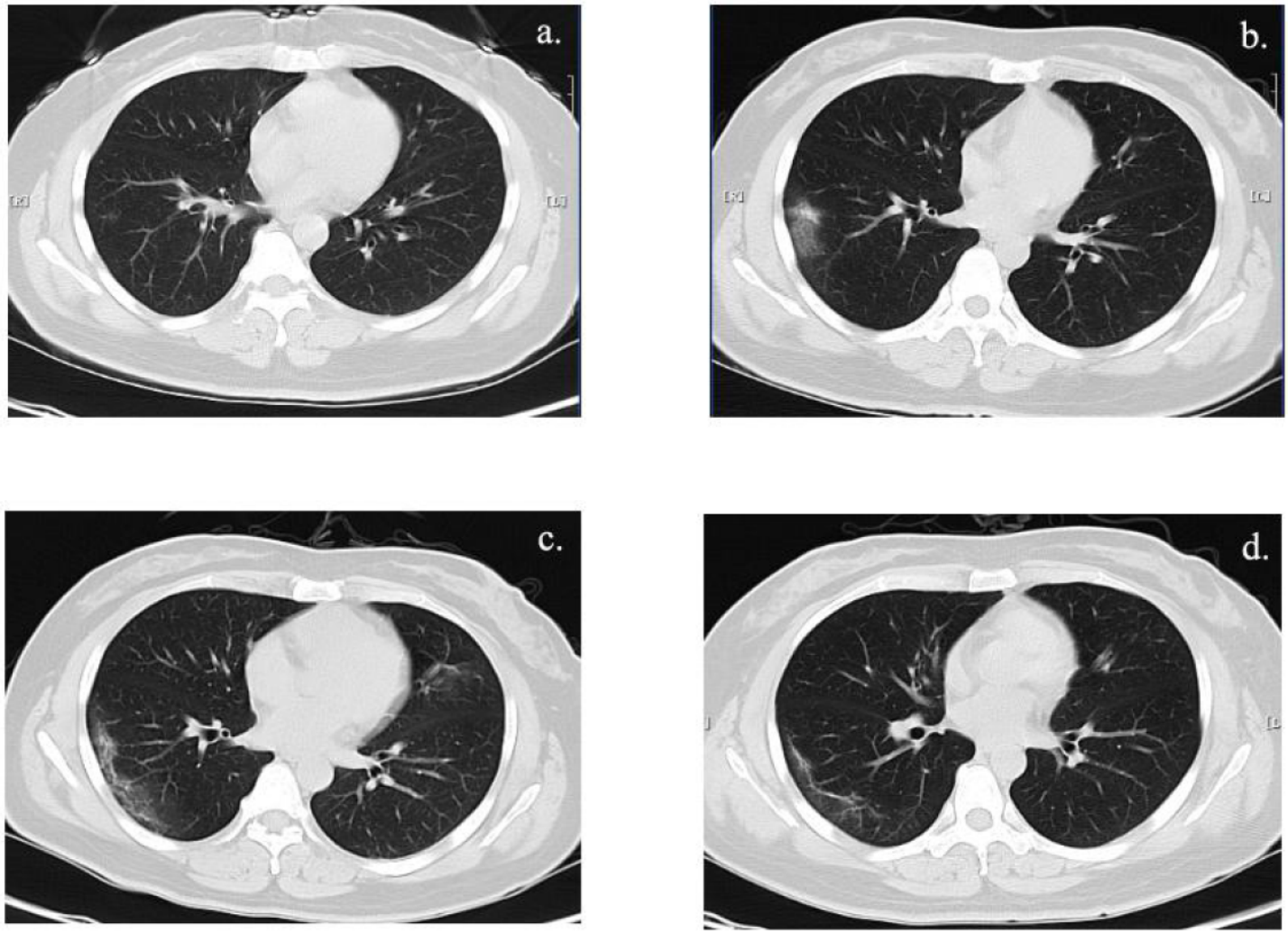

Figure 3

Dynamic change image of chest CT in case 6 (a) Day 1 of hospitalization. (b) Day 5 of hospitalization. (c) Day 8 of hospitalization. (d) Day 14 of hospitalization.