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Research Article

Correlation of Clinical Findings with Innate Immunity Against SARS-CoV-2 and Nucleic Acid Expression of SARS-CoV-2 Among Patients in Mongolia

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Abstract

Estimating the extent of COVID-19 pandemic and the severity of the disease needs accumulation of real-time data, which is currently insufficient in Mongolia. Here, we observed viral load in upper respiratory tract, generation of specific anti-SARS-CoV-2 immunoglobulins in blood, and pathological changes in lung in 32 patients reported at the time of the first outbreak in Mongolia. The results showed that the viral load in the upper respiratory tract appeared for four weeks after SARS-CoV-2 infection, while IgG level increased in second week. However, IgM was developed in 2nd to 3rd week and its serum level decreased further. The CT images showed that the patients with severe disease have severe pulmonary infiltration and decreased ventilation of the lobes compared with patients with mild symptoms. Our study provides important information for diagnosis of COVID-19 infection, evaluation of stage of the disease, and the criteria for evaluating cure of the disease.

Keywords: COVID-19; SARS-CoV-2; Specific immunity; Computed tomography; Ground-glass opacity

Introduction

COVID-19 infection (Coronavirus disease 2019; cause: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; firstly named as 2019-nCoV) was first reported in the end of December in 2019 in Hubei province in the People's Republic of China and has rapidly spread around the world [1-5]. As of 01 October 2022, 618 million people got COVID-19 infection and 6.55 million people died. SARS-CoV-2 is reported as the seventh variant of coronavirus that has infected human [6]. SARS-CoV-1 infection was reported in 2002-2003 in the People's Republic of China while MERS-CoV (Middle East Respiratory Syndrome Coronavirus) was reported in Middle eastern countries in 2012 [7,8]. SARS-CoV-1, SARS-CoV-2, and MERS-CoV are considered as driven from zoonotic and caused severe respiratory disease and mortality [8,9].

SARS-CoV-2 infects humans by binding to the angiotensin-converting enzyme receptor 2 (ACE2) on the epithelial cell surface of the lungs [10]. When the virus enters the human body, mediators increased the dendritic cell induction and activation as well as IFN1, which is responsible for retarding the viral transmission and immunity response [11,12]. During SARS-CoV-2 infection, both innate and acquired immunity are activated. IgG and IgM are secreted after CD4+T cells induce B cells, and the cell immunity is activated when CD8+ T cells remove the virus infected cells. T helper cells are responsible for supporting other immune cells by secreting inflammatory cytokines and mediators. SARS-CoV-2 inhibits the immunity against the virus by suppressing the T cell activity and inducing the apoptosis [13-15].

In Mongolia, 0.983 million cases with COVID-19 were reported by first of October in 2022. Understanding immunity response to the virus, and the findings on computed tomography (CT) is essential to diagnose and monitor the patients with COVID-19 infection. Therefore, this study evaluated the immunity against the virus, clearance time of the virus from the body, and its clinical correlation among the first cases of COVID-19 in Mongolia.

Material and methods

32 patients with COVID-19 infection among the first COVID-19 cases in Mongolia, who were admitted to the National Center for Communicable diseases in November 2020 were involved in this study. They were prospectively enrolled and followed up until being discharged.

Sample collection

32 people who were admitted to the National Center for Communicable diseases in November were selected in this study. Nasopharyngeal swab was collected every 2-5 days and serum were collected every 3-5 days, respectively. Then, viral load of SARS CoV-2 was determined by RT-PCR while IgM and IgG were detected by ELISA. We followed all the patients for 15-42 days and clinical findings were compared in this study. Clinical findings were classified as mild, moderate, and severe according to the clinical guideline for coronavirus infection. Mild disease presents no respiratory symptoms, no pneumonia, and no abnormalities on CT scan. Moderate disease presents certain respiratory symptoms, abnormal findings on the lung CT and no respiratory failure. Severe disease presents pneumonia, respiratory failure, and needs oxygen and supports respiration by invasive and noninvasive ventilators. Very severe disease presents patients with severe pneumonia who need respiratory ventilators [16]. The patients were classified into 2 groups: mild and moderate to severe. Analysis was done based on the clinical findings on the lung images taken by Philips CT scanner.

RT-PCR

RNA was extracted from nasopharyngeal swab by QIAamp®96 Virus QIAcube®HT (5) kit and fully automated QIAcube HT machine for RNA/DNA extraction. PCR was performed using SARS-CoV-2 viral E gene (Roche, Berlin, Germany), internal control EAV (LightMix® SarbecoV E-gene plus EAV) multiplex primer/probe and Applied Biosystems AgPath-ID™ One-Step RT-PCR (Thermo Fisher Scientific) according to the previously described protocol.

EAV (horse arteritis virus) was used as an internal control. Viral load was determined by Ct value and greater than ≥40 was considered as negative.

Detection of IgG and IgM antibodies against SARS-CoV-2

The levels of IgM and IgG against SARS CoV-2 were determined by ELISA for detecting surface S spike protein manufactured by Wantai Biological Pharmacy in the Republic of China according to the manufacturer's protocol. Greater than OD≥1.0 was considered as positive and less than OD <1.0 was considered as negative according to the manufacturer's protocol.

Results

Severity of the disease was correlated with older age

A total of 32 patients with confirmed COVID-19 infection were involved in our study. 20 (62.5%) of them were male whereas 12(37.5%) were female. Average age was 41 years old.

20–29-year-old patients accounted for 28% (9), 30-29-year-old patients accounted for 28% (9), 40–49-year-old patients were accounted for 19% (6),40-49 years old, 5(16%) was 50-59 years old and 3(9%) was older than 60 years old (Table 1). All patients were divided into 2 groups based on the severity: 1) mild and 2) moderate to severe. 23(72%) of the patients had mild symptoms while 9(28%) of them had moderate to severe symptoms. Average age of moderate to severe group was 56 while of mild group was 37. Our results also showed that the older the people, the more severe and slower the recovery process was. It suggests that severity of disease was related to the older age (Figure.1A). There was no difference between the hospital admission days between the mild and severe groups (Figure.1B). This may be related to the current criteria for hospital discharge and recovery after coronavirus.

Classification	ID		Age	Gender	Hospital stays	Severity of respiratory
Mild (n=23)	Case 1		21	male	25	Not severe
	Case 2		20	male	25	Not severe
	Case 3		29	male	19	Not severe
	Case 4		30	male	31	Not severe
	Case 5		29	male	23	Not severe
	Case 6		26	male	23	Not severe
	Case 7		47	male	28	Not severe
	Case 8		31	male	27	Not severe
	Case 9		40	male	21	Not severe
	Case 10		38	female	26	Not severe
	Case 11		34	male	28	Not severe
	Case 12		31	male	28	Not severe
	Case13		34	female	25	Not severe
	Case 14		50	male	25	Not severe
	Case 15		54	male	28	Not severe
	Case 16		31	male	28	Not severe
	Case 17		49	male	34	Not severe
	Case 18		48	female	28	Not severe
	Case 19		27	female	29	Not severe
	Case 20		29	male	31	Not severe
	Case 21		39	female	28	Not severe
	Case 22		36	male	28	Not severe
	Case 23		51	female	28	Not severe
moderate-to severe n=9)	Case 24		21	male	38	Severe

	Case 25		50	female	31	Severe
	Case 26		28	male	31	Severe
	Case 27		70	female	28	Severe
	Case 28		46	female	18	Severe
	Case 29		52	female	21	Severe[#]
	Case 30		56	female	25	Severe
	Case 31		91	male	22	Severe
	Case 32		68	male	28	Severe
"#" used ventilator						

Table 1: Demography of participants.

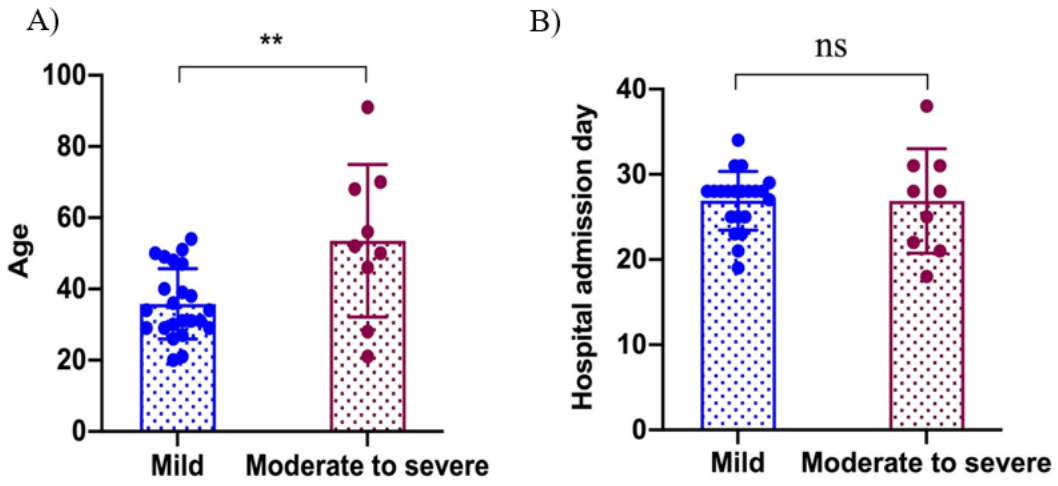

Figure 1: A) Correlation between severity of the disease and age. B) Correlation between severity of the disease and hospital admission days. **P<0.01

Correlation between viral load and antibodies against SARS-CoV-2

The nasopharyngeal swab collected every 2-5 days and serum collected every 3-5 days. The viral load of SARS-CoV-2 was detected by RT-PCR and levels of IgM and IgG were measured by ELISA, respectively (Figure.2).

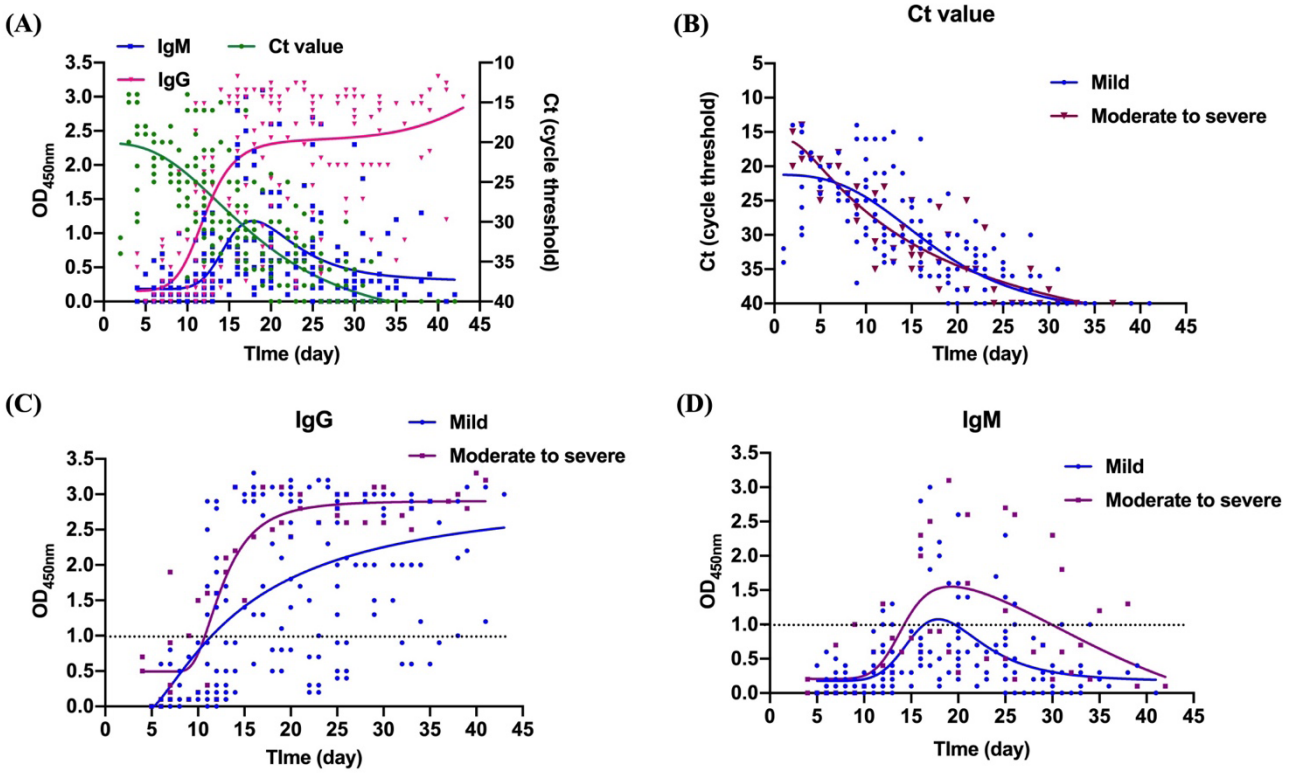

Figure 2: Dynamic changes of upper respiratory viral load and serum antibodies (IgM and IgG) in patients with SARS-CoV-2 infection. (A) Dynamic changes of viral load (Ct value) and generation of antibodies (IgM, IgG) in all patients during SARS-CoV-2 infection. Viral load dynamics (B) and generation of antibodies (C, D) by clinical evaluation of the patients with SARS-CoV-2.

The mean CT value was 19(14-24) for moderate to severe cases, and 24 (15-33) for mild cases in the first 7 days. Viral load was higher in severe cases than mild cases. During the first 7 days, viral load was stable; however, CT value gradually decreased starting from the second week. Then, on the week 4, viral RNA was not present in 90% of all the patients. Seroconversion of IgG started and increased during the beginning of the COVID-19 infection while seroconversion of IgM started on the second week after the infection and then slowly decreased (Figure.2A). We found that when SARS-CoV-2 viral load got lower, antibody expression was increased, suggesting a strong reverse correlation between viral CT value and IgG expression (correlation coefficient (r)= 0.8951; IC 95%, 0.8025. to 0.9456; p<0.0001). Our results showed that there was no correlation between Ct value and clinical findings (Figure.2B). In severe cases, IgG level against SARS-CoV-2 was markedly elevated and was stable while IgG level was gradually elevated in mild cases (Figure.2C). However, the level of IgM was high for 2 to 3 weeks and then declined while IgM showed slight increase during 16 to 20 days and then slowly declined in mild cases (Figure.2D). Ct value from nasopharyngeal swabs was related to the age in some studies [17] whereas our result showed that Ct value was not related to the age (Figure.3A, B). It might be due to limited number of patients involved in our study. There is no statistically significant difference between age and IgG level. There was statistically significant difference between IgM level of severe cases and mild cases (*P<0.005)*. Our result showed that differences in level of IgG between severe and mild cases at 14-28 days were statistically significant (*P<0.05)*. There was no statistically significant difference between these two groups since the second and the fifth week. IgG against SARS-CoV-2 was present in 30(93.75%) patients while 2(6.25%) was not met the criteria that was greater than 1 (≥1) of all the people involved in our study. Among these 30 patients, mild cases with no symptoms had low expression of specific antibody against SARS-CoV-2 (Figure.4D).

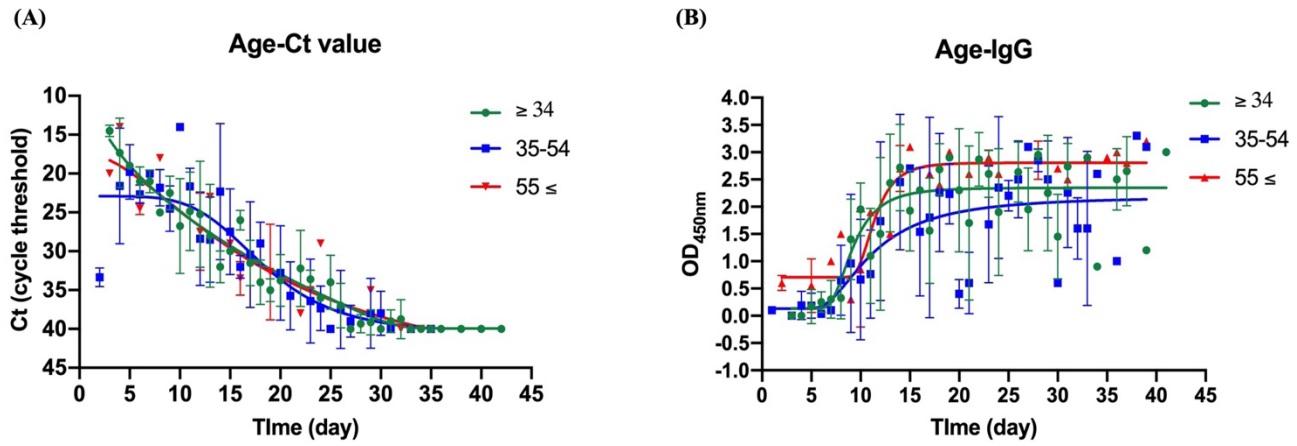

Figure 3: Dynamics of Ct value (A) and IgG (B) by age groups.

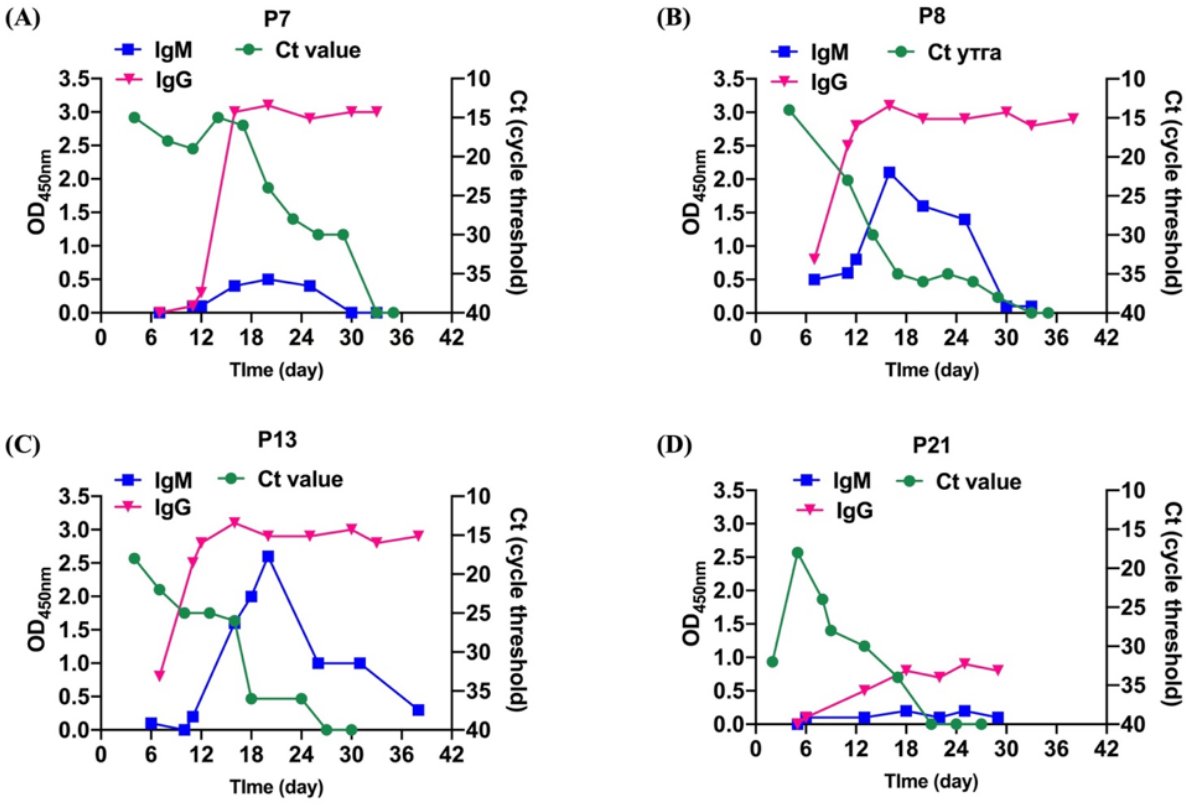

Figure 4: Determination of viral load and titers of antibodies (IgM and IgG) in some mild cases with SARS-CoV-2 infection.

Abnormal findings on CT scan

Furthermore, we chose 4 severe and 4 mild cases from all the patients as representative cases to show their viral load, clinical findings, and changes on the lung CT scan from the time of the admission to the discharge from the hospital. Results for viral load and antibody in mild cases were shown in Figure 4 and in severe cases in Figure 7.

Case 1

47-year-old male patient had mild clinical presentation after getting COVID-19 infection, but viral RNA was present for 30 days. IgG titer was remarkably elevated from day 12 and IgM titer was very low and gradually decreased. However, the level of IgM did not reach the positive point of the kit which was greater than 1 (≥1) (Figure.4A). During the first 7 days, there was no changes on CT images while on day 16, CT result showed that 1.4 cm mass with less density was found in the 6th segment of lower lobe in the left lung (Figure.5).

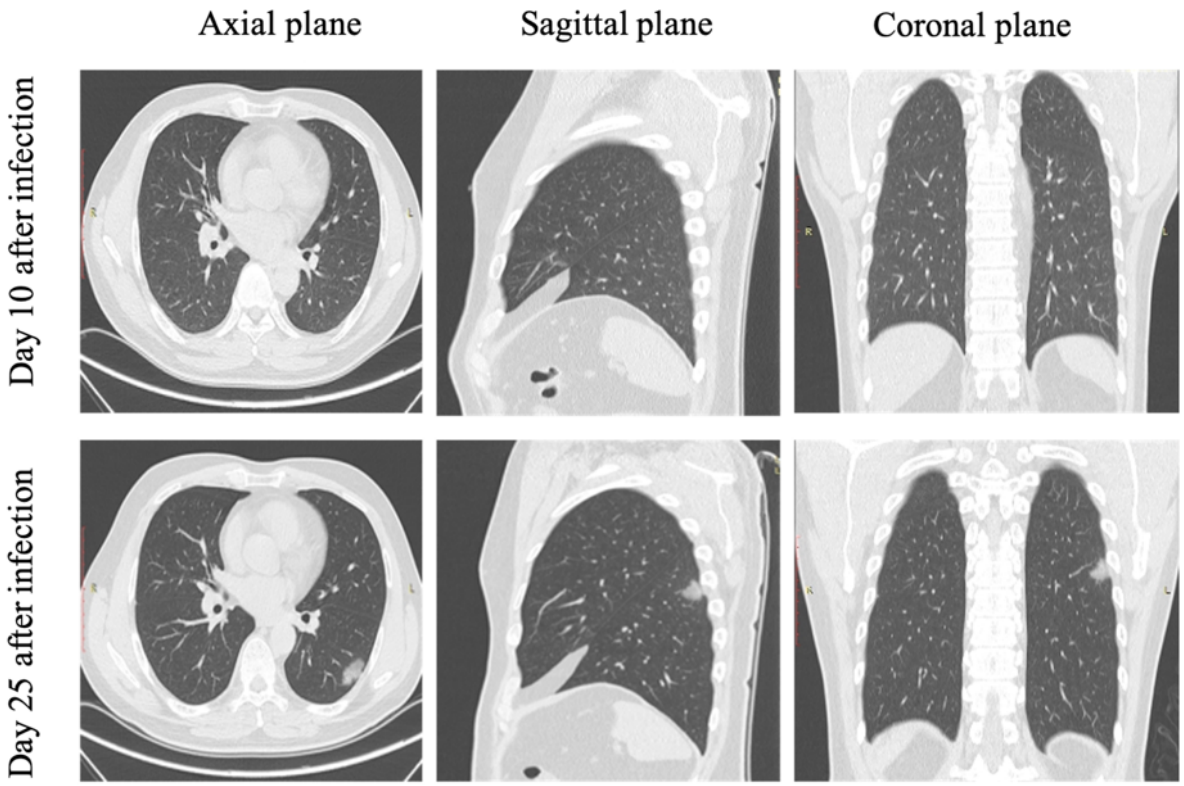

Figure 5: CT scan showed that 1.4 cm mass with less density was found in the 6th segment of lower lobe in the left lung. Upper panel: axial plane, sagittal plane and coronal plane of a patient 10 days after infection. Lower panel: axial plane, sagittal plane and coronal plane of a patient 25 days after infection.

Case 2

34-year-old female patient had mild clinical presentation. Viral load was high for 2 weeks and decreased on the third week and no virus was detected at day 27 and afterward. IgG titer was increased after day 6. IgM was detected from day 6 and started to decrease on the third week (Figure.4B). On day 8 after infection, CT result showed that there was a less density infiltration on a subpleural ground-glass opacity in the lower lobe of right lung (Figure.6). There was subpleural ground-glass opacity in the upper lobe of left lung and air-filled opacity was observed in the lower lobe of left lung. After 8 days, size of the ground-glass opacity got bigger in both lungs whereas size of the infiltration in the lower lobe of the lung was resolved and decreased (Figure.6).

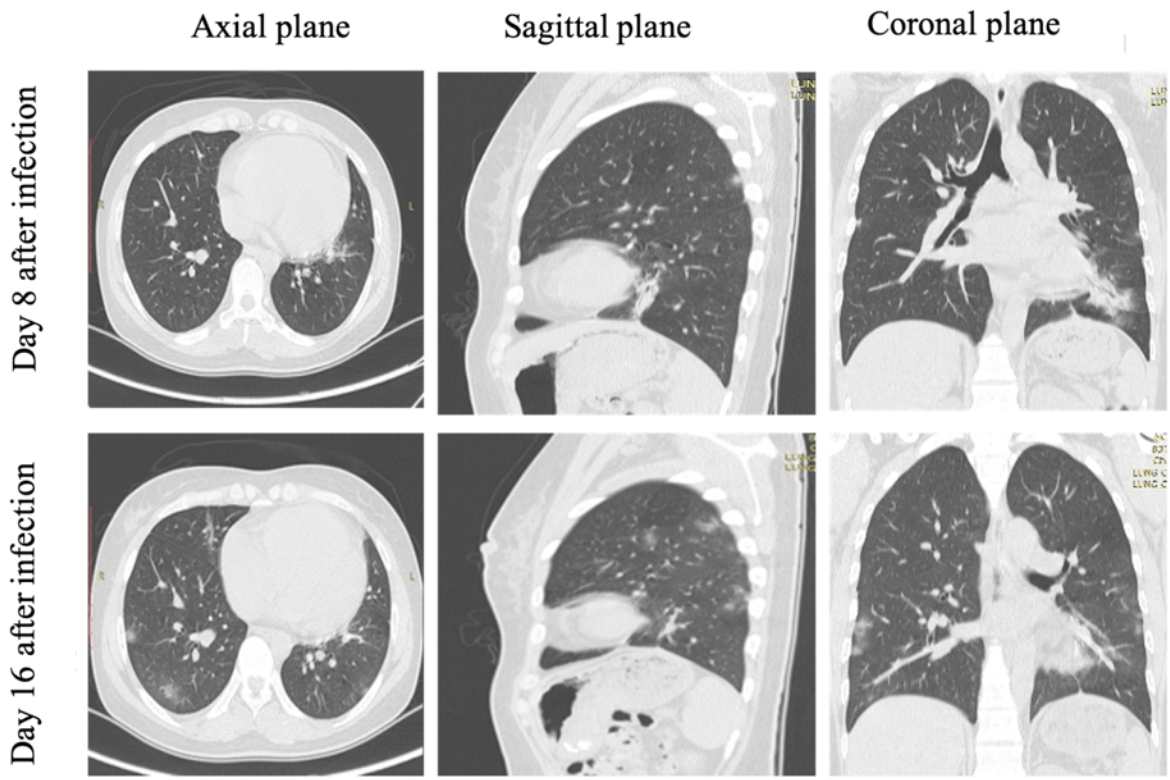

Figure 6. CT scan of case 2. CT scan showed subpleural band with low density and a ground glass opacity in the lower lobe of right lung on day 8. Consolidation was present in the lower lobe of lung. On day 16, size of the ground glass opacity got bigger in both lungs whereas size of the mass in the lower lobe of the lung was broken and decreased.

Case 3

47-year- old female with no comorbidity had severe clinical presentation. Viral load in the airway and antibody titer against virus was shown in Figure 7B. Nasopharyngeal swab was taken on day 9 or day 10 after exposure to the COVID-19. SARS-CoV-2 infection was confirmed after RT-PCR. Viral load was markedly decreased on day 12 and was not detected on day 35. Seroconversion of IgM and IgG started in the first week of the disease onset. IgM was decreased from day 15 and IgG was gradually increased and became plateau (Figure.7B). CT scan showed the diffuse consolidation and ground-glass opacity in both lungs on first day of COVID-19 infection. All the abnormal findings were resolved after 18 days, and fibrosis was observed in the posterior and lower segments of upper and lower lobes of both lungs. (Figure.8).

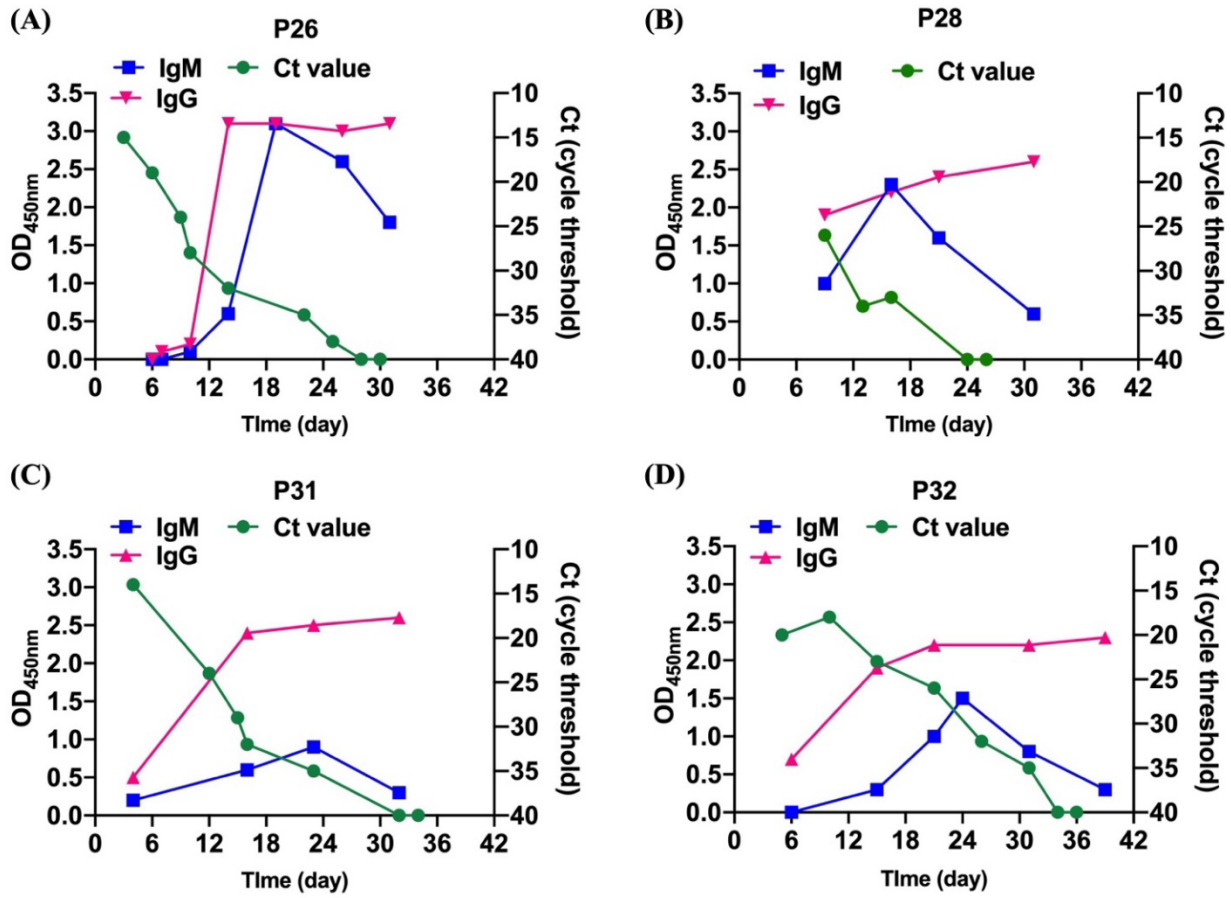

Figure 7: Determination of viral load and titers of antibodies (IgM and IgG) in some severe cases with SARS-CoV-2 infection.

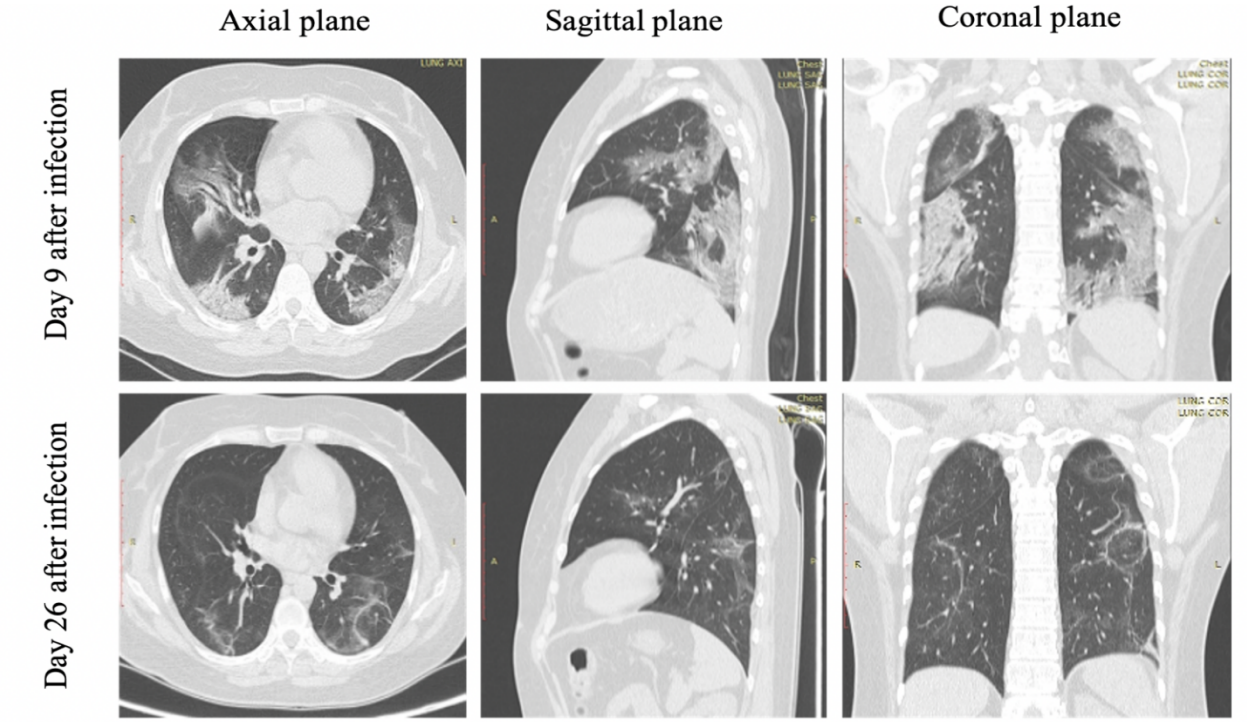

Figure 8. The results of CT of case 3.

Figure 8: CT scan of case 3. CT scan showed the bilateral ground-glass opacities, consolidation and diffuse infiltration. On day 26, consolidation was resolved, and fibrosis was observed in the posterior and bottom segments of upper and lower lobes of both lungs.

Case 4

66-year-old male patient had major complaints of coughing, fatigue, no appetite after 2 days of infection. Viral RNA was present for 31 days and gradually reduced and then not detected. During early infection, IgM was not detected while IgG was detected early (Figure 7D). The previous study for determining immunity against SARS-CoV-2 reported that IgG titer was higher than IgM in the blood [19]. After 9 days of infection or on day 7 after symptoms onset, CT result showed that there was mixed density consolidation on the ground-glass opacity in the upper lobe of the right lung, the upper and lower lobes of the left lung and decreased ventilation in the lungs. Pleural effusion was present in both lungs and lymph nodes was enlarged to 1.6cm. After 10 days, comparing with the previous CT images, infiltrations started to be resolved and density of other changes was increased. Ground glass opacity, symptom reversed halo sign, air bronchogram sign, and pleural effusion indicated the severity of the disease. After 30 days, changes were resolved, and density was decreased in both upper and lower lobes of the lungs (Figure.9). Pleural effusion was resolved, and size of the lymph nodes was decreased to 1.4 cm. RT-PCR showed that virus was present for 30 days and it was related to severity of the disease. Although Ct value was not correlated with severity, CT scan can serve as the most reliable diagnostic method for determining severity of COVID-19 [18]. In addition, level of IgM and IgG cannot be the factor for determining recovery from the disease. Comorbidities such as hypertension, diabetes II and aging might be the main cause of the disease severity.

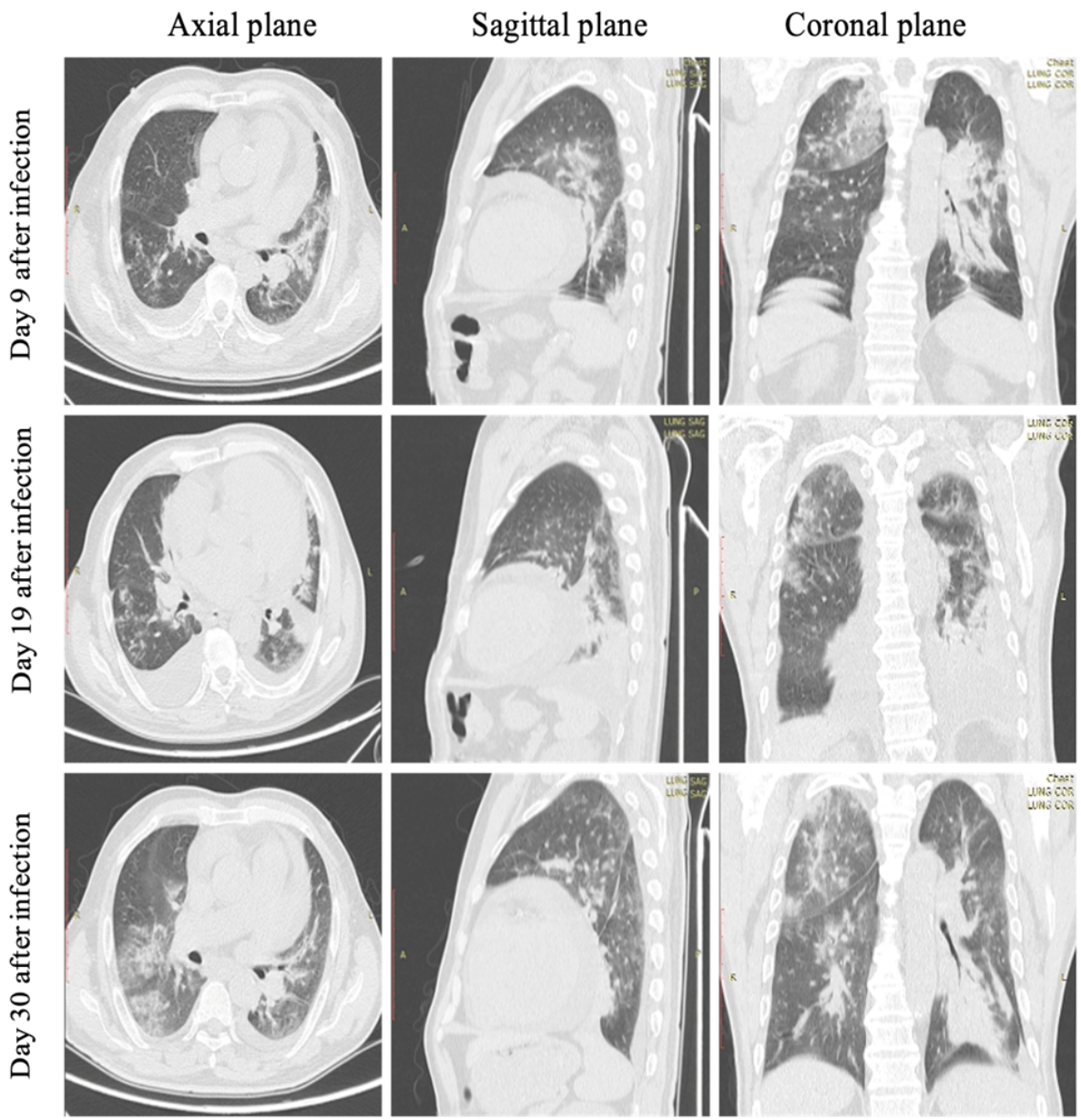

Figure 9: CT scan of case 4. On day 9 after infection, CT scan showed that there was mixed density consolidation on the ground glass opacity in the upper lobe of the right lung, the upper and lower lobes of the left lung. Pleural effusion was present and lymph nodes was enlarged to 1.6cm. On day 19, lesions started to be resolved and density of other changes was increased. Ground glass opacity, symptom reversed halo sign, air-bronchogram sign, and pleural effusion are the sings for disease severity. After 30 days, changes were resolved, and density was decreased in upper and lower lobes of the lungs.

Discussion

The present study showed the correlation between clinical findings and levels of antibodies as well as abnormalities on CT. It was reported that older people with COVID-19 had more severe clinical findings [19] and mortality risk was much higher for older people[1]. Wu et al reported that case fatality ratio was higher in older patients than in younger patients [20]. Results of the present study showed that the older people had severe disease. Therefore, our results were consistent with the previously published results by other researchers, who reported that IgG was produced during the early stages of the infection [21] and increased starting from the first week to fifth week and then stable until the seventh week [22]. We found that high IgG titer was correlated with low viral load, which were consistent with previous studies. Our study showed that the level of IgG was higher than the IgM during early stages of COVID-19 infection. Young et al reported that the IgG was correlated with days from symptom onset [23]. It was reported that levels of antibodies against SARS-COV-2 S1 were not associated with ages [23], similar to what our study found.

Furthermore, our results showed that there was no correlation between Ct value and clinical findings. In contrast, Wang Y et al found that after SARS-CoV-2 infection, viral load was higher in severe cases [24]. It might be related to a smaller number of severe patients involved in our study. According to Berislav study, patients with mild disease had low expression of specific antibody against surface S protein of SARS-CoV-2 [25] that were same as what we found.

We selected the symptomatic severe patients with COVID-19 for determining the abnormalities on chest CT [26]. It was reported that CT findings were mixed with other chronic lung diseases of the patients [26]. Previous studies reported that the CT findings for COVID-19 were similar as the CT findings for SARA-CoV-1 and MERS-CoV [27]. Abnormalities on chest CT in COVID-19 depends on the stage and severity of the disease [28]. Our result suggests that abnormalities on CT were present approximately on day 7 after symptom onset. Want Y et al reported that CT abnormalities were observed well during 6-11 days of infection and most common finding was ground-glass opacity [29]. Huang et al found that the consolidation was present on both lungs among the severe patients with COVID-19 at intensive care unit at Wuhan hospital while ground glass opacity was present among mild patients with COVID-19 [30]. We also found that ground glass opacity was the main findings on CT scan for patients with severe symptoms of COVID-19. However, these findings can be present in other viral pneumonia. Therefore, confirming the COVID-19 infection is needed.

Conclusion

RT-PCR is the main method for detecting SARS-CoV-2. Ct value and dynamics of antibody against SARS-CoV-2 virus might be the important criteria for evaluation for post infection. CT findings for complications of COVID-19 infection include low density consolidations in the lungs and pleural effusion, suggesting that CT scan is an important tool for controlling recovery, and severity of COVID-19 disease. Therefore, this study provides important information for the diagnosis of COVID-19 infection, post infection evaluation, and the criteria for recovery from the disease.

Conflict of Interests

The authors have declared that no competing interest exists

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