

Title	Novel Coronavirus Infection and Acute Kidney Injury in Two Renal Transplant Recipients: Case Report
Running Title	Novel coronavirus Infection and Acute Kidney Injury in Two Renal Transplant Recipients
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Abstract

Novel coronavirus infection is a recent infective agent that causes severe potentially fatal pneumonia. The clinical presentation includes asymptomatic infection, severe pneumonia, and acute respiratory failure. Data pertaining to the clinical presentation of solid organ transplant recipients are scarce. Two cases of novel coronavirus infection in two recipients of renal transplant with variable clinical presentations and outcomes are reported. The first patient presented with progressive respiratory symptoms, acute renal failure, and passed away, whereas the second one, although presented with respiratory tract symptoms and hypoxemia remained stable and exhibited an excellent clinical recovery despite recent reception of thymoglobulin induction. This paper reports rare cases of novel coronavirus infection in renal transplant recipients. For an enhanced insight of the novel coronavirus infection and acute kidney injury on the clinical presentation, severity, and outcome in solid organ transplant recipients, further investigations are required.

Keywords: novel coronavirus infection; renal transplant; acute kidney injury;

Case 1

A 59-year-old male was admitted to the hospital with complaints of “fever with cough and expectoration for 8 days”. There was no particular cause of fever eight days prior to reporting, as on February 1st, 2020. The body temperature recorded at night was 38.2° C, along with symptoms such as dyspnea, headache, and myodynia, but none of the other symptoms such as palpitation, chest pain, chills, fatigue, and night sweat were experienced. He was hospitalized in another hospital six days prior to the admission, as on February 3rd, 2020. The common blood count was observed to be normal, and the total number of lymphocytes was $1.28 \times 10^9/L$. Influenza A and B tests were negative. A ground glass shadow was seen in the CT scan of the lung in the upper and lower regions of the left lung (Figure 1). He was administered arbidol hydrochloride tablets, cephalosporin, proprietary Chinese medicine, and antipyretic drugs (from Feb. 4 to 8). He coughed a small amount of white sputum and suffered intermittent fever four days prior to the admission, as on February 5th, 2020. He also experienced nausea without vomiting, abdominal pain, diarrhea, and exertional dyspnea without obvious aggravation, hemoptysis, and chest pain. The 2019-nCov nucleic acid test was found to be positive. He used the abovementioned drugs regularly, which relieved the symptoms of coughing and expectoration. The patient’s wife had novel coronavirus pneumonia and he was in close contact with her. He had no history of Southern China seafood market contact. Ever since he was infected, he has had a poor appetite, poor sleep quality, and poor mental health.

Past medical history : The patient had hypertension for 20 years, for which he was under the medication of oral valsartan and bisoprolol fumarate tablets. He also had a history of 6 years of coronary heart disease, for which he was using oral bisoprolol fumarate tablets, betaloc. He was undergoing a long-term anti-rejection treatment for 5 years post right kidney transplantation with cyclosporine and bradinine. It had been discontinued at the time of being presented.

The data recorded at physical examination are as follows: nasal catheter flow at

5L/min, SpO₂ 82%, HR 77bpm, BP 136/76mmHg, RR 24bpm, temperature 36.5℃, height 168cm, and weight 75kg.

The relevant examination and body temperature of the patient after admission is shown in the Figure2 and 3. Angiotensin-converting enzyme (ACE) test 28U/L, Mycoplasma pneumoniae, chlamydia, respiratory syncytial virus, adenovirus, influenza A virus, influenza B virus, parainfluenza virus, and Legionella pneumophila IgM antibody were found to be negative. IL1β<5.0pg/ml, IL2 receptor 659U/ml, IL6 57.47pg/ml↑, IL 8 16.4pg/ml, IL 10 9.6pg/ml↑, and Tumor necrosis factor (TNF-α) 8.4pg/ml↑. G, GM and Candida mannan test was found negative. The patient continued to use the anti-rejection drugs administered for renal transplantation, and was on nasal catheter 5L/min for oxygen inhalation. The next day, the patient's blood oxygen level could not be maintained, which was therefore replaced with noninvasive ventilation. Parameters: S/T mode: IPAP should be 14cm H₂O, EPAP should be 8cmH₂O, FiO₂ 90%, f=12 times/min. Fat emulsion amino acids and glucose injections were administered for intravenous nutritional support. The blood pressure was controlled by urapidil hydrochloride injection pump point, and the urine volume by furosemide. The patient suffered from acid reflux, heartburn, chest distress and suffocation, progressive dyspnea, and progressive deterioration of renal function while undergoing the treatment, 3 days post admission. The renal function was reinvestigated (Figure 2): Serum creatinine(sCr) 467μmol/L, blood urea nitrogen(BUN) 25.8mmol/L, glomerular filtration rate (eGFR) 11mmol/L, bicarbonate (HCO₃) 12.7mmol/L, K 5.41mmol/L, alanine aminotransferase (ALT) 61IU/L, aspartate aminotransferase(AST) 87IU/L, ALB 38.4g/L, and hs-CRP 96.7mg/L.

The patient seemed to be in a state of delirium on the 5th day after admission. The saturation of the patient dropped to 10% all of a sudden, his consciousness was lost, and his heart rate and blood pressure could not be measured. The noninvasive auxiliary ventilation was continued, the oxygen absorption concentration was set at 100%, and the patient was administered continuous external pressure. Once the

patient was recovered from the heart rate, blood pressure reappeared a minute later, but the heart rate could not be measured. By 6:17 am, the patient's consciousness and vital signs could not be recovered. Repetitive administration of epinephrine and dopamine did not help in raising the patient's blood pressure, and the heart rhythm was not detected. Intermittent administration of epinephrine, atropine, and cardiopulmonary resuscitation were rendered useless. At 6:52 am, the ECG of the patient exhibited a straight line, indicating clinical death.

Case 2

A 37-year-old female was admitted to hospital, owing to "fever with cough for 8 days" The patient had experienced fever without obvious stimulus 8 days prior to admission, as on February 5th 2020. The peak temperature had reached 40°C at night, accompanied by chills, dry cough without phlegm, mild dyspnea with obvious after activity, along with muscle pain, dizziness, headache, poor tolerance, chest pain, chest distress, pharyngeal pain, no fatigue, and night sweat. The patient visited Wuhan Union Medical College Hospital, where a chest CT scan revealed novel coronavirus infection in the lower region of her left lung on the abovementioned date (Figure 4), with positive 2019-nCov nucleic acid. The patient was administered arbidol hydrochloride tablets (from February 5th–13), moxifloxacin (from February 5th–13), ceftriaxone (from February 5th–12), and propylene spheres (from February 8th–12th). With the described treatment symptoms alleviated, body temperature was nearly stable for 3 days, and the chest CT scan indicated lesion progression on February 12th, 2020.

Past medical history : The patient had suffered hypertension for a year, for which he used metoprolol tartrate tablet 47.5mg Qd and 20mg Qd of Adalat. During pregnancy in 2009, the patient found urinary protein 2+, mild lower extremity edema and no blood pressure rise. During the period, the patient had hematuria with naked eyes when he had a "cold". She had not diagnosis and treatment. In 2014, due to

headache, dizziness, nausea and vomiting, the blood pressure rise was found, with the highest blood pressure of 200/160mmhg and blood creatinine of 180umol/L. With mild lower extremity edema, she had been treated with traditional Chinese medicine, and IgA nephropathy was indicated by renal puncture. After three times pulse therapy of hormone and cyclophosphamide, she was gradually reduced to oral prednisone 10mg QD and then serum creatinine increased. In 2019, the serum creatinine was reexamined to be about 500umol/L. At the same time, there was systemic edema, hypoproteinemia, increased urine protein and poor diuretic effect. After right internal jugular vein catheterization, the left forearm arteriovenous fistula was performed. Hemodialysis lasted for 3 months. In August 2019, kidney transplantation was performed successfully. The serum creatinine was maintained at 130-140umol/L after operation. The urine volume was normal and oral administration was strong. It was treated with 20 mg QD of prednisone, 2 mg of tacrolimus in the morning, 1.5 mg in the evening and mycophenolate mofetil was used.

Diagnosis and treatment process:

The relevant examination and change in body temperature of the patient after admission is shown in the Figure 5 and 3. Urine routine: RBC 2+ and pro 2+. Biochemical tests: sCr 167μmol/L, BUN 7.7mmol/L, eGFR 33.4ml/min/1.73, and HCO₃⁻ 19.5mmol/L; Tacrolimus was discontinued post admission, although methylprednisolone 40mg Qd and moxifloxacin against infection was continued; furosemide 40mg was administered after daily albumin according to the urine volume of the patient. The serum creatinine exhibited progressive upward trend. Patients had a good rest, adequate nutrition, oxygen inhalation, and gamma globulin infusion, avoiding nephrotoxic drugs, Giving appropriate diuretic treatment according to the amount of urine. Methylprednisolone was changed from 40mg Qd per days to oral prednisone 25mg Q12h and gradually reduced to 5mg Qd oral maintenance. 11 days after admission, it began to add tacrolimus 2mg in the morning, 1mg in the evening for treatment. Then the patient had an excellent clinical recovery in body temperature, absorption of lung lesions (Figure 6) and renal function (Figure

5 and 3).

Informed consent for the collection of his medical history and blood samples was obtained in compliance with the Declaration of Helsinki and approved by the local ethical committee (Peking University Third Hospital medical science research ethics committee approve, IRB00006761-M2020060), and the patient provided informed consent for publication of the case.

Discussion:

Novel Coronavirus was discovered in a series of tests conducted on respiratory tract specimens collected from Wuhan, Hubei, China. This pathogen was found in December 2019, which mainly infected the respiratory tract, causing novel coronavirus pneumonia and serious life-threatening complications. Novel coronavirus spread rapidly as an epidemic in several provinces and cities in China and abroad. It was included in the class B infectious diseases as specified in the infectious disease prevention act of People's Republic of China. The World Health Organization (WHO) included the epidemic of COVID-19 as an international public health emergency on January 31, 2020. COVID-19 is a common complication among renal transplant recipients. Thus, it becomes imperative to report the clinical features of COVID-19 in renal transplant recipients.

The long-term intake of immune agents by renal transplant recipients although may reduce the rejection of the body effectively, but significantly reduces the body's immunity to virus, bacteria, and certain other pathogens. Pulmonary infection is one of the major kinds of infections that may occur post renal transplantation, with the features of occult onset, rapid progress, and serious complications[1, 2]. The symptoms of the two renal transplant recipients discussed in this paper were initially moderate, with low fever and no cough or expectoration. Diet, sleep, spirit, and self-comfort were normal. Chest CT scan exhibited patchy and flaky ground glass shadows. In the first case, the symptoms quickly deteriorated, hypoxemia occurred rapidly, and renal function worsened gradually, resulting in death.

The mortality due to the occurrence of severe pneumonia in renal transplant recipients was 46.2% to 78.3%. The infection commonly occurred from 1 to 6 months after renal transplantation. The patient reported in the first case had a 5-year history of kidney transplantation, and COVID-19 had manifested after a long time of transplantation. Respiratory failure follows in the courses of the disease and calls for long-term respiratory support, which may be linked to the low immunity of the body. It is speculated that the infection rate and incidence of COVID-19 are associated with the immune system and the target organ damage occurs due to virus toxicity, but not the time after kidney transplantation.

Wuhan Institute of Virology and other researchers have recently proved that novel coronavirus entered into the host body by infecting the epithelial cells by way of binding with angiotensin I converting enzyme 2 (ACE2) receptor on the cell surface [3-5]. The first COVID-19 patient suffered progressive deterioration of renal function. Certain current studies have evidenced that, in addition to respiratory system damage, there also occurs renal function abnormalities or even renal damage in some patients. Studies have indicated that 3% to 10% of the patients infected with the novel coronavirus suffer renal function abnormalities, such as an increase in sCr or urea nitrogen, and 7% of the patients suffer acute renal damage. Certain research groups relied on online datasets to comprehend the expression level of ACE2 in the renal system and the findings were as expected that is the expression level of ACE2mRNA in healthy renal cells was relatively high. The immunohistochemistry outcomes indicated that the expression level of ACE2 protein in kidney, especially in the renal tubular cells was not as high, and the expression of ACE2 was not observed in immune cells and glomerular epithelial cells in the case of COVID-19 patients. Renal tubular cells function to reabsorb and excrete, and have a crucial role in the excretion of metabolites, the maintenance of body fluid, and acid–base balances. The novel coronavirus may enter renal tubular cells through binding with ACE2, thus resulting in cytotoxicity and renal dysfunction. The kidney of the transplant patients is more fragile as compared with the normal kidney, which may easily cause kidney

damage [6].

It has been found that acute kidney injury (AKI) caused due to coronavirus is common, as these two patients, which mainly manifests as renal tubular injury. Recently, 1099 COVID-19 patients as reported by Guan indicated that the incidence of AKI was 0.5%, and 5 of 173 severely affected patients showed AKI (2.9%) [7]. The most recent investigation by Cheng et al. [8] reported an incidence of AKI to be 3.2% among 710 consecutive patients diagnosed with COVID-19. Nevertheless, the mechanism of how coronavirus leads to AKI is yet to be illuminated. As per recent studies, it may be linked to the direct mediation and immune activation of the abovementioned coronavirus. Regarding the immune activation, earlier studies have found that SARS-Cov and MERS-Cov infections can remarkably raise the level of inflammatory factors and chemokines [9]. Its major secretions include chemokines, proinflammatory cytokines, and inducible nitric oxide synthetase through M1 subtype of macrophage to form cytotoxic peroxynitrite and mediate renal injury. Moreover, dendrites release TNF- α for additional promotion of the inflammatory response [10]. It has been recently reported that cytokine storm syndrome has a crucial role in various infection-mediated multiple organ failure. It can promote the activation of cytokine cascade reaction and release a large number of cytokines to cause systemic inflammation. Clinically, the TNF- α , IL-1, and IL-6 levels in the abovementioned patients increased remarkably, indicating that there may be cytokine storm syndrome. IL-6 and GM-CSF in a group of 29 COVID-19 patients were further found to release inflammatory factors by activating monocytes as reported by Chen Lei et al., thus amplifying the immune effects and eventually causing AKI.

Considering this, it is possible to use the blood purification technology such as plasma exchange and hemofiltration may possibly be used to actively start blood purification treatment for the purpose of clearing inflammatory factors in an early stage in case of critically ill patients with high inflammatory response.

COVID-19 is caused by coronavirus, which has become a major public health

hazard to human society. COVID-19 in combination with AKI is a clinical problem that not only increases the mortality rate but may also cause chronic kidney disease, and calls for immediate attention. As its investigations are just beginning, adequate active exploration and multidisciplinary cooperation are essential.

References

- [1].Oliva, A., et al., Severe Bloodstream Infection due to KPC-Producer E coli in a Renal Transplant Recipient Treated With the Double-Carbapenem Regimen and Analysis of In Vitro Synergy Testing. *Medicine*. 95(7): p. e2243.
- [2].Zarauza Santove A, A., et al., BK Virus Infection in Pediatric Renal Transplantation. *Transplantation Proceedings*. 47(1): p. 62-66.
- [3].Zhou, P., et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 2020
- [4].Wu, F., et al., A new coronavirus associated with human respiratory disease in China. *Nature*, 2020.
- [5].Xu, X., et al., Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci*, 2020.
- [6].Fan Caibin, et al, ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection. *medRxiv* 2020
- [7].Guan WJ, et.al, Clinical characteristics of 2019 novel coronavirus infection in China. *medRxiv* print first posted online Feb.9,2020
- [8].Cheng Y, et.al, Kidney impairment is associated with in-hospital death of COVID-19 patients *medRxiv* print
- [9].Arabi YM, et al, Middle East Respiratory syndrome. *N Eng J Med* 2017 ; 376(6):584-594.
- [10].Singbartl K, et al, Kidney-Immune System Crosstalk in AKI. *Semin Nephrol*. 2019;39(1):96-106.

Figure legend

Figure 1. Case 1: 59-year male with fever, cough and expectoration. Non-enhanced chest computed tomography (CT) showed multiple, bilateral, small nodular ground glass opacities and patchy ground glass opacities , with a subpleural distribution.

Figure 2. Changes in critical lab test results during hospital stay of case 1 : there was a progressive increase in creatinine with a significant decrease in eGFR after admission. With the progressive increase of leukocytes, the lymphocyte count dropped from $0.8 \times 10^9/L$ to $0.4 \times 10^9/L$ and stabilized at this level. At the same time, CRP level increased significantly to 100mg/L on the 4th day of hospitalization, with platelet showing a downward trend.

Figure 3. Changes in body temperature. Case 1: The body temperature was normal (36.5°C) at the time of admission, followed by fever in the daytime, which fluctuated from 37.5°C to 38.0°C . On the second day, the body temperature dropped to normal in the morning and then lasted for 70 hours. On the 5th morning, the body temperature rose to 38.8°C and then fell to normal. Case 2: The body temperature was normal (36.0°C) at the time of admission, and the fever of remittent appeared from the next day. The body temperature fluctuated from 37.9°C to 38.8°C . Since the 7th day of hospitalization, the body temperature dropped to normal and fluctuated at 35.8°C - 36.7°C .

Figure 4. Case 2: 37-year female with fever and cough. Non-enhanced chest computed tomography (CT) showed multiple, bilateral, peripheral, patchy ground glass opacities, with a subpleural distribution, slight thickening of the adjacent pleura and interlobular septa. This is her CT scan at the time of onset.

Figure 5. Changes in critical lab test results during hospital stay of case 2. Case 2

was in CKD3 stage at the time of admission, and on the 9th day of hospitalization, there was a progressive decrease in serum creatinine with eGFR returning to 50ml/(min.1.73m²). After admission, leukocytes fluctuated from $1.0 \times 10^9/\text{L}$ to $8.0 \times 10^9/\text{L}$, and that of platelets increased from $120\text{--}220 \times 10^9/\text{L}$. Lymphocytes decreased from $0.4 \times 10^9/\text{L}$ to $0.2 \times 10^9/\text{L}$, and continued to rise to $1.5 \times 10^9/\text{L}$ on the 7th day. Meanwhile, CRP decreased to normal after reaching a peak (35mg/L) on the 5th day.

Figure 6. Case 2: Chest CT images of a 37-year-old female, with pneumonia caused by coronavirus disease-19 (COVID-19). (A) Chest CT with axial planes shows multiple mixed ground-glass opacities and linear opacities in the bilateral lung lobes. (B) Chest CT with axial planes shows the improvement of pneumonia with decreased ground-glass opacities and linear opacities in the subpleural area. (C) Chest CT with axial planes shows the minimal absorption of both ground-glass opacities and linear opacities in the bilateral lung lobes.

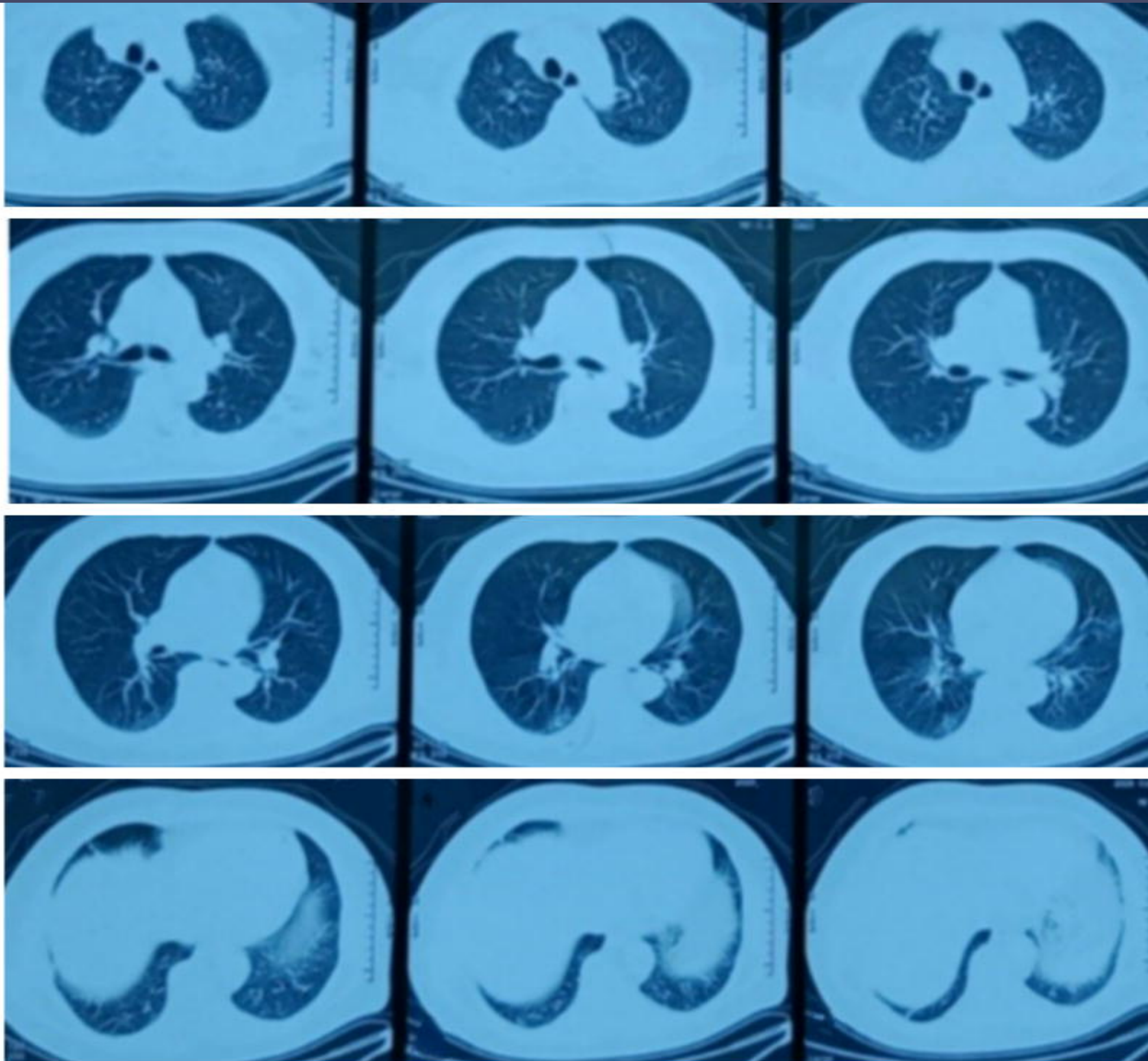
Abbreviation: Cr: serum creatine; eGFR: estimated glomerular filtration rate; hs-CRP: high sensitivity C-reactive protein; WBC: white blood cell; LY: lymphocyte; PLT: Platelet

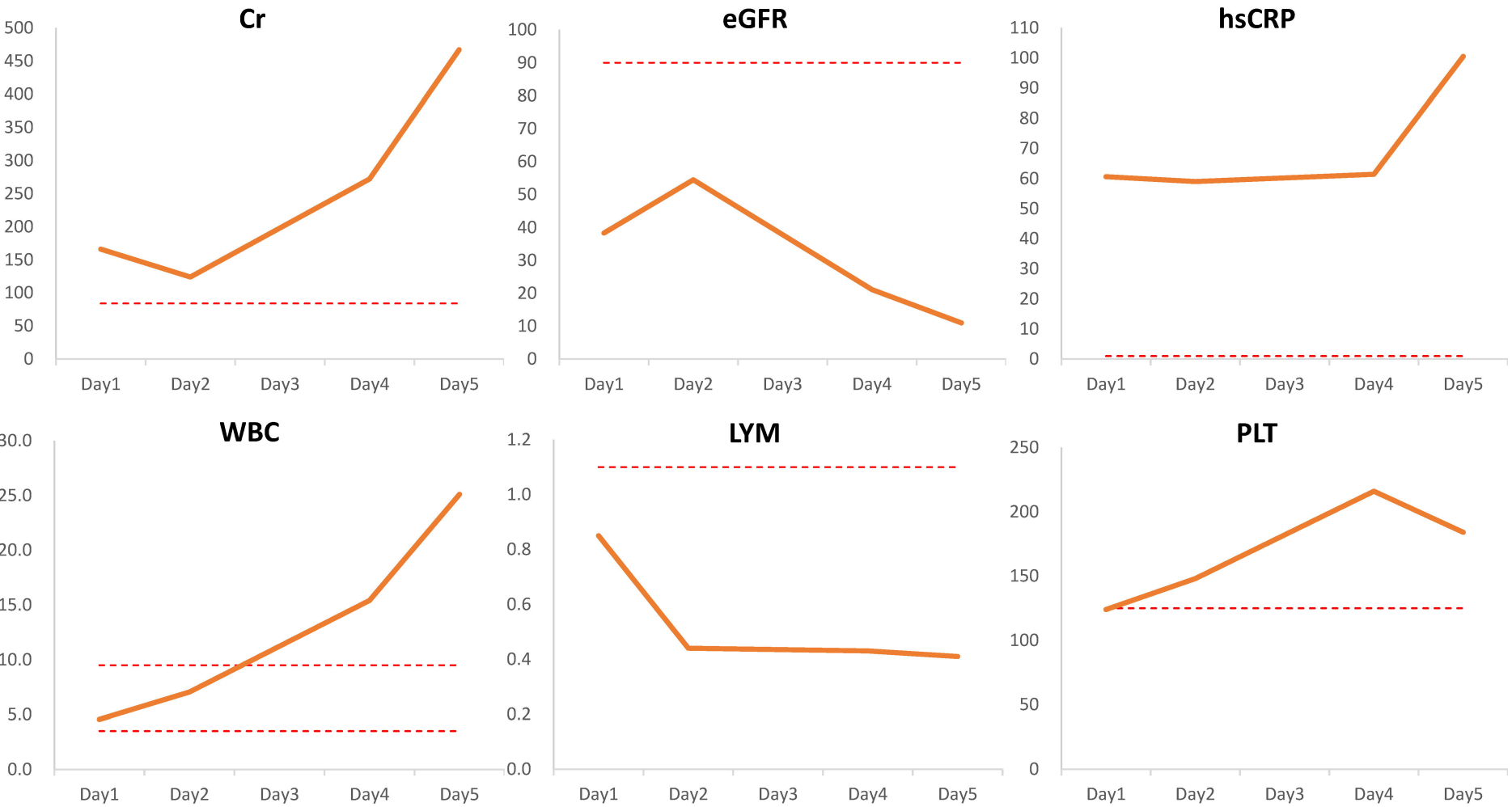
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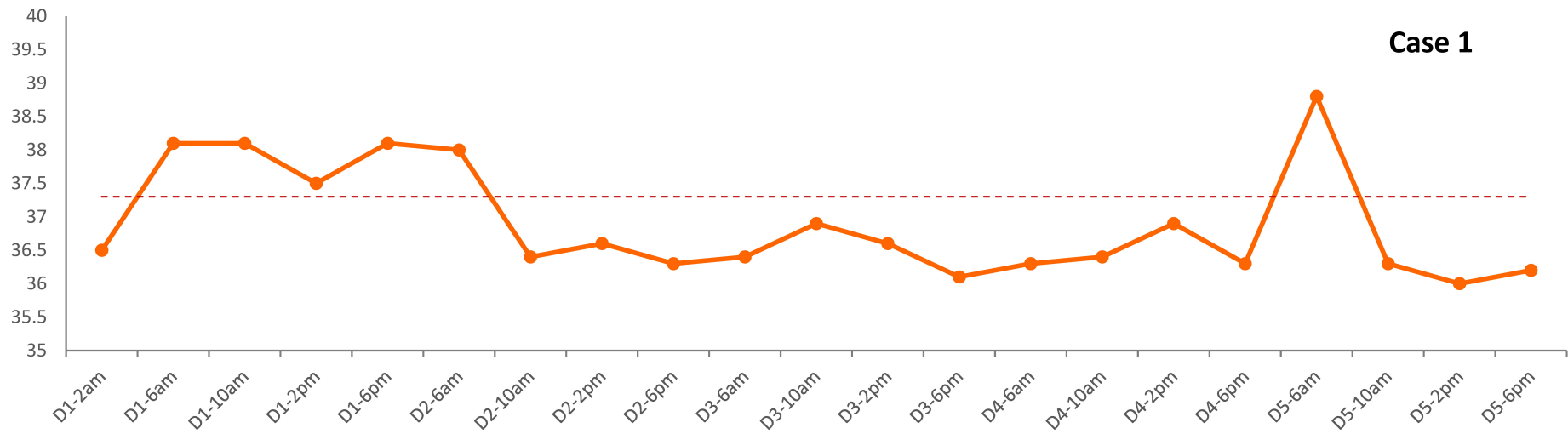
Disclosures

None.

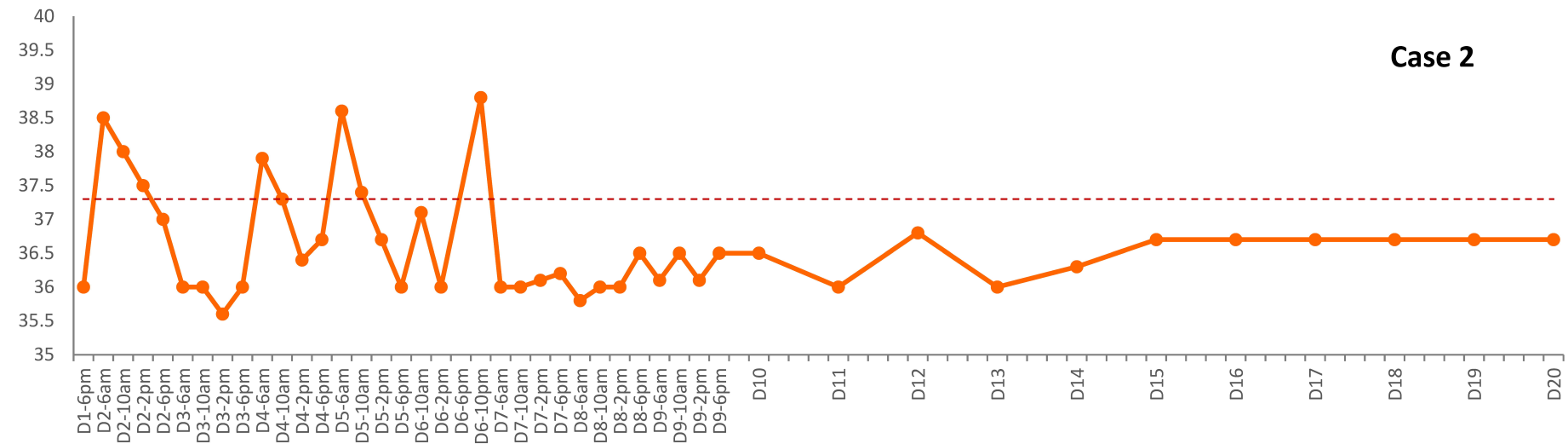


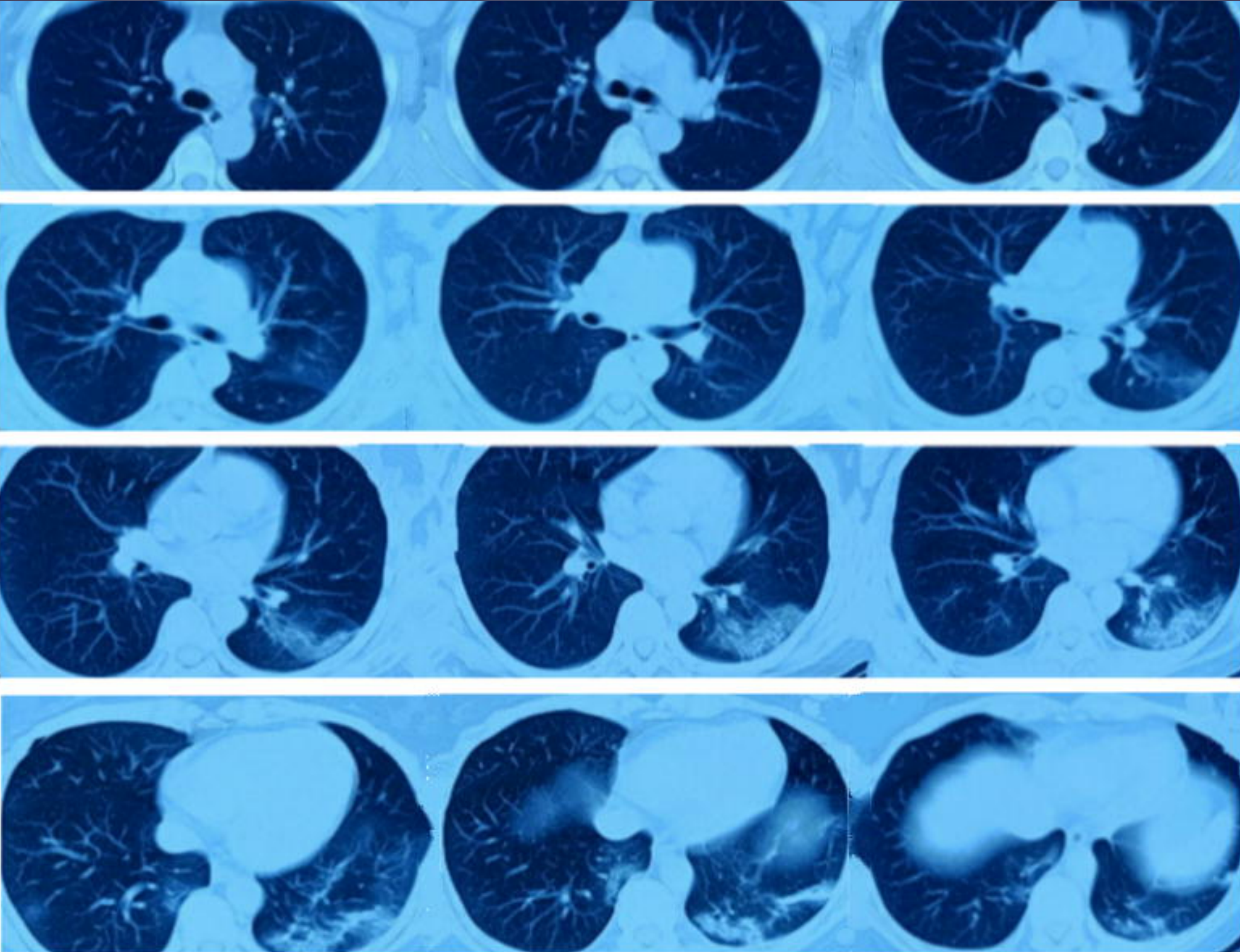


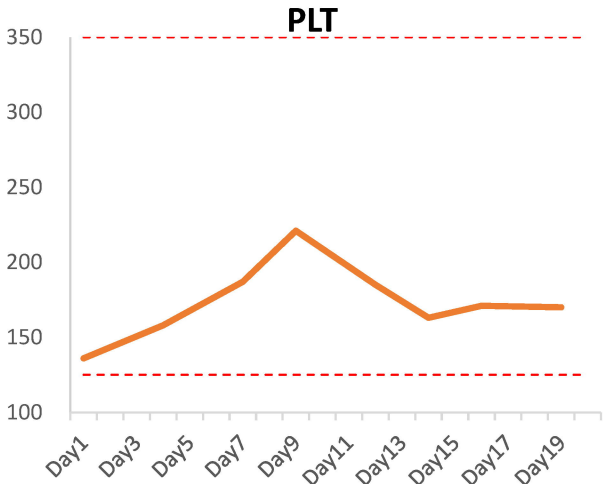
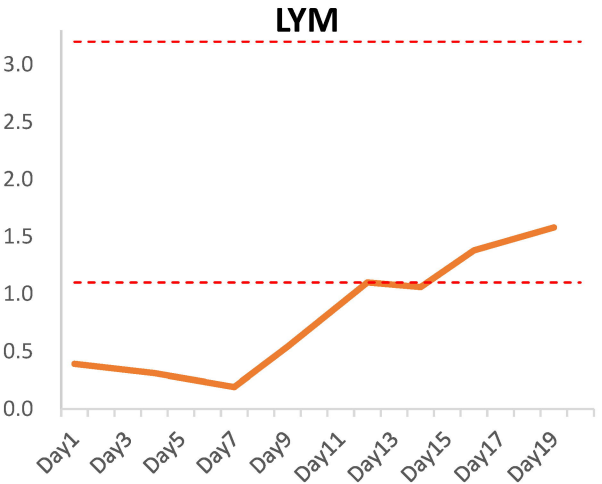
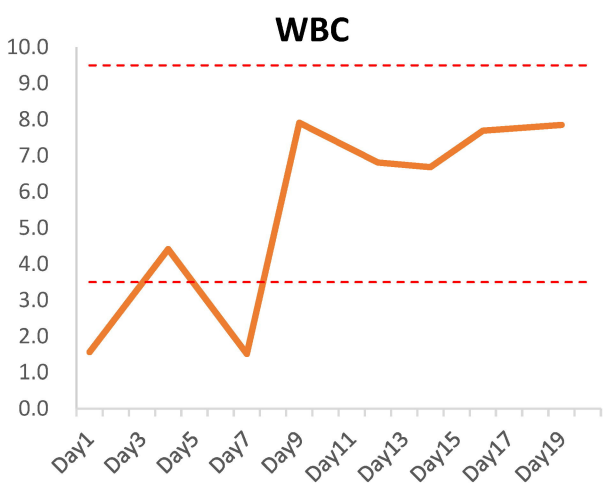
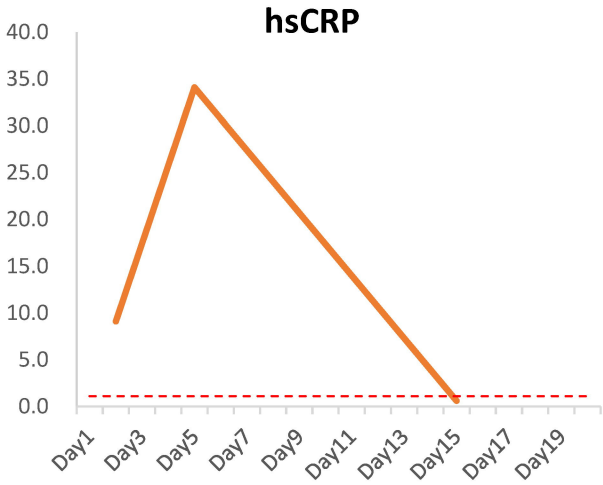
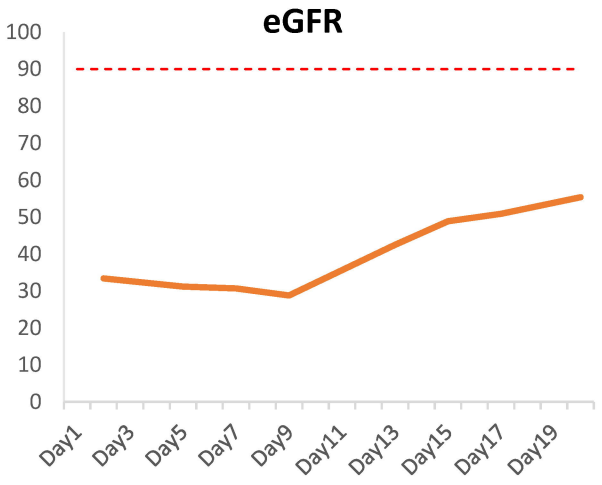
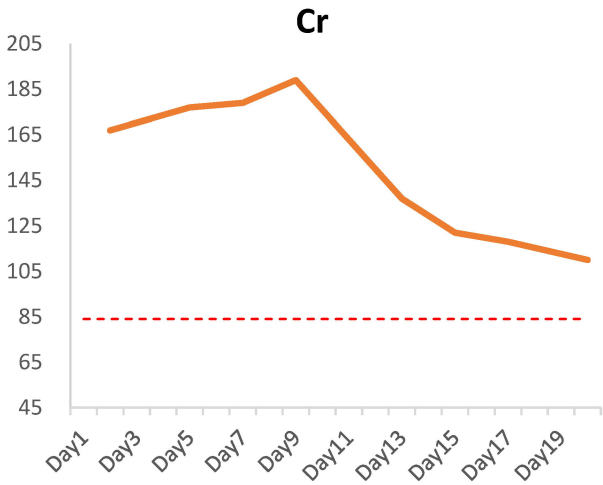
Case 1

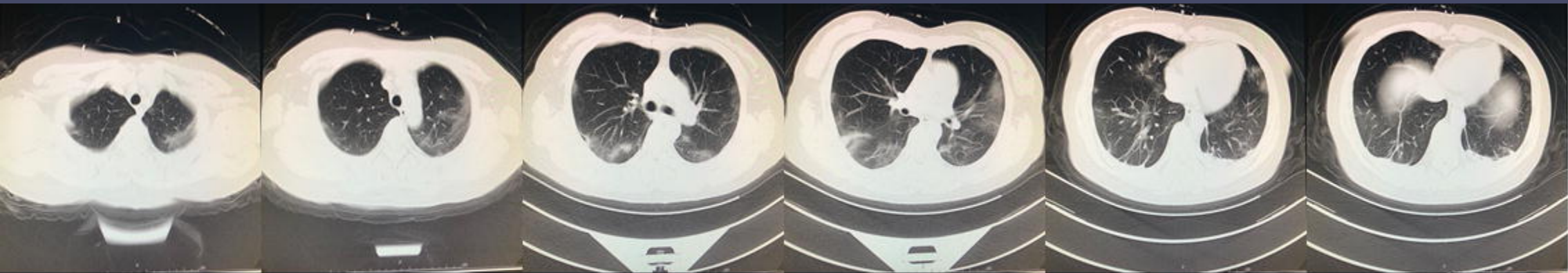


Case 2

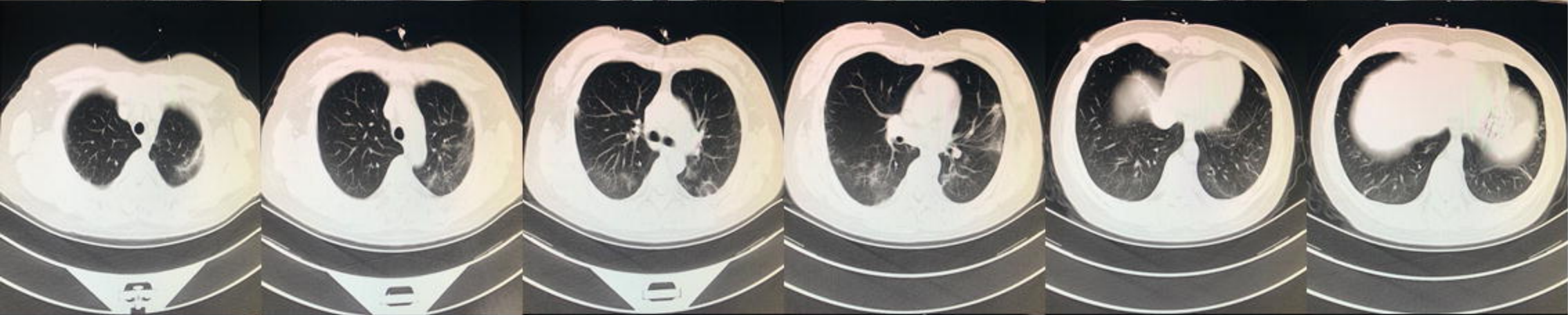




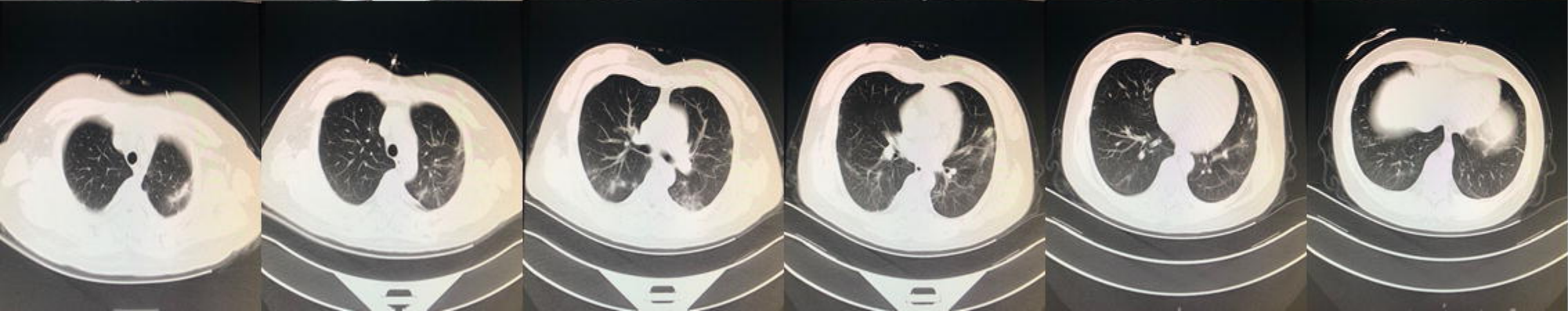




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(B)
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(C)
2020-3-4