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Different clinical presentations of two renal transplant recipients with Coronavirus Disease 2019: a case report

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Abstract

Background: The Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus-2 has spread rapidly worldwide and disease spread is currently increasing. The clinical picture of transplant recipients and the effect of the anti-rejection immunosuppressive regimens on the clinical course of COVID-19 are lacking.

Case presentation: We report two cases of COVID-19infection in renal transplant recipients with variable clinical presentations. The first patient presented with mild respiratory symptoms and a stableclinical course. The second patient had more severe clinical characteristics and presented with severe pneumonia and multi-organ failure. Both patients received a combination therapy including antiviral treatment and reducedimmunosuppressiontherapy and finally recovered.

Conclusions: We report COVID-19 infectionin two renal transplant recipients with a favorable outcome but different clinical courses, which may provide a reference valuefor treating such patients. Additional data are needed to gain a better understanding of the impact of immunosuppressive therapy on the clinical presentation, severity, and outcome of COVID-19in solid organ transplant recipients.

Background

As of mid-March 2020, Coronavirus Disease 2019 (COVID–19) caused by severe acute respiratory syndrome Coronavirus–2 (SARS-CoV–2) has expanded to include over 234,000 confirmed cases and over 9800 deaths, involving 176 countries around the world. Analysis of the epidemiological pattern curve of COVID–19 showed that the overall epidemic pattern was an aggregation outbreak. Patients with COVID–19 may develop severe symptoms of acute respiratory infection, particularly those with comorbid conditions tend to have a high mortality rate [1].

Thus far, there are no specific therapeutic agents for COVID–19, and supportive care is the mainstay of management strategies. Clinical trials evaluating potential therapies, including remdesivir and chloroquine, are being conducted. Lopinavir and ritonavir are not only limited in transplantation due to drug-drug interactions with calcineurin inhibitors [2], but have also been reported to have no benefit beyond standard care in a recent study [3].

To the best of our knowledge, there has only been one previously reported case of a transplant recipient with COVID–19 [4]. The clinical picture of transplant recipients and the effect of the anti-rejection immunosuppressive regimens on the clinical course of COVID–19 are lacking. We report two cases of COVID–19 in renal transplant recipients with variable clinical presentations.

Case Presentation

Case 1

A 57-year-old man who underwent a renal transplant from his father due to chronic renal failure in 2013, was admitted to Union hospital in Wuhan on February 11, 2020, complaining of an unexplained fever (up to a maximum of 39.2°C) for 6 days. This was followed by cough, fatigue, nausea, and shortness of breath, while no chest pain, sore throat, diarrhea, or abdominal pain were present. The patient had no history of smoking or alcohol abuse, cardiovascular disease, or pulmonary disease. His immunosuppressive regimen consisted of tacrolimus 1.5 mg orally twice daily, and mycophenolate mofetil 0.75 g twice daily until 2 days prior to his visit.

On admission, his chest computed tomography (CT) scan showed multiple patchy ground-glass opacities in the bilateral lungs (Fig. 1A). Laboratory testing revealed an absolute lymphocyte count of 0.98 10^9/L (normal range, 1.1–3.2 10^9/L), serum creatinine 142 μmolL (normal range, 59–104 μmolL), and estimated glomerular filtration rate (eGFR) of 49.3 ml/min/1.73 m^2 (normal range, □90 ml/min/1.73 m^2). A nasopharyngeal swab specimen was obtained and sent for detection of SARS-CoV–2 according to the CDC guidelines [5]. In brief, throat-swab specimens from the upper respiratory tract were obtained and maintained in a viral-transport medium. SARS-CoV–2 was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) as previously reported [6]. The patient was diagnosed with COVID–19 according to the positive detection of SARS-CoV–2 and chest CT display.

Combination therapy was initiated with immunoglobin (10 g per day), methylprednisolone (40 mg daily), recombinant human interferon-alpha 2b (10 million IU daily), arbidol hydrochloride (0.6 g daily), and biapenem (0.6 g daily), for 12 days, in order to inhibit virus replication and implement empirical antibiotic treatment. Four days after admission, the alanine aminotransferase level

increased to 76 U/L (normal range, 0–40 U/L), and by day 8 it had increased further to 93 U/, which indicated hepatic damage. Glutathione was then initiated by 1.8 g intravenous injection daily for 9 days. Immunosuppression was resumed on day 2 after admission, including tacrolimus 1 mg twice daily, and mycophenolate mofetil 0.375 g twice daily (adjusted to 0.75 g twice daily on day 10). High-flow humidification oxygen inhalation therapy was used to prevent acute hypoxic respiratory failure. During treatment, the patient's symptoms resolved with body temperature falling to between 36.3°C and 37.1°C, and his cough, nausea, and shortness of breath disappeared. The laboratory results were also improved, in particular, the lymphocyte count, serum creatinine, eGFR, and alanine aminotransferase (Fig. 2). On day 4, the second chest CT scan indicated that his pneumonia had aggravated (Fig. 1B). On day 9, the third chest CT scan (Fig. 1C) showed significant absorption of bilateral ground glass opacities compared to the previous scans. Based on the persistent negative results of SARS-CoV–2 RT-PCR on days 7 and 9, as well as the lung lesions partially absorbed, the patient was discharged on day 13.

Case 2

A 55-year-old man, who underwent a renal transplant in 2013 due to chronic kidney disease presented to the emergency department of Tongji Hospital on February 13, 2014, complaining of oliguria (400 ml) and a cough for 10 days, and shortness of breath for 2 days. He did not complain of fever, sore throat, or diarrhea. The patient had a history of surgery for urinary tract obstruction due to kidney stones and concomitant myocardial infarction in 2019. His immunosuppression was mycophenolate mofetil 0.5 g twice daily, tacrolimus 2.5 mg twice daily, and methylprednisolone 8 mg once daily.

On admission, he required 7 L/min of oxygen through a facemask to maintain an oxygen saturation of 95%, with a blood pressure of 82/50 mmHg and a heart rate of 99 bpm. His chest CT scan showed bilateral diffuse ground-glass changes (Fig. 3A). Laboratory testing revealed an absolute lymphocyte count of 0.31 10^9/L, serum creatinine 247 μmolL, eGFR 24.4 ml/min/1.73 m^2, high-sensitivity troponin I (hsTNI) 312.8 pg/mL (normal range, 34.2 pg/mL), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) 70000 pg/mL (normal range, 161 pg/mL). Nasopharyngeal swabs on admission were positive

for SARS-CoV–2 RT-PCR. Continuous veno-venous hemodialysis and hemofiltration were promptly started. He developed arrhythmia (atrial fibrillation with rapid ventricular rate) on day 3 and initially received synchronized cardioversion and noninvasive mechanical ventilation with bi-level positive airway pressure therapy. On day 5, the level of hsTNI increased to 1580.3 pg/mL and the NT-proBNP level was 70000 pg/mL, which indicated acute congestive heart failure. After diuresis, cardiotonics, steroids, and respiratory support, the patient's clinical condition improved and he was transferred to the general ward for infectious diseases.

The patient received treatment with immunoglobin, arbidol hydrochloride, recombinant human interferon-alpha2 b, and antimicrobial therapy consisting of biapenem and micafungin according to the clinical events. Antimicrobial doses were adjusted to the patient's creatinine clearance, and the immunosuppressive regimen was adjusted to the clinical condition, including CT scans, laboratory results, FK506 blood concentration, and symptoms (Fig. 4). On day 14, due to the persistent lymphocyte depletion and an abnormal ratio of lymphocyte subsets, the dose of immunoglobin was reduced to 5 g per day, and mycophenolate mofetil to 0.5 g daily. On day 16, mycophenolate mofetil was discontinued and tacrolimus was reduced to 3 mg daily due to the development of bacterial and mycotic pneumonia, and re-adjusted on day 22 due to the negative results of SARS-CoV–2 RT-PCR (Fig. 4).

During treatment, the patient's symptoms resolved and laboratory tests, including D-dimer, C-reactive protein (CRP), and interleukin 6 (IL–6), were improved significantly with days, although the lymphocyte count did not change significantly until the day of discharge (Fig. 5A). However, when comparing the lymphocyte subsets, the percentages of $CD3^+$ T cells, CD3+CD4+ T cells (helper/inducer T cells), and the ratio of CD3+CD4+ T cells/CD3+CD8+ T cells decreased with the clinical course of the disease, while the percentage of CD3+CD8+ T cells (suppressor/cytotoxic T cells) and CD16+CD56+ T cells (natural killer cells, NK) increased with the clinical course of the disease (Fig. 5B). On day 10, the second chest CT scan indicated that his pneumonia aggravated with multiple patchy opacities and local consolidation (Fig. 3B). On day 18, the third chest CT scan showed significant absorption of multiple patchy opacities (Fig. 3C). On day 25, the fourth chest CT scan

showed absorption of local consolidation compared to the third scan (Fig. 3D). In addition, the high flow humidification oxygen inhalation therapy was removed until the 26th day of treatment, based on the markedly improved respiratory function. Given the remission of the disease, as well as the persistent negative results of SARS-CoV–2 RT-PCR, the patient was discharged on day 28.

Discussion

Transplant recipients have a high susceptibility to viral pneumonia, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and now COVID–19. Here, we report two cases of COVID–19 in renal transplant recipients with variable clinical presentations. Diagnosis was based on symptoms and chest CT scan, and was confirmed using real-time RT-PCR assays according to the Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection (Trial Version 5) issued by the National Health Commission of the People's Republic of China. The severity of COVID–19 is classified as asymptomatic, mild, severe, and critical cases of pneumonia (acute respiratory distress syndrome, sepsis, septic shock). In this report, the first patient was a mild case, and the second patient was a critical case.

In case 1, the patient had a stable clinical course. Although his pneumonia was aggravated on day 4 and an abnormal increase in serum creatinine and ALT indicated kidney and liver injury on day 8, his symptoms were relieved and the laboratory results improved after treatment, which may be associated with the continuous rise in lymphocyte count during treatment. We speculate that the activation of lymphocytes may be due to the withdrawal of immunosuppressive drugs for 3 days at the early stage of the disease.

In case 2, the patient had more severe clinical characteristics, presenting with severe pneumonia and multi-organ failure. The patient's heart failure was probably in part related to the excess fluid volume caused by his renal failure and myocardial infarction. Although there is currently no evidence to suggest that viral tropism to uroepithelial cells plays a role in causing acute renal failure in COVID–19, it has been confirmed as a cause of MERS CoV infection [7]. Secondary mixed bacterial-fungal pneumonia was confirmed on day 16 after admission, and was accompanied by a positive result for SARS-CoV–2 RT-PCR, which reduced or even eliminated the dosage of anti-rejection medications. On

day 22, the test was negative and the patient's condition improved markedly, which indicated that temporary cessation of immunosuppression was effective at that time.

In these two cases, we observed different profiles of lymphocyte counts, which fluctuated below the normal range in case 2 and continuously rose within the normal range in case 1. Similarly, previous studies have suggested that lymphocytopenia is a typical laboratory abnormality and considered disease severity related to highly pathogenic coronavirus infections [8, 9]. As the disease progressed and the clinical status deteriorated, the levels of lymphocytes progressively decreased, which may explain why the clinical course of the two patients was so different [10]. In addition, kinetic changes in lymphocyte subsets in case 2 showed that the percentage of CD3+CD4+ T cells decreased and the percentage of CD3+CD8+ T cells and NK cells increased as the disease improved. When CD4+ T cells are below 200 cells/mm^3, patients with lymphocyte depletion have increased susceptibility to fungal infections[11], as was observed on day 16. Although dramatic loss of CD4+ and CD8+T cells in COVID–19 patients has been reported previously, it is unclear whether the increase in CD8+ T cells and NK cells were responsible for the recovery.

Inflammatory cytokine storm is another important characteristic in patients with severe COVID–19, which can rapidly cause severe immune damage to multiple organs and can ultimately be life-threatening. In line with this, we observed that the levels of D-dimer, CRP, and IL–6 were elevated initially and then decreased significantly during recovery, as evidenced by relieving pulmonary lesions on chest CT scan in case 2. It is also supported by a previous study that demonstrated that the decrease in IL–6 was closely related to treatment effectiveness, while an increase in IL–6 indicated disease exacerbation [12]. A cytokine storm is directly or indirectly caused by SARS-CoV–2 infection, which can activate pathogenic T cells and produce IL–6 and granulocyte-macrophage colony stimulating factor (GM-CSF). Together, these changes further activate CD14+CD16+ inflammatory monocytes and produce more IL–6 and other inflammatory factors [13]. We suggest that IL–6 might be a valuable candidate for monitoring severe type COVID–19.

Due to the small number of patients, it remains unclear whether the natural history of COVID–19 is altered in transplant recipients. However, it appears that it may be similar to that of the non-

transplant population based on the variable clinical presentation of these two cases.

Conclusion

We report COVID–19 infection in two renal transplant recipients with a favorable outcome but different clinical courses, which may provide a reference value for treating such patients. Additional data are needed to gain a better understanding of the impact of anti-rejection immunosuppressive therapy on the clinical presentation, severity, and outcome of COVID–19 in solid organ transplant recipients.

Abbreviations

ALT: Alanine aminotransferase; COVID–19: Coronavirus Disease 2019; CRP: C-reactive protein; CT: Computed tomography; eGFR: Estimated glomerular filtration rate; IL–6: Interleukin 6; RT-PCR: Reverse transcription polymerase chain reaction; SARS-CoV–2: Severe acute respiratory syndrome coronavirus 2; hsTNI: High-sensitive troponin I; NT- proBNP: N-terminal pro-B-type natriuretic peptide; NK: Natural killer cell; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; GM-CSF, Granulocyte-macrophage colony stimulating factor

Declarations

Ethics approval and consent to participate

Not applicable, consent was obtained from both patients described in this report.

Consent for publication

Written informed consent was obtained from both patients for publication of this case report and any accompanying details and images. Written consent is available by request.

Availability of data and materials

All material and data described in the manuscript are available upon request to the corresponding author of the present article.

Competing interests

The authors declare that they have no potential conflicts of interest to disclose.

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Authors' contributions

JL, GC and CC collected the patients’ health related data. MZ and ST analyzed and interpreted routine diagnostic results. JL, GC and CC wrote the manuscript. All authors read and approved the final manuscript.

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Figures

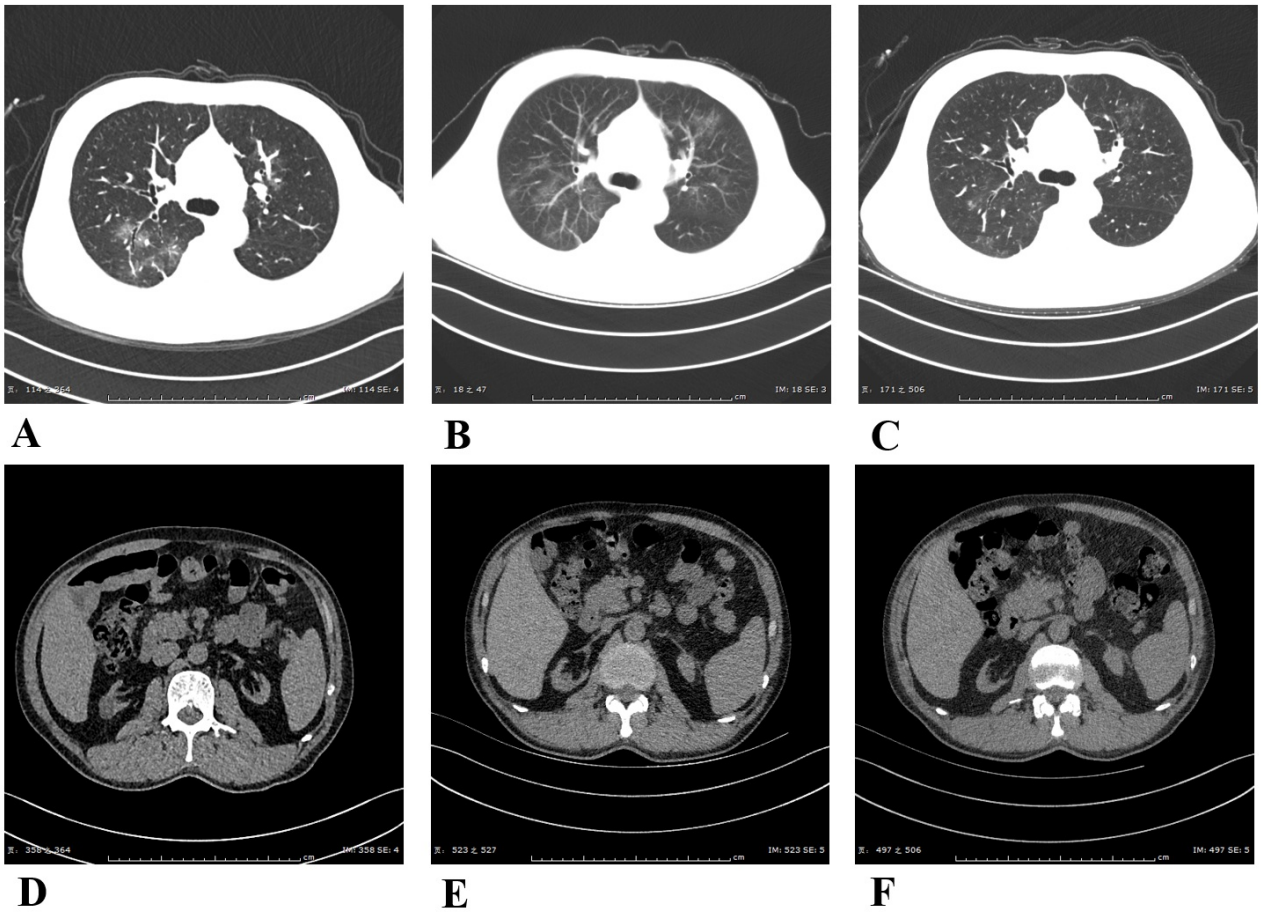

Figure 1

The chest computed tomography (CT) scan showed multiple patchy ground-glass opacities on admission (A), aggravation on day 4 (B), and significant absorption on day 9 (C). Bilateral renal atrophy was observed on admission (D), day 4 (E), and day 9 (F).

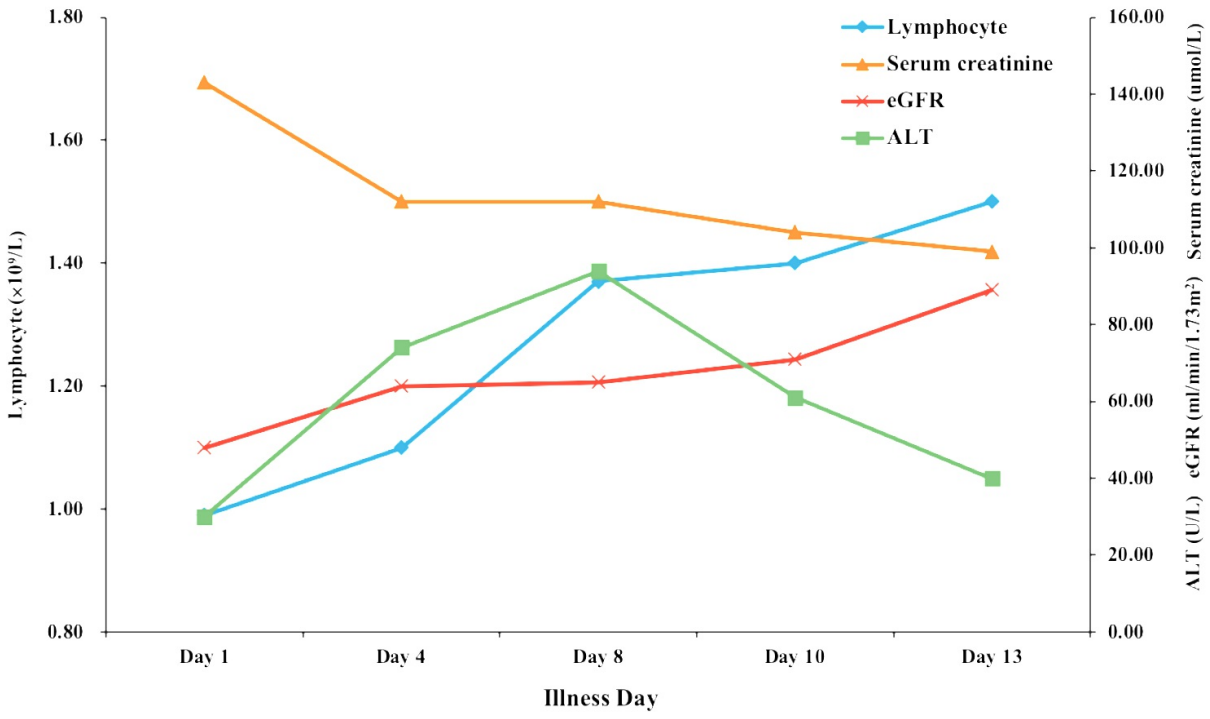

Figure 2

The lymphocyte count and estimated glomerular filtration rate (eGFR) is continuously increasing and serum creatinine is decreasing. The level of alanine aminotransferase (ALT) initially increased and then decreased during treatment.

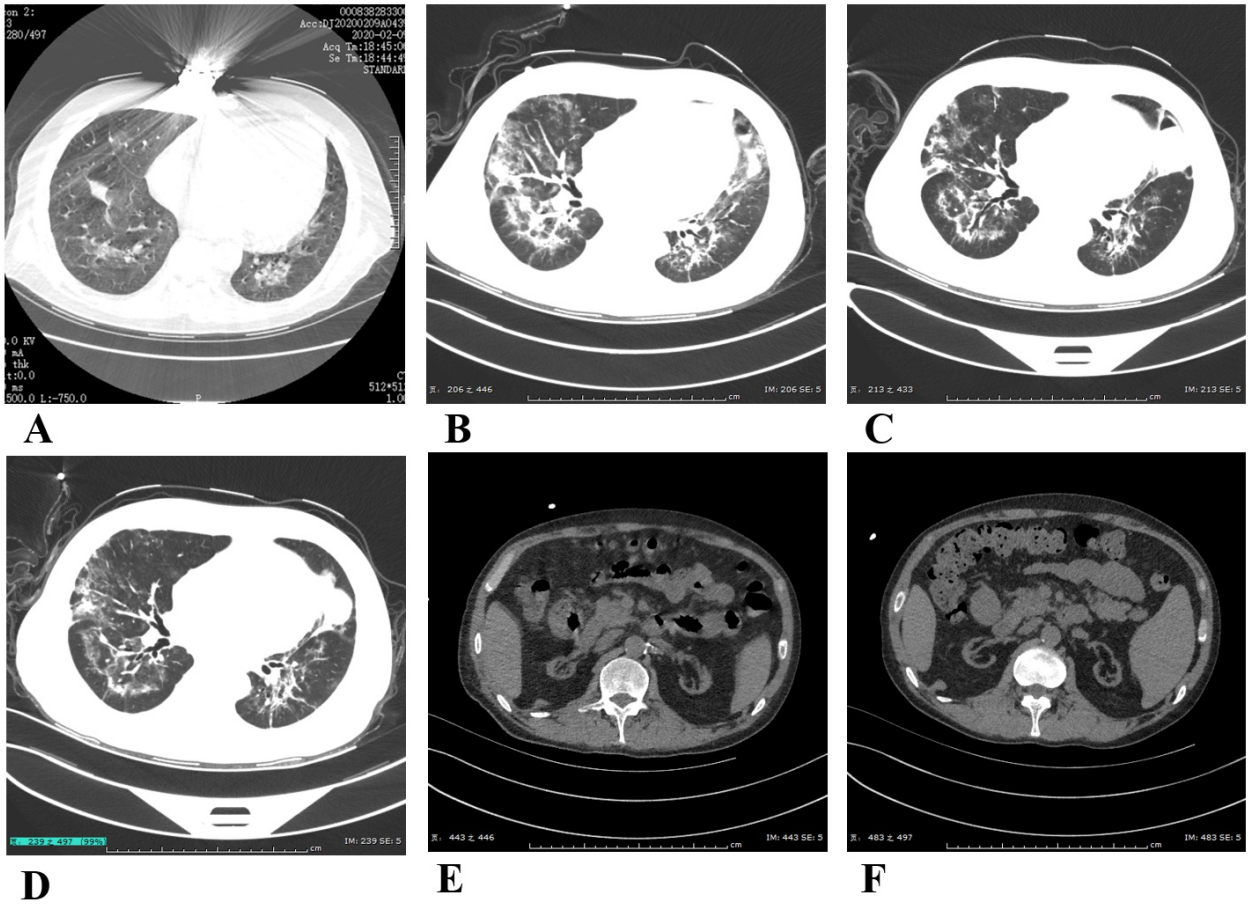

Figure 3

The chest computed tomography (CT) scan showed bilateral diffuse ground-glass changes on admission (A), aggravation on day 10 (B), significant absorption on day 18 (C), and absorption of local consolidation on day 25 (D). Bilateral renal atrophy was observed on admission (E) and day 25 (F).

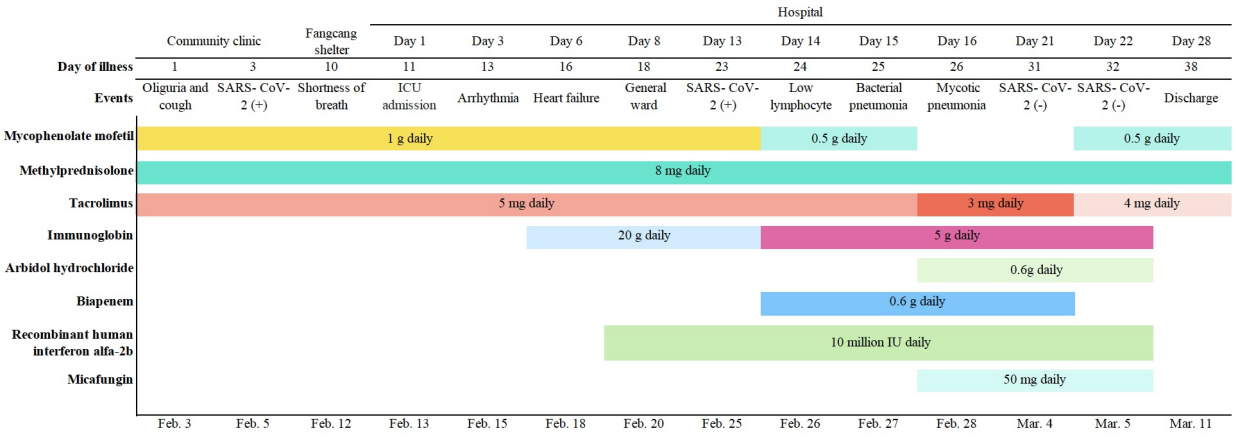

Figure 4

Medication strategy according to day of illness and day of hospitalization, February 3 to March 11, 2020.

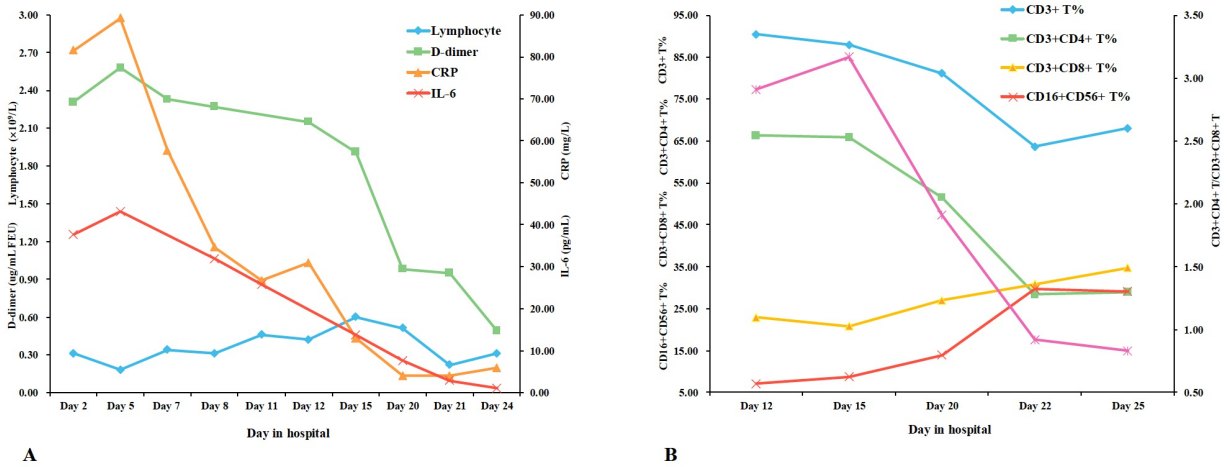

Figure 5

The levels of D-dimer, C-reactive protein (CRP), and interleukin 6 (IL-6) decreased, and the lymphocyte count fluctuated during treatment (A). The percentage of CD3+ T cells, CD3+CD4+ T cells, and the ratio of CD3+CD4+ T cells/CD3+CD8+ T cells decreased, and the percentage of CD3+CD8+ T cells and CD16+CD56+ T cells increased during treatment (B).