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LETTER TO THE EDITOR

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# COVID-19 and liver transplantation: Lessons learned from three reported cases

To the Editor,

During the COVID-19 pandemic, transplant recipients have been recognized as more susceptible to infection, to have greater severity of disease, and prolonged shedding of this highly transmissible virus.[1] However, there is limited information on the impact of COVID-19 in liver transplant (LT) recipients. We reviewed three reported cases with detailed treatment information from China to better understand the features and associated therapeutic strategies used in transplant recipients with COVID-19.[2-4]

As summarized in Table 1, three patients all received immunosuppressive therapy after transplantation and were initially diagnosed as having mild disease and then progressed to severe illness. High fever (ie, >39°C) was common in the patients, which differed from previous reports that organ transplant recipients present with only low-grade or no fever. Similar to the general population, lymphopenia was common, while multiple peripheral pulmonary ground-glass opacities were the typical radiological findings during progressive infection.

Two patients (cases 1 and 2) of similar age with post-transplant infections had opposite outcomes. The first patient (case 1) was infected by his wife.[2] During hospitalization, immunosuppressive therapy with maintained with tacrolimus and mycophenolate. He also received standard methylprednisolone therapy. Despite antibacterial treatment, he succumbed to secondary bacterial and fungal infection. The second patient (case 2) was suspected of having opportunistic infections; treatment was subsequently changed to discontinuation of tacrolimus and addition of cefoperazone.[3] After a month of treatment, he successfully recovered and was discharged. Unlike these two patients, the third (case 3) was infected with COVID-19 during the perioperative period.[4] Antimicrobial agents were started immediately following transplantation because of persistent fever. When COVID-19 was confirmed, tacrolimus and glucocorticoids were titrated to lower doses. After 60 days of hospitalization, he was successfully discharged.

Current data suggest that an exaggerated innate immune response is important in instigating severe illness in patients with COVID-19. In this context, the immunocompromised host may be protected by a weaker innate response against severe COVID-19. However, this ignores the fact that recipients are more likely to develop secondary bacterial or fungal infections, which was found in all three of the cases.[5]

Successful treatment of opportunistic infection is important in the context of transplantation. Insufficient immunosuppression might result in acute graft rejection, whereas excessive immune suppression can lead to secondary nosocomial infections. Thus, healthcare professionals need to carefully balance the risks and benefits of altering immunosuppressive regimens in LT recipients. Based on the cases presented, a reduction or temporary halt to immunosuppressive agents might be considered in patients with serious infections who have a low risk of rejection. According to the current literature, LT recipients with serious infections are rare in the context of acute graft rejection.

Previous experience from SARS indicated that treatment with high-dose corticosteroids yielded little benefit in transplant recipients. Similarly, the WHO recommends avoiding the use of corticosteroids in the treatment of patients with COVID-19.

Prevention is the best "treatment." In epidemic hotspots with high risk of SARS-CoV-2 transmission, transplant recipients should practice social distancing even with family members in the same household.

## KEYWORDS

COVID-19, liver transplantation

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

## AUTHORS' CONTRIBUTIONS

Feng Gao and Ming-Hua Zheng conceived and designed the study. Fen Gao and Jin-Yang Gu interpreted and analyzed the data. Feng Gao and Kenneth I. Zheng drafted the manuscript. Jacob George critically revised the manuscript for important intellectual content. Ming-Hua Zheng supervised the study. All authors contributed to the manuscript for important intellectual contents and approved the submission.

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**Abbreviations:** COVID-19, coronavirus disease 2019; LT, liver transplantation; SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus 2.

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**TABLE 1** Characteristics of the three patients

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Age (year)/sex | 59/Male | 50/Male | 37/Male |
| Co-morbidities | Obstructive jaundice | Nil | Nil |
| Indication for liver transplant | Hepatocellular carcinoma | Hepatitis B cirrhosis | Hepatocellular carcinoma |
| Duration of liver disease prior to transplant | Diagnosed HBV infection 25 y ago and hepatocellular carcinoma 3 y previously | Unknown | Diagnosed HBV infection 19 y ago and multiple hepatic masses 3 mo previously |
| Post-transplant complications | Several episodes of jaundice after transplantation | Nil | Nil |
| Maintenance immunosuppression | Tacrolimus and mycophenolate (unknown dosage) | Tacrolimus (at a mean dose of 0.03 mg/kg/d) monotherapy | Tacrolimus and systemic glucocorticoids (unknown dosage) |
| Interval from transplant to onset of COVID-19 symptoms | Two years and nine | Two and a half years | 3 d before transplantation (during the perioperative period) |
| Interval from onset of symptoms to admission | 3 d | 6 d | 4 d after admission (during the perioperative period) |
| Exposure history | Close contact with his wife who was diagnosed with COVID-19 | A resident of Wuhan, exposure history uncertain | A resident of Wuhan, exposure history uncertain (fever on the fourth day of admission) |
| Symptoms and signs on admission | Fever (up to 40°C), jaundice, splenomegaly, and ascites | Fever (up to 39.6°C) | Fever (up to 39°C) on day 4 |
| Abnormal biochemical indicators on admission | White cell count: $3.2 \times 10^9$/L;<br>Lymphocyte count: $0.7 \times 10^9$/L;<br>C-reactive protein: 35.1 mg/L;<br>Total bilirubin: 83.9 μmol/L;<br>ALT: 60 U/L;<br>GGT: 1087 U/L | White cell count: $5.9 \times 10^9$/L;<br>Lymphocyte count: $0.42 \times 10^9$/L;<br>High sensitivity C-reactive protein: 32.1 mg/L;<br>Liver transaminases: normal | Neutrophil count: $7.51 \times 10^9$/L;<br>Lymphocyte count: $0.64 \times 10^9$/L |
| Chest computed tomography (CT) scan | Day 1: Bilateral ground-glass opacities;<br>Day 12: Significant worsening of bilateral lung inflammation. | Day 1: Multiple peripheral patchy ground-glass shadows in both lungs;<br>Day 8: Mixed diffuse ground-glass opacities with multifocal patchy consolidation involving both lungs and bronchiectasis in left lower lobe;<br>Day 28: Bilateral peripheral distribution of small patchy consolidations and reticular fibrosis and exudative lesions—improved | Day 9: Bilateral hypostatic change and minor pleural effusion in the right thoracic cavity;<br>Day 28: Multicentric subpleural ground-glass opacification in the left lobe;<br>Day 36: Resolution of the infiltrate in the left lobe and progression of pleural effusion in the right lung |
| Microbiologic cultures | Blood culture was positive for candida albicans, and alveolar lavage and pleural fluid were positive for pseudomonas aeruginosa (d12);<br>Bile duct pus was positive for pseudomonas aeruginosa (d23) | Not mentioned | Sputum culture was positive for gram-positive cocci and gram-negative bacilli (d9) |

(Continues)

**TABLE 1** (Continued)

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Changes in patients' conditions during hospitalization | Developed respiratory failure (d4); multiple organ failure (d37) | Presented with progressive dyspnea (d5); clinical symptoms resolved (d24) | ALT and AST levels gradually elevated (d26); fever subsided (d33); and suspected acute cellular rejection (d40); |
| Immunosuppressants | Tacrolimus and mycophenolate were maintained | Discontinued tacrolimus for 4 wks (d2-29); | Tacrolimus gradually titrated to lower doses (d19-39); |
| Glucocorticoid | Standard methylprednisolone (d4) | Systemic methylprednisolone (d2) | Glucocorticoids were gradually titrated to lower doses (d19) |
| Antiviral agents | α-interferon, arbidol and lopinavir/ritonavir | α-interferon, umifenovir, and lopinavir/ritonavir | Oseltamivir |
| Antimicrobial agents | Piperacillin-tazobactam (d1); cefoperazone-sulbactam and caspofungin (d12); and meropenem and voriconazole (d23) | Cefoperazone (d1) | Cefdinir (d4-6); imipenem and cilastatin (d7-21); caspofungin (d7-21); and linezolid (d8-21) |
| Intravenous immunoglobulin | Yes | Yes | Yes |
| Repeat COVID-19 RT-PCR test | Negative on days 33 and 35 | Two consecutive negative nucleic acid tests before discharge | Negative on days 34 and 52; Positive on day 53 and returned to negative on day 56 |
| Outcome | Died on day 45 | Alive and discharged on day 31 | Alive and discharged on day 60 |

*Note:* The first day of hospital admission was assumed as day 1 (d1).

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