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# Recovery of Moderate Coronavirus Disease 2019 in a Liver Transplant Recipient on Continued Immunosuppression: A Case Report

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## ABSTRACT

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had an enormous impact on the world. Owing to limited data available, it remains unclear to what extent liver transplant recipients should be considered at a higher risk of severe disease.

We describe a moderate course of coronavirus disease 2019 (COVID-19) in a patient who underwent a liver transplant 2 years earlier because of Budd-Chiari syndrome. The patient presented with malaise, headache, dry cough, and fever for 4 days. Immunosuppressive therapy with tacrolimus and mycophenolate mofetil was continued throughout the course of infection. Oxygen therapy was given for a single night, and the patient gradually recovered with supportive care only.

With this case report, we demonstrate that liver transplantation and immunosuppression is not necessarily associated with severe COVID-19 and emphasize that more information on this matter is urgently required. Withdrawal of immunosuppressive therapy could be associated with higher mortality.

**T**HE global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has had an enormous impact on the world. Since the beginning of the outbreak, researchers worldwide have tirelessly tried to understand the disease. However, owing to the limited availability and quality of studies, it remains unclear to what extent liver transplant recipients should be considered at a higher risk of severe disease [1,2]. Further, the implications of immunosuppressive therapy are poorly understood. Consequently, we describe and discuss a case of moderate COVID-19 in a liver transplant recipient on continued immunosuppressive therapy.

## CASE PRESENTATION

A 58-year-old woman who had a liver transplantation 2 years earlier because of Budd-Chiari syndrome was admitted to the Department of Hepatology and Gastroenterology with 4 days of malaise, headache, dry cough, and fever. The patient denied other symptoms. She had no recent travel history or any known exposures to SARS-CoV-2. The patient had a medical history of hypertension, hypercholesterolemia, and obesity (body mass index [BMI] 37.1 kg/m<sup>2</sup>), and she had been treated for cholangitis shortly after her liver transplantation. The patient had no alcohol abuse and was a

previous smoker but stopped before transplantation. At admittance, the patient had been on stable immunosuppression with tacrolimus 4 mg daily and mycophenolate mofetil 500 mg twice daily for more than 1 year. Antihypertensive therapy consisted of amlodipine 5 mg and bendroflumethiazide with potassium 2.5+573 mg once daily.

On admission, the patient had a temperature of 38.6°C, blood pressure of 129/88 mm Hg, heart rate of 90 beats per minute, respiratory rate of 12 breaths per minute, and oxygen saturation of 96% on ambient air. Her physical examination was inconspicuous, and subsequent biochemistry showed only modest signs of COVID-19 with C-reactive protein of 9.8 mg/L (reference range < 8), creatinine of 97 μmol/L (reference range, 45-90), and alkaline phosphatase of 120 U/L (reference range, 35-105). Leukocytes were within normal ranges (reference range, 3.5-10.0). White blood cell differential was not conducted initially. Liver parameters were normal, and plasma tacrolimus was within therapeutic range (5.1 μg/L). A supine chest radiograph was without evident infiltrates. Urinary dipstick was normal. An oropharyngeal swab tested positive

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for SARS-CoV-2 RNA using reverse transcriptase polymerase chain reaction (PCR), and a nasopharyngeal swab was negative for influenza. Blood cultures were negative. Because of immunosuppression, suspicion of infection, and penicillin allergy, the patient was empirically treated with meropenem intravenously 1000 mg 3 times daily for 2 days. On day 6 after onset of symptoms, the patient was clinically stable and discharged to self-isolation with continued immunosuppressive therapy without further treatment. The patient denied cardiopulmonary symptoms but reported headache.

On day 11 after onset of symptoms, the patient was readmitted to the Department of Infectious Diseases with symptoms of increased fever, fatigue, headache, and dyspnea while walking on stairs. Her temperature was 38.6°C, and her oxygen saturation on ambient air was 92%. Vital parameters were stable. During the first night, meropenem was reinitiated, and the patient was given 1 L of nasal oxygen per minute, resulting in a saturation increase to 97%. C-reactive protein was 5.1 mg/L, leukocytes were  $5.1 \times 10^9/L$ , and lymphocytes were  $1.41 \times 10^9/L$ . Over the following 3 days, biochemistry was only modestly affected, with a maximum C-reactive protein level of 37.2 mg/L, mild lymphopenia ( $1.11 \times 10^9/L$ , reference range 1.30-3.50), erythrocyte sedimentation rate of 48 mm (reference range, < 30), albumin level of 32 g/L (reference range, 36-45), alkaline phosphatase level of 107 U/L, D-dimer level of 1.0 mg/l fibrinogen equivalent units (reference range, <0.60), and normal liver parameters. Chest radiograph was still without infiltrates. Sputum culture was negative, and PCR was negative for *Mycoplasma pneumoniae* and *Legionella pneumophila* DNA. After 3 days (day 14 after onset of symptoms), the patient improved, meropenem was discontinued as bacterial superinfection was unlikely, immunosuppressive therapy was still continued, and the patient was sent home to self-isolation.

Fifty days after onset of symptoms, the patient expressed a high degree of symptomatic improvement, although fatigue and dyspnea was still present when walking outdoors and doing physical activities. Hypogeusia and anosmia had resolved spontaneously 2 weeks after discharge.

## DISCUSSION

We describe a case of moderate COVID-19 in a liver transplant recipient who recovered during continued immunosuppressive therapy. Definition of disease severity was based on World Health Organization's guidelines [3]. In addition to showing that SARS-CoV-2 infection in liver transplant recipients on immunosuppressive therapy is not necessarily associated with severe COVID-19, the case demonstrates that these patients also present with a biphasic disease pattern as commonly described in COVID-19 and with clinical features similar to nonimmunosuppressed individuals [4-6].

While the literature on COVID-19 is rapidly accumulating, it remains unclear whether liver transplant recipients are at higher risk of severe COVID-19 compared with nontransplant patients and the background population. However, limited data suggest that COVID-19 may lead to more severe disease outcomes in liver and other solid organ transplant recipients, with overall mortality rates up to 28% [6-12]. However, a recent systematic review including 154 adult liver transplant recipients with COVID-19 demonstrated a mortality rate of only 2.6%, lower than the

mortality in many background populations [13]. Nonetheless, pre-existing medical conditions associated with severe COVID-19 such as hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, and obesity [5] may be more prevalent in liver transplant recipients [14], potentially increasing the risk of severe SARS-CoV-2 infection and blurring the impact assessment of immunosuppressive therapy. A recent nationwide study from Denmark found organ transplantation to be a significant but minor predictor for hospitalization and fatal outcome in SARS-CoV-2 PCR-positive patients, although only adjusting for sex and age [15].

While elevated alanine aminotransferase levels, reduced platelet counts, and reduced levels of albumin have been associated with an increased mortality [5], it has not yet been clarified whether these findings reflect underlying liver disease, direct liver damage, or immune-mediated cell-injury. Yet, abnormal liver parameters seem to be frequent in COVID-19 patients [16].

Despite the presence of comorbidity such as obesity and hypertension in our case, which is normally associated with worse outcome in COVID-19, one could speculate whether her current immunosuppressive treatment actually protected her from the severe outcome. In line with those considerations, it is currently being discussed whether immunosuppression may induce protection from the viral-induced hyperinflammatory syndrome characterized by cytokine storms and multiorgan failure or whether chronic immunosuppression constitutes a risk factor for severe disease [6,17]. It has been suggested that all patients with severe COVID-19 should be screened for hyperinflammatory biomarkers to identify subgroups of patients for whom specific immunosuppression could improve outcome [17]. For our patient, the course of disease was moderate and elaborated biomarker analysis was unfortunately not conducted, although that might potentially have been useful to predict disease outcome [18]. Moreover, a chest computed tomography scan was not conducted because of the relatively fast recovery and mild to moderate course of disease.

Preliminary data from Lombardy, Italy did not indicate an increased risk of severe COVID-19 in liver transplant recipients on immunosuppression and reported a low mortality rate of 3% in long-term liver transplant recipients [19]. In our case, the patient was continued on immunosuppressive therapy without any adjustments. However, among the first published reports of SARS-CoV-2-infected liver transplant recipients, temporary withdrawal of tacrolimus and administration of methylprednisolone 40 mg/day in a patient with severe lymphopenia was presented [20]. We speculate that increased mortality rates seen among organ transplant recipients could be associated with a reduction of immunosuppressive therapy. A recent systematic review of 89 studies on cancer and transplant patients with COVID-19 concluded that low-dose prednisolone and tacrolimus may have beneficial effects on SARS-CoV-2 infection, while the effects of mycophenolate mofetil are more unclear [21].

Another recent review concludes that, for now, it is not possible to provide evidence-based recommendations regarding the use of immunosuppressants in transplanted patients with COVID-19 [22].

A position paper from The European Association for the Study of the Liver and the European Society of Clinical Microbiology and Infectious Diseases has advised against reduction of immunosuppressive therapy and suggested that reduction should be considered only under certain circumstances [23], while other societies seems more inclined to favour reduction [24]. More studies are urgently needed to determine the implications of immunosuppressive therapy on COVID-19 [25]. As recently pointed out [26], there may be a trend toward reducing immunosuppressive therapy, particularly antimetabolites, in transplant recipients, although strong supporting evidence is not currently available [27]. For now, adjustments should be carefully individualized, and factors such as COVID-19 disease severity, degree of lymphopenia, type of immunosuppressive regimen, time from transplantation, and risk of acute graft rejection should be considered.

## CONCLUSIONS

In conclusion, more evidence on COVID-19 in liver transplant patients is urgently needed to guide clinical management, as these patients represent a potentially vulnerable cohort of patients. We suggest more studies should be conducted rapidly to determine the significance of immunosuppressive therapy.

## PATIENT'S PERSPECTIVE: MY EXPERIENCE WITH COVID-19

It all started with a fever. Sunday, day 0. I just thought I've had too much to do lately and took it a little easier.

Monday, day 1. I had a temperature of 38°C. I went to work, but after midday I felt ill and went home and rested. By early evening, a fever re-emerged (38.7°C), and I tried contacting the Department of Hepatology and Gastroenterology. As I could not reach them, I went to bed.

Tuesday, day 2. I contacted the outpatient clinic. My temperature was 38.5°C, and I was admitted to the ward. I tested negative for influenza.

Wednesday, day 3. I still had a fever and headache, and I now also had a slight cough. I went for a walk.

Thursday, day 4. I still had a fever, headache, and a discrete cough. At the ward rounds, I was offered testing for coronavirus. I thought: "Well... why not? Just in case." I was pretty calm because I was sure the test would come out negative. In the evening around 7:30 p.m., the answer came. The test was positive. I was very sad and worried what would happen to me. I was totally unprepared for that answer. However, under the circumstances I was alright, so I wanted to go home and was instructed on how to act and behave: isolation!

Friday, day 5. I was discharged and picked up by my husband, and we tried adapting to the situation. The

weekend went on, but my temperature increased, and my breathing was getting strenuous.

Tuesday, day 9. I was admitted to the COVID-19 ward. I was tired and slept most of the time. I was given oxygen. My temperature was fluctuating, and I was freezing. I didn't really think about what was going to happen; I guess I felt indifferent.

Friday, day 12. The fever seemed to be abating, and I got back home with still a bit of fever and coughing.

Wednesday, day 31. I felt a relief in the coughing and the feeling of having a cold. I isolated for an additional 48 hours. Finally, soon I was free!

After the course of the illness, I have been feeling fortuitous under the circumstances. I'm grateful for the help I've been given. I also think that if I didn't have the history of organ transplantation and contacted the department, I would've been told that it was just the flu!

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