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**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 80129

**Manuscript Type:** MINIREVIEWS

## **Liver Transplantation Amidst the COVID-19 Era; Our Centre Experience**

Liver Transplantation during COVID-19 Era

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## **Abstract**

The Coronavirus disease (COVID-19) significantly impacted the liver transplant (LT) process worldwide. Consequently, it brought significant challenges and limitations to transplant policies and organ allocation forcing LT centers to adjust their protocols to ensure maximum benefit and avoid harm to their patients. Our center, like many others, was obliged to adapt to the challenges. This paper provides an overview of the effects of COVID-19 on LT and details our center's experience and efforts during this unprecedented pandemic and hopes to serve as a guide for future public health crises.

**Key Words:** COVID-19; liver transplantation; immunosuppression; experience; mortality

Khazaaleh S, Suarez ZK, Alomari M, Rashid MU, Handa A, Gonzalez AJ, Zervos XB, Kapila N. Liver Transplantation Amidst the COVID-19 Era; Our Centre Experience. *World J Clin Cases* 2022; In press

**Core Tip:** The COVID-19 pandemic gave rise to an exceptional situation for LT around the world, initially leading to a decline in liver transplantation followed by a rapid recovery. This robust response resulted from extensive efforts by various LT centers to offset these challenges in addition to emerging evidence and the provision of appropriate guidelines from major LT societies. It is of the utmost importance to share experiences among LT centers to improve outcomes and reduce graft loss.

## **INTRODUCTION**

The Coronavirus (COVID-19) pandemic represented an unforeseen crisis to healthcare systems and transplant centers around the world, resulting in significant changes to solid organ transplant (SOT) practices<sup>1,2</sup>. At the beginning of the pandemic, a decrease in SOT was observed and attributed to multiple factors, which included a shortage of resources and staff, a saturation of critical care beds, changes to the donor pool, and

uncertainty regarding optimal post-transplant immunosuppressive therapy. The stress on the health care system forced most of the transplant centers to reduce liver transplant (LT) activity to best utilize scarce resources.

LT centers that continued their activity had to adjust their policies<sup>3</sup> and develop strategies that ensured the safety of their patients, including protocols regarding testing of donors and candidates<sup>4,5</sup>, reorganization of clinical and isolation protocols to establish a coronavirus-free-pathway, rearrangement of waitlist based on priority, and promotion of telemedicine to minimize exposure to the virus. The United States was not the exception, and the initial reduction in the number of LT performed at the beginning of 2020, was followed by a brisk comeback in the second half of 2020 and early 2021.<sup>6</sup> The emergence of evidence and recommendations by the international transplant societies was crucial in guiding LT programs during these unprecedented times.

In this article, we will discuss our center's experience with COVID-19 regarding its effects on LT patients, including the pre-transplant, peri-operative and post-transplant periods.

### **COVID-19 EFFECTS ON LT VOLUME AT OUR CENTER**

Similar to other LT centers across the nation, soon after the pandemic was declared<sup>7</sup>, we observed a decline in the number of LT performed at our center. From March 2020 to February 2021, 42 LT were performed, representing a reduction of 14.28% of the cases when compared to the same period one year earlier. Subsequently, from March 2021 to February 2022, a 38.77% decrease in LT was noted when compared to the period between March 2019 and February 2020, and a reduction of 28.57% when compared to the period between March 2020 and February 2021 [Figure 1].

### **COVID-19 RELATED LT CONSIDERATIONS**

#### *Prevention*

General COVID-19 preventive measures for LT candidates are similar to those established for the general public. We continue to recommend LT recipients maintain personal measures to minimize exposure to COVID-19, such as social distancing, masking, and avoiding gatherings whenever possible, regardless of vaccination status.

LT centers faced significant ethical challenges of vaccine skepticism and uncertainty regarding if it should be mandatory for all candidates on the waitlist<sup>8</sup>. Based on guidance from international transplant societies, vaccination against COVID-19 was strongly recommended for patients with chronic liver disease<sup>9</sup>. However, SOT recipients were found to mount a lower humoral response to COVID-19 vaccination<sup>10</sup>, for which the administration of booster doses was deemed necessary to achieve acceptable immunity<sup>11</sup>.

On August 12th, 2021, the FDA approved a three-dose mRNA vaccine series for immunocompromised patients, including SOT recipients<sup>12</sup>. In addition, the Advisory Committee on Immunization Practices (ACIP) recommended that all immunocompromised adults should be vaccinated at least three months after the third inoculation of the mRNA vaccine or two months after the initial sequence of the Johnson & Johnson vaccine<sup>13</sup>. We agree with these recommendations, and in our center, we highly recommend that all patients listed for LT receive at least three doses of an mRNA vaccine before transplant.

At the beginning of 2022,<sup>3</sup> the Food and Drug Administration (FDA) published an Emergency Use Authorization for tixagevimab/cilgavimab (Evusheld), a long-acting monoclonal antibody for pre-exposure prophylaxis of COVID-19 in patients with moderate to severe immunosuppression<sup>14</sup>. Evusheld became an attractive armamentarium for protection against COVID-19 infection in LT recipients who may not be able to mount an appropriate immune response to the vaccine<sup>15</sup>. In a retrospective study that followed 378 patients with hematologic malignancies, less than

60% of patients seroconverted after the third vaccine dose, regardless of the therapy used. Thirty-three patients (8.8%) eventually developed COVID-19 infection, and among them, three died due to severe infection. Importantly, no deaths occurred among patients who achieved seroconversion, and none of the patients who received Evusheld ( $n = 25$ ) developed COVID-19 infection<sup>10</sup>. Although data on the use of Evusheld may be lacking in the SOT population, at our center, we adopted the use of Evusheld in all patients who undergo LT, irrespective of vaccination status.

#### *COVID-19 in LT candidates*

Early case reports from Korea<sup>16</sup> and India<sup>17</sup> studied the viability of conducting a LT after 14 to 28 days of a positive COVID-19 infection in asymptomatic or minimally symptomatic patients. Also, a retrospective multicenter study from 11 European countries reported 26 patients who received a LT after a median of 78.5 days from an initial positive test for COVID-19. Even though LT candidates with symptomatic COVID-19 were at higher risk of early mortality when compared to counterparts with similar MELD scores, those who underwent LT had a favorable short-term survival of 96%. This study showed that once patients recover from COVID-19, LT is safe and encouraged<sup>18</sup>.

In our center, patients on the waitlist who test positive for COVID-19 in a PCR test are temporarily inactivated until becoming asymptomatic; and three weeks have elapsed since their initial positive test. Subsequently, if the patient had respiratory symptoms, we perform a contrast-enhanced computed tomography of the chest and pulmonary function tests before reactivation. Conversely, if the patient did not develop any respiratory symptoms, they are reactivated without further testing.

#### *Donor COVID-19 positivity*

During the beginning of the pandemic, transplant societies recommended against SOT in situations where donors tested positive for COVID-19 due to the likelihood of developing complications, such as acute respiratory distress syndrome or thrombosis of the graft. However, as the pandemic continued, the Organ Procurement and Transplantation Network Ad Hoc Disease Transmission Advisory Committee (OPTN DTAC) recommended that the decision to transplant organs from donors with active infection of COVID-19 should take into consideration the likelihood of death of the recipient for delaying the procedure and the risk of transmission to members of the transplant team.

Nevertheless, studies revealed that, unlike lung transplant recipients, the chance of disseminating COVID-19 infection from the donor to the recipient was low in LT patients<sup>19</sup>. The degree of viral load in the blood is usually low, and therefore blood-borne transmission does not represent a significant risk<sup>20</sup>. In our center, we actively consider liver grafts from donors who are COVID-19 positive at the time of organ donation.

#### *COVID-19 in LT recipients*

Initial reports suggested that LT recipients could be at an increased risk of acquiring severe COVID-19, given their immunosuppressed status, with the inherent risk of long-term viral shedding<sup>21,22</sup>. Although some studies showed an increased infection rate among SOT recipients, this was not associated with worse clinical outcomes. The Spanish Society for Liver Transplantation conducted a prospective nationwide study that included 111 Liver transplant recipients and concluded that these patients are twice as likely to be infected with COVID-19 compared to age- and gender-matched individuals (standardized incidence: 191.2; 95%CI 190.3-192.2)<sup>23</sup>. However, another prospective study from Italy followed 30 LT recipients with COVID-19 and suggested that LT recipients were more symptomatic, yet with no increased risk of hospitalization or death<sup>24</sup>.

The approach to management varies based on the severity of the COVID-19 infection and largely stems from experts' opinions. It is generally advised to lower the cumulative dose of immunosuppression, particularly mycophenolate mofetil, if possible<sup>23</sup>. Immunosuppression was found to be an independent predictor of severe COVID-19 disease as it may interfere with mounting a humoral response to COVID-19 vaccination<sup>25</sup>. Commonly used agents for outpatient management of COVID-19 infection include oral antivirals such as Molnupiravir and Nirmatrelvir/ritonavir (Paxlovid). Molnupiravir appears to be effective, safe, and well-tolerated in LT patients<sup>26</sup>. Nonetheless, Paxlovid strongly interacts with calcineurin inhibitors (CNI), so concomitant use is contraindicated due to the potential for CNI toxicity<sup>27</sup>. For those requiring inpatient management of COVID-19, the nucleotide analog Remdesivir is our preferred therapeutic option. It has been shown to shorten the duration of illness and hospitalization, especially when given to patients on supplemental oxygen within ten days of symptom onset<sup>28</sup>.

We also use COVID-19-specific antibodies in LT recipients with COVID-19, mainly in the outpatient setting and selected patients in the inpatient setting. In a single-center, retrospective study that included liver and kidney transplant recipients, COVID-19 monoclonal antibody (Casirivimab-imdevimab or Bamlanivimab) reduced hospitalization from 32% to 15% ( $P = 0.045$ ) with no mortality (13% vs 0%,  $P = 0.04$ )<sup>29</sup>.

#### *Impact on LT medical staff*

Healthcare providers are well-known to be at an additional risk of contracting COVID-19 when compared to the general population<sup>30</sup>. At our center, we adopted a strategy of decreasing interactions among team members to mitigate the risk of COVID-19 transmission. All meetings, including LT selection and multidisciplinary tumor boards, were transitioned to an online platform. A strict departmental protocol was implemented for caregivers who developed symptoms to allow them to undergo testing



and appropriate isolation. Outpatient visits, when necessary, were shifted to an online platform to minimize unnecessary exposure and protect patients and staff members.

### **CONCLUSION**

The COVID-19 pandemic has impacted transplant centers globally, and despite the burden, LT centers have been forced to adopt protocols to ensure patient and caregiver safety. The limitations of our study include that it only provides the experience of one LT center in the United States. In the future, emerging evidence will further guide LT centers toward the creation of contingency plans to provide optimal pre-transplant, peri-operative and post-transplant care in future public health crises.

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PRIMARY SOURCES

1	Christine E. Koval, Mohamed Eltemamy, Emilio D. Poggio, Jesse D. Schold, Alvin C. Wee. " Comparative Outcomes for Over 100 Deceased Donor Kidney Transplants from - 2 Positive Donors: A Single Center Experience ", American Journal of Transplantation, 2022 <small>Crossref</small>	15 words — 1%
2	<a href="#">f6publishing.blob.core.windows.net</a> <small>Internet</small>	12 words — 1%
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