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BRIEF REPORT

Outcomes of liver transplantation in recipients with previous coronavirus disease 2019 infection

To the editor,

As the pandemic continues, the number of patients with liver disease who have recovered from coronavirus disease 2019 (COVID-19) is also likely to increase significantly. Nonetheless, the impact of this infection on patients receiving a transplant after recovering from it is relatively less studied. Concerns include those with regard to the timing of transplant, issues of hypercoagulability, and the immunomodulatory effect of the virus.[1,2] Another undefined peril is that of reactivation/reinfection of the virus in an immunosuppressed recipient. We aim to bridge this shortfall in literature by presenting the largest series to date of post–COVID-19 patients who have undergone liver transplantation (LT). We address the likely issues that this exceptional situation may present.

A review of all adult patients who underwent LT at our unit between September 2020 and June 2021 was performed. The study covered a period when our region was facing the peak of the second COVID-19 wave attributed to the delta variant. All patients with a previous history of COVID-19 infection were included in the study (COVID-19–LT group). Their preoperative demographics, details of COVID-19, time to transplantation, and operative and postoperative outcomes were noted. To understand the relative impact of COVID-19 on patients undergoing LT, a comparison was made with a pre-COVID control group of LT recipients (pre–COVID-19–LT group) from October 2018 to March 2020.

Of the 51 LT recipients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at various time points prior to transplant, 48 and three patients underwent living donor LT (LDLT) and deceased donor LT, respectively. The median interval from COVID-19 to LT was 99 days (interquartile range, 15–329 days), and the earliest a patient underwent LT was 15 days. A total of nine patients had asymptomatic COVID-19, 26 patients had mild disease, moderate infection was seen in 11 patients, and four patients developed a severe disease. Prolonged hospitalization with liver decompensation was seen in two, six, and two patients following mild, moderate, and severe COVID-19 infection, respectively. Of the four patients who had severe disease, two required invasive ventilation and two were on noninvasive ventilatory support. Of the ventilated patients, the first patient underwent LT 5 months following COVID-19 infection. This patient also became COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR)–positive 8 months after LT. He made an uneventful recovery. The other patient who required invasive ventilatory support went on to develop post–COVID-19 cholangiopathy (Table 1) and ultimately required LT 110 days following COVID-19. He had an uneventful postoperative period and was well on follow-up. Explant histopathology of all the other recipients was unremarkable. Our standard immunosuppression protocol including its dosing (triple immunosuppression with calcineurin inhibitors, antimetabolites, and steroids), as described elsewhere, was not modified in the COVID-19–LT group.[3] None of the patients received induction immunosuppression.

There were three mortalities in the COVID-19–LT group, none of which were directly attributable to the COVID-19 infection. Patients from the COVID-19–LT group were compared with the pre–COVID-19–LT group (Table 2). The preoperative demographics were comparable. A numerically higher incidence of early allograft dysfunction (13.7% vs. 5.1%; $p = 0.06$) was noted in the COVID-19–LT group. Other outcomes with regard to pulmonary and vascular complications were comparable between the groups (Table 2, Supplement S1). Critically, LT in our patients appeared safe, with comparable outcomes in those recovering from COVID-19.

Of the 48 living donors, 18 had a previous history of COVID-19. All of the donors had an interval of at least 4 weeks between the infection and their operation. They had two negative COVID-19 RT-PCR tests and normal chest scans prior to the donation. All of the donors had COVID-19 neutralizing antibodies. All 18 had an uneventful postoperative period and remain well on routine postdonation follow-up. Anticoagulation protocol followed as per our standard unit protocol for both the recipients and donors. No COVID-19–specific modifications were made to the anticoagulation protocol.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 1 Etiology and comorbidities of post–COVID-19 patients undergoing LDLT ($n = 51$)

Etiology and comorbidities	*n* (%)
Etiology	
Nonalcoholic steatohepatitis	17 (33.3)
Cryptogenic liver disease	8 (15.7)
Alcohol-related liver disease	7 (13.7)
Hepatitis B virus	7 (13.7)
Autoimmune hepatitis	3 (5.9)
Wilson's disease	2 (3.9)
Hepatitis C virus	2 (3.9)
Hepatitis B virus—acute liver failure	1 (1.9)
Hepatocellular carcinoma	1 (1.9)
Primary sclerosing cholangitis	1 (1.9)
Drug-induced liver injury	1 (1.9)
Post–COVID-19 cholangiopathy	1 (1.9)
Comorbidities	
Diabetes mellitus	24 (47.1)
Acute kidney injury	13 (25.5)
Coronary heart disease	12 (23.5)
Smoking	10 (19.6)
Hypertension	10 (19.6)
Hypothyroidism	9 (17.7)
Asthma	3 (5.8)

Abbreviations: COVID-19, coronavirus disease 2019; LDLT, living donor liver transplantation.

TABLE 2 Comparison of demographics and LDLT postoperative outcomes between post–COVID-19 and non–COVID-19 cohorts

	Post–COVID-19 cohort ($n = 51$)	Non–COVID-19 cohort ($n = 215$)	*p* value
Demographics			
Age, years	50.7 ± 10.1	50.9 ± 11.3	0.82
BMI, Kg/m^2	26.1 ± 5.5	27.17 ± 4.8	0.16
MELD score	18 (8–34)	17 (13–23)	0.72
Postoperative outcomes			
Length of hospital stay, days	14 (11–21)	15 (12–19)	0.84
Length of ICU stay, days	7 (4–12)	6 (5–8)	0.22
Day of extubation	1 (1–1)	1 (1–1)	0.89
Prolonged mechanical ventilation, >24 h from arrival to ICU	7 (13.7)	21 (9.8)	0.41
Early allograft dysfunction	7 (13.7)	11 (5.1)	0.06
Acute rejection	3 (5.9)	11 (5.1)	0.71
Hepatic artery thrombosis	1 (1.9)	1 (0.4)	0.08
Chest infection	4 (7.8)	29 (13.6)	0.37
Death within 90 days	3 (5.9)	13 (6.1)	0.99

Note: Data are provided as mean ± standard deviation, number (percentage), or median (interquartile range). $p < 0.05$ is considered significant.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease.

As the waves of the COVID-19 pandemic continue unabated, the transplant community is faced with an increasing number of recipients and donors who have recovered or are recovering from COVID-19. The implications of this disease on the peri-LT period have not been clearly understood.

In addition to recognized pulmonary complications, it continues to be unknown how long a post–COVID-19 hypercoagulable state remains. Nonetheless, the recommended duration of thromboprophylaxis by various hematological and cardiac societies has been between 30 and 45 days.[4] Apart from one patient who developed hepatic artery thrombosis (LT 5 months after COVID-19 infection), which appeared unrelated to the viral infection, no other venous or arterial thrombotic complications were noted.

As a result of SARS-CoV-2 infectivity, transplant societies recommend a "cooling-off period" after pulmonary symptom resolution.[3,5] However, patients with a Model for End-Stage Liver Disease (MELD) score greater than 15 remain at high risk of liver failure and early death, making a stringent application of this cooling-off period impracticable. Nevertheless, the risk of mortality without LT in these patients needs to be balanced against the risk of post-LT mortality. Other small case series have demonstrated the safety of performing LT before a mandatory 4-week interval. Although only six of our recipients received transplants earlier than this, outcomes appeared generally consistent with the greater cohort. More data are needed to understand the optimal LT timing.[1,5]

As presented in the data from the European Liver and Intestine Transplant Association/European Liver Transplant Registry (ELITA/ELTR) multicenter cohort study, reinfection with COVID-19 does not appear to be a major concern.[1] In our case series, apart for one patient who had reinfection 8 months after LT, none of the other recipients developed COVID-19. A multicenter study noted that LT did not increase the risk of death in patients with COVID-19.[1] Reduction of immunosuppression is therefore not routinely recommended but needs to be made on a case-by-case basis, especially in patients admitted to the intensive care unit (ICU).[5] Our patients received the standard immunosuppression, and no difference in the rates of rejection were noted between the COVID-19 and pre–COVID-19–LT groups (Table 2).

It is crucial to acknowledge that a progressively increasing number of patients with liver disease are likely to have had a past history of COVID-19. We present the largest outcome data of LT recipients who have recovered from COVID-19. We demonstrate that

when COVID-19 symptoms resolve and the severity of underlying liver disease is considered, patients are at no higher risk than those with no prior COVID-19 infection. However, large, international, multicenter registry data are needed to help provide robust data allowing for evidence-based guidelines.

CONFLICT OF INTEREST

Nothing to report.

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SUPPORTING INFORMATION

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