Liver Transplantation Services During the Time of COVID-19

Parita Patel and Anjana Pillai*

Section of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, The University of Chicago Medicine, Chicago, IL, USA

Received: 16 March 2021  |  Revised: 12 April 2021  |  Accepted: 8 May 2021  |  Published: 31 May 2021

Abstract

The coronavirus disease 2019 (COVID-19) is associated with high morbidity and mortality, prompting overwhelmed hospital systems to reallocate resources to those stricken with the disease. In response, many liver transplantation programs unexpectedly came to an abrupt halt, significantly affecting the lives of living donors and recipients around the world. As the risk-benefit scale of liver transplantation has changed in the era of COVID-19, it is prudent to understand the impact of COVID-19 on those with underlying liver disease and those in need of a liver transplant. In this review, we discuss recommendations put forth by hepatology and transplant societies, summarize results from emerging studies, and propose strategies to appropriately risk stratify patients prior to transplantation.

Citation of this article: Patel P, Pillai A. Liver transplantation services during the time of COVID-19. J Clin Transl Hepatol 2021;9(4):587–591. doi: 10.14218/JCTH.2021.00095.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has affected over 72 million patients around the world as of December 2020.1 Due to the rapid rise of COVID-19, hospitals and policy makers implemented drastic changes to allow for resource reallocation aimed at treating patients stricken by the virus. Surgical operating rooms were transformed into intensive care units (ICUs), specialty providers were deployed to COVID-19 units, and lifesaving ventilators were rationed due to overwhelmed healthcare systems. As a result, organ transplantation centers were brought to an abrupt halt in the wake of a quickly growing pandemic. Undoubtedly, the COVID-19 pandemic has shifted the risk-benefit scale of liver transplantation.2 Reliability of diagnostic testing, risk of infection, transmission in the perioperative setting, and the impact of immunosuppression are all major concerns.3 Additionally, increased perioperative complications in patients infected with COVID-19 at time of surgery have also been reported.4 As transplant programs safely reopen, modifications to standard protocols are necessary to provide safe and effective methods of organ transplantation for both deceased and living donors. In this article, we explore how this pandemic has affected and changed liver transplantation and summarize recommendations from multiple health organizations.

COVID-19 and liver disease

Data on the effect of COVID-19 on patients with chronic liver disease is growing exponentially. In a study of over 2,500 patients with COVID-19 in the United States, patients with chronic liver disease and COVID-19 were almost five times more likely to die than those without COVID-19 (relative risk [RR]=4.6, 95% confidence interval [CI]=2.6–8.3, p<0.001).5 Similarly, in a study of over 88,000 patients in the Veterans Affairs national healthcare system, COVID-19 infection was associated with a 3.5-fold increase in mortality in patients with cirrhosis and cirrhosis was associated with a 1.7-fold increase in mortality in patients with COVID-19 infection.6 Preliminary data suggest mortality attributable to COVID-19 is higher in patients with more advanced liver disease and is strongly correlated with Child-Pugh (CP) class.7 Mortality rates were 12.2% in patients without cirrhosis compared to 23.9% in patients with CP Class A vs. 43.4% in patients with CP Class B, and 63% in those with CP class C.7 In addition to baseline liver disease stage, analysis of an international registry of patients with chronic liver disease and COVID-19 found that age (odds ratio [OR] 1.02, 95% CI=1.01–1.04, p=0.011) and alcohol-related liver disease (OR 1.79, 95% CI=1.00–3.03, p=0.040) were also factors associated with death.8 Conversely, Bajaj and colleagues8 observed in a multicenter trial that, when matched for age and gender, patients with cirrhosis and COVID-19 may have similar mortality compared to patients with cirrhosis alone, although higher than in patients with COVID-19 without cirrhosis.

COVID-19 and liver transplantation outcomes

The initial paucity of data left clinicians uncertain about the
impact of COVID-19 in solid organ transplant (SOT) recipients. Early single-center reports, limited by small sample sizes and restricted geographic domains, published variable mortality rates, leaving providers unsure about the safety of transplantation during this time.10,11 As a result, many transplant centers around the world were suspended during the initial wave of the pandemic. Lombardy, Italy was drastically affected by COVID-19, with hospitals required to expand the total number of ICU beds from 724 to 1,381 to accommodate patients with the virus.12 Although authorities had not formally halted the transplant programs across Lombardy, there was a temporary decrease in liver transplantation due to several reasons, including an overwhelming influx of COVID-19 patients to ICU beds, redeployment of ICU doctors (leaving a paucity of specialists to care for liver transplant recipients), lack of data regarding the risk of nosocomial COVID-19 in recipients, and concerns regarding the safety of the procurement teams who may be exposed to potentially infected patients.12 A similar decline in solid organ transplantation procedures was seen in France, with a 90.6% reduction in deceased donor transplantation since the COVID-19 outbreak.13

Countries with large living donor programs were similarly affected. In a study conducted in India, the effects of the COVID-19 pandemic on living donor liver transplantation (LDLT) were evaluated from March to June 2020 and compared to a pre-COVID period in 2019. LDLTs in COVID-19 times decreased to 58.9% of the previous year, with no significant difference in age, gender or indication of LDLT. One of twenty-three post-transplant recipients, three of seventy-one recipients and donors during evaluation, and one of one hundred and twenty-five healthcare workers developed COVID-19 during this time, all with uneventful recovery.14

Although transplantation rates initially decreased during the height of the pandemic, growing collaborations among researchers worldwide has since led to multicenter data on outcomes in SOT recipients and has improved risk stratification in this patient population. In a study of 482 SOT recipients from over 50 transplant centers, the 28-day mortality rate after COVID-19 diagnosis was 18.7%. In that study, independent risk factors for mortality included age > 65 years (OR 3.2, 95% CI=1.4–7.0, p=0.004), chronic lung disease (OR 2.5, 95% CI=1.2–5.2, p=0.018) and obesity (OR 1.9, 95%CI 1.0–3.4, p=0.039).10 Immunosuppression was not found to be a risk factor for mortality in any similar rate. Mortality rates and risk factors for death were identified in other large-sample studies. In a large, national cohort study performed in England, 597 of the 46,789 SOT (1.3%) recipients who tested positive for COVID-19 had a mortality rate of 25.8%. Increasing recipient age was the only variable independently associated with death after a positive COVID-19 test in that study.15

As more data became available, the impact of COVID-19 was specifically evaluated in liver transplant recipients. In a prospective study of 19 European centers, 12 centers had registered 57 cases of liver transplant recipients who contracted COVID-19.16 The most common symptoms were fever (79%), cough (55%), dyspnea (46%), fatigue or myalgia (56%), and gastrointestinal symptoms (33%). Immunosuppression was reduced in 22 recipients (37%) and discontinued in 4 (7%), but no impact on outcome was observed. The estimated case fatality rate was 12% (95% CI=5% to 24%), and notably five of the seven patients who died had a history of cancer.16

Similar data were seen in a prospective nationwide study in Spain, which found fever and cough to be the most common symptoms of COVID-19 in liver transplant recipients.17 In that study, the mortality rate was 18%, which was lower than in the matched general population (standardized mortality ratio 95.5, 95% CI=94.2–96.8).17 Clinical predictors of severe COVID-19 among hospitalized patients included higher Carlson co-morbidity index (RR=1.28, 95% CI=1.05–1.56, p=0.015), male gender (RR=2.49, 95% CI=1.14–5.41, p=0.021), and dyspnea at diagnosis (RR=7.25, 95% CI=2.95–17.82, p<0.001). White et al.17 also found that increased age and presence of comorbidities carry more risk than the liver transplantation itself. In a multicenter trial of 151 adult liver transplant recipients from 18 countries and 627 patients who had not undergone liver transplantation, there was no difference in proportion of patients hospitalized (124 [82%] patients in the liver transplant cohort vs. 474 [76%] in the comparison cohort, p=0.106), or who required intensive care (47 [31%] vs. 185 [30%], p=0.837). ICU admission (43 [28%] vs. 52 [8%], p<0.0001) and need for invasive ventilation (30 [20%] vs. 32 [5%), p<0.0001), however, were more frequent in the liver transplant cohort. There was no difference in death between the two groups (19% in the liver transplant group vs. 27% in the non-transplant group, p=0.46), and in a propensity score matched analysis, liver transplant did not increase the risk of death in patients with COVID-19 (absolute risk difference 1.4%, 95% CI=−7.6 to 10.4). Only advanced age, serum creatinine, and non-liver cancer were associated with increased risk of death in the liver transplantation group.18 A Swedish study also found older age, male sex, and greater body mass index at presentation to be associated with adverse outcomes.19

With new potential treatment options, vaccinations, and emerging data on the safety of liver transplantation, more programs around the world have begun to reopen and increase their transplant volumes. The reopening of transplant programs in England was addressed by the National Health Services Blood and Transplant (NHSBT) unit.20 Given the challenges faced by units vary by geographical location, organ type and local resource environments, NHSBT felt these considerations were best evaluated at the local level. As these challenges are in constant flux, especially with the new strains of the virus and multiple waves of the pandemic, the NHSBT has proposed guidelines to consider prior to reopening of programs. These include assessing the availability of adequate resources (multidisciplinary team input, number of ward beds, anesthestia availability, personal protective equipment, blood products, etc.) and microbiology and infection control policies meeting national standards. The impact of reopening transplant programs around the world, particularly with new strains of the virus emerging, has yet to be seen.

Liver transplant evaluation in the COVID-19 era

The COVID-19 pandemic has admittedly affected the evaluation and listing process for liver transplantation. During the height of the pandemic, many transplant centers restricted transplants to their sickest patients or completely halted their transplant programs, significantly decreasing organ procurements and thereby adversely affecting transplant wait times and wait list mortality.21 While there is no universal policy on how to best utilize resources and ensure patient and healthcare provider safety, it is imperative for centers to critically and carefully develop policies and protocols that best fit their patient population and consider the prevalence of COVID-19 in their area.21 For patients undergoing liver transplant evaluation, multidisciplinary care teams, such as those involving transplant education, social work, nutrition, and pharmacy, and financial consults, should be conducted via telemedicine whenever possible.21 For patients who are scheduled for in-person visits, precautions should be made in advance to
limit exposure, including staggering patient arrival times, decreasing congregation in patient waiting rooms, ensuring appropriate use of masks, screening for symptoms, and limiting the number of family members/friends that accompany the patient. When the determination is made to proceed with transplantation efforts, the American Association for the Study of Liver Disease (AASLD) recommends ensuring appropriate resource utilization (ICU beds, ventilators, personal protective equipment, and supply of blood products) and frequent re-evaluation of these resources. In centers with protective equipment, and supply of blood products) and frequent re-evaluation of these resources. In centers with ongoing resource limitations, the European Association for the Study of Liver Disease (EASL) suggests prioritizing liver transplantation in patients with poor short-term prognosis (i.e. those with acute liver failure, acute-on-chronic liver failure, high model for end-stage liver disease [MELD] scores and hepatocellular carcinoma [HCC] at the upper limits of the Milan criteria). Other additional considerations include accepting only grafts with a low risk of delayed graft function, as this can minimize complications and avoid prolonged hospital stays and implementing perioperative management in a specific, designated clean ICU. Prioritized patients should be triaged appropriately (as discussed below) and telemedicine visits should be utilized when appropriate.

Waiting on the transplant list during COVID-19

For outpatient management of those on the transplant list, AASLD recommends scheduling specific patients, particularly those with HCC or high MELD scores, for in-person clinic visits while using telemedicine for patients with less urgent issues. Outpatient labs and imaging should be obtained only as clinically necessary. During the height of the pandemic, the Organ Procurement and Transplantation Network (OPTN) temporarily enacted policy changes where centers and patients were no longer required to update labs or imaging as a means to maintain MELD score. During this time, clinical data and imaging from previous evaluation and pre-transplantation periods, including any previous recipient status, could be maintained if updated data could not be obtained. These policies were implemented by OPTN to help prevent unnecessary exposure to transplant recipients and living donors and to alleviate data burden for transplant centers during the initial wave of the pandemic. However, in patients listed with HCC, Mehta and colleagues recommend obtaining preoperative imaging at time of admission for liver transplant, if not done within 3 months, to ensure tumor characteristics meet standard liver transplant criteria. Additional measures to reduce transmission during the peri-transplant period include social isolation for waiting list patients, telephone screening for symptoms and exposures before admission, and staggering patient arrival times to avoid congregating in waiting area.

COVID-19 diagnosis and testing

The risk of COVID-19 infection from an infected living donor or deceased donor is limited at this time and is evolving as more data becomes available. Furthermore, it is essential to recognize that while testing is helpful, no laboratory test is 100% specific or sensitive, allowing for false positives and false negatives. The positive and negative predictive values are determined by a specific assay performance, taking into account the amount of locally circulating virus and specimen quality. Ultimately, the risks and benefits should be considered on a case-by-case basis prior to performing or denying a transplant.
age, serum creatinine and non-liver cancer were associated with death among liver transplant recipients. Another prospective nationwide study of 111 liver transplant recipients in Spain with COVID-19 also demonstrated that chronic exposure to immunosuppressive agents did not increase standardized mortality rates. However, findings did suggest that high doses of mycophenolate could increase the risk of severe COVID-19 among hospitalized liver transplant patients.

With the evidence and data that are available, AASLD and EASL recommend not changing immunosuppressive regimens in post-transplant patients without COVID-19, while emphasizing general precautionary measures such as maintaining social distancing, wearing masks, and avoiding travel. In post-transplant patients with COVID-19, adjustment of immunosuppression should be individualized with severity of COVID-19 weighed against risk of graft rejection. Minimizing immunosuppression, particularly antimetabolite medications, should be considered as would be done with contraction of other infections.

Potential treatment options for COVID-19 are under review, but the effect of these medications on liver transplant recipients remains unknown. Given the paucity of data, close monitoring is recommended for possible drug-drug interactions and adverse reactions.

**Fig. 1. Proposed approach to COVID-19 testing for liver transplantation.** *Data on organ donation from previous COVID-19-infected donors are limited and decision to proceed with transplantation should occur on a case-by-case basis. Discussions with the transplant recipient should be arranged and risks and benefits of transplantation vs. no transplantation should be thoroughly explained. Repeat positive PCR within 90 days most likely reflects persistent shedding or viral RNA rather than new infection, but organ acceptance should only be considered after consultation with ID experts. Figure adapted from the AST. SARS-COV2: Recommendations and Guidance for Organ Donor Testing. Available at: https://www.myast.org/sites/default/files/Donor%20Testing_100520_revised_ReadyToPostUpdated10-12.pdf. ID, infectious disease; COVID-19, coronavirus disease 2019.*

**Conclusion**

The COVID-19 pandemic has had a dramatic impact on transplant programs, recipients and donors around the world. Resource reallocation during the height of the pandemic brought many transplant programs to a halt. Although data continues to evolve, this review summarizes the available evidence and society recommendations to help liver transplant programs safely perform organ transplantation. Appropriate risk stratification of patients with liver disease, methodological testing of donors and recipients prior to transplantation, and minimizing transmission are key components in providing a safe and effective method to resume deceased donor and living donor liver transplantation around the world.

**Funding**

None to declare.

**Conflict of interest**

AP is on the Speaker’s Bureau for Simply Speaking Hepatitis (CME) and Medical Advisory Board for Eisai Inc, Exelixis, and Genentech. PP has no disclosures.

**Author contributions**

Drafted the paper and approved the final version (PP), revised and approved the final version of the manuscript (AP). AP is the guarantor of the article.
References

[1] Gardner L, Dong E. Johns Hopkins Coronavirus Resource Center.

[2] Lembach H, Hann A, McKay SC, Hartog H, Vasanth S, El-Dali P, et al. Severe liver disease among the COVID-19 pandemic, Lancet Gastroenterol Hepatol 2020;5(6):725–726. doi:10.1016/S2468-1253(20)30187-4.

[3] Di Maria T, Berenguer M. COVID-19 and liver transplantation. Nat Rev Gastroenterol Hepatol 2020;17(9):526–528. doi:10.1038/s41575-020-0347-z.

[4] Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgery during the incubation period of COVID-19 infection. EClinicalMedicine 2021;21:100331. doi:10.1016/j.eclinm.2020.100331.

[5] Singh S, Khan A. Clinical characteristics and outcomes of COVID-19 in the United States: a multicenter research network study. Gastroenterology 2020;159(2):768–771.e3. doi:10.1053/j.gastro.2020.04.064.

[6] Ioannou GN, Liang PS, Locke E, Green P, Berry K, O’Hare AM, et al. Cirrhosis and SARS-CoV-2 infection in U.S. Veterans: risk of infection, hospitalization, ventilation and mortality. Hepatology 2020.

[7] Moon AM, Webb GJ, Alomar C, Armstrong MJ, Cargill T, Dhanasekaran R, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry. J Hepatol 2020;73(3):705–708. doi:10.1016/j.jhep.2020.05.013.

[8] Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Alomar C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. J Hepatol 2021;74(3):567–577. doi:10.1016/j.jhep.2020.09.024.

[9] Bajaj JS, Garcia-Tsao G, Biggins SW, Kamath PS, Wong F, McGeorge S, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. Gut 2021;70(3):531–536. doi:10.1136/gutjnl-2020-322118.

[10] Kate Os, Haydel BM, Floroman SS, Rana MM, Chaudhry ZS, Ramesh MS, et al. COVID-19 in solid organ transplant: a multi-center cohort study. Clin Infect Dis 2020;ciaa1097. doi:10.1093/cid/ciaa1097.

[11] Pereira MR, Mohan S, Cohen DJ, Husain SA, Dubé GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant 2020;20(7):1800–1808. doi:10.1111/ajt.15941.

[12] Maggi U, De Carlo L, Ippolito C, Colledan M, Regalia E, Rossi G, et al. The impact of the COVID-19 outbreak on living liver transplantation programs in Northern Italy. Am J Transplant 2020;20(7):1840–1848. doi:10.1111/ajt.15948.

[13] Loupy A, Aubert O, Reese PP, Bazin O, Bayer F, Jacquelin C. Organ procurement and transplantation during the COVID-19 pandemic. Lancet 2020;395(10237):e95–e96. doi:10.1016/S0140-6736(20)31040-0.

[14] Soin AS, Choudhary NS, Yadav SK, Saigal S, Saraf N, Rastogi A, et al. Restructuring living donor liver transplantation at a high volume center during the COVID-19 pandemic. J Clin Exp Hepatol 2020. doi:10.1016/j.jceh.2020.09.009.

[15] Ravanah R, Calaghan CJ, Humford L, Ushiro-Limb J, Thorburn D, Casey J, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: a national cohort study. Am J Transplant 2020;20(11):3218–3221. doi:10.1111/aert.13747.

[16] Becchetti G, Zambelli MJ, Pascual L, Donato MF, Invernizzi F, Detry O, et al. COVID-19 in an international European liver transplant recipient cohort. Gut 2020;69(10):1832–1840. doi:10.1136/gutjnl-2020-321923.

[17] Colmenero J, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. J Hepatol 2021;74(1):148–155. doi:10.1016/j.jhep.2020.07.040.

[18] Webb GJ, Marjot T, Cook JA, Alomar C, Armstrong MJ, Brenner EJ, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. Lancet Gastroenterol Hepatol 2020;5(11):1008–1016. doi:10.1016/S2468-1253(20)30271-5.

[19] Softeland JM, Friman G, von Zur-Mühlen B, Ericzon BG, Wallquist C, Karason K, et al. COVID-19 in solid organ transplant recipients: a national cohort study from Sweden. Am J Transplant 2021. doi:10.1111/ajt.16596.

[20] Transplant Programmes: Issues for Consideration for Future Infection Surges. 2021.

[21] Fivy K, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology 2020;72(1):287–304. doi:10.1002/hep.32181.

[22] Boettler T, Marjot T, Newsome PN, Mondelli MU, Cordero E, et al. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. J Hepatol 2020;21(5):100169. doi:10.1016/j.jhep.2020.100169.

[23] Updates to Candidate Data during 2020 COVID-19 Emergency. Available from: https://optn.transplant.hrsa.gov/governance/policy-notices/.

[24] Mehta N, Parikh N, Kelley K, Hameed B, Singal AG. Surveillance and monitoring of hepatocellular carcinoma during the COVID-19 pandemic. J Clin Exp Hepatol 2020. doi:10.1016/j.jceh.2020.09.009.

[25] American Society of Transplantation. SARS-CoV-2 (Coronavirus, 2019-nCoV): Recommendations and Guidance for Organ Donor Testing. Available from: https://www.myast.org/sites/default/files/Donor%20Testing_10052020_revised_ReadyToPostUpdated10-12.pdf.

[26] Donato MF, Invernizzi F, Lampertico P, Rossi G. Health status of patients who underwent liver transplantation during the coronavirus outbreak at a large center in Milan, Italy. Clin Gastroenterol Hepatol 2020;18(9):2131–2133.e1. doi:10.1016/j.cgh.2020.04.041.

[27] Mirjalili M, Shafiekhani M, Vazin A. Coronavirus disease 2019 (COVID-19) and transplantation: pharmacotherapeutic management of immunosuppression regimen. Ther Clin Risk Manag 2020;16:617–629. doi:10.2147/TCRM.S256246.