



Clinical Practice Issues for Liver Transplantation in COVID-19 Recovered Recipients

Progress in Transplantation
2022, Vol. 32(2) 148-151
© 2022, NATCO. All rights reserved.
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15269248221092742
journals.sagepub.com/home/pit



Kirti Shetty, MD^{1,2} , Zurabi Lominadze, MD^{1,2},
Kapil Saharia, MD^{2,3}, Suryanarayana Reddy Challa, MD⁴,
Maria Montenegro, MSN^{2,5}, Raphael P. H. Meier, MD, PhD^{2,5} ,
Saad Malik, MD^{2,5}, Josue Alvarez-Casas, MD^{2,5}, Sasan Sakiani, MD^{1,2},
Neha Jakhete, MD^{1,2}, Nathalie Urrunaga, MD^{1,2},
Stephen H. Gray, MD^{2,5}, and Daniel G. Maluf, MD^{2,5}

Abstract

The ongoing burden of COVID-19 in persons with end stage liver failure necessitates the development of sound and rational policies for organ transplantation in this population. Following our initial experience with two COVID-19 recovered recipients who died shortly after transplant, we adjusted our center policies, re-evaluated outcomes, and retrospectively analyzed the clinical course of the subsequent seven COVID-19 recovered recipients. There were two early deaths and 5 successful outcomes. Both deceased patients shared common characteristics in that they had positive SARS-CoV2 PCR tests proximal to transplant (7-17 days), had acute on chronic liver failure, and suffered thromboembolic phenomena. After a careful review of clinical and virological outcome predictors, we instituted policy changes to avoid transplantation in these circumstances. We believe that our series offers useful insights into the unique challenges that confront transplant centers in the COVID-19 era and could guide future discussions regarding this important area.

Keywords

liver transplantation, COVID-19, outcomes

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in a decrease in solid organ transplants performed in 2020.¹ Infection of waitlist candidates with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has also affected transplant policies, given concerns about respiratory, cardiovascular, and thrombotic complications, as well as the effect of immunosuppression on recovery and viral shedding. There have been reports of successful outcomes following liver transplantation in COVID-19 recovered recipients.²⁻⁷

Clinical Relevancy to Practice

Barriers to liver transplantation in those who have been infected with SARS-CoV2 include uncertainties regarding multisystem involvement, recrudescence of infection with immunosuppression, and risk of nosocomial transmission. As we enter the third year of this pandemic and despite the availability of effective vaccines, a significant disease burden persists and places those with end stage organ damage at risk. Importantly, COVID-19 has been shown to cause hepatic decompensation in 46% of those with cirrhosis, half of whom develop

acute-on-chronic liver failure.⁸ It is anticipated that there will be a continued need for transplantation in those who recover from COVID-19. The development of rational policies enabling the safe and efficacious utilization of donor organs in such individuals is therefore necessary.

We report our program's experience on posttransplant outcomes in COVID-19 recovered liver transplant recipients... Our objective was to highlight clinical predictors of outcome,

¹ Department of Medicine, University of Maryland Medical Center, Baltimore, MD, USA

² Program in Transplantation, University of Maryland Medical Center, Baltimore, MD, USA

³ Institute of Human Virology, University of Maryland Medical Center, Baltimore, MD, USA

⁴ Department of Medicine, University of Maryland Medical Center Midtown Campus, Baltimore, MD, USA

⁵ Surgery, University of Maryland Medical Center, Baltimore, Maryland, USA

Corresponding Author:

Kirti Shetty, Division of Gastroenterology and Hepatology, N3W50, University of Maryland Medical Center, 22 S Greene Street, Baltimore, MD 21201, USA. Email: kshetty@som.umaryland.edu

Table 1. Clinical Characteristics And Outcomes Of 7 Patients Undergoing Liver Transplantation Following COVID-19.

Case	Age/ gender	Transplant Indication	MELD-Na	Pretransplant LOS	First positive PCR prior to transplant (days)	Last PCR prior to transplant interval (days)		ICU LOS	Posttransplant disposition	Patient outcome (days posttransplant as of 10/28/21)
						Pos	Neg			
1	58/M	Acute HAV	40	16	102	7	1	105(58)	Deceased	105
2	43/M	Alcohol cirrhosis	40	7	22	17	7	24(3)	Deceased	24
3	50/M	Alcohol/ HCV cirrhosis	40	7	61	60	7	14(8)	Home	262
4	72/M	NASH	29	0	224	201	182	7(3)	Home	364
5	66/M	HCC/NASH	26	0	58	58	8	7(5)	Home	237
6	59/F	Autoimmune cirrhosis	23	0	98	83	50	7(3)	Home	91
7	29/M	Alcohol cirrhosis	29	0	122	89	66	9(2)	Home	162

LOS: length of stay; HAV: hepatitis A virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; NASH: non-alcoholic steatohepatitis.

specifically delineating factors that portend poor prognosis and mortality risk.

We performed a retrospective chart review of the 7 patients who underwent transplantation following COVID-19 from November 2020 to July 2021. This review received exemption from full review by our Institutional Review Board. All transplants were done under a protocol for SARS-CoV2-infected individuals.

Our first two COVID-19 recovered recipients died at days 105 and 24 posttransplant, respectively. This negative experience led to a reappraisal and revision of our protocol and practices. After multidisciplinary consultations and reviews, policy changes were implemented. The clinical outcomes of the next 5 COVID-19 recovered recipients were studied. Our final cohort comprised 6 males and 1 female, between the ages of 29 and 72. Indications for transplant, viral kinetics and outcome are summarized in the Table 1.

Patient Summaries:

Our first two patients died following transplant and we will describe each patient's individual course in detail. Patients' next of kin approved publication of individual cases.

Patient 1. Pretransplant: This 58-year-old male was admitted with acute hepatitis A, which followed a sub-acute course. He had tested positive for SARS-CoV2 four months prior to his transplant admission, which resulted in mild disease without hospitalization. At the time of transfer to our center, he was negative for SARS-CoV2 RNA by nasopharyngeal swab polymerase chain reaction (PCR), however, he tested PCR positive at a high cycle threshold 7 days before transplant., repeat PCR one day before transplant was negative. He had a prolonged pre-transplant ICU admission of 17 days, developing acute on

chronic liver failure (ACLF), grade 3. He had clinically improved at the time of transplant.

Posttransplant: He was transferred to the floor on post-op day 14 and developed hepatic artery thrombosis on post-op day 30. Celiac/hepatic arteriogram showed right hepatic artery occlusion immediately distal to its origin, and not at the anastomosis. Selective catheterization of the right hepatic artery and angioplasty was attempted but was unsuccessful. Computerized tomographic (CT) angiogram of the chest on post-op day 32 showed right lower lobe segmental and subsegmental pulmonary emboli. Anticoagulation was initiated, but he developed recurrent, significant bleeding episodes (hemoperitoneum, gastrointestinal bleeding) which necessitated its discontinuation. He had persistent renal failure, respiratory failure, and ischemic cholangiopathy, and developed profound septic shock requiring high dose pressors. The family decided to transition to comfort care and he passed away in the hospital on post-op day 105.

Patient 2. Pretransplant: This 43-year-old male was admitted to his local hospital with COVID-19 pneumonia 22 days prior to transplant, and treated with dexamethasone and remdesivir, before being transferred to our center for worsening hepatic dysfunction. He had a remote history of heavy alcohol use but no prior decompensations. He developed left lower lobe pulmonary embolism (PE) 20 days prior to transplant. He was administered IV heparin for 7 days, but developed variceal hemorrhage, for which anticoagulation was stopped and endoscopic variceal ligation was performed. He was in the ICU for 7 days with ACLF grade 3). He gradually improved and was weaned off pressors, extubated and was on room air prior to transplant. Chest CT scan showed resolution of pulmonary infiltrates, and SARS-CoV2 PCR was negative 7 days prior to an uncomplicated transplant.

Posttransplant: He was initiated on low molecular weight heparin, but developed hemoperitoneum on post-op day 9, requiring discontinuation of anticoagulation. Ultrasound of lower extremities showed no deep vein thrombosis and repeat chest CT showed no PE. He was discharged to acute rehabilitation at an affiliated hospital. On post-op day 24, he reported pleuritic left sided chest pain. Chest/upper extremity CT showed right pleural effusion and patchy left ground glass opacities. He was given IV antibiotics and pain medications. A CT angiogram was ordered to rule out PE, but before the CT could be completed, he was found pulseless and apneic. Resuscitation was unsuccessful.

The next five patients are alive and well at a mean of 163 days from transplant (range 31-304) as of August 28, 2021. The mean number of days from first positive SARS-CoV2 PCR to transplant is 222 (range 82-284), and from last positive PCR to transplant is 98 (range 58-201). All had mild COVID-19 symptoms and were transplanted either from the nursing floor (N = 1) or from home (N = 4) with no thromboembolic (TE) phenomena noted pre- or posttransplant. All had uneventful perioperative and postoperative courses, were discharged home, and are currently doing well with no thrombotic complications. Consents were obtained from all patients.

Practice Issues Our single-center experience of liver transplant in 7 previously SARS-CoV2 infected individuals offers the largest case series of deceased donor liver transplantation following COVID-19, augmenting a recent report on living donor living transplant from India.³ Since the decision-making process in deceased donation is often more pressured, and potential candidates are sicker, our experience highlights important differences in approach. Of our 7 recipients, 5 are alive and well at a mean of 163 days from transplant (range 31-304 days). The 2 early deaths offer a cautionary tale and underline the limits of our understanding of this novel infection, unguided as we currently are by the traditional tools of evidence-based medicine.

The Following is a Summary of Practice Implications

1. Deciding on transplant candidacy: We undertook transplantation in these candidates cautiously, and with multidisciplinary input. The decision to proceed was made with an emphasis on individual risk-benefit analysis, and the certainty of liver-related death without transplant.

2. Identification of risk factors for poor outcome: We tried to understand the commonalities between the 2 patients who died shortly after transplant. Both were very sick in the ICU, although all objective parameters had improved by the time of transplant. Both tested positive for SARS-CoV2 PCR within a short interval prior to transplant (7-17 days). Patient #1 had asymptomatic COVID-19 4 months prior to his transplant admission, had 2 subsequently negative nasopharyngeal PCR swabs, but he then tested positive by qualitative PCR with a high cycle threshold of 38 seven days before transplant.

The consensus opinion of our team was that this low quantitative value denoted remnant viral RNA, and not active infection. The occurrence of significant TE phenomena in both deceased patients led us to believe that this hallmark of COVID-19 may represent the most significant deterrent to successful transplantation. TE complications are an important predictor of overall mortality in COVID-19. Human coronaviruses have been demonstrated to enter cells of the alveolar epithelium and endothelium through the binding of angiotensin-converting enzyme 2 (ACE-2). Activation of endothelial cells is believed to drive thrombosis (both venous and arterial). Recognized predisposing factors are ICU admission, stage of COVID-19 (early vs late), immobility, and sepsis. Additionally, patients with liver disease have complex alterations in their coagulation profiles and those with ACLF are at particular risk for bleeding and thrombotic complications.^{9,10} The intersection between known hypercoagulable states of COVID-19 and ACLF therefore produces a high-risk situation for the development of TE events posttransplant, which can have disastrous consequences. Of our 2 patients who suffered TE events, both had recent COVID-19 infection (as defined by a short interval between positive PCR testing and transplantation) and they were the only ones in our series transplanted from the ICU with grade 3 ACLF, leading us to postulate that the combination of ACLF in a recently infected COVID-19 patient may be associated with TE events. Neither of these patients had other hypercoagulable risk factors by history or pretransplant laboratory testing. Standard immunosuppression was used and no infectious complications were noted posttransplant in any of the recipients.

3. Protocol changes: We now require potential candidates to be at least 28 days from the initial diagnosis of COVID-19, have 2 negative nasopharyngeal swab PCR tests at least 24 hours apart, and no evidence of COVID-19 pneumonia at the time of transplant listing. For patients urgently in need of transplant who are within 4 weeks of initial COVID-19 diagnosis, we consider those with 2 negative PCR tests at least 24 hours apart on a case-by-case basis for listing after consultation with the transplant infectious disease team. Antibody testing is used in potential candidates over 4 weeks from COVID-19 diagnosis, but with at least one positive PCR test. We take an individualized approach to risk-benefit considerations, in particular the risk of liver-related death without a transplant using ACLF grade, MELD score, and clinical judgment.

Implications for Practice This series represents an important learning experience for our program, and one which we hope will provide insights into the unique challenges that confront transplant centers in the pandemic era. Liver transplantation may be successfully carried out in patients who have recovered from COVID-19. However, the presence of ACLF, ICU needs, and TE events pre- or posttransplant was associated with compromised outcomes in our cohort, and if present, may suggest a cautious approach to transplantation. Transplant decision making must be informed not only by center-specific resources, but also by the underlying ethical principles of beneficence, distributive justice, and respect for autonomy that are

inherent in the practice of transplantation. As our experience with this pandemic matures, future research will be required to delineate strategies that could be utilized to successfully transplant high-risk individuals such as those identified by our series.

Abbreviations

KiS	Professor of Medicine
ZL	Assistant Professor of Medicine
KaS	Assistant Professor of Medicine
SRC	Internal Medicine Resident Physician
MM	Liver Transplant Nurse Practitioner
RM	Assistant Professor of Surgery
SM	Instructor of Surgery
JAC	Assistant Professor of Surgery
SS	Assistant Professor of Medicine
NJ	Assistant Professor of Medicine
NU	Assistant Professor of Medicine
SG	Associate Professor of Surgery
DM	Professor of Surgery

Authors' Note

- Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work: KShetty, ZL, KSaharia, SRC, MM, SG, DGM
- Drafting the work and revising it critically for important intellectual content: KShetty, ZL, KSaharia, SRC, MM, RPHM, SM, JAC, SS, NJ, NU, SG, DGM
- Final approval of the version to be published: KShetty, ZL, KSaharia, SRC, MM, RPHM, SM, JAC, SS, NJ, NU, SG, DGM
- Agreement to be accountable for all aspects of the work and ensuring that questions related to its accuracy and integrity are investigated and resolved: KShetty, ZL, KSaharia, SRC, MM, RPHM, SM, JAC, SS, NJ, NU, SG, DGM


Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Kirti Shetty  <https://orcid.org/0000-0002-7725-6050>

Raphael P. H. Meier  <https://orcid.org/0000-0001-9050-0436>

References

1. UNOS. COVID-19 and solid organ transplant. Updated April 18, 2021. Accessed February 15, 2022. <https://unos.org/covid/>
2. Dhand A, Bodin R, Wolf DC, et al. Successful liver transplantation in a patient recovered from COVID-19. *Transpl Infect Dis.* 2021;23(2):e13492. doi:10.1111/tid.13492
3. Kulkarni AV, Parthasarathy K, Kumar P, et al. Early liver transplantation after COVID-19 infection: the first report. *Am J Transplant.* 2021;21(6):2279-2284. doi:10.1111/ajt.16509
4. Manzia TM, Gazia C, Lenci I, et al. Liver transplantation performed in a SARS-CoV-2 positive hospitalized recipient using a SARS-CoV-2 infected donor. *Am J Transplant.* 2021;21(7):2600-2604. doi:10.1111/ajt.16548
5. Martini S, Patrono D, Pittaluga F, et al. Urgent liver transplantation soon after recovery from COVID-19 in a patient with decompensated liver cirrhosis. *Hepatol Commun.* 2020;5(1):144-145. doi:10.1002/hep4.1580
6. Roupheal C, D'Amico G, Ricci K, et al. Successful orthotopic liver transplantation in a patient with a positive SARS-CoV2 test and acute liver failure secondary to Acetaminophen overdose. *Am J Transplant.* 2021;21(3):1312-1316. doi:10.1111/ajt.16330
7. Yohanathan L, Campioli CC, Mousa OY, et al. Liver transplantation for acute liver failure in a SARS-CoV-2-PCR-positive patient. *Am J Transplant.* 2021;21(8):2890-2894. doi:10.1111/ajt.16582
8. Marjot T, Moon AM, Cook JA, 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. Klok FA, Kruijff MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147. doi:10.1016/j.thromres.2020.04.013
10. Lisman T, Bernal W. Management of hemostatic disorders in patients with advanced liver disease admitted to an intensive care unit. *Transfus Med Rev.* 2017;31(4):245-251. doi:10.1016/j.tmr.2017.06.002