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Brief Report

Novel Study of SARS-CoV-2 RNA in Post-Reperfusion Liver Biopsies after Transplantation Using COVID-19-Positive Donor Allografts

Jenna N. Whitrock [1], Michela M. Carter [1], Adam D. Price [1], Aaron M. Delman [1], Catherine G. Pratt [1], Jiang Wang [2], Divya Sharma [2], Ralph C. Quillin III [1,3] and Shimul A. Shah [1,3,*]

[1] Cincinnati Research in Outcomes and Safety in Surgery (CROSS) Research Group, Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA; whitroja@ucmail.uc.edu (J.N.W.)
[2] Department of Pathology, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA
[3] Division of Transplantation, Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA
* Correspondence: shahsu@ucmail.uc.edu

Abstract: The utilization of COVID-19-positive donors has expanded the donor pool for transplantation since the initiation of COVID allograft utilization protocols. However, the biopsy-proven PCR transmission rate of COVID-19 from these allografts has not been well documented. In August 2021, an institutional COVID-19-positive allograft protocol was implemented for liver and kidney transplants. Post-reperfusion liver biopsies were obtained intra-operatively to evaluate for COVID-19 RNA, and post-operative day 7 nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) swabs were collected. The primary endpoints evaluated included COVID-19 RNA on biopsy and COVID-19 detected via nasopharyngeal RT-PCR swab on post-operative day 7. A total of 20 vaccinated recipients underwent transplantation (17 liver only, 3 simultaneous liver and kidney) with whole liver allografts from 20 COVID-19-positive deceased donors between August 2021 and April 2022. 95% (19/20) of donors were asymptomatic at the time of donation. On post-reperfusion liver allograft biopsies, COVID-19 RNA was found in 10% (2/20) of the samples. All the recipients were COVID-19-negative on post-operative day 7 nasopharyngeal RT-PCR, showing a 0% transmission rate of COVID-19 from the positive allografts. The use of COVID-19 allografts appears to be a safe practice, with no PCR-detectable transmission of COVID-19 despite 10% of the liver allografts having COVID-19 RNA present on post-reperfusion biopsy.

Keywords: COVID-19; liver transplantation; transmission; liver biopsy

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1. Introduction

The transplant population was disparately impacted by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the Coronavirus Disease 2019 (COVID-19) pandemic. COVID-19 is a contagious respiratory disease that can lead to an array of symptoms, ranging from mild to severe. Symptoms of COVID-19 may include fever, chills, cough, shortness of breath, respiratory failure, sepsis, thromboembolism, multiorgan failure, and death [1]. The United States experienced a 51% drop in transplant activity [2] and a 2.2-fold increase in waitlist mortality due to the COVID-19 pandemic, which began in 2019 [3]. This decrease in transplant activity was likely a result of multiple factors including scarce hospital resources, changes in processes of care for organ donation and allocation, and concerns for the potential for poor outcomes in recipients with COVID-19. Despite transplant recipients being at risk for complications from COVID-19 infection due to their medical comorbidities and immunosuppression, it was discovered, as the pandemic progressed, that the incidence of COVID-19 infection was lower in transplant recipients compared to those on the waitlist [4]; however, both populations were at an

excess mortality risk due to infection, which initially lead to hesitancy in the utilization of these otherwise appropriate allografts early during the pandemic [5].

Mechanisms of potential infection transmission by organ donation were theorized, and SARS-CoV-2 was detected in lung, bowel, kidney, liver, and heart on autopsy studies [6], which resulted in early recommendations against the use of organs from donors with active COVID-19. However, as our understanding about the virus and the management of its complications developed, a necessary debate occurred within the transplant community regarding the ethics of withholding allografts from COVID-19-positive donors, especially when it is known that liver allografts are a scarce resource, and withholding allografts increases waitlist mortality. In the time since the initiation of COVID-19 allograft utilization protocols in 2020 and 2021, the safety of COVID-19 allografts has been shown. However, many questions persist. Particularly, uncertainty remains regarding whether the tissue-based virus in SARS-CoV-2-positive non-lung allografts is replication-competent. Furthermore, uncertainty endures about best practices regarding the utilization of and long-term outcomes associated with the use of SARS-CoV-2-positive allografts. This study sought to analyze the rate of donor-derived transmission events and to determine if the presence of SARS-CoV-2 RNA within donor allografts impacts the risk of experiencing adverse events such as death, graft loss, biliary complications, COVID-related illness, respiratory complications, and vascular complications.

2. Materials and Methods

In August 2021, the University of Cincinnati Medical Center developed an institutional protocol to help guide the use of allografts from COVID-19-positive deceased donors. From August 2021 through April 2022, all recipients of COVID-19-positive liver allografts underwent intra-operative post-reperfusion liver biopsies to evaluate for SARS-CoV-2 RNA on droplet digital polymerase chain reaction (PCR) testing. They subsequently underwent post-operative day 7 nasopharyngeal reverse transcriptase PCR (RT-PCR) testing and were monitored for any signs or symptoms of clinical COVID-19 transmission.

This is a retrospective cohort study of 20 vaccinated recipients who underwent transplantation (17 liver only, 3 simultaneous liver and kidney) with whole liver allografts from 20 COVID-19-positive deceased donors between August 2021 and April 2022. This study was approved by the University of Cincinnati Institutional Review Board (IRB#: 2023-0081). Statistical analysis was carried out using JMP Pro16.

Throughout the study period, comfort levels with COVID-19 improved as virulence appeared to decline. Protocols evolved based on new information available. Initially, potential donors were excluded if they had imaging that raised concerns of COVID-19-induced pneumonia or ARDS or their cause of death was COVID-19. However, as more information became available, these exclusion criteria were eliminated. In addition, recipients were initially given monoclonal antibodies after transplant; although, this practice also evolved as recommendations changed.

3. Results

3.1. Donors

The mean number of days from the diagnosis of COVID-19 to organ donation for donors was 4.0 $\pm$ 3.1 days. Most of the donors were diagnosed with COVID-19 via nasopharyngeal RT-PCR (80%, n = 16) and the others were diagnosed via bronchoalveolar lavage RT-PCR (20%, n = 4). One donor (5%) died directly from a COVID-19-related illness with anoxia reported as the cause of death. The remaining donors were asymptomatic at the time of donation (95%). The donors' cause of death was listed as anoxia for 13 of the donors (65%), stroke for 4 donors (20%), and traumatic brain injury for 3 donors (15%).

When evaluating procurement trends, liver perfusion pumps were not used for any of the allografts, and all were from brain-dead donors. The mean cold ischemia time was 366.9 min (5.8 h) with a standard deviation of 102.2 min. The mean warm ischemia time was 31.2 min with a standard deviation of 4.8 min.

3.2. Recipients

The recipients of the COVID-19-positive liver allografts had a mean age of 54.1 (±10.3) years with mean MELD scores of 21.2 (±8.7) (Table 1). Indications for liver transplant included alcoholic cirrhosis (n = 9, 45%), primary sclerosing cholangitis/primary biliary cholangitis (n = 3, 15%), hepatitis C cirrhosis (n = 3, 15%), nonalcoholic steatohepatitis (n = 2, 10%), autoimmune hepatitis (n = 1, 5%), drug-induced liver injury (n = 1, 5%), and alpha-1 antitrypsin deficiency (n = 1, 5%).

Table 1. Population characteristics of donors and recipients.

Donor Characteristics	**n = 20**
Age (years), mean ± SD	data
Days from diagnosis of COVID-19, mean ± SD	4.0 ± 3.1
Expedited placement, n (%)	7 (35%)
Recipient Characteristics	**n = 20**
Age (years), mean ± SD	54.1 ± 10.3
Male, n (%)	7 (35%)
BMI, mean ± SD	26.8 ± 3.8
MELD, mean ± SD	21.2 ± 8.7
Retransplant, n (%)	2 (10%)
COVID-19 vaccination	20 (100%)
Boosted (>2 doses), n (%)	12 (60%)
Complete (2 doses), n (%)	8 (40%)

COVID-19: Coronavirus Disease 2019, BMI: Body Mass Index, MELD: Model for End-Stage Liver Disease, SD: standard deviation.

All patients who received COVID-19-positive allografts had been fully vaccinated, and 60% (n = 12) had received booster vaccinations. All the recipients were tested per institutional protocol for COVID-19 pre-operatively and were negative; however, three patients did not receive pre-operative testing due to recent COVID-19 infection within the 90 days pre-operation.

On the post-reperfusion liver allograft biopsies, COVID-19 RNA was found in only 10% (2/20) of the samples (Table 2). All the recipients were COVID-19-negative on post-operative day 7 nasopharyngeal RT-PCR, showing a 0% transmission rate of COVID-19 from the positive allografts. No additional scheduled COVID testing was completed. Twelve patients (60%) received post-operative monoclonal antibody treatment for COVID-19. All the patients received induction therapy with solumedrol and were discharged home on a steroid taper, tacrolimus, and mycophenolate mofetil per our institution's protocol.

Table 2. Recipient outcomes.

Outcomes	**n (%)**
COVID-19 RNA Present on Post-Reperfusion Biopsy	2 (10%)
Post-Operative Day 7 Nasopharyngeal RT-PCR COVID-19 Testing (Positive Result)	0
Early Allograft Dysfunction	2 (10%)
Biliary Complications	0
Deep Vein Thrombosis	0
Respiratory Complications	4 (20%)
Vascular Complications	1 (5%)
30-Day Graft Survival	20 (100%)
30-Day Patient Survival	20 (100%)
1-Year Patient Survival	19 (95%)
Median survival	685.5 days [IQR: 669.7–733.5]

COVID-19: Coronavirus Disease 2019, IQR: Interquartile Range, RNA: Ribonucleic Acid, RT-PCR: Reverse Transcriptase Polymerase Chain Reaction.

Respiratory complications occurred in four (20%) recipients, though these did not occur in the patients with COVID-19 RNA found on biopsies nor were any of the complications related to COVID-19 (three cases of aspiration pneumonia, one case of pulmonary edema). One case of hepatic artery thrombosis occurred, though this was likely related to a donor-derived hepatic artery injury. No cases of deep vein thrombosis or biliary complications occurred.

The median follow up was 685.5 days [IQR 669.7–733.5 days]. There were no cases of graft loss or subject deaths within the first 30 days; however, one subject died at 154 days of aspiration while recovering at a rehabilitation facility with a functioning liver allograft.

4. Discussion

This is the first study to evaluate donor-derived transmission events and the presence of SARS-CoV-2 RNA in post-reperfusion liver biopsies after the transplantation of liver allografts from COVID-19-positive donors. We found that despite 10% of the livers testing positive for SARS-CoV-2 RNA on droplet digital PCR testing at the time of reperfusion biopsy, there were no cases of donor-derived transmission events to any of the 20 vaccinated recipients. At 30 days, all the grafts were functioning, and at 1 year, 95% of the patients were alive with functioning grafts.

Despite the concerns expressed in the prior literature regarding safety of the utilization of COVID-19-positive liver allografts due to many tissue-level changes seen in various cadaveric and tissue studies [6], our study did not demonstrate any signs that these changes occurred in our vaccinated recipients. We noted one (5%) vascular complication, though this was likely technical in nature, and four (20%) respiratory complications, and none were determined to be related to COVID-19 disease. We found only 10% of the allografts had SARS-CoV-2 RNA, which suggests that although SARS-CoV-2 RNA may be transmitted via solid organs, it is unlikely that this will occur in liver transplantation [6].

Our study does have limitations that we would like to address. First, both the donor and recipient protocols evolved throughout the time studied, which could have affected the data; however, we do not believe these changes impacted our major findings. Next, we acknowledge that this is a single-center study, and our sample size is inherently power-limited, though we believe these findings remain impactful given the novel nature of our methodology. Finally, we did not have donor SARS-CoV-2 viral load data or vaccination status available, which could have provided insight into the donors' burden of disease.

Overall, with no PCR-detectable transmission of COVID-19 despite 10% of the liver allografts having COVID-19 RNA present on post-reperfusion biopsy, we support the use of COVID-19 allografts as it appears to be a safe practice. The ability to utilize these allografts increases the rate of transplantation and therefore decreases the waitlist time and mortality for patients in need of life-saving liver transplants without compromising graft or patient outcomes in appropriately selected patients.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available.

Conflicts of Interest: The authors declare no conflicts of interest.

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