



BRIEF COMMUNICATION

When is it safe to perform abdominal transplantation in patients with prior SARS-CoV-2 infection: A case series

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Abstract

Background: The Coronavirus disease 2019(COVID-19) pandemic has negatively impacted worldwide organ transplantation. However, there is limited information on recipients transplanted after SARS-CoV-2 infection. A full understanding of this scenario is required, as transplantation is a life-saving procedure and COVID-19 remains an ongoing threat.

Methods: Abdominal organ transplant recipients diagnosed with COVID-19 prior to transplantation were identified by chart review and clinical data were collected. The primary outcome was the transplant outcome including graft loss, rejection and death, and reactivation of infection post-transplant.

Results: We identified 14 patients who received abdominal organ transplants after symptomatic PCR confirmed SARS-CoV-2 infection; four patients had a positive PCR at the time of admission for transplantation. The median time of follow-up was 79 (22–190) days. One recipient with negative PCR before transplant tested positive 9 days after transplant. One of 14 transplanted patients developed disseminated mold infection and died 86 days after transplant. During the follow-up, only one patient developed rejection; thirteen patients had favorable graft outcomes.

Conclusions: We were able to perform abdominal transplantation for patients with COVID-19 before transplant, even with positive PCR at the time of transplant. Larger studies are needed to determine the time to safe transplant after SARS-CoV-2 infection.

KEYWORDS

abdominal transplantation, coronavirus disease 2019, PCR

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1 | INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has burdened health care systems worldwide and negatively impacted organ donation and transplantation.¹ A significant decrease in the number of transplants and an increased waitlist mortality was initially reported from US transplant regions. However, deceased donor transplant activity is now coming back at or above pre-pandemic levels.² There is a large volume of data regarding managing post solid organ transplant (SOT) recipients with COVID-19,³ but it is still uncertain when patients with a previous history of COVID-19 can proceed with transplantation, especially since 20% of the US population has been exposed to the virus.⁴

When conducting transplants, we need to assess the risks versus benefits of each transplant case, especially with regards to specific organ types. After induction, T-cell- and B-cell-mediated immunity is reduced, which may result in a relapse of SARS-CoV-2 infection, even though there is no conclusive evidence of the latter. COVID-19 is also associated with secondary infections, such as invasive pulmonary aspergillosis, which can increase mortality post-transplant. To undergo a safe transplant, preventive measures must be taken.^{5,6}

On the other hand, there is a significant benefit from SOT that improves the quality of life and is also a life-saving procedure. There is also evidence of an increase in mortality in pre-kidney transplant recipients on the transplant waitlist^{7,8} amidst a pandemic, thus, transplantation is still the best therapeutic option for end-organ failure.

Although a limited number of lung transplantations were performed for the recipients who developed COVID-19 while SARS-CoV-2 polymerase chain reaction (PCR) positivity,^{9,10} only a few were reported for abdominal transplant for patients with a previous history of COVID-19 infection.¹¹⁻¹⁴

To provide some guidance on the safety of procedures and promptness to abdominal transplant after infection, we present our pilot experience for patients with a history of COVID-19, who subsequently received liver and/or kidney transplants.

2 | MATERIAL AND METHODS

This was a single-center retrospective cohort study conducted at the Miami Transplant Institute, Jackson Health System, Miami, Florida, USA. We included all patients diagnosed with SARS-CoV-2 infection before abdominal transplant between March and December 2020. We excluded patients who showed antibody positivity without having documented PCR positive test results.

Our center implemented a strict protocol to test all recipients with nasopharyngeal (NP) swab PCR on the day of admission for transplant since April 10, 2020, along with antibody testing for SARS-CoV-2. All documented Cycle threshold (Ct) value was analyzed via Cepheid platform. Antibody testing targeting spike protein was performed via an ortho-diagnostics platform to measure IgG and total antibodies, expressed in signal/cutoff ratio (s/co) (lower

limit of positivity: 1.0). All potential transplant recipients who had a history of COVID-19 were assessed for transplant candidacy in the institutional committee. For non-urgent transplants, based on the infectivity studies,^{15,16} we used 35 as a threshold to proceed to transplant. For urgent liver transplants, we used a lower threshold, which was 25, to get listed. However, the final decision to proceed with transplantation was made on a case-by-case basis as determined by the severity of the disease, the duration from the diagnosis, radiological findings, and symptoms. During transplant surgery, for PCR positive recipients, we implemented active SARS-CoV-2 infection precaution methods including wearing N95 masks and using negative pressure surgery rooms. After the transplantation, for surveillance purposes, we repeated PCR testing. This study was approved by the University of Miami research ethics board (research ethics board number: 20150360) as well as the institutional research committee and conducted consistent with principles embodied in the Declaration of Helsinki.

3 | RESULTS

During the study period, we tested patients for COVID-19 within 12 h prior to transplant. The median time of follow-up and graft survival was 79 (22-190) days. Four patients had positive NP swab PCR 12 h prior to transplant. One patient with a negative PCR developed a reactive PCR in the immediate post-transplant period. In addition to that, nine patients who showed negative NP swab PCR yet showed positive antibody testing with a previous history of PCR positivity (Table 1). We excluded four patients who showed antibody positivity without having documented PCR positive test results. Here, we describe in detail the four patients who showed positive PCR at the time of transplant and one additional case who achieved negative PCR at the time of transplant but turned positive soon after transplant.

3.1 | Case 1

A 37-year-old woman, with a history of overlap syndrome including autoimmune hepatitis and primary biliary cholangitis being treated with mycophenolate and prednisone, was diagnosed with COVID-19, 90 days prior to liver transplantation. Clinical symptoms of infection included fever, cough, and shortness of breath that progressed to pneumonia and were treated with hydroxychloroquine. Respiratory symptoms continued for one week and after that, she was asymptomatic. Repeated PCR 33 days after diagnosis was negative. At the time of admission for a liver transplant, repeat NP swab PCR was positive, with a Ct value of 35. We also confirmed IgG (24.8 s/co) and total immunoglobulin positivity (88.1 s/co). High-dose methylprednisolone was used for induction immunosuppression. Five days after transplant, NP swab PCR was negative. Follow-up at 190 days revealed stable allograft function, no signs of infections nor surgical complications.

TABLE 1 Summary of abdominal transplant recipients who developed SARS-CoV-2 infection prior to transplant

Age/Gender	Transplant type	SARS-CoV-2 PCR at transplant (if positive, cycle threshold) [†]	COVID-19 to transplant (days)	Antibody testing for SARS-CoV-2 result at transplant (IgG/Total)	Repeated PCR (days, result)	Induction immunosuppression	Rejection/Outcome	Follow-up period
1 37/Female	Liver	Positive, 35.5	90	24.8/88.1	5 and 7 days, negative	High-dose steroid	No/Survive	190
2 55/Male	Liver/Kidney	Positive, 25	53	10.9/85.5	9 and 20 days, negative	ATG, Basiliximab, Solumedrol	No/Death	86
3 63/Male	Kidney	Positive, 32.5	64	30.9/392	4 days positive, 11 days negative	ATG, Basiliximab, Solumedrol	No/Survive	129
4 66/Male	Kidney	Positive, 35.2	60	5.8/104	6 and 10 days, negative	ATG, Basiliximab, Solumedrol	No/Survive	24
5 65/Male	Liver/Kidney	Negative	61	0.13/4.9	9 days positive, 35 days negative	ATG, Basiliximab, Solumedrol	No/Survive	105
6 66/Female	Liver	Negative	202	22/97.1	8 and 14 days, negative	High-dose steroid	Yes/Survive	100
7 50/Male	Liver	Negative	165	8.1/260	11 days, negative	High-dose steroid	No/Survive	39
8 51/Male	Liver	Negative	107	2.1/36	10 days, negative	High-dose steroid	No/Survive	46
9 55/Male	Kidney	Negative	61	31/856	14 days, negative	ATG, Basiliximab, Solumedrol	No/Survive	113
10 31/Male	Kidney	Negative	113	12.9/106	14 days, negative	ATG, Basiliximab, Solumedrol	No/Survive	135
11 65/Male	Kidney	Negative	113	29/482	7 days, negative	ATG, Basiliximab, Solumedrol	No/Survive	68
12 56/Male	Kidney	Negative	147	8.0/220	32 days, negative	ATG, Basiliximab, Solumedrol	No/Survive	41
13 30/Male	Kidney	Negative	149	0.02/0.68	4 days, negative	ATG, Basiliximab, Solumedrol	No/Survive	72
14 43/Female	Kidney(Living donor)	Negative	172	0.23/19.7	3 and 16 days, negative	ATG, Basiliximab, Solumedrol, Rituximab	No/Survive	22

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; PCR, polymerase chain reaction; ATG, anti-thymocyte globulin.

[†]PCR platform: Cepheid

3.2 | Case 2

A 55-year-old man with acute alcoholic hepatitis was transferred to our center for transplant evaluation. NP swab PCR at the time of admission was negative. Six days after admission, after known nosocomial exposure, a repeated SARS-CoV-2 PCR became positive. Six days after diagnosis, he was febrile and hypoxic with bilateral opacities in chest X-ray. He received dexamethasone, remdesivir, convalescent plasma along with empiric antibiotics. Unfortunately, he also developed kidney failure secondary to acute tubular necrosis. Thirty-five days after diagnosis, this patient was asymptomatic from COVID-19 and was actively listed for a simultaneous liver-kidney transplant. Transplantation took place 53 days after diagnosis; and at that time, PCR still resulted positive with a Ct value of 25 with positive antibody testing (IgG 10.9 s/co, Total 85.5 s/co). The post-transplant course was complicated by infected hematoma as well as septic thrombophlebitis from a peripherally inserted central catheter. Eventually, this patient developed a severe disseminated mold infection. Pathology from the skin and amputated foot tissue showed non-septated hyphae with greater than 90 degrees angles branches, but culture showed negative. This patient died 86 days after the transplant.

3.3 | Case 3

A 63-year-old man, with end-stage renal disease secondary to type one diabetes, contracted SARS-CoV-2 infection 64 days prior to kidney transplant. He was symptomatic with fever and shortness of breath but never required hospitalization. Twenty-four days after diagnosis, NP swab PCR was reported negative. At the time of transplant, we repeated SARS-CoV-2 PCR testing to be positive with Ct value of 32.5. Also, the COVID-19 IgG of 30.9 s/co ratio and total antibody was 392 s/co. Kidney transplant was conducted, and thymoglobulin 3mg/kg total dose, along with basiliximab and high-dose steroids were given as induction immunosuppression. No reduction in induction or maintenance regimens took place. Repeated NP swab was positive 4 days after transplant with Ct value of 41 and achieved negativity at post-operative day 11. As a follow-up on day 129, the patient remained asymptomatic and graft function normal.

3.4 | Case 4

A 66-year-old man, with end-stage renal disease from hypertension, contracted SARS-CoV-2 infection 60 days prior to his kidney transplant. His symptoms included fever and cough, which resolved in two weeks. No COVID-19 specific therapies were given. Repeated NP swab PCR was negative after 52 and 55 days after diagnosis. SARS-CoV-2 PCR test at the time of transplant was positive with Ct value of 35.2 while antibodies were detected; COVID-19 IgG of 5.82 s/co ratio and total antibody of 104 s/co ratio. Hence, the kidney transplant surgery took place and thymoglobulin 3 mg/kg,

basiliximab, and high-dose steroids were given as per protocol. Again, no deviation from standard induction and maintenance immunosuppression occurred. Repeat NP swabs performed on days 6 and 10 were negative. No surgical nor infectious complications were noted during the post-operative period.

3.5 | Case 5

A 65-year-old man with alcoholic liver cirrhosis was diagnosed with COVID-19, 61 days prior to his kidney and liver transplant. He required admission to our hospital and received convalescent plasma and dexamethasone. NP swab PCR was positive at day 40 and negative at day 60 of diagnosis. All symptoms resolved within two weeks. Of note, prior to transplant, this patient did not develop antibodies against SARS-CoV-2. Nine days after transplant, NP swab PCR was repeated and showed positive with Ct value of 41, but finally achieved negativity on day 35 of transplant. The post-transplant course was complicated by *Candida auris* candidemia, which required a prolonged ICU stay. The patient was still in ICU 105 days after transplant at the end of the follow-up period.

Table 1 shows additional data for all patients. Of note, for the rest of the nine patients including three deceased donor liver, five deceased donor kidney, and one living donor kidney transplant, had a median time from the diagnosis of COVID-19 to transplant of 147 (range 61-202) days. We did not change the induction or maintenance immunosuppressive regimen due to the previous history of COVID-19. Only one liver transplant recipient developed T-cell-mediated rejection and was managed with an increased dose of steroids. The rest of them had good graft function, and no death was seen during follow-up.

4 | DISCUSSION

This case series demonstrates the possibility of performing abdominal SOT safely in recipients diagnosed with COVID-19 within a short time period to transplantation. Among 14 patients, 12 had favorable outcomes, with one mortality and one prolonged ICU admission. Unexpectedly five recipients had PCR positivity in the perioperative period, of which two developed significant infections and one died within 3 months post-transplant.

There has been a significant decrease in deceased donor and living donor transplantation worldwide due to the pandemic.^{1,2} Ravanan et al suggested there is an increased mortality on the waiting list, in the COVID-19 era.⁷ Even with the COVID-19 pandemic, kidney and liver transplantation still remains a life-saving procedure and should be considered in selected cases. However, there are other risks to performing transplantation during a pandemic. Being admitted to the hospital itself presents a risk for contracting SARS-CoV-2, even with personal protective equipment utilization. In addition, finding resources to take care of transplant patients has been challenging due to the hospital system-wide reallocation, or

personnel and equipment to meet the needs of COVID-19 patients. Besides reallocation of resources, the rate of infection can be higher post-transplant due to their immunocompromised state. There are reports of prolonged shedding of infective SARS-CoV-2 in immunocompromised individuals^{17,18} yet no large studies have proven this to be the case in SOT individuals. Also, one patient was diagnosed with mold infection soon after transplant. Eventhough there are several reports of post COVID-19 associated pulmonary Aspergillosis,¹⁹ we could not identify if this was due to post-COVID-19 or prolonged immunosuppressive situation as there were no positive respiratory cultures. Hence, it is challenging to quantify and compare the risks and benefits of transplantation during the pandemic and critical for transplant physicians to safely attempt to continue to perform this life-saving procedure on a one-to-one basis.

To further complicate the situation, prolonged PCR positivity has been well-documented, especially in immunocompromised patients.²⁰ Some reports showed prolonged viral culture positivity in immunocompromised hosts. Viral culture would be a more accurate test; however, viral culture requires extensive resources, including a biosafety level 3 microbiology laboratory. To date, PCR is recognized as the gold standard, and even if PCR is negative, no established rule exists to precisely determine the safe period of time to proceed with transplantation because of concern for relapse due to immunosuppression. We decided to use the PCR Ct value to determine the timing for the transplant. Ct value has been reported as a more validated indirect measure of infectivity compared to others^{9,16,21} but not established to assess the degree of disease severity or potential for recurrence after immunosuppression. At this time, in patients with resolution of clinical infection and high Ct values, there is no supporting data that predicts disease relapse after induction immunosuppression therapy for transplantation. In our health system and the state of Florida, routine viral cultures for SARS-CoV2 are not available. We used Ct values as a surrogate marker of culture negativity to determine the timing for abdominal transplant for pre-transplant recipients whose PCR was still positive. Of note, two patients who had a poor outcome showed PCR positivity at the time or soon after transplant, which was lower than the other two patients who did well after transplant. In addition to Ct values, we measured antibody titers to ensure the potential recipients have mounted a significant immune response against SARS-CoV-2 prior to transplant. For PCR negative patients, positive antibody was not a requirement to get listed for transplant at our institute.

It is important to note that this study has several limitations. First, this is a single-center analysis with a limited number of cases. Second, the background of the potential recipients, treatment methods including immunosuppression protocols and surgical procedures, are different among SOT centers. We only had 14 patients and thus the power is too small to validate any significant conclusions, yet as a case series, some trends may be inferred. Also, the use of Ct values to guide clinical decision-making may contain some problems as there are several factors related to the patient, specimen, and specific PCR assay that can result in significant inter- and

intra-patient variability in Ct values. In addition to this, given that the patients were all at least 53 days from the initial diagnosis, it might be unlikely that any had an actual active viral infection that would become more apparent post-transplant. Lastly, the follow-up period was short so long-term outcomes including the incidence of rejection, graft loss, or other late-onset opportunistic infections are not available; yet, we believe we had enough follow-up period to monitor for recurrence of SARS-CoV-2.

In conclusion, we were able to perform abdominal transplantation for patients who developed COVID-19 prior to transplant, even with positive PCR at the time of transplant. To validate this model, we will need a larger sample size study and longer follow-up.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Y.N., S.A., and G.G. performed the data analysis. All authors were responsible for the study design, data interpretation, and writing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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