










CASE REPORT

Liver transplantation performed in a SARS-CoV-2 positive hospitalized recipient using a SARS-CoV-2 infected donor

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The coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 currently affected more than 108 million people worldwide with a fatality rate of 2.2%. Herein, we report the first case of liver transplantation (LT) performed with a liver procured from a SARS-CoV-2 positive donor. The recipient was a 35-year-old SARS-CoV-2 positive female patient affected by severe end-stage HBV-HDV-related liver disease (model of end-stage liver disease = 32) who had neutralizing SARS-CoV-2 antibodies (titers 1:320) at time of LT. The LT was successful, and the graft is functioning two months after surgery. The recipient cleared the SARS-CoV-2 infection 1 month after LT. The current case shows that the prompt use of SARS-CoV-2 infected liver donors offers an invaluable life-saving opportunity for SARS-CoV-2 positive wait-listed patients who developed neutralizing SARS-CoV-2 antibodies.

KEYWORDS

clinical research/practice, donors and donation: extended criteria, infection and infectious agents - viral, infectious disease, liver transplantation/hepatology, organ procurement and allocation

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rapidly spreading among humans, causing a mild-to-severe, cold-like, respiratory tract infection,^{1,2} known as coronavirus disease 2019 (COVID-19).³ As of February 15, 2021, more than 108 millions of people have been infected, and more than 2.0 (2.2%) million deaths were globally detected since the start of the pandemic.⁴ The clinical spectrum of COVID-19 widely differs among infected individuals, including from asymptomatic to patients with severe and quickly progressing lethal pneumonia.⁵

In Italy, as December 1, 2020, the National Transplant Center (CNT), jointly with the National Institute of Health, established that the heart and the liver from SARS-CoV-2 infected donors can be procured and transplanted, yet only in waitlisted patients who are SARS-CoV-2 positive, or with a previous history of COVID-19. The liver transplant team must provide clear-cut evidence that patients suffer of severe end-stage liver or heart disease, with high likelihood of death on the waiting list, making therefore the potential risks due to donor-to-recipient viral transmission acceptable.

On December 2020, at Tor Vergata University, Rome, Italy, a liver from a SARS-CoV-2 positive donor was transplanted in a

Abbreviations: BAL, bronchoalveolar lavage; BAR, balance of risk; CNT, National Transplant Center; COVID-19, coronavirus disease 2019; Ct, cycle thresholds; CVVH, continuous veno-venous hemofiltration; DRI, donor risk index; ICU, intensive care unit; LT, liver transplantation; MELD, Model for End-stage Liver Disease; POD, postoperative day; P-SOFT, predict survival outcome following liver transplantation; RT-PCR, real-time reverse transcription; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSO, transplantable solid organs; UNOS, United Network for Organ Sharing.

SARS-CoV-2 recipient who developed neutralizing SARS-CoV-2 antibodies.

2 | CASE REPORT

A 33-year-old female (weight: 48 kg; height: 160 cm; body mass index: 19) patient with end-stage HBV-HDV-related cirrhosis, with a biochemical Model for End-stage Liver Disease (MELD) score of 30, was listed for LT in November 2020, at the Tor Vergata University Transplant Center in Rome, Italy. Five days after listing, the patient underwent a routine SARS-CoV-2 nasopharyngeal swab, and all 2019 nCoV genes (E/N/S) were detected at real-time polymerase chain reaction (RT-PCR), indicating an ongoing infection according to the detected cycle thresholds (Ct)⁶ (Table 1). The patient had no respiratory symptoms, but the chest CT scan showed features of ground glass pneumonia. The patient was thus suspended from the LT waiting list and transferred to a nonsurgical COVID-19 ward for the clinical care (oxygen administration, enoxaparin [0.5 mg/kg/day], steroids [dexamethasone, 6 mg/day], azithromycin) and the SARS-CoV-2 monitoring. SARS-CoV-2 IgG antibodies and nasopharyngeal swabs were routinely tested (Tables 1 and 2). After the publication of the new CNT rules (protocol 1951/CNT 2020, December 1, 2020),⁷ the patient was reactivated on the LT waiting list with a MELD score of 29. In the following week, the patient had a significant clinical deterioration, including grade II/III encephalopathy, with total bilirubin rising to 36.8 mg/dL and the MELD score to 32 (indicating an estimated 3-month mortality of 52.6%). The patient was therefore listed in the national organ sharing urgency program for LT (United Network for Organ Sharing [UNOS] Status 1).

The day after listing, a liver graft from a 65-year-old brain-dead female donor (weight: 65 kg; height: 165 cm; body mass index: 24) was offered for our patient. The donor risk index (DRI)⁸ was 1.94 and the graft-to-recipient weight ratio was 2.8.

During the donor screening procedures, the bronchoalveolar lavage (BAL) for SARS-CoV-2 resulted positive for all three genes (RT-PCR, Allplex SARS-CoV-2 Assay Seegene; gene E Ct = 24; gene S Ct = 27; gene N Ct = 24). The donor had no previous medical history of COVID-19. Due to the severely impaired clinical status of our

recipient, implying an exceedingly high risk of death, we decided to accept the organ offer and to proceed with the LT. The preallocation score to predict survival outcome following liver transplantation (P-SOFT) was 12 and the balance of risk score (BAR) was 10,^{9,10} corresponding to an estimated prediction of 6- and 12-month survival of 92% and 86%, respectively.

All of the personnel involved in the LT were adequately equipped with surgical caps, protective N95 filtering and surgical facemasks, isolation gowns, and double gloves. The LT recipient was provided with surgical cap and surgical mask. None of the involved personnel ever tested positive for SARS-CoV-2 after LT.

The intraoperative BAL for detection of for SARS-CoV-2 was positive (Table 1). The patient remained stable intraoperatively, and the surgical procedure was completed uneventful. An induction therapy with 5000 IU of hepatitis B immunoglobulin was administered at LT, followed by 2000 IU daily until Day 4 after LT. The patient was then transferred to the intensive care unit (ICU) and extubated immediately after. Due to the lack of clear-cut guidelines, the immunosuppression was based on our center protocol (tacrolimus 0.09 mg/kg/day, once a day, and everolimus 0.01 mg/kg/day, twice daily). After surgery, the patient was treated with tenofovir disoproxil fumarate (245 mg/day). The graft showed a rapid recovery after LT. The aspartate aminotransferase peak and PT-INR within the first week after LT were 1298 IU/L and 2.00, respectively, while bilirubin dropped from 36.8 mg/dL at transplant to 18.9 mg/dL on postoperative day (POD) 10. The clinical course was characterized by significant leucopenia, renal impairment, and obstructive jaundice managed by appropriate everolimus dose adjustments (0.25 mg/bid), tacrolimus withdrawal for 1 week, and bile duct stenting, respectively. A SARS-CoV-2 nasopharyngeal swab tested positive on POD 5, yet there was no clinical evidence of respiratory symptoms and fever nor of radiological findings suggestive for COVID-19. On POD 7, the patient was discharged from the ICU in good clinical conditions and admitted to a COVID-19-dedicated area, with specialized healthcare personnel. The patient turned out to be negative at SARS-CoV-2 molecular testing 30 days after LT (a detailed timeline is summarized in Table 1) without ever developing signs of COVID-19. The last chest CT scan showed no features of ground glass pneumonia, and 2 months after LT, the graft is well functioning. Interestingly, the day of LT the

TABLE 1 Timeline of the patient SARS-CoV-2 real-time PCR molecular exams, measured in cycles threshold (Ct)

Pre-LT/POD	-30 Pre-LT ^a	-23 Pre-LT	-17 Pre-LT	-11 Pre-LT	-9 Pre-LT	LT	V POD	X POD	XVIII POD	XXIV POD	XXXI POD	XXXII POD	XXXIII POD
COVID-19 Exam	NPS	NPS	NPS	NPS	NPS	BAL	NPS	NPS	TA	TA	BAL	BAL	BAL
Envelope (E) protein	17.12	25.23	27.24	29.94	29.31	25.7	33.16	37.23	0	39.14	NEG	NEG	NEG
Nucleocapsid (N) protein	13.44	24.06	26.34	28.51	27.5	24.94	31.9	37.52	37.12	37.88	NEG	NEG	NEG
Spike (S) protein	16.49	25.56	27.01	29.99	29.14	26.7	35.04	39.43	0	0	NEG	NEG	NEG

Abbreviations: BAL, bronchoalveolar lavage; LT, liver transplantation; NPS, nasopharyngeal swab; POD, postoperative day; TA, tracheoaspirate.

^aReferred to 11/11/2020, when the patient was temporarily suspended from LT waiting list after the detection of a positive COVID-19 NPS.

TABLE 2 Timeline of the patient SARS-CoV-2 IgG and IgG neutralizing antibodies quantification detection

	Timeline						
	-30 Pre-op	-23 Pre-op	-17 Pre-op	-11 Pre-op	-9 Pre-op	LT	10 days after LT
SARS-CoV-2 IgG (AU/ml) ^a	Neg (0.02)	Neg (0.03)	Neg (0.26)	Neg (1.38)	Neg (1.42)	Pos (4.48)	N/A
SARS-CoV-2 IgM (AU/ml) ^b	N/A	N/A	N/A	N/A	N/A	Pos (1.2)	Pos (1.3)
SARS-CoV-2 IgA (AU/ml) ^c	N/A	N/A	N/A	N/A	N/A	Pos (9.1)	Pos (6)
Neutralizing SARS-CoV-2 IgG titer ^d	N/A	N/A	N/A	N/A	N/A	Pos (1:320)	Pos (1:160)

Abbreviation: LT, liver transplantation.

^aResults obtained with chemiluminescence immunoassay (CLIA) (Positive IgG: >1.4 AU/mL); ^bResults obtained with enzyme-linked immunosorbent assay (ELISA) (Positive IgM: >1.1 AU/mL); ^cResults obtained with enzyme-linked immunosorbent assay (ELISA) (Positive IgA: >1.1 AU/mL); ^dResults obtained with enzyme-linked immunosorbent assay (ELISA) (Positive IgG titer: >1:10).

patient had neutralizing SARS-CoV-2 antibodies (SARS-CoV-2 IgG positive [titer of 1:320]), which were confirmed at POD 10 (titer of 1:160) (Table 2).

3 | DISCUSSION

The COVID-19 pandemic has strongly affected plenty of lives worldwide as well as the transplant community, including transplant recipients in urgent need for organs. Since the pandemic started, more and more ICU beds were occupied by a rising number of COVID-19 patients, thus reducing the chance to procure transplantable solid organs (TSO) from suitable donors. Consequently, patients on the waiting list are nowadays less likely to be transplanted in due time and more prone to develop life-threatening disease complication.¹¹ In Italy, the COVID-19 pandemic had a deleterious impact on LT programs, generating a severe dearth of TSO, which resulted in longer waiting times and an exceeding number of deaths on the waiting lists.¹ This underlines the need of using even more stringent prioritization criteria to select transplant candidates in this changed COVID-19 scenario, including the evaluation of organ donors.¹

We hereby present the first case of LT in a young SARS-CoV-2 positive female recipient who had neutralizing SARS-CoV-2 antibodies at time of transplant, performed using an organ procured from a SARS-CoV-2 positive donor.

The recipient was listed for LT due to severe deterioration of her clinical conditions (high priority MELD score and encephalopathy), further complicated, during hospitalization, by SARS-CoV-2 infection. Because of the lack of clear-cut guidelines during the early period of the COVID-19 pandemic, the patient was initially withdrawn from the waiting list as soon as SARS-CoV-2 positivity was ascertained. Yet, she was promptly relisted after the release of specific rules from the CNT,⁷ allowing to transplant life-saving organs (namely, heart and liver) procured from SARS-CoV-2 positive donors to wait-listed recipients at high risk of death with ongoing, or previous, COVID-19. The rationale behind this choice relies on

the potential presence of neutralizing antibodies in the candidates because of the natural infection in order to prevent SARS-CoV-2 transmission or reactivation.

Our recipient had a good neutralizing antibodies titer (1:320) on the day of transplant which was protective against a superinfection. In addition, despite the prolonged positivity of the RT-PCR, our patient underwent LT a month after the first detection of SARS-CoV-2 infection (specifically with a high Ct value for all genes) (Table 1). According to recently published papers, this positivity probably does not reflect an ongoing active infection but simply the amplification of nonreplicating virus.^{12,13}

For this reason, we believe that transplanting patients with long-lasting asymptomatic infection with high neutralizing antibodies titer is a reasonable option for urgent candidates.

Once the MELD score had reached 32, the patient was further prioritized in the transplant list by granting an urgency status at the national level, which allowed to be successfully transplanted the following day.

This case report shows that detection of SARS-CoV-2 positivity in waitlisted patients with end-stage liver disease who present neutralizing SARS-CoV-2 antibodies and normal respiratory function should no longer be considered a contraindication to LT. In our patient, the MELD-estimated 3-month risk of death while remaining on the waiting list was more than 50%; hence, the patient had much less life expectancy compared to a post-LT 6-month survival rate greater than 90%, according to P-SOFT and BAR.^{9,10} It should also be noted that in Italy the overall risk of death due to COVID-19 is 3.5%,⁴ a remarkably lower figure compared to the estimated mortality due to the underlying end-stage liver disease in our patient. Clearly, to ensure the greatest degree of safety for both healthcare providers and other patients, LT in SARS-CoV-2 infected patients must be performed only in dedicated Institutions with stringent respect of the regional/national rules against the spread of the pandemic in hospital settings, such as the use of dedicated COVID-19 areas (Operating Theatre, ICUs, wards) and pathways, and the extended use of personal protection.¹⁴

Although a long-term follow-up of this patient is definitely needed, we feel that the pioneering approach hereby used may prove to be of relevant benefit to the transplant activity in the current pandemic scenario. In the current absence of specific guidelines, we would recommend a close monitoring of the virological and the immunological status of SARS-CoV-2 both during the waiting list and after transplantation (at least weekly). It would also be important to determine the viral SARS-CoV-2 strain involved in the donor as in the recipient, a relevant information that unfortunately was not available in the present case.

Even if there is not yet enough experience on the type of immunosuppression (IS) to prefer in LT recipients with COVID-19, Belli et al.¹⁵ suggested to adopt a tacrolimus-based IS, as emerging from European Liver Transplant Registry data. Interestingly, recent studies in the nontransplant population suggest that IS may be beneficial in SARS-CoV-2 infection, yet these findings await confirmation in *de novo* LT recipients.^{16,17}

Neither definite therapies nor secure prophylaxis against COVID-19 is currently available. However, we are now just entering the era of vaccination for SARS-CoV-2 infection, which is expected to become a concrete option already in the early 2021.¹⁸⁻²⁰ We can argue that the SARS-CoV-2 immunity, whether from a previous infection or vaccination should protect transplant candidates from a superinfection. Nevertheless, specific studies are clearly needed to confirm the effectiveness of the immunization in the transplant recipients.

4 | CONCLUSION

This case report breaks down a number of barriers which have so far discouraged the practice of transplantation in donors and recipients with SARS-CoV-2 infection. It shows that we may safely expand the donor pool including SARS-CoV-2 infected donors, thus creating a larger network of suitable organs -namely liver, heart, and kidney that could be of great benefit to SARS-CoV-2 patients that have developed immunity.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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