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ORIGINAL ARTICLE

Liver transplantation from active COVID-19 donors: A lifesaving opportunity worth grasping?

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COVID-19 pandemic dramatically impacted transplantation landscape. Scientific societies recommend against the use of donors with active SARS-CoV-2 infection. Italian Transplant Authority recommended to test recipients/donors for SARS-CoV-2-RNA immediately before liver transplant (LT) and, starting from November 2020, grafts from deceased donors with active SARS-CoV-2 infection were allowed to be considered for urgent-need transplant candidates with active/resolved COVID-19. We present the results of the first 10 LTs with active COVID-19 donors within an Italian multicenter series. Only two recipients had a positive molecular test at LT and one of them remained positive up to 21 days post-LT. None of the other eight recipients was found to be SARS-CoV-2 positive during follow-up. IgG against SARS-CoV-2 at LT were positive in 80% (8/10) of recipients, and 71% (5/7) showed neutralizing antibodies, expression of protective immunity related to recent COVID-19. In addition, testing for SARS-CoV-2 RNA on donors' liver biopsy at transplantation was negative in 100% (9/9), suggesting a very low risk of transmission with LT. Immunosuppression regimen

Abbreviations: BAL, bronchoalveolar lavage; CNT, Italian Transplant Authority; COVID-19, coronavirus disease 2019; Ct, cycle threshold; ICU, intensive care unit; LT, liver transplantation; NPS, nasopharyngeal swabs; NT-Abs, neutralizing antibody; POD, postoperative day; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

remained unchanged, according to standard protocol. Despite the small number of cases, these data suggest that transplanting livers from donors with active COVID-19 in informed candidates with SARS-CoV-2 immunity, might contribute to safely increase the donor pool.

KEYWORDS
cirrhosis, clinical research/practice, donors and donation: deceased, donors and donation: donor evaluation, donors and donation: donor-derived infections, ethics and public policy, infection and infectious agents - viral, infectious disease, liver transplantation/hepatology, organ procurement and allocation

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic dramatically impacted the landscape of organ donation and transplantation in Europe and United States.[1,2]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes for cellular entry the angiotensin converting enzyme 2 which is mostly expressed in lungs, explaining why the respiratory system involvement predominates.[3] Nevertheless, organ dysfunction beyond the lungs has been described as well, in particular liver injury was seen in 14%–53% of patients due to infection of liver cells, drug-induced or within a systemic inflammatory syndrome.[4]

European and American scientific societies recommend against the use of organs from donors with active SARS-CoV-2 infection and recommend donor SARS-CoV-2 screening to prevent inadvertent positive organ transplant.[5,6] On the other hand, the Organ Procurement and Transplantation Network Ad Hoc Disease Transmission Advisory Commitee reviewed published literature until April 2021 and suggested that the decision to recover organs from donors with active COVID-19 should evaluate the recipient's risk mortality and the risk of transmission to surgical teams.[7] The pro-con debate is going on, waiting for real-life data.[8,9] The current recommendations are based on the assumptions that (1) SARS-CoV-2 could be transmitted to the recipient through organ transplantation, (2) it could result in severe manifestations in immunosuppressed patients, (3) there are only limited targeted treatment options, and (4) long-term allograft outcomes related to the use of such organs are largely unknown. So far, 11 SARS-CoV-2 infected donors (active COVID-19), diagnosed after donation, without transmission to 18 different recipients have been published (one living liver donor, one platelet transfusion, two allogenic hematopoieticstem cell transplantations, and 13 kidneys and one liver from deceased donors).[7,10-14]

Unfortunately, three cases of proven SARS-CoV-2 transmission from lung donor to recipient (despite negative donor upper respiratory tract testing) have been reported.[7,14,15] However, donor-derived infection with viruses that infect the respiratory tract has been already described in the past and almost exclusively detected in lung recipients.[16] These risks must be balanced against the lifesaving benefit of organ transplantation to patients who might otherwise have limited opportunities for transplant, due to disease acuity, limited matches related to blood type or sensitization, and may not survive to receive another organ from a non-infected donor. Furthermore, wait-listed patients are at risk for COVID-19 due to multiple comorbid conditions and frequent healthcare contacts.

Italy has been the first European country to face the severe COVID-19 pandemic since February 2020 and our National Healthcare System is enduring a tremendous pressure. In order not to compound the outbreak lethality with risking the lives of patients who need a lifesaving liver transplant (LT), all transplant Centers remained open, although a reduction in the activity was noted due to donor shortage.[17] Italian Transplant Authority (Centro Nazionale Trapianti, CNT) recommended to test all recipients and donors for SARS-CoV-2 RNA immediately before LT and, to expand the donor pool, starting from November 2020 grafts from deceased donors with active SARS-CoV-2 infection were allowed to be considered for urgent-need transplant candidates, who were known to be SARS-CoV-2 positive or with past COVID-19, and were able to sign an informed consent.

As scanty data exist regarding the safety of transplanting organs recovered from donors with active COVID-19, we present here the results of the first 10 consecutive LT cases with such donors within an Italian multicenter (five centers involved) national series.

2 | MATERIALS AND METHODS

2.1 | Study period

We enrolled patients from November 20, 2020, to February 8, 2021. Follow-up was closed on July 18, 2021.

2.2 | Definitions

The Organ Procurement and Transplantation Network Ad Hoc Disease Transmission Advisory Committee[7] defined active COVID-19 an immunocompetent donor with a history of confirmed COVID-19, less than 21 days from the date of disease onset and SARS-CoV-2 detected in a respiratory sample *or* an asymptomatic donor with detection of SARS-CoV-2 in a respiratory sample without a reliable

history to determine the timeline of past symptoms of COVID-19; mild COVID-19 as detection of SARS-CoV-2 in a respiratory sample in subjects with symptoms consistent with COVID-19 infection who did not require oxygen supplementation or inpatient hospitalization for COVID-19; severe COVID-19 as detection of SARS-CoV-2 in a respiratory sample in subjects with symptoms consistent with COVID-19 infection who required oxygen supplementation or inpatient hospitalization for COVID-19.

2.3 | Donors

The donors underwent detection of SARS-CoV-2 nucleic acid in nasopharyngeal swabs (NPS) or bronchoalveolar lavage (BAL) and detection of IgG anti SARS-CoV-2 at recovery. According to clinical history, they underwent SARS-CoV-2 RNA evaluation before recovery, as reported in Table 1.

SARS-CoV-2 nucleic acid was tested on liver biopsy collected at back-table, before graft reperfusion.

2.4 | Recipients

All recipients were tested at LT for SARS-CoV-2 nucleic acid in NPS and/or in BAL and for IgG anti-SARS-CoV-2. For the first month after LT, they underwent weekly evaluation of SARS-CoV-2 RNA in NPS and SARS CoV-2 IgG (Table 1 and Supportive Table S1).

In Turin LT Center, starting from November 20, 2020, all recipients were also tested for SARS-CoV-2 IgG at registration on the LT waiting list.

2.5 | SARS-CoV-2 tests

IgG antibodies against SARS-CoV-2 have been tested with Liaison® SARS-CoV-2 anti-S1/S2 IgG test (DiaSorin, Saluggia Italy), cut-off value for positivity of 15 AU/ml. Sensitivity and specificity of the test is 75.6% and 100%, respectively[18]; the positive and negative agreement with Plaque Reduction Neutralization Test is 94.4% and 97.8%, respectively, according to the manufacturer; or ARCHITECT® SARS-CoV-2 IgG immunoassay (Abbott, Milan, Italy) with a cut-off value for positivity of 1.4 AU/ml. Sensitivity and specificity of the test is 70% and 100% respectively.[19]

Neutralizing antibody (NT-Abs) against SARS-CoV2 test was performed in BSL-3 suite adapting an in-house previously reported neutralization assay.[20] Vero E6 cells were seeded at 2×10^4 cells/well concentration in a 96-well microtitre plate, 24 hours before the assay. Briefly, 50 μl of plasma samples from each patient were serially diluted (from 1:10 to 1:5120) in sextuplicate and mixed with 100 median tissue culture infectious doses (TCID50) of SARS-CoV-2 virus (human strain VR PV10734, gently provided by INMI L. Spallanzani). After 1 hour incubation at 37°C, plasma and virus were transferred to Vero E6 microplates. Cells were incubated at 37°C in 5% CO_2, for 5 days prior to microscopic evaluation of the cytopathic effect (CPE). Neutralization titer was determined by the highest plasma dilution showing a 50% reduction of CPE and evaluated according to the Reed-Muench formula.[21] Positive and negative controls were included in all test runs. The recipient 9 was tested for NT-Abs, as recently published.[22]

SARS-CoV-2 nucleic acid was detected in NPS or BAL by using direct real-time PCR assay for in vitro qualitative detection: Simplexa® COVID-19 Direct (DiaSorin) or Xpert® Xpress SARS-CoV-2 (Cepheid Europe SAS) or GeneFinder™ COVID-19 Plus RealAmpKit (OSANG Healthcare Co. Ltd.). SARS-CoV-2 nucleic acid was detected in liver tissue by using Simplexa® COVID-19 Direct (DiaSorin) or GeneFinder™ COVID-19 Plus RealAmpKit (OSANG Healthcare Co. Ltd.).

2.6 | Liver transplant and study procedures

During organ procurements and LT, the liver teams used protective equipment such as filtering face masks (NK-92, N95, FFP2, and FFP3), eye goggles and standard gloves and gowns. The organ procurements were performed using standard technique, and the livers were preserved in cold storage with Celsior solution. Immunosuppression regimen was detailed for each patient.

By Italian law, Regional Transplantation Centers are the custodians of donor/recipient biomedical data also for research purposes. All study procedures complied with the ethical standards of the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008.

3 | RESULTS

3.1 | Donors

During the study period we enrolled 10 brain-dead donors (Table 1) with a median age of 61 years (range 14–82), median body mass index 24.5 kg/m^2 (range 20–29), donor risk index 2.0 (range 1.11–2.41). All the subjects were affected by active COVID-19: five donors were SARS-CoV-2 RNA positive in NPS with pneumonia (four patients) or anosmia/fever (one patient) within 21 days before organ recovery; the five remaining donors tested SARS-CoV-2 RNA positive in BAL at recovery without a reliable history to determine the timeline of past symptoms of COVID-19. At recovery, IgG anti SARS-CoV-2 tested negative in seven of eight donors and SARS-CoV-2 RNA on liver biopsy was negative in nine of nine (Table 1).

3.2 | Recipients

The median recipient age was 56 years (range 1–70); median body mass index 25 kg/m^2 (range 16–34); half of them were affected by alcohol cirrhosis and 40% by hepatocellular carcinoma. The median Model for End Stage Liver Disease score at LT was 13 (range 7–35) and patient 1 had a Pediatric End Stage Liver Disease score of 29.

TABLE 1 Donor and recipient characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Donors										
Age, years	17	51	62	51	66	60	77	14	65	82
Body Mass Index, kg/m^2	21	25	25	24	29	28	20	20	24	28
Cause of brain death	Trauma	CBV	CBV	CBV	Meningitis	CBV	CBV	Trauma	CBV	CBV
Donor Risk Index	1.70	1.57	2.28	1.90	2.16	2.41	2.1	1.11	1.9	2.35
Time between the first detection of SARS CoV-2 RNA and organ recovery, days	5	0	10	1	0	3	2	6	1	0
Before organ recovery										
SARS-CoV-2 RNA[1] in NPS	Positive	/	Positive	Negative	/	Positive	Positive	Positive	Positive	/
SARS-CoV-2 RNA in BAL	Positive	/	NA	NA	/	Positive	NA	NA	Positive	/
COVID-19 symptoms	Pneumonia	Unknown	Pneumonia	Unknown	Unknown	Pneumonia	Pneumonia	Anosmia/ fever	Unknown	Unknown
At organ recovery										
SARS-CoV-2 RNA in BAL	Negative	Positive	Positive	Positive	Positive	Negative	NA	Positive	Positive	Positive
SARS-CoV-2 RNA in NPS	NA	NA	NA	NA	NA	NA	Positive	Positive	Positive	NA
IgG[2] anti SARS-CoV-2	Negative	Negative	Negative	Negative	Negative	Negative	Positive	NA	NA	Negative
COVID-19	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active
SARS-CoV-2 RNA liver biopsy	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	NA	Negative
Recipients										
Liver disease	Sclerosing cholangitis	Biliary cirrhosis	Non-alcoholic steatohepatitis	Alcohol	Alcohol	Polycystic liver disease	Alcohol	Alcohol	HBV+HDV	Alcohol
Hepatocellular carcinoma	No	No	Yes	Yes	Yes	No	No	Yes	No	No
COVID-19 hospitalization, days	0	7	13	0	10	0	0	0	29	30
Pre-LT COVID−19 pneumonia	no	yes	no	no	no	no	no	no	yes	yes
First SARS-CoV-2 RNA[1] positive – LT, days	22	47	51	/	31	/	85	45	30	61
SARS-CoV-2 RNA negative – LT, days	19	14	4	/	0	/	31	30	0	36
SARS-CoV−2 RNA in NPS at LT	Negative	Negative	Negative	Negative	Indeterminate	Negative	Negative	Negative	Positive	Negative
IgG[2] anti SARS-CoV-2 at LT	Negative	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive
MELD at LT	29 (PELD)	19	11	9	13	7	25	8	35	16
Post-LT hospitalization, days	140	16	11	7	13	10	28	15	75	18
Follow-up, days	239	233	229	222	219	161	162	237	75	194
Outcome	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Dead	Alive

Abbreviations: BAL, bronchoalveolar lavage fluid; CBV, cerebrovascular; LT, liver transplantation; MELD, Model for End Stage Liver Disease; NA, not available; NPS, nasopharyngeal swabs; PELD, Pediatric End Stage Liver Disease.

[1]Cases from 1 to 7; 9, 10: Simplexa® COVID-19 Direct (DiaSorin) or Xpert® Xpress SARS-CoV-2 (Cepheid Europe SAS); Case 8: GeneFinder™ COVID-19 Plus RealAmpKit (OSANG Healthcare Co. Ltd.).

[2]Cases from 1 to 7: Liaison® SARS-CoV-2 S1/S2 IgG test (DiaSorin); positive >15 AU/ml. Capses from 8 to 10: ARCHITECT® SARS-CoV-2 IgG immunoassay (Abbott); positive >1.4 AU/ml.

Five patients had a history of severe COVID-19 which required inpatient hospitalization, with oxygen supplementation (one non-invasive ventilation) and lung CT scan showing pneumonia in three of them; only patient 9 was treated with heparin and steroids; none of them received remdesevir. Three patients (1, 7, and 8) were affected by mild COVID-19 (with fever, anosmia, fatigue), which did not require oxygen supplementation or hospitalization. These eight patients underwent LT after a median time of 46 days (range 22–85) from the first available SARS-CoV-2 RNA positive test (Table 1).

Patients 4 and 6 tested IgG anti-SARS-CoV-2 positive (titer 47 and 103 AU/ml, respectively) with negative SARS-CoV-2 RNA on NPS at registration on the LT waiting list (1 day and 47 days before LT, respectively); both of them reported an undefined history of fatigue in the previous month, but they did not perform at that time a SARS-CoV-2 RNA test. At LT their IgG titres persisted positive (48.5 and 110 AU/ml, respectively) with persistent negative RNA on NPS.

SARS-CoV-2 RNA in NPS at LT was negative in all candidates except for patient 5 who was indeterminate in NPS and positive in BAL, and patient 9 who was positive in NPS. Both patients tested RNA positive for the first time one month before LT and became persistently negative at NPS starting from postoperative day (POD) 28. All the others tested SARS-CoV-2 RNA negative on weekly NPS during the first month after LT (Supportive Table S1). None of the LT recipients developed COVID-19 symptoms.

At LT, 8 of 10 patients tested SARS-CoV-2 IgG positive. Case 1 (a pediatric patient who was affected by Wiedemann-Steiner syndrome and combined immunodeficiency with low immunoglobulin levels needing replacement therapy) and case 8 were IgG negative at LT and during the first-month follow-up. Case 4 lost IgG positivity starting from POD7. NT-Abs against SARS-CoV-2 were evaluated in seven patients at LT and tested positive in five of them (71%) (Supportive Table S1).

None of the enrolled subjects received anti-SARS-CoV-2 vaccination during the study period.

Immunosuppression was based on basiliximab induction and tacrolimus for two patients (1 and 7), steroids, mycophenolate mofetil and tacrolimus for seven patients and tacrolimus plus everolimus in the remaining one (9).

The median post-LT hospital length of stay was 16 days (range 7–140).

After a median follow-up of 221 days (range 75–239), patient 9 died on POD75 due to sepsis caused by multidrug-resistant *Acinetobacter baumannii*; alpha-fetoprotein serum levels of patient 3 were found to be elevated at 3-month follow-up and chest/abdomen CT scan showed lung nodular areas which are currently treated with everolimus and sorafenib. The liver function of the nine surviving patients is satisfactory.

4 | DISCUSSION

The COVID-19 pandemic dramatically impacted the landscape of organ donation and transplantation globally.[23,24] This new epidemic has overwhelmed healthcare resources in some regions and forced rationing of care, including Intensive Care Unit (ICU) beds and ventilatory supports. As a consequence, organ donation and transplantation have been reduced in many countries. Overall, the progression of disease has varied but appears to be more rapid in immunocompromised hosts with greater rates of ICU admission and death.[25-28]

All transplantation societies strongly recommend universal screening (nucleic acid testing [NAT]) of potential deceased organ donors before procurement.[29] Donors with positive SARS-CoV-2 testing or donors with exposure risk criteria regardless of laboratory finding are generally excluded by most transplant organizations. Transmission from infected donors to immunosuppressed recipients has been recently described with lung transplantation.[7,14,15,30]

In both cases, the donor tested negative for SARS-CoV-2 with upper respiratory tract sampling for nucleic acid testing, however, BAL in case 1 and bronchial wash in case 2 tested positive immediately after transplantation.[14,15] Only lungs were transplanted from the first donor while the second donated the kidneys and the liver too. No transmission occurred to two kidney recipients (one had previous COVID-19 vaccine and one had previous COVID-19 infection) and one liver recipient. SARS-CoV-2 has not been detected from liver tissue; SARS-CoV-2 has only been detected from cardiac tissue in one patient with severe cardiac dysfunction, who would not be a candidate for donation.[8]

In Italy more than 4 million COVID-19 cases have been reported by the end of May 2021 and about 260 000 are still positive. In order to maintain organ transplantation for lifesaving organs, in November 2020 the CNT decided to allow the use of livers and hearts from donors with active SARS-CoV-2 infection, documented by positive NAT testing in NPS or BAL at the time of donor evaluation. Antibody testing against SARS-CoV-2 is not required by the Italian rules for deceased organ donor evaluation and no decision is taken based on their presence or not. However, IgG anti-SARS-CoV-2 were tested in 8 of 10 donors but the results were available only after the transplant procedures and did not influence in any way the use of the organs. As expected, seven of eight tested donors resulted anti-SARS-CoV-2 IgG negative. This is consistent with the median time required for developing a detectable serological response[31] and supports the hypothesis of an early infection of the donors, most of them died for causes unrelated to COVID-19.

These organs can be transplanted into informed recipients with ongoing or resolved COVID-19. Candidates with recent COVID-19 are in fact very likely protected by natural immunity and we assumed that there was a very low risk of SARS-CoV-2 transmission. Convalescent individuals from COVID-19 have in fact a significantly lower risk of reinfection.[32,33]

Starting from November 2020 to May 2021, 19 organs (17 livers and 2 hearts) from SARS-CoV-2 positive donors have been transplanted in Italy in recipients with ongoing or past COVID-19. In the present paper we report the outcome of the first 10 LTs with at least 5 months of follow-up. Only two recipients had a positive molecular test on NPS at the time of organ transplantation. Case 5 with a history of COVID-19 in early November 2020, was relisted after two negative

NPS; just before transplantation he had indeterminate SARS-CoV-2 RNA in NPS but positive in BAL. This patient at the end of LT, was transferred to a COVID-dedicated ICU, where BAL confirmed to be positive for SARS-CoV-2 RNA on POD 1 and 3. However, three consecutive NPS tested negative on POD 3, 4, and 7. The second recipient (case 9) had a history of asymptomatic COVID-19 in November 2020 and high cycle threshold (Ct) at the time of liver transplantation (gene E Ct = 24; gene S Ct = 27; gene N Ct = 24),[22] whose significance in terms of viral infectivity is controversial.

Testing for antibodies against SARS-CoV-2 just before LT was positive in 8 of the 10 recipients and the in vitro viral neutralizing capacity of sera was ascertained in 5 of the 7 cases in which it was investigated, confirming, as expected, the presence of a potential protective immunity related to the recent SARS-CoV-2 infection in most of the patients. In addition, testing for SARS-CoV-2 on donors' liver biopsy before transplantation was negative in nine of nine tested donors suggesting a very low risk of transmission with LT. Only one recipient (case 9), who tested positive at the time of LT remained persistently positive up to 21 days after transplantation but with very high Ct.[22] None of the remaining recipients was found to be positive for SARS-CoV-2 during the follow-up.

Immunosuppression regimen remained unchanged, according to each Center standard protocol and no anti-SARS CoV-2 therapy was used after LT.

The study has limitations mostly due to the small number of patients and the different methods used to assess the immunological status of the recipients. In addition, it is unclear if the lack of transmission was due to the immune protection of the recipients or to the lack of replicating virus in the liver grafts. However, despite the small number of cases we believe that transplanting livers from donors with positive SARS-CoV-2 in upper and/or lower respiratory tract, in informed candidates with immunity due to past COVID-19, might contribute to safely increase the donor pool during the COVID-19 pandemic.

The increasing number of vaccinated candidates might allow the use of organs from donors with active COVID-19 in recipients with prior vaccination. To date there are no correlates of antibody response and protection against SARS-CoV-2 infection and therefore we did not consider vaccination sufficient to guarantee protection. Furthermore, it is well known that patients with chronic liver disease have a poor response to vaccines, including anti-COVID-19 vaccines[34] and therefore the use of these organs for vaccinated recipients is something that needs to be explored. In addition, the growing number of variants which may evade the individual natural or vaccine induced immunity is one of the major challenges we have to face in the near future. Finally, our results and the current limited published evidence suggest that organs from donors with active COVD-19 could also be used for non-immune recipients, in particular for recipients at high risk for mortality on the waitlist. However larger studies are needed to confirm these results before recommending this possibility.

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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*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the Corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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