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# COVID-19 positive donor for solid organ transplantation

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## Summary

The COVID-19 pandemic has significantly changed organ donation and transplantation worldwide. Since the beginning of the pandemic, the uncertainty regarding the potential route of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created tremendous pressures on transplantation communities, and international organisations have advised against using organs from deceased donors who have tested positive for SARS-CoV-2. The possibility of SARS-CoV-2 transmission through organ donation has only been reported for lung transplantation; hence, based on current experience, transplantation of non-lung organs from donors with active SARS-CoV-2 infection has been considered possible and safe, at least over short-term follow-up. As the evolving outbreak of SARS-CoV-2 continues, alongside the presence of vaccines and new treatment options, clinicians should consider transplanting organs from deceased donors with active SARS-CoV-2 infection to recipients with limited opportunities for transplantation and those with specific natural or vaccine-induced immunity. This article proffers an expert opinion on the use of organs from deceased donors with resolved or active SARS-CoV-2 infection in the absence of more definitive data and standardised acceptance patterns.

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## Introduction

The COVID-19 pandemic has posed significant global challenges for solid organ transplantation due to the spread of the disease, the overload of healthcare systems and the need to maintain both procurement and transplant activity, without compromising safety and quality of organs.<sup>1</sup> Since the beginning of the pandemic, uncertainties regarding the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission from donors to recipients have been a matter of controversy among the scientific community and have substantially influenced transplantation practices.<sup>2–5</sup>

Early in the outbreak, international transplantation societies and organ procurement organisations recommended screening donors for SARS-CoV-2 and advised against the use of organs from SARS-CoV-2-positive donors.<sup>4,6</sup> However, restrictive policies have led to the loss of a substantial number of potentially lifesaving organs, and based on the persistence of the ongoing pandemic, the emerging literature and critical evaluation of the biology of SARS-CoV-2 and the related disease, these recommendations have been critically questioned.<sup>3,6</sup> More than 2 years into the pandemic, many questions remain about how to approach the risk of SARS-CoV-2 transmission from donors to recipients, but we must balance the risk of donor-derived infection with the risk of mortality on the waiting list.<sup>7</sup> In this article we provide our expert opinion and perspective on the use of organs from deceased donors with previous or active SARS-CoV-2

infection based on the Italian experience in the absence of more definitive data and international standardised protocols.

## Impact of the COVID-19 pandemic on worldwide organ transplantation

During the pandemic, various adaptation strategies have been established worldwide in different organ groups in relation to waiting list management and transplantation activity.<sup>4</sup> At the beginning, an overall decline of transplant work was observed worldwide, with kidney transplantation being the most affected, followed by lung, liver, and heart transplantation. With regard to the COVID-19 pandemic, almost all live kidney donation procedures were postponed and deceased donor kidney transplantation was recommended to be reserved for likely lifesaving indications.<sup>1,5</sup>

Time-based trends showed a significant reduction in transplant activity during the initial phase of the pandemic (February 2020 to April 2020), with losses stabilising during the summer of 2020, but decreasing again during the second wave (October 2020 to December 2020). The reduction in transplants converted to significant waitlisted patient life-years lost, especially for kidney transplant recipients.<sup>1</sup> Currently, despite uncertainties and pandemic-related disruptions more than 2 years into the COVID-19 outbreak, transplant activity is almost back to the pre-pandemic period in most countries.<sup>8</sup>

Italy was the first country in Europe to be hit by the virus and has been one of the worst affected



countries in the world. In March 2020, a national state of alarm was declared, with rules targeted to control the spread of COVID-19, including a national contingency plan and lockdown measures.<sup>5,9</sup> From the perspective of transplantation, Italy presented a less significant than expected decrease in organ transplant activity (9.8% in 2020 compared with the mean activity of 2019), despite the absolute number of diagnosed cases and COVID-19-related mortality, since the Italian healthcare system classified donation and transplantation activities as essential.<sup>1</sup>

Based on the epidemiological evolution of the spread of SARS-CoV-2 in our country and the growing evidence related to the transmission of SARS-CoV-2, the Italian Transplant Authority (Centro Nazionale Trapianti-CNT), in association with the National Institute of Health, has adopted evolving strategies and a pioneering approach.<sup>10</sup> Early in the pandemic, the CNT recommended universal mandatory donor and recipient SARS-CoV-2 screening, with the objective of both preventing donor-derived SARS-CoV-2 infections and protecting the transplant and organ procurement teams. Transplantation of organs from deceased donors with previous SARS-CoV-2 infection was implemented both for abdominal and thoracic transplants starting in May 2020. Lastly, Italy was the very first country in the world to carry out a protocol to use organs from donors with active SARS-CoV-2 infection for liver and heart transplant recipients (November 2020), which was also subsequently extended to kidney recipients (January 2022).<sup>11</sup> In our country, the COVID-19 vaccination campaign started at the end of December 2020 and priority access to SARS-CoV-2 vaccination for waitlisted patients and for transplant recipients was recommended.

## **SARS-CoV-2 and implications for transplantation**

### **Biology of SARS-CoV-2**

As the SARS-CoV-2 pandemic evolves, we have gained important insights into the epidemiology and biology of this infection, which have implications for solid organ transplantation.<sup>2,3,12</sup>

The risk of a donor-derived infection may be a condition of the donor exposures and the incubation period, which is estimated to last mostly 3-5 days after exposure (range 2-14 days).<sup>13</sup> If the donor has a previous or active SARS-CoV-2 infection, we also need to consider the risk of infectivity, making a distinction between viral RNA detection and viable virus. Prolonged SARS-CoV-2 RNA respiratory shedding after clinical recovery has not been clearly associated with sustained infectiousness. Immunocompetent individuals with SARS-CoV-2 infection are most infectious in the earlier phases of infection (beginning a few days before the start of symptoms), with a median duration of

SARS-CoV-2 positivity in respiratory samples of around 18 days and viable virus detected up to 20 days after the start of symptoms. However, in patients with non-severe clinical presentations, infectivity beyond 7-10 days after the onset of symptoms is unlikely.<sup>13</sup>

The degree and duration of viral load and viability of the virus in blood or specific organs may also influence the risk of a donor-derived transmission. SARS-CoV-2 RNA has been detected in bodily fluids, including blood (10%), stool and urine during acute infection, but this is not a demonstration of infectious virus.<sup>14,15</sup> The presence of sub-genomic SARS-CoV-2 RNA, which is only produced in actively infected cells, has been described in the heart, kidney and liver of patients dying predominantly of severe COVID-19<sup>14</sup> and may be a matter of concern both regarding the risk of transmission and the unknown long-term organ-specific sequelae of COVID-19.<sup>2,3</sup> However, it remains unclear whether the vital transmissible virus can exist in non-respiratory organs and if these data can be extrapolated to patients with asymptomatic or mild infection.

### **Hospital setting preventive measures**

Transplantation from SARS-CoV-2-positive donors poses the risk of SARS-CoV-2 transmission to the recipient, the procurement teams, and to other patients in the hospital. Therefore, it must only be performed in dedicated institutions with rigorous preventive measures, the use of personal protective equipment (PPE) and dedicated areas (operating room, intensive care units, and wards).<sup>16</sup>

During organ procurement and transplant, optimal infection control measures are recommended; PPE, such as filtering facemasks (N95, FFP2 and FFP3), eye protection, and standard gloves and gowns. Organ procurement can be performed using a standard technique. After transplantation, positive recipients may be placed in a COVID-19 area, whereas it would be prudent to place negative recipients in isolation in an individual room in a non-COVID-19 area but with isolation procedures. In our experience, no transmissions to healthcare workers have occurred.<sup>16</sup>

### **Improving safety and eligibility of waitlisted patients**

Candidates on the waiting list are at increased risk of becoming infected with COVID-19, and of developing severe disease owing to several comorbidities, impaired immunity, and frequent contacts with the healthcare system.

Waitlisted candidates should have priority access to SARS-CoV-2 vaccination irrespective of past infection or the presence of serological response and should ideally be fully vaccinated (with at least 3 doses) for COVID-19 at least 2 weeks prior to transplantation. Available data on a fourth booster

dose (at least 3 months after the third dose) is still limited.<sup>17</sup>

Active immunisation against SARS-CoV-2 in transplant candidates should be strongly encouraged not only because of the expected reduction in the risk of complications and improvement of immune responses to vaccination compared with naïve recipients vaccinated after transplant, but also because it might allow for the use of organs from SARS-CoV-2-positive donors.<sup>18</sup> Patient removal from the transplant list for refusing COVID-19 vaccination and vaccine mandates is a timely and controversial ethical topic. Based on our current protocol, we recommend patients be vaccinated and tested for SARS-CoV-2 IgG and/or virus-specific cell-mediated immunity at waiting list registration or thereafter, but ideally before transplantation.

#### Donor and recipient SARS-CoV-2 screening

Current strategies for donor and recipient screening for SARS-CoV-2 include evaluation by history (identification of exposures to and symptoms compatible with COVID-19), chest imaging (if indicated) and microbiologic testing.<sup>10</sup> Regarding the samples for SARS-CoV-2 reverse-transcription PCR (RT-PCR) testing, our recommendation is to collect samples from the lower respiratory tract, preferentially bronchoalveolar lavage taken within 24-48 hours prior to organ recovery for each deceased organ donor. For living donors, a nasopharyngeal swab has to be collected within 72 hours of organ recovery (but ideally as close to procurement as possible).<sup>19</sup> Recipients should always be tested by SARS-CoV-2 RT-PCR assay using a nasopharyngeal swab and/or a sample from the lower respiratory tract on admission for transplant.

#### The use of organs from deceased donors with previous SARS-CoV-2 infection

Existing data suggest satisfactory infectious outcomes in recipients of non-lung and lung organs

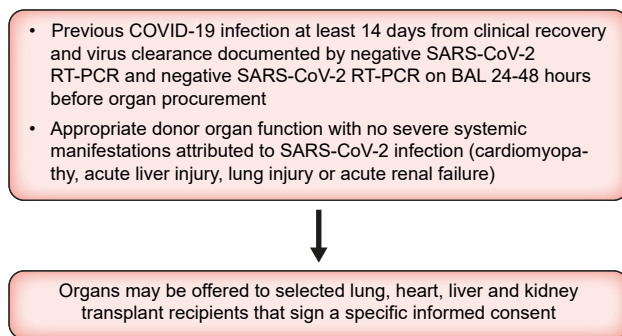
from donors who had recovered from COVID-19, because no cases have resulted in proven transmission.<sup>6</sup> The American Society of Transplantation recommended waiting for 21-90 days after an initial diagnosis of COVID-19 prior to considering organs from donors with previous SARS-CoV-2 infection.<sup>20</sup> However, the available literature is limited, and many variables remain unexamined regarding SARS-CoV-2 transmission, standardisation of degree of COVID-19 severity, selection of recipients and impact of natural or vaccine-induced immunity.<sup>6,21</sup>

In our current national protocol, organ procurement is allowed from a deceased donor who died at least 14 days after the resolution of symptoms and had viral clearance documented by a negative SARS-CoV-2 RT-PCR. In addition, a negative SARS-CoV-2 RT-PCR from the lower respiratory tract must be obtained 24-48 hours prior to organ recovery. These donors may be carefully evaluated prior to donation and ultimately be considered eligible if no long-lasting organ damage has resulted from COVID-19 and appropriate organ function is established. The transplant centre should have a discussion with the recipient regarding the risk-benefit of transplantation, and the recipient must sign a specific informed consent. In our opinion, deceased organ donors with past SARS-CoV-2 infection can be considered both for lung transplant and non-lung transplant recipients. The summary of Italian recommendations for the evaluation and testing of deceased organ donors with previous SARS-CoV-2 infection is listed in Fig. 1.

#### The use of organs from deceased donors with active SARS-CoV-2 infection

Transplantation of non-lung organs can be considered from highly selected deceased donors with active SARS-CoV-2 infection. Cases of non-lung solid organ and haematological transplantation from SARS-CoV-2-infected donors to different recipients occurred inadvertently without transmission of the virus.<sup>6</sup> Unfortunately, cases of transmission from SARS-CoV-2-infected donors (with negative upper respiratory tract testing) to lung transplant recipients have been reported and were associated with poor outcomes.<sup>19</sup> Pilot experiences with SARS-CoV-2-positive donors occurred in Italy in November 2020, when the first transplant of a liver from a SARS-CoV-2-positive donor was performed with no transmission to the recipient with resolved SARS-CoV-2 infection.<sup>22</sup> Since then, several transplants have been performed, most of which were liver, kidney, and (to a lesser extent) heart. To date, no cases of SARS-CoV-2 transmission after non-lung transplant have been reported.<sup>6,7,16,21,23-25</sup>

Donors who died of other causes may be considered eligible if they had mild or asymptomatic SARS-CoV-2 infection incidentally found



**Fig. 1. Summary of Italian recommendations for selection of deceased donors with previous SARS-CoV-2 infection and target recipients.** BAL, bronchoalveolar lavage; NPS, nasopharyngeal swab; RT-PCR, real time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

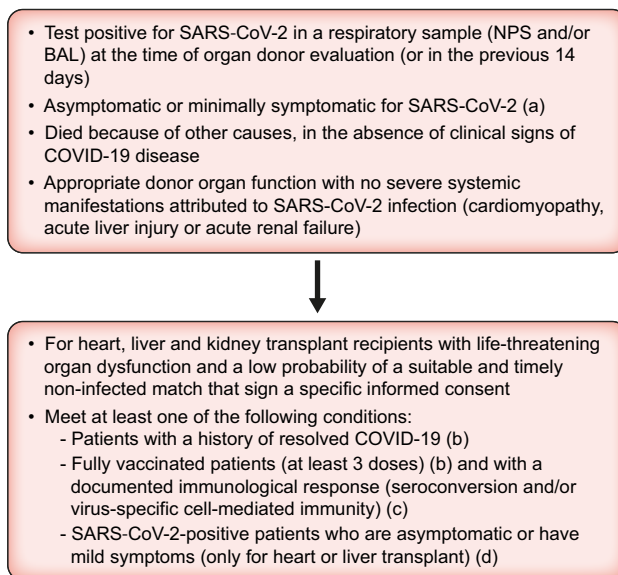
during screening, without severe organ dysfunction or COVID-19-related inflammatory syndromes (Fig. 2).<sup>10</sup>

The cycle threshold (Ct) may help determine the likelihood of transmissibility (Ct levels >35 tend to correlate with culture negativity) and influence clinical decision-making. However, in our current protocol, we do not utilise the Ct in the decision-making process because it is not available from many testing platforms and the values are not necessarily comparable between different tests.<sup>6</sup>

In addition, it is recommended (if possible) to perform biopsies on donor liver and kidney to search for SARS-CoV-2 RNA and histopathologic changes and to test for SARS-CoV-2 RNA in the preservation fluid. As regards heart transplant, biopsy should be performed at the sole discretion of the transplant centre.<sup>16</sup>

Carefully selected deceased donors with active SARS-CoV-2 infection may be considered for liver, heart and kidney recipients with life-threatening organ dysfunction and a low probability of a suitable and timely non-infected match (related to blood type or a condition of hyperimmunization). To receive an organ from a deceased SARS-CoV-2-positive donor, recipients must have natural or vaccine-induced immunity (Fig. 2). Patients who meet these characteristics should be referred for the transplant procedure on a case-by-case basis after contacting the national transplant centre and obtaining a second opinion from the national infectious diseases expert. Transplant candidates must receive clear and comprehensive counselling regarding the uncertainty of SARS-CoV-2 transmission and the possible unknown short- and long-term consequences.<sup>10</sup>

Patients receiving an organ from a deceased SARS-CoV-2-positive donor should be tested for anti-SARS-CoV-2 IgG and SARS-CoV-2 neutralising



**Fig. 2. Summary of Italian recommendations for selection of deceased donors with active SARS-CoV-2 infection and target recipients.** (A) Asymptomatic COVID-19 Infection: Detection of SARS-CoV-2 in a respiratory sample without current or past symptoms compatible with COVID-19. Mild COVID-19: Detection of SARS-CoV-2 in a respiratory sample in patients with symptoms consistent with COVID-19 who did not require oxygen supplementation or inpatient hospitalisation for COVID-19. (B) Elapsed time should be evaluated on an individual basis with a second opinion from an infectious diseases specialist. (C) In case of absence of available immunological response, it is recommended not to increase the ischaemic time while waiting for the result and to evaluate indication on an individual basis with a second opinion from an infectious diseases specialist. (D) Kidney recipients who are candidates for kidney transplantation and who test positive for SARS-CoV-2 must be suspended from the waiting list and can be re-entered 14 days after documented virological cure. BAL, bronchoalveolar lavage; NPS, nasopharyngeal swab; RT-PCR, real time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

antibodies at the time of transplant (ideally results should be available before transplant). The motivation behind this choice relies on the potential presence of neutralising antibodies to prevent SARS-CoV-2 transmission. Overall, recipients are not required to undergo anti-SARS-CoV-2

**Table 1. Summary of Italian recommendations for sample collection and monitoring of the recipient of organs from a donor with active SARS-CoV-2 infection.**

	Before transplant	After transplant			
		Day 7	Day 14	Day 21	Day 28
<b>Donor</b>					
SARS-CoV-2 RT-PCR on NPS and BAL (a)	X				
SARS-CoV-2 RT-PCR on donor graft biopsy (b) and preservation fluid	X				
<b>Recipient</b>					
SARS-CoV-2 RT-PCR on NPS	X	X	X	X	X
SARS-CoV-2 RT-PCR on BAL (c)		X	X	X	X
SARS-CoV-2 serology (d)	X		X		X
SARS-CoV-2 RT-PCR on graft or other donor samples (biopsies) (e)		X	X	X	X

BAL, bronchoalveolar lavage; COVID-19, coronavirus disease 2019; NPS, nasopharyngeal swab; RT-PCR, real time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(a) Taken ≤24 hours from every donor; (b) recommended for liver and kidney transplants and performed at the sole discretion of the transplant centre for hearts; histopathologic examination of biopsy is also recommended; (c) if the patient is intubated; (d) anti-SARS-CoV-2 IgG and + SARS-CoV-2 neutralising antibody assay; if possible, it should be obtained ideally before transplant (specify the type of test and cut-offs for positivity); (e) biopsies if indicated according to standard practise and availability of validated tests.

**Table 2. Recommendations by main international transplantation societies of factors related to solid organ donation for non-lung transplant recipients from donors with SARS-CoV-2 infection.**

Requirements by transplantation societies	Italy CNT	Spain ONT	United Kingdom NHSBT	United States OPTN	Canada CST	Australia New Zealand TSANZ
LRT donor SARS-CoV-2 PCR test for non-lung donation	Yes	Yes	Yes	No	Yes	No
Minimum duration from donor symptom onset to allow transplant (days)	0	0	28	10	28	0
Donor symptom resolution	No	No	Yes	Yes	Yes	No
Donor SARS-CoV-2 PCR Ct value	No	No	No	No	No	No
Systematic donor CT scan	No	No	No	No	No	No
Donor negative SARS-CoV-2 PCR	No	No	Yes	No	Yes	No
Analysis of donor organ quality	No	No	Yes	Yes	No	Yes
Minimum duration from recipient symptom onset to allow transplant (days)	0*	14	28	ND	30	ND
Mandatory recipient vaccine	No	No	No	No	No	No
Routine screening of SARS-CoV-2 antibody for donor and/or recipient	No	No	No	No	No	No
Post exposure prophylaxis suggested	No	No	No	No	No	No
Immunosuppression change suggested	No	No	No	No	No	No
Specific recipient informed consent	Yes	Yes	Yes	Yes	Yes	Yes

CNT, Centro Nazionale Trapianti; CST, Canadian Society of Transplantation; Ct, Cycle threshold; LRT, lower respiratory tract; ND, not defined; NHSBT, National Health Service Blood and Transplant; ONT, Organización Nacional de Trasplantes; OPTN, organ procurement and transplantation network; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSANZ, The Transplantation Society of Australia and New Zealand.

\*SARS-CoV-2-positive recipients who are asymptomatic or have mild symptoms (only for heart or liver transplant). Modified from Boan *et al.*<sup>27</sup>

treatment, but anti-SARS-CoV-2 monoclonal antibodies have been used at the time of transplant for asymptomatic candidates who were incidentally found to be positive for SARS-CoV-2 on admission for transplantation and for selected non-immune recipients. The need for post-transplant antiviral therapy could be considered, including intravenous (remdesivir) and oral formulations (molnupiravir and nirmatrelvir/ritonavir) for selected patients. However, drug–drug interactions between nirmatrelvir/ritonavir and calcineurin inhibitors may limit the use of nirmatrelvir/ritonavir early after transplantation.

After transplantation, standard induction or a maintenance immunosuppression regimen is recommended. In our experience, we would suggest close monitoring of the clinical, virological, and immunological status of SARS-CoV-2 in the recipient after transplantation (at least weekly) (Table 1).<sup>10</sup> It is mandatory to report to the national transplant authority any adverse events in the recipient and monitor any potential negative long-term impact. As of today, based on our national experience (71 organ transplants) and the current literature (455 non-lung organ transplants: 278 kidneys, 125 livers, 41 hearts, and 11 pancreases) on organ transplantation from donors with a

positive lower respiratory tract SARS-CoV-2 test, no recipients acquired SARS-CoV-2 infection through non-lung transplantation. In contrast there have been 3 unexpected donor-derived transmissions to lung recipients, because the donor tested negative for SARS-CoV-2 in an upper respiratory tract specimen but retrospectively tested positive in a lower respiratory tract specimen.<sup>6,7,16,21,23–26</sup>

In summary, non-lung organ transplantation can be performed using organs from deceased donors with active SARS-CoV-2 infection, but active infection prohibits lung donation. In the current absence of specific guidelines, applicable recommendations are listed in Fig. 2 and Table 1.

### Worldwide policies for using SARS-CoV-2-positive donors

Due to the uncertainties regarding the risk of SARS-CoV-2 transmissibility from donors to recipients, worldwide centres have adopted variable transplantation practices and policies. As things stand, most transplant societies have issued regularly updated guidance for practice during the evolving pandemic but are still not using organs from donors with active SARS-CoV-2 infection or are currently more conservative, requiring a

negative SARS-CoV-2 PCR to consider proceeding to solid organ transplantation. Increasing evidence of the absence of SARS-CoV-2 transmission and good short-term outcomes has led to increasing support for the acceptance of grafts from deceased donors with resolved or active SARS-CoV-2 by national organisations from Italy, Spain, the United Kingdom, Australia, the United States and Canada. The similarities and the differences in management between countries are summarised in [Table 2](#).<sup>11,21,27,28</sup>

### Future perspective

As the pandemic is ongoing, we should update the current recommendations in real time. It is likely that organs from donors with active SARS-CoV-2 infection may also be used for non-immune recipients with end-stage organ dysfunction who are at risk of mortality, especially considering new effective targeted treatments and prophylaxis. In addition, donors with active SARS-CoV-2 infection may be used both with immediate and non-immediate life-saving potential to prevent loss of waitlisted patients.

Although we are currently accepting only donors who are incidentally found to be SARS-CoV-2-positive, in the near future, donors with a wider clinical spectrum of COVID-19 may also be considered after careful assessment of potential organ damage and systemic complications.

The increasing number of SARS-CoV-2 variants is of concern. The surge of the recent Omicron and related variants that may evade the natural or vaccine-induced immune response is a major challenge which we must deal with. Lastly, the long-term consequences of using organs from SARS-CoV-2-positive donors, graft quality, and unknown subclinical effects of COVID-19 on organ function still need to be determined.

### Conclusions

Transplantation in the setting of the current pandemic is an ever-changing landscape, and it is vital for the transplant community to adapt to the evolving conditions and evidence. The acceptance of donors with previous or active SARS-CoV-2 will help to expand the pool of lifesaving organs, although

more studies are needed to develop standardised management protocols and confirm these initially promising results with prolonged follow-up.

### Abbreviations

CNT, Centro Nazionale Trapianti; Ct, cycle threshold; PPE, personal protective equipment; RT-PCR, reverse-transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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### Conflict of interest

PAG has the following conflict of interest: Consulting fees from Merck, Sharp & Dohme, Gilead Sciences, Takeda, Shionogi, Allovir; member of speakers bureau for Merck, Sharp & Dohme, Gilead Sciences, Takeda, Atara; MP has no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

PG and MP performed the literature research and wrote the manuscript. PG is the infectious diseases second opinion of the Italian National Center for Transplantation and was the one who suggested to start using organs from donors with active SARS-CoV-2 infection and wrote the Italian protocol.

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2022.06.021>.

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*Author names in bold designate shared co-first authorship*

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