Current Transplantation Reports (2021) 8:281–292
https://doi.org/10.1007/s40472-021-00343-0

COVID19 AND TRANSPLANTATION (R AVERY, SECTION EDITOR)

Use of Organs from SARS-CoV-2 Infected Donors: Is It Safe? A Contemporary Review

Vivek B. Kute[1] · Vidya A. Fleetwood[2] · Hari Shankar Meshram[1] · Alexis Guenette[2] · Krista L. Lentine[2]

Accepted: 7 September 2021 / Published online: 26 October 2021

Abstract

Purpose of Review As the prevalence of individuals with recovered coronavirus disease 2019 (COVID-19) increases, determining if and when organs from these donors can be safely used is an important priority. We examined current knowledge of outcomes of transplant using donors with recovered COVID-19.

Recent Findings A literature search of PubMed and Google scholar databases was conducted to identify articles with terms "SARS-CoV2," "COVID-19," "donor recovered," and "transplantation" published through 08/10/2021. We identified 25 reports detailing 94 recipients of both abdominal and thoracic transplants from donors with both prior and active COVID-19 infection. Rates of transmission to the recipient and of transplanted organ dysfunction were low among reports of donors with prior COVID-19 infection. End organ dysfunction and transmission were more common with active infection, although few reports are available. Standardized reporting is needed to better assess the impact of donor symptomatology, cycle thresholds, and individual recipient risk factors on postoperative outcomes.

Summary Available reports suggest that transplantation from COVID-19 donors may be feasible and safe, at least in short term follow-up. Nevertheless, there is a need for standardized testing and management protocols which should be tailored for available resources. While increased availability of COVID-19 vaccinations will mitigate risks of donor-derived COVID-19 and simplify management, continued vigilance is warranted during the ongoing public health emergency.

Keywords COVID-19 · SARS-CoV-2 · Living donors · Deceased donors · Organ donation · Transplantation · Screening · Pandemic

Abbreviations

AST	American Society of Transplantation
BAL	Broncho-alveolar lavage
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-19
DD	Deceased donor
DGF	Delayed graft function
DM	Diabetes mellitus
FDA	Food and Drug Administration
ESLD	End stage liver disease
LD	Living donor
LDKT	Living donor kidney transplantation
LRT	Lower respiratory tract
MSOF	Multi-system organ failure

Vivek B. Kute and Vidya A. Fleetwood are co-first authors.

Krista L. Lentine is the senior author.

This article is part of the Topical Collection on *COVID19 and Transplantation*

✉ Vivek B. Kute
drvivekkute@rediffmail.com

Vidya A. Fleetwood
vidyaratna.fleetwood@health.slu.edu

Hari Shankar Meshram
hsnephrology@gmail.com

Alexis Guenette
alexis.guenette@health.slu.edu

Krista L. Lentine
krista.lentine@health.slu.edu

[1] Department of Nephrology, Institute of Kidney Diseases and Research Center, Dr HL Trivedi Institute of Transplantation Sciences (IKDRC-ITS), Civil Hospital Campus, Asarwa, Ahmedabad, India

[2] Center for Abdominal Transplantation, Saint Louis University School of Medicine, Saint Louis, MO, USA

OPTN	Organ Procurement and Transplantation Network
PCR	Polymerase chain reaction
RT-PCR	Reverse real-time polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
URT	Upper respiratory tract

Introduction

The coronavirus disease 2019 (COVID-19) pandemic substantially impacted organ donation, including donor evaluation and selection, candidacy for and timing of transplantation, and clinical management after transplantation [1–9]. The global impact of COVID-19 in transplantation has been most severe in regions with highest COVID-19 burden and fewest resources [10, 11]. Case series, cohort studies, and database analyses have demonstrated that severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection-associated mortality is higher in organ transplant recipients compared to the general population [12–14]. As the prevalence of COVID-19 rises, transplant centers across the world must balance the need to continue live-saving transplantation against the concern for the risk of donor-derived COVID-19 infection [11]. To maintain transplant volumes without compromising safety in the COVID-19 era, a number of factors must be examined. These include the criteria for accepting organs with suspected, confirmed, or cleared COVID-19 infection; the probability of waitlist mortality without transplantation; the timing of recipient vaccination with regard to transplant and the appropriate precautions after vaccination; the ideal immunosuppression regimen; and the treatment protocol should COVID-19 infection occur. To date, multiple professional societies including the American Society of Transplantation (AST), the British Transplantation Society, the International Society for Heart and Lung Transplantation, The Transplantation Society (TTS), and the Indian Society of Organ Transplantation (ISOT) have worked to generate frequently updated guidance for transplant practice in the context of an evolving pandemic [15–19]. In this review, we examine the state of current evidence related to the safety of transplantation from donors with prior or current COVID-19.

Review Methodology

A literature search was conducted of several comprehensive databases including MEDLINE, PubMed Central, and Google Scholar on 8/10/2021 for published research articles using the search terms of "SARS-CoV-2," "COVID-19," "donor recovered," "transplantation," and "COVID-19 recovered," "SARS-CoV-2 recovered" with no language or date restrictions. Studies were examined for relevance. The sole inclusion criterion was containing information on the post-transplant course of a recipient who had received an organ from a donor either currently or previously infected with COVID-19. Of the 1,182 studies extracted, 25 reports of 94 recipients contained information relevant to our review. One report was excluded for detailing a duplicate case. An additional SRTR review was excluded due to the possibility of duplicate reporting of published cases.

Donor Testing Utility and Accuracy

The use of organs during the pandemic relies on readily available, reliable, and accurate donor COVID-19 testing, along with accessible communication of testing results to transplant teams [5]. Currently, testing specimens can be obtained from several sources, with lower respiratory tract (LRT) samples demonstrating higher viral loads and therefore more likely to yield positive tests than upper respiratory tract (URT) specimens [20]. The highest rates of positive tests have been obtained from broncheoalveolar lavage (BAL) specimens (95% positive) versus sputum (72%) and oropharyngeal swab (32%) [20]. The sensitivity and specificity of tests from different specimen sources are difficult to specify as they vary depending on the source and the platform. Antigen and serology testing are available; however, in the setting of pre-transplant screening, nucleic acid amplification testing is recommended and preferred as per AST guidelines [15].

With a wide variety of specimen sources available for testing, the need for an accurate diagnosis must be balanced against the need for safety. Although LRT specimens more frequently detect viral particles than URT specimens, the BAL necessary to obtain these specimens is an aerosolizing procedure, which carries increased risk of transmitting disease to all persons present in the room [21]. As of March 2021, only 50–60% of potential lung donors were undergoing LRT testing prior to donation. Following a series of four cases of lung donors with negative nasopharyngeal specimens and subsequently positive LRT specimens obtained from BAL, the OPTN Ad Hoc Disease Transmission Advisory Committee approved a proposal for emergency action mandating that all potential lung donors undergo LRT testing [22]. For non-lung donors, AST guidelines recommend at least one negative COVID-19 test from the respiratory tract within the three days prior to donation [15].

Samples are evaluated through reverse transcriptase polymerase chain reaction (RT-PCR) with the potential to utilize the cycle threshold in the decision-making process. RT-PCR cycle threshold (Ct) values refer to the number of PCR

cycles needed to amplify the viral nucleic acid to a detectable level; lower Ct levels—indicating less amplification required—correlate with higher viral density [23]. These values were initially identified as a potential marker of active COVID-19 infection. However, not all tests produce an actual value; of those that do, the values are not necessarily comparable given the possibility of different targets. Current approved tests under emergency use authorization (EUA) by the US Food and Drug Administration (FDA) are qualitative assays that target multiple different SARS-CoV-2 genes simultaneously, allowing each target to generate a different Ct value from the same specimen. These tests are not constructed to report a quantitative measurement of nucleic acid in a sample due to the lack of standardized controls of known concentration, as well as the poor optimization of linear relationships between the Ct value and the concentration of target nucleic acid in the specimen. Finally, the blood is the ideal specimen for quantitative viral load testing; respiratory specimens are less ideal due to inherent variability of the collection process and testing. In acknowledgement of the wide variability of Ct values, IDSA-AMP has released a statement including the wide variety of factors that affect the Ct values. These include patient factors (symptoms, immune status, and age), specimen factors (collection method, specimen type, transport and storage conditions), and test factors (sample volume, gene target, primer/probe design, nucleic acid extraction and amplification efficiency) [24].

Donor testing is currently performed using a number of possible specimens; blood and BAL specimens have the highest likelihood of capturing a positive COVID-19 test in the donor. At least one negative test from the URT is advised for non-lung donors; a negative LRT specimen is mandatory for assessing the infectious status of potential lung donors. Ct values may be useful for trending in the same patient if other variables remain fixed (constant specimen type, use of same machine, same target evaluated), but are not yet thought to be reliable for comparing degree of infection among Sars-CoV-2-positive patients.

Infectious Outcomes in Donors with Resolved SARS-CoV-2 Infection

Although some evidence shows that many centers are willing to consider organs from donors with prior COVID-19 infection, acceptance patterns and protocols are not standardized among centers. A national survey of US living donor kidney transplant programs between 9/2020 and 11/2020 demonstrated wide variability in acceptance of organs from living donors with evidence of prior COVID-19 infection across the responding centers ($n = 115$) [8]. Overall, 42 living donations from individuals with cleared COVID-19 infection were identified. Over 93% of centers were willing to allow living donors who had previously experienced COVID-19 infection to donate, although almost 40% were only willing to consider donation on a case-to-case basis. The majority of centers (50.8%) preferred to wait at least three months after donor recovery from COVID-19 before proceeding with transplantation. The most common reason for excluding potential living donors with recovered COVID-19, endorsed by 59.8%, was a history of either current or resolved acute kidney injury (AKI). However, no literature has evaluated program willingness to accept organs from donors with active Sars-CoV-2 infection. For living donors with a history of COVID-19, AST recommends considering donation if the donor is at least 28 days from symptom resolution with a negative NAT [16].

Multiple case reports and three case series have shown acceptable infectious outcomes in recipients of non-lung organs from donors with resolved SARS-CoV-2 infection (Tables 1 and 2). Reports detail the postoperative course of the recipients of 45 kidney transplants (Table 1), 14 liver transplants (Table 2), and 6 heart transplants (Table 3) from 55 donors with prior COVID-19. The median time from first documented PCR-confirmed infection to time of organ donation was 54 days (range 3–140). In all cases but one, the donors' symptoms were absent or mild. None of the transplants resulted in symptomatic COVID-19 transmission to the recipient; however, not all the recipients were tested in the absence of symptoms to confirm that transmission had not occurred. Notably, few recipients were considered to have any degree of Sars-CoV-2 immunity: fifteen recipients were reported to have had prior COVID-19, and an additional three were at least partially vaccinated. Few were checked for neutralizing antibodies, and only one recipient was seropositive. A single liver recipient was reported to have respiratory failure in the context of multisystem organ failure [25], but three nasopharyngeal swabs were negative for COVID-19 post-transplant in this patient.

Use of lungs for transplantation from donors with prior COVID-19 appears more uncommon: three case reports have addressed lung transplantation from patients with recovered COVID-19 (Table 4). Ceulemans et al. [26] reported the first double lung transplant from a Donation after Circulatory Death (DCD) donor who had recovered from COVID-19 three months earlier and presented with a superior P/F ratio and negative testing. Two subsequent reports [27, 28] detailed cases in which the donor had been diagnosed 90 and 49 days before with similarly negative repeat testing, excellent lung function, and good postoperative outcome. None of these recipients has tested positive; however, two of the three had been previously infected with Sars-CoV-2, causing their progression to lung transplantation, and may have had a degree of immunity.

From the available evidence, it appears that use of both abdominal and thoracic organs from donors with prior COVID-19 is not associated with high rates of SARS-CoV-2

Table 1 Kidney transplants from donors with resolved or active SARS-CoV-2 infection. Symptoms are considered mild if present but not life-threatening, and severe if resulting in organ failure. Abbreviations: *ACR*, acute cellular rejection; *AKI*, acute kidney injury; *BAL*, broncheoalveolar lavage; *cr.*, creatinine; *Ct*, cycle threshold; *d*, days; *DD*, deceased donor; *DGF*, delayed graft function; *LD*, live donor; *NP*, nasopharyngeal; *SGF*, slow graft function. *Donors from manuscript by Kute et al. were summarized for clarity. **Specimen source not reported

Author	Donor					Recipient				
	Type	Time from diagnosis (day)	Infection documentation	Symptom severity	Serum Cr	Age	Prior infection/vaccination	IgG	Graft dysfunction	Follow-up (day)
Prior infection										
Neidlinger et al., Nov 2020 [25]										
1	DD	98	NP, BAL	Mild	NR (all)	NR (all)	NR (all)	NR (all)	DGF None	42 NR
2	DD	120	NP, BAL	Asymptomatic					None None	28 28
3	DD	Unknown	NP, BAL	Asymptomatic					None None	30 30
Safa et al., Jan 2021 [60]	LD	140	NP	Mild	Normal	60+	None	NR	SGF	28
Kanchi et al., Jan 2021 [54]	LD	42	NP	Mild	NR	35	Infection	(+)	None	98
Kucuk et al., Feb 2021 [23]	LD	30	NP	Mild	NR	31	Infection	(-)	None	45
Kute et al.,*April 2021 [39]										
1 (…) 31	LD	54 (median)	NP	23/31 Asymptomatic 8/31 Mild	Normal	39 (11–59)	9/31 Infection 22/31 None	NR	2/31 ACR	44 (all)
Meshram et al., June 2021 [30]										
1	DD	30	NP	Severe	NR	14 48	Infection None	NR NR	None None	60 60
Koval et al., July 2021 [61]										
1	DD	3	NP	Asymptomatic	Normal	40 27	Fully vacc Partial vacc	NR NR	AKI (Cr. 2.1) None	84 84
Frattaroli et al., July 2021 [62]	DD	NR	PCR**	Asymptomatic	NR	22	Partial vacc None	NR	None	84
Active infection										
Perlin et al., May 2021 [55]										
1	DD	0	NP Ct NR	Mild	Normal	49 45	None None	NR NR	DGF None	240 240
Puodziukaite et al., June 2021 [63]										
1	DD	0	NP Ct 32–33	Mild	Normal	38 36	Infection Infection	(+) (+)	None DGF	90 90

Table 1 (continued)

Author	Donor					Recipient					
	Type	Time from diagnosis (day)	Infection documentation	Symptom severity	Serum Cr	Age	Prior infection/vaccination	IgG	Graft dysfunction	Follow-up (day)
Koval et al., July 2021 [61]										
1	DD	0	NP Ct NR	Mild	Normal	35	None	NR	None	84 (all)
						29	None	NR	None	
2	DD	3	NP Ct 38–40	Mild	Normal	44	Infection	NR	None	
						38	None	NR	None	
3	DD	1	NP Ct NR	Mild	Severe AKI	66	Partial vacc	NR	None	
						55	Fully vacc	NR	DGF	
4	DD	0	NP Ct 31–41	Mild	Normal	24	Partial vacc	NR	None	
						41	None	NR	None	
Frattaroli et al., July 2021 [62]										
1	DD	0	NP Ct 40.2	Asymptomatic	NR	21	Partial vacc	NR	None	84
						33	None	NR	None	84
Sigler et al., July 2021 [64]										
1	DD	0	NP Ct 29.4	Mild	NR	27	Fully vacc	(-)	None	7
						28	None	(-)	None	7

transmission to the recipient, as no cases have resulted in a demonstrated transmission.

Many variables remain unexamined regarding the safety of using non-lung organs from donors with recovered COVID-19. The impact of prior infection or vaccination, present in 18 of the 65 recipients, cannot be estimated from this data, especially in the absence of neutralizing antibody testing in the majority of cases.

Additionally, the studied sample includes patients largely at low risk of symptomatic or severe COVID-19: [10] the median age of the recipients examined is 39, and only three of the patients are older than 60 years of age. Few authors report the incidence of diabetes, hypertension, cardiac disease, and elevated body mass index (BMI) in these recipients, factors known to elevate the risk of COVID-19-associated illness and complications [29]. As not all of the recipients underwent COVID-19 testing postoperatively, patients may have experienced transmission resulting in undetected asymptomatic infection. Further data is necessary to determine whether COVID-19 is more transmissible in higher risk recipients or may cause more severe illness in similarly immunosuppressed recipients of higher age and comorbidity index than the examined patients.

The dearth of reports of donors with prior severe COVID-19 symptomatology suggests that organs have only been accepted from highly selected donors. Of the reviewed reports, only one donor [30] experienced COVID-19 characterized as severe based on profound respiratory failure; there was no evidence postoperatively of COVID-19-associated injury or graft dysfunction. However, the degree of COVID-19 severity is not reported in a standardized fashion across the examined cases, limiting assessment of the impact of more critical illness on disease transmissibility. Longer-term follow-up and a standardized characterization of the severity of donor COVID-19 is necessary to better understand the impact of prior Sars-CoV-2 infection on solid organ transplant recipients.

Infectious Outcomes in Organ Recipients from Donors with Active SARS-CoV-2 Infection

Many organ procurement organizations responded to the onset of the pandemic with rapid implementation of donor testing and reporting policies [5]. In most cases, organs from donors with active COVID-19 were not transplanted. However, negative donor serology does not guarantee absence of infection, and some organs were transplanted from Sars-CoV-2-positive donors after false negative testing. Additionally, some organs from Sars-CoV-2-positive donors were transplanted intentionally, either to recipients with evidence of prior infection or to COVID-19-naïve recipients considered at too high a risk of waitlist

Table 2 Liver transplants from donors with resolved or active SARS-CoV-2 infection. Symptoms are considered mild if present but not life-threatening, and severe if resulting in organ failure. Abbreviations: *ACR*, acute cellular rejection; *BAL*, broncheoalveolar lavage; *BW*, bronchial washings; *Ct*, cycle threshold; *d*, days; *DD*, deceased donor; *LD*, live donor; *MSOF*, multi-system organ failure; *NP*, nasopharyngeal

Author	Donor					Recipient				
	Type	Time from diagnosis (day)	Infection documentation	Symptoms	LFTs	Age	Prior infection/ vaccination	IgG	Graft dysfunction	Follow-up (day)
Prior infection										
Neidlinger et al., Nov 2020 [25]										
1	DD	98	NP, BAL	Mild	NR	NR	NR	NR	None	NR
2	DD	38	NP, BW	Mild	NR	NR	NR	(-)	None	21
3	DD	Unknown	NP, BAL	Asymptomatic	NR	NR	NR	NR	MSOF	30
4	DD	48	NP, BAL	Asymptomatic	NR	NR	NR	NR	None	14
Tuncer et al., Feb 2021 [65]	LD	32	NP	Asymptomatic	Normal	60	Infection	NR	None	16
Malleeswaran et al., July 2021 [66]										
1	LD	92	NR (all)	Asymptomatic (all)	NR (all)	41	7/9 None	NR (all)	None (all)	75
2	LD	72				9	2/9 Infection			30
3	LD	64				47				60
4	LD	53				2				30
5	LD	27				48				120
6	LD	15				8				30
7	LD	49				12				45
8	LD	22				35				30
9	LD	87				3				30
Active infection										
Heinz et al., June 2020 [31]	LD	0	NP Ct NR	Mild	NR	< 1	None	NR NR	COVID hepatitis	30
Hong et al., Oct 2020 [40]	LD	0	NP Ct NR	Mild	NR	57	None	NR	Hepatic artery thrombosis	69
Manzia et al., Feb 2021 [67]	DD	0	NP Ct 25–27	NR	NR	33	Infection	(+)	None	60
Dhand et al., June 2021 [68]	DD	0	NP Ct 38.5	Mild	NR	54	Fully vacc	NR	None	28
Nguyen et al., August 2021 [41]	LD	0	NR	Mild	NR	24	None	(-)	Mild ACR	26
Barros et al., August 2021 [69]	DD	0	NP 12.0	Mild	NR	48	Infection	NR	None	120

Table 3 Heart transplants from donors with resolved or active SARS-CoV-2 infection. Symptoms are considered mild if present but not life-threatening, and severe if resulting in organ failure. Abbreviations: *BAL*, broncheoalveolar lavage; *Ct*, cycle threshold; *d*, days; *DD*, deceased donor; *EF*, ejection fraction; *NP*, nasopharyngeal

Author	Donor					Recipient				
	Type	Time from diagnosis (day)	Infection documentation	Symptoms	EF (%)	Age	Prior infection/vaccination	IgG	Graft dysfunction	Follow-up (day)
Prior infection										
Neidlinger et al., Nov 2020 [25]										
1	DD	98	NP, BAL	Mild	NR	NR	NR	NR	None	42
2	DD	38	NP, BW	Mild	NR	NR	NR	(-)	None	NR
3	DD	Unknown	NP, BAL	Asymptomatic	NR	NR	NR	NR	None	NR
Active infection										
Reparaz et al., Feb 2021 [70]	DD	0	NP Ct 35–37	Mild	NR	NR	NR	NR	None	51
Dhand et al., June 2021 [68]	DD	0	NP Ct 38.5	Mild	NR	57	None	NR	None	28
Sigler et al., July 2021 [64]	DD	0	NP Ct 29.4	Mild	NR	21	None	NR	None	7

Table 4 Lung transplants from donors with resolved or active SARS-CoV-2 infection. Symptoms are considered mild if present but not life-threatening, and severe if resulting in organ failure. Abbreviations: *AR*, acute rejection; *BAL*, broncheoalveolar lavage; *BW*, bronchial washings; *Ct*, cycle threshold; *d*, days; *DD*, deceased donor; *EF*, ejection fraction; *NP*, nasopharyngeal; *POD*, postoperative day

Author	Donor					Recipient				
	Type	Time from diagnosis (day)	Infection documentation	Symptoms	Lung function	Age	Prior infection/vaccination	IgG	Graft dysfunction	Follow-up (day)
Prior infection										
Ceulemans et al., March 2021 [26]	DD	90	BAL	Mild	PaO2 402 mmHg	61	None	NR	Minimal AR	53
Kim et al., July 2021 [71]	DD	90	BW	Mild	PaO2 402 mmHg	56	Infection	NR	None	90
Querrey et al., July 2021 [28]	DD	49	BAL	Mild	P/F ratio 280–474	65	Infection	NR	None	40
Active infection										
Kumar et al., March 2021 [32]	DD	0	NP negative BW (POD 0) Ct 26–28	Asymptomatic	NR	70	NR	NR	Prolonged intubation	25
Kaul et al., March 2021 [33]	DD	0	NP negative BAL (POD 3) Ct 8.1	Mild	NR	NR	NR	NR	Graft failure	61

mortality to wait for an uninfected donor. Transplantation of non-lung allografts from donors actively infected with SARS-CoV-2 at the time of organ procurement comprises 26.4% of the examined cases.

Fifteen donors yielding a total of 25 transplanted organs (16 kidneys, six livers, and three hearts) have been described. None of the donors presented with severe infection. Of the recipients, twenty patients were intentionally transplanted with non-lung organs from donors with active SARS-CoV-2 infection (Tables 1, 2, and 3). As many as eleven of these recipients may have had some degree of COVID immunity, as three of the recipients had prior COVID-19 and six were at least partially vaccinated; additionally, two recipients were themselves actively infected with SARS-CoV-2 as confirmed by PCR. Among these recipients, no transmissions have occurred.

Five recipients were transplanted unintentionally when COVID-19 testing resulted positive after transplantation had occurred. Of the recipients unintentionally exposed by missed donor infection, one liver recipient developed positive PCR testing postoperatively and has been presumed a donor-derived infection [31]. The recipient additionally developed COVID-associated hepatitis in the transplanted split liver allograft. However, the transplant took place at the start of the pandemic before widely available testing, and neither recipient nor donor was tested pre-transplant. In addition, the donor was the mother of the recipient and in close contact with the patient prior to transplantation; it is difficult to exclude transmission having occurred pre- or post-operatively rather than through organ transmission. Finally, both donor and recipient tested positive days after the transplant had occurred, raising the possibility that both had acquired the infection within their hospital stay.

While no reports have been made of the intentional transplantation of Sars-CoV-2-infected lungs, two recipients have received lung allografts from actively infected donors with poor outcomes (Table 4). In the first case [32], the donor presented without COVID-19 symptoms and nasopharyngeal PCR tests resulted negative twice prior to donation. However, intra-operative bronchial washings during the recipient transplantation were positive for COVID-19 PCR; the recipient remained persistently positive after transplantation and has developed respiratory failure with bilateral airspace disease persistent to two months post-transplantation. The second [33] had a similar course: the donor presented with a cerebrovascular accident and was noted to have a right lower lung consolidation attributed to atelectasis with no other COVID-19 symptoms. Nasopharyngeal PCR was negative, and the lungs were transplanted; on post-operative day 2, the recipient had worsening respiratory distress and cardiogenic shock, prompting COVID-19 testing with a low-level positive result. The recipient developed multisystem organ failure and care was withdrawn at two months post-transplant. Of note, in neither of these cases was donor BAL NAT performed or required prior to lung procurement from the donor.

All lung recipients who received Sars-CoV-2-positive organs immediately developed positive NAT and COVID-19-related end-organ dysfunction. ACE-2 receptors, the target of the SARS-CoV-2 virus [34], are expressed more densely in the lungs than other tissues [35], which may favor easier transmission from infected lung donors. Based on the limited information examined here, use of infected lungs should be avoided until more data is gathered. Additionally, given the higher incidence of ACE-2 receptors in the lower respiratory tract and the viral persistence there after nasopharyngeal clearance [28], proceeding with lung transplantation after a negative nasopharyngeal swab without further lower respiratory tract investigation should be avoided.

The presence of neutralizing antibodies was considered by the authors who intentionally used Sars-CoV-2-positive organs as a safety valve for transplanting infected allografts; however, given the development of Sars-CoV-2 variants which may evade antibody protection [36], confidence in antibody protection to allow safe use of organs from Sars-CoV-2-positive donors may be premature.

Graft Outcomes

Due to the relative novelty of the SARS-CoV-2 pandemic and the rarity of organ use from donors with prior or active COVID, long-term graft outcomes cannot yet be assessed. Some evidence suggests that even in the absence of severe disease, patients who develop COVID-19 have a higher incidence of delayed development of end-organ dysfunction. A retrospective cohort study of over 47,000 patients demonstrated increased rates of diabetes and cardiovascular disease in patients with prior COVID-19 [37]. Similarly, markers of compromised renal function have been detected in other post-COVID patients, even in those whose symptomatology had not included acute kidney injury [38]. The possibility of occult organ dysfunction in patients with active or resolved COVID-19 should be a factor in considering organ acceptance.

Graft dysfunction in recipients of donors who have recovered from COVID-19 is uncommonly reported in the cases examined. Among kidney recipients (Table 1) of donors who have recovered from COVID-19, a single case of delayed graft function (DGF) was reported [25], corresponding to an incidence of 2.2%. A large-series report of 31 living donor kidney transplants from COVID-19-cleared donors in India published by Kute et al. [39] made note of 100% graft and patient survival, a low acute cellular rejection rate of 6.4%, and a median serum creatinine of 1.0 mg/dL with no cases of delayed graft function. Among those who received kidney allografts from

donors with active COVID-19 infection, the incidence of DGF is higher at 18.75% (Table 1). Notably, Koval et al. described a 33-year-old Sars-CoV-2-positive donor with a terminal creatinine of 5.7 mg/dL, both of whose kidneys were transplanted; the recipient creatinine measurements at 12 weeks were 1.4 mg/dL and 1.1 mg/dL, respectively, suggesting that it is possible to achieve good outcomes in a young donor with COVID-induced AKI. However, sample sizes are too limited to draw conclusions, and data on cold ischemic time, donor age, and other relevant factors are commonly unreported, limiting the generalizability of the data.

Among the 14 recipients of livers from donors with cleared infection (Table 2), a single case of multisystem organ failure—including liver allograft dysfunction—was reported [25]. In that patient, multiple postoperative nasopharyngeal swabs were negative for Sars-CoV-2, indicating that the organ damage was independent of active infection but not ruling out the possibility of COVID-19 sequelae. Of six recipients of livers from actively infected donors, three reported graft complications: one hepatic artery thrombosis [40], ascribed to technical factors; one mild presumed acute cellular rejection; [41] and one biopsy-proven COVID-19 hepatitis [31].

No graft dysfunction has been reported in recipients of heart or lung allografts from donors with cleared COVID-19 infection (Tables 3 and 4). However, as described above, case reports document catastrophic outcomes of lung transplantation from actively infected donors, emphasizing the need for avoidance or substantial caution.

Persistence of SARS-COV-2 in Organ Tissue and Associated Dysfunction

COVID-19 is characterized most frequently by an acute respiratory illness, but multiple studies suggest the presence of virus in other organs, particular kidneys. Entry of the virus into cells is facilitated by multiple genes, including most prominently that expressing the Angiotensin Converting Eznyme (ACE-2) receptor [42]. The ACE-2 receptor is found in vascular endothelium in type I and II pneumocytes and in smooth muscle cells of the pulmonary vasculature, but it has also been demonstrated in epithelial cells of the bile duct, heart, intestine, and kidneys [43]. The presence of the ACE-2 receptor provides a gateway for the virus and suggests that these tissues may carry viral particles in patients with demonstrated SARS-CoV-2 infection.

Few studies have substantiated the presence of viral particles within fluids and tissues. Clinical samples sometimes display evidence of viral presence: SARS-CoV-2 appears rarely in the blood, seen in 1–15% of patients with severe infection [20, 44]; but RNA has also been detected in the stool [20] and in urine [45]. Viral particles and high levels of RNA have been isolated from lung tissue [42, 46, 47]; exponentially lower levels of RNA have been detected in the kidneys, liver, and heart tissues [42]; Viral particles require electron microscopy to detect; no studies have detected SARS-CoV-2 particles in the liver or pancreas [48] and only a single study has identified virions in the myocardium [49], but microscopy has detected the virus in several instances in every compartment of the kidney [42].

The presence of viral RNA in organ tissue is concerning both for transmission of the disease and for the unknown long-term organ-specific sequelae of COVID-19. Even in cases with no damage to the transplantable organ, it has not yet been determined whether subclinical damage that may later become clinically significant has occurred. Microscopic proteinuria has been demonstrated in the setting of normal creatinine in non-transplant patients who have previously recovered from COVID-19 [50]. Similarly, low estimated glomerular filtration rate at 6 months after recovery from COVID-19 has been reported in patients who did not experience acute kidney injury during their index admission for COVID infection [38].

Further study is needed to determine the long-term clinical impact of COVID-19 on organ function and whether accepting allografts from infected donors will affect post-transplant outcomes.

Ideal Immunosuppression Regimen in Donation with COVID-19 Donors

Currently, there are no evidence-based recommendations for managing immunosuppression in the context of the pandemic, either for prevention or as part of the management of patients with confirmed COVID-19. The AST has stated that the decision to reduce immunosuppression during the pandemic should consider the balance between disease severity and risk of rejection [16].

Survey studies have demonstrated a trend toward the decreased use of depleting antibodies for induction therapy in general during the COVID era [51, 52]. The consequences of such modification are yet to be determined; however, a UNOS review comparing early post-transplant outcomes by immunosuppression regimen during the pandemic era showed no change in mortality with the use of lymphocyte depleting agents [51].

In cases of transplantation from donors with prior COVID-19, there is no specific regimen which should be uniformly applied. In the studies reviewed, induction therapy was omitted entirely in two cases [53–55]; in the remaining cases, the immunosuppression regimen was either unchanged or not reported.

At this time, no evidence supports changing post-transplant induction or maintenance immunosuppression in the

case of donor infection; however, many programs preferentially omit induction immunosuppression or use a non-depleting form of induction in recipients either suspected of or confirmed to have COVID-19 infection [51].

Society Guidelines and Recommendation for Transplantation from COVID-19 Donors

The AST offers considerations for proceeding in light of a positive test from a previously infected potential donor if (1) the donor is between 21 and 90 days from initial symptoms, (2) symptoms have resolved, and (3) an infectious disease expert is consulted [15, 56]. These recommendations acknowledge that positive RT-PCR tests beyond this timeframe from asymptomatic patients most likely represent persistent viral shedding of little significance rather than active infection.

Ritschl et al. [57] identified 19 national organ societies with position statements in December 2020 on the use of organs from donors with COVID-19. Sixteen of these societies strongly supported avoidance of organs from donors with positive testing or a high clinical suspicion of infection. Although only three societies recommended proceeding with transplantation using organs from donors with resolved infection, most did not comment, and none recommended against the use of these allografts. With the mounting data on the use of organs from donors with prior or current COVID-19 and the increasing availability of vaccination, professional society guidelines may be updated serially over time.

Conclusions

Available evidence suggests that organ use may be safe from donors who have recovered from COVID-19 and have negative testing; case reports and series to date have shown no increase in adverse outcomes and no donor-derived infections with these allografts. The AST recommends waiting 21–90 days [15] after an initial diagnosis of COVID-19 prior to considering organs from donors with resolved infection, and most of the cases published to date followed this timeframe. While a shorter timeframe may be safe in some carefully selected donors with currently negative testing, current data on such practice is limited, and caution and recipient informed consent is advised.

Few reports and no series or trials have examined the outcomes of using organs from donors with active infection. No conclusions can be drawn on the transplant-specific outcomes of the use of non-lung organs with active infection, but donor-derived transmission has been reported and should be a considered a risk even for vaccinated recipients. The use of lung allografts from donors with active infection has been associated with unacceptable outcomes in two reported cases, and should be avoided in the absence of further evidence. In addition, to avoid inadvertent transmission due to false negative URT testing, a LRT specimen should be obtained for every lung donor as is now mandated by the OPTN [22].

Efforts to optimize protocols for donor COVID-19 testing, organ evaluation, and immunosuppression management in the recipient are critical priorities to support safe transplantation during the pandemic. While increased availability of COVID-19 vaccinations will mitigate the risk of donor-derived COVID-19, transplant physicians, primary care physicians, health educators and policy makers must collaborate to maximize access to and patient acceptance of vaccination prior to transplant [58], and evidence-guided use of boosters in immunocompromised patients who begin vaccination after transplant [59].

Author Contribution All authors have contributed to the work, and reviewed and approved the final version.

Funding K.L.L. is supported by the Mid-America Transplant/Jane A. Beckman Endowed Chair in Transplantation and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant R01DK120551.

Declarations

Conflict of Interest The authors declare no competing financial interests. K.L.L. is a member of the American Society of Nephrology (ASN) COVID-19 Response Team.

References

1. Lentine KL, Mannon RB, Josephson MA. Practicing with uncertainty: kidney transplantation during the COVID-19 pandemic. Am J Kidney Dis. 2021;77(5):777–85.
2. Boyarsky BJ, Werbel WA, Durand CM, et al. Early national and center-level changes to kidney transplantation in the United States during the COVID-19 epidemic. Am J Transplant. 2020;20(11):3131–9.
3. Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant. 2021;21(3):925–37.
4. Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. Lancet. 2020;395(10237):e95–6.
5. Lentine KL, Singh N, Woodside KJ, et al. COVID-19 test result reporting for deceased donors: emergent policies, logistical challenges, and future directions. Clin Transplant. 2021;35(5):e14280.
6. Lentine KL, Vest L, Schnitzler MA, et al. Survey of U.S. living kidney donation and transplant practices in the COVID-19 era. Kidney Int Rep. 2020.
7. Chang SH, Wang M, Lentine KL, Merzkani M, Alhamad T. Solid organ transplantation during the COVID-19 pandemic in the United States. Transpl Int. 2021.

8. Jan MY, Jawed AT, Barros N, et al. A national survey of practice patterns for accepting living kidney donors with prior Covid-19. Kidney Int Rep. 2021;6(8):2066–74. https://doi.org/10.1016/j.ekir.2021.05.003.
9. Zaidi H, Klassen AC, Fleetwood J, et al. Living organ donor health care priorities during the COVID-19 pandemic. Kidney Int Rep. 2021;6(4):1151–5.
10. Ahn C, Amer H, Anglicheau D, et al. Global Transplantation COVID Report March 2020. Transplantation. 2020;104(10):1974–83.
11. Salvalaggio PR, Ferreira GF, Caliskan Y, et al. An international survey on living kidney donation and transplant practices during the COVID-19 pandemic. Transpl Infect Dis. 2021;23(2):e13526.
12. Caillard S, Chavarot N, Francois H, et al. Is COVID-19 infection more severe in kidney transplant recipients? Am J Transplant. 2021;21(3):1295–303.
13. Hadi YB, Naqvi SFZ, Kupec JT, Sofka S, Sarwari A. Outcomes of COVID-19 in solid organ transplant recipients: a propensity-matched analysis of a large research network. Transplantation. 2021;105(6):1365–71.
14. Kute VB, Bhalla AK, Guleria S, et al. Clinical profile and outcome of COVID-19 in 250 kidney transplant recipients: a multicenter cohort study from India. Transplantation. 2021;105(4):851–60.
15. American Society of Transplantation (AST). 2019-nCoV (Coronavirus): recommendations and guidance for organ donor testing. Updated 10/05/2020. Available at: https://www.myast.org/covid-19-information. Accesed: 07/04/2021. Accessed.
16. American Society of Transplantation (AST). 2019-nCoV (Coronavirus): 2019-nCoV (Coronavirus): FAQs for Organ Transplantation. Updated 04/12/2021. Available at: https://www.myast.org/covid-19-information. Accessed: 07/04/2021.
17. Kute VB, Guleria S, Bhalla AK, Sharma A, Agarwal SK, Sahay M, et al. ISOT consensus statement for the kidney transplant recipient and living donor with a previous diagnosis of COVID-19. Indian J Transplant. 2021;15(2):131. https://doi.org/10.4103/ijot.ijot_26_21.
18. The British Transplantation Society. COVID-19 Information Web site. Published 2021. Updated 4/19/2021. Accessed 6/21/2021, 2021.
19. COVID-19 Information for Transplant Professionals Web site. Updated 07/08/2021. Accessed 07/10/2021.
20. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323(18):1843–4.
21 Bolton L, Mills C, Wallace S, Brady MC, Royal College of S, Language Therapists C-AG. Aerosol generating procedures, dysphagia assessment and COVID-19: A rapid review. Int J Lang Commun Disord. 2020;55(4):629–36.
22. Organ Procurement and Transplantation Network (OPTN). Notice of OPTN emergency policy change: lower respiratory SARS-CoV-2 testing for lung donors Web Site. https://optn.transplant.hrsa.gov/media/4576/policy_notice_lunglowerrespiratorytesting_20210426.pdf. Published 2021. Accessed 08/29/2021.
23. Kucuk EV, Sit D, Kayabasi H, et al. The first kidney transplantation after recipient and living donor recovered from COVID-19. North Clin Istanb. 2021;8(2):187–9.
24. Infectious Disease Society of America. IDSA and AMP joint statement on the use of SARS-CoV-2 PCR cycle threshold (Ct) values for clinical decision-making Published 2021. Updated 3/12/2021. Accessed 8/6/2021.
25. Neidlinger NA, Smith JA, D'Alessandro AM, et al. Organ recovery from deceased donors with prior COVID-19: a case series. Transpl Infect Dis. 2021;23(2):e13503.
26. Ceulemans LJ, Van Slambrouck J, De Leyn P, et al. Successful double-lung transplantation from a donor previously infected with SARS-CoV-2. Lancet Respir Med. 2021;9(3):315–8.
27. Kim H-J, Shin DH, Cho WH, Kim D, Yeo HJ. Successful lung transplantation from a donor who had recovered from SARS-CoV-2 pneumonia. Ann Thorac Surg. 2021;S0003–4975(0021):01265–1260.
28. Querrey M, Kurihara C, Manerikar A, et al. Lung donation following SARS-CoV-2 infection. Am J Transplant. 2021.
29. Preskorn SH. The 5% of the population at high risk for severe COVID-19 infection is identifiable and needs to be taken into account when reopening the economy. J Psychiatr Pract. 2020;26(3):219–27.
30. Meshram HS KV, Chauhan S, et al. A Case Report of transplantation from a deceased donor with critical COVID-19: ongoing dilemma between discarding and accepting organs in COVID-19 era! TID-21-CRRL-048.R1. Accepted 21 June 2021.
31. Heinz N, Griesemer A, Kinney J, et al. A case of an infant with SARS-CoV-2 hepatitis early after liver transplantation. Pediatr Transplant. 2020;24(8):e13778–e13778.
32. Kumar D, Humar A, Keshavjee S, Cypel M. A call to routinely test lower respiratory tract samples for SARS-CoV-2 in lung donors. Am J Transplant. 2021.
33. Kaul DR, Valesano AL, Petrie JG, et al. Donor to recipient transmission of SARS-CoV-2 by lung transplantation despite negative donor upper respiratory tract testing. Am J Transplant. 2021.
34. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–4.
35. Gaussen A, Hornby L, Rockl G, et al. Evidence of SARS-CoV-2 infection in cells, tissues, and organs and the risk of transmission through transplantation. Transplantation. 2021;105(7):1405–22.
36. Weisblum Y, Schmidt F, Zhang F, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife. 2020;9.
37. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021;372:n693.
38. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220–32.
39. Kute VB, Godara S, Guleria S, et al. Is it safe to be transplanted from living donors who recovered from COVID-19? Experience of 31 Kidney Transplants in a Multicenter Cohort Study From India. Transplantation. 2021;105(4):842–50.
40. Hong HL, Kim SH, Choi DL, Kwon HH. A case of coronavirus disease 2019-infected liver transplant donor. Am J Transplant. 2020;20(10):2938–41.
41. Nguyen MC, Lee EJ, Avery RK, et al. Transplant of SARS-CoV-2-infected living donor liver: case report. Transplant Direct. 2021;7(8):e721.
42. Puelles VG, Lutgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med. 2020;383(6):590–2.
43. Loganathan S, Kuppusamy M, Wankhar W, et al. Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes. Respir Physiol Neurobiol. 2021;283:103548–103548.
44. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
45. Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl). 2020;133(9):1039–43.
46. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;382(12):1177–9.
47. Perrucci GL, Sommariva E, Ricci V, et al. Presence of SARS-CoV-2 Nucleoprotein in cardiac tissues of donors with negative COVID-19 molecular tests. Diagnostics (Basel). 2021;11(4).

48. Kates OS, Fisher CE, Rakita RM, Reyes JD, Limaye AP. Use of SARS-CoV-2-infected deceased organ donors: should we always "just say no?" Am J Transplant. 2020;20(7):1787–94.
49. Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;22(5):911–5.
50. Huart J, Bouquegneau A, Lutteri L, et al. Proteinuria in COVID-19: prevalence, characterization and prognostic role. J Nephrol. 2021;34(2):355–64.
51. Bae S, McAdams-DeMarco MA, Massie AB, et al. Early changes in kidney transplant immunosuppression regimens during the COVID-19 pandemic. Transplantation. 2021;105(1):170–6.
52. Sandal S, Boyarsky BJ, Massie A, Chiang TP, Segev DL, Cantarovich M. Immunosuppression practices during the COVID-19 pandemic: a multinational survey study of transplant programs. Clin Transplant. 2021:e14376.
53. Perlin D, Shmanev A, Perlina A, Kulikov P. Kidney transplantation from COVID-19 deceased donor. Urol Case Rep. 2021;37:101617.
54. Kanchi P, Sambandam S, Siddhan R, Soundappan S, Vaseekaran VP, Gupta A. Successful kidney transplantation after COVID-19 infection in two cases. Nefrologia (Engl Ed). 2021.
55. Perlin DV, Dymkov IN, Terentiev AV, Perlina AV. Is kidney transplantation from a COVID-19-positive deceased donor safe for the recipient? Transplant Proc. 2021;53(4):1138–42.
56. Information C-. American Society of Transplantation.
57. Ritschl PV, Nevermann N, Wiering L, et al. Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: a by-proxy society recommendation consensus approach. Am J Transplant. 2020;20(7):1826–36.
58. Axelrod DA, Ince D, Harhay MN, et al. Operational challenges in the COVID era: asymptomatic infections and vaccination timing. Clin Transplant. 2021.
59. Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. N Engl J Med. 2021.
60. Safa K, Elias N, Gilligan HM, Kawai T, Kotton CN. Successful living kidney donation after COVID-19 infection. Transplantation. 2021;105(1):e4–5.
61. Koval CE, Poggio ED, Lin YC, Kerr H, Eltemamy M, Wee A. Early success transplanting kidneys from donors with new SARS-CoV-2 RNA positivity: a report of 10 cases. Am J Transplant. 2021.
62. Frattaroli P, Anjan S, Coro A, et al. Is it safe to perform abdominal transplantation from SARS-CoV-2 polymerase chain reaction positive donors? Transpl Infect Dis. 2021.
63. Puodziukaite L, Serpytis M, Kundrotaite A, et al. Kidney transplantation from a SARS-CoV-2-positive donor for the recipients with immunity after COVID-19. Transpl Infect Dis. 2021:e13666.
64. Sigler R, Shah M, Schnickel G, et al. Successful heart and kidney transplantation from a deceased donor with PCR positive COVID-19. Transpl Infect Dis. 2021;n/a(n/a).
65. Tuncer A, Akbulut S, Baskiran A, et al. A recipient and donor both have COVID-19 disease. Should We Perform a Liver Transplant? J Gastrointest Cancer. 2021.
66. Malleeswaran S, Mohanka R, Yalakanti RB, et al. Living donor hepatectomy after proven SARS-CoV-2 infection: first report of 9 cases from 3 centers. Transplantation. 2021;105(7):e70–1.
67. Manzia TM, Gazia C, Lenci I, et al. Liver transplantation performed in a SARS-CoV-2 positive hospitalized recipient using a SARS-CoV-2 infected donor. Am J Transplant. 2021.
68. Dhand A, Gass A, Nishida S, et al. Successful transplantation of organs from a deceased donor with early SARS-CoV-2 infection. Am J Transplant. 2021.
69. Barros N, Ermel A, Mihaylov P, Lacerda M, Fridell J, Kubal C. Deceased donor liver transplantation from a SARS-CoV-2 positive donor to a SARS-CoV-2 positive recipient. Liver Transpl. 2021.
70. Royo-Villanova Reparaz M, Dominguez-Gil B, Moreno Docón A, Cánovas López SJ, Pastor Pérez FJ, Ortín Freire AJ. Organ donor with PCR positive for SARS-CoV-2, it has been always no? Med Intensiva (Engl Ed). 2021.
71 Kim HJ, Shin DH, Cho WH, Kim D, Yeo HJ. Successful lung transplantation from a donor who had recovered from SARS-CoV-2 pneumonia. Ann Thora Surg. 2021. https://doi.org/10.1016/j.athoracsur.2021.06.045.