



## BRIEF COMMUNICATION

# Real-time transcription polymerase chain reaction cycle threshold values as criteria for utilization of incidental COVID-19 positive lung donors

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**KEYWORDS:**

lung transplant;  
COVID-19;  
donor selection;  
infection;  
survival

Shortage of organ donors is an ongoing limiting factor in lung transplantation (LT). Despite increasing prevalence of asymptomatic COVID-19 infection, positive COVID-19 testing from a potential donor remains a contraindication at many LT centers.

In this report, we present the outcomes of LT utilizing an algorithm based on donor clinical presentation, and COVID-19 real-time reverse transcription polymerase chain reaction (RT-PCR) with cycle threshold (Ct) values evaluation. The Ct value threshold for organ acceptance was  $>35$ . A total of 8 COVID-positive donors were included. No donor-to-recipient transmissions of COVID-19 were observed. Short-term outcomes were comparable to those reported in pre-COVID literature. Survival-to-date is 100% with median POD of 161 days. Our findings support the safety and efficacy of utilizing our algorithm including Ct value threshold for selection of donors with incidental COVID-19 positive testing.

J Heart Lung Transplant 000;000:1–4

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## Brief communication

The emergence of the COVID-19 pandemic placed significant strain on solid organ transplantation.<sup>1,2</sup> As a consequence of the pandemic in 2020, there was a decline in both the number of lung transplants (LTs) performed as well as the number of recovered lung donors.<sup>1</sup> A potential explanation is related to the safety of utilizing of COVID-19 positive donors due to the risk of transmission of COVID-19

infection.<sup>3</sup> Outcomes have been reported in other solid organs, yet there remains paucity of LTs described.<sup>2,4</sup>

Following 3 donor derived COVID-19 transmissions to LT recipients from donors with initial negative nasopharyngeal (NP) testing that retrospectively tested positive in lower respiratory tract (LRT) samples, the Organ Procurement and Transplantation Network (OPTN) required LRT SARS-CoV-2 testing for all potential lung donors. In its current iteration, the OPTN guidance on SARS-CoV-2 screening and donor organ acceptance identifies COVID-19 positive donors as low risk if the test was performed between 21 and 90 days after disease onset in the setting of resolved COVID-19.<sup>5</sup> For donors who test positive with no known history of infection, it is recommended that organs be considered for non-lung recipients only. However, these guidelines can decrease the number of organ acceptance

*Abbreviations:* LT, lung transplant; NP, nasopharyngeal; LRT, lower respiratory tract; Ct, cycle threshold; PGD, primary graft dysfunction; ACR, acute cellular rejection; DSN, donor sequence number

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without considering quality of the lungs and our evolving knowledge of COVID-19 risk of transmission and severe disease. Therefore, we present our center's experience utilizing an algorithm based on donor clinical presentation, and COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) with cycle threshold (Ct) values (Figure 1).

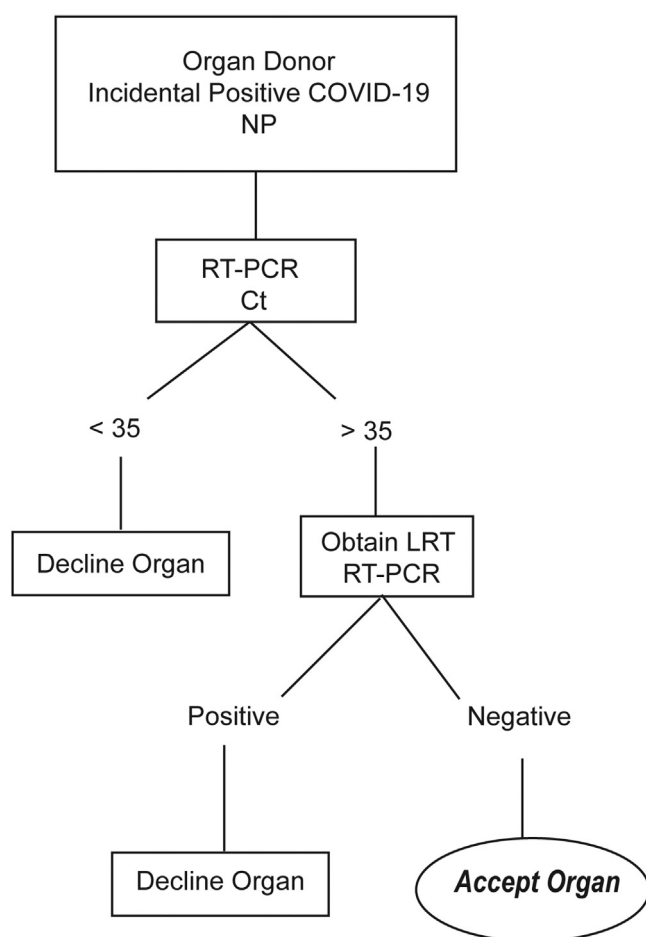
This is a single-center case series evaluating LT outcomes utilizing donors with incidental positive SARS-CoV-2 RT-PCR with Ct >35 via NP or LRT testing at any point during hospitalization between October 2021 and August 2022. SARS-CoV-2 RT-PCR testing per organ acceptance algorithm was ordered by the organ procurement organization as requested by our center and performed at the donor hospital facility. The primary outcome was COVID-19 transmission based on positive COVID-19 testing within 30 days of transplant. Secondary outcomes were primary graft dysfunction (PGD) grading at 72 hours,

incidence of acute cellular rejection (ACR), 30-day survival, and 90-day survival. All LT recipients had received vaccination against COVID-19 prior to listing and signed informed consent to the use of lungs from donors with COVID-19 RT-PCR Ct values >35.

As of October 30, 2022, there have been a total of 8 COVID-positive donors meeting criteria. Donor and recipient clinical characteristics are described in Table 1. All donors were male. Donor median age was 24.5 years (y) (range 17-32y) and median BMI was 27.9 (range 20.7-31.1). No donors had history of diabetes or smoking greater than 20 packs/y. The median donor sequence number (DSN), which represents the number of recipients to whom the organ had been offered prior to acceptance for transplantation, was 7.5 (range 1-75). All offers prior to acceptance (7 out of 8) had been declined due to NP COVID-19 positive testing. Median Ct value of SARS-CoV-2 RT-PCR testing was 36.4 (range 35.7-37.5), with 7 (87.5%) detected from NP sampling. Median number of days between positive donor testing and transplantation was 4 (range 3-5). Median number of chest imaging tests, including chest X-rays and at least 1 computed tomography, was 12 during donor admission. All images were reviewed by transplant surgeons and pulmonologist prior to acceptance. Cause of deaths included drug intoxication (2), motor vehicle accident (2), suicide (2), head trauma (1), and cardiovascular (1). All 8 LT recipients underwent bilateral lung transplants. The median age of LT recipients in years was 44.5 (range 34.5-50.3) and median lung allocation score (LAS) was 46 (range 37-85). There was no donor-derived COVID-19 transmission to recipients based on LRT SARS-CoV-2 RT-PCR testing post-transplant. At 72 hours, 3 (37.5%) developed Grade 1 PGD, 1 (12.5%) Grade 3 PGD, and 4 (50%) had no evidence of PGD. One recipient (12.5%) developed Grade A1 rejection. All recipients are alive to date, corresponding to 30-day survival of 100% for 8 recipients and 90-day survival of 100% for 7 thus far (Table 2).

There is currently no consensus for determining the safety of utilization of donors for LT with incidental positive COVID-19 testing. Only 2 LTs have been described at a single center, where donor eligibility required initial positive NP testing to be >20 days from procurement and a negative LRT testing.<sup>6</sup> However, it does not include evaluation of the cycle threshold (Ct) value. In fact, Ct values are presently not recommended for assessment of infectivity by the Centers for Disease Control and Prevention and the Food and Drug Administration due to test variability.<sup>6,7</sup> However, other single center experiences using Ct threshold greater than 35 have reported successful organ transplantations.<sup>7,8</sup> Ct values represent the number of amplification cycles needed on a RT-PCR sample to breach the threshold for positivity. They have been inversely correlated to viral load and mortality and used clinically to reduce isolation period for COVID-19 infected individuals.<sup>6,9</sup>

Our experience based on an evaluation of the RT-PCR Ct values contributes to the available evidence of safety of utilizing donors with incidental positive COVID-19 testing. Across our 8 cases, all donors had Ct values greater than 35, a threshold that has been shown to correlate with inability to detect culturable virus.<sup>5</sup> Based on our algorithm, only



**Figure 1** Algorithm for organ evaluation for lung transplantation in donors with incidental positive COVID-19 testing. For donors with incidental positive COVID-19 testing by NP swab, evaluation of the Ct was completed. If Ct threshold was < 35, organ was declined. If Ct threshold was >35, LRT testing was performed. If LRT RT-PCR was positive, organs were declined. If the LRT RT-PCR was negative or met Ct threshold >35, organ would be accepted. LRT = lower respiratory tract; NP = nasopharyngeal swab; Ct = cycle threshold; RT-PCR = reverse transcriptase polymerase chain reaction.

**Table 1** Donor and Recipient Characteristics

Case	Donor									Recipient				
	Age (y)	Sex	BMI	Cause of death	P/F ratio at offer	CT chest	NP Ct	LRT Ct	Time to transplant (d)	Age (y)	Sex	Disease	LAS	Offers prior to acceptance
1	29	M	31.6	Drug intoxication	408	Ground-glass and patchy alveolar opacities are present within RUL and bilateral lobes	35.8	Negative	5	45	M	PF	38	11
2	20	M	20.7	MVA	520	Patchy infiltrate in LUL. Ground-glass infiltrate in LLL	39.3	Negative	6	68	M	IPF	37	12
3	17	M	25.6	Suicide	496	Mild dependent aspiration and atelectasis.	35.3	Negative	4	35	M	COVID-19 PF	94	21
4	19	M	31.1	Suicide	457	Dependent atelectasis is present at RLL	36.7	Negative	2	51	F	NSIP	49	4
5	32	M	25.0	Cardiovascular	539	Minimal ground-glass density in RUL. Minimal atelectasis in LLL	Negative	35.12	3	50	M	PH	43	75
6	18	M	30.9	Head trauma	485	Consolidation in RLL. A small dependent left basilar consolidation is also present.	36.1	Negative	4	33	F	PF	94	1
7	30	M	23.3	MVA	419	Minimal bilateral effusion, no opacities	37.1	Negative	7	44	M	IPF	37	4
8	29	M	30.1	Drug intoxication	447	Consolidation in RLL, scattered small consolidation LLL	38.6	Negative	3	27	F	PH	82	2

Abbreviations: Ct, cycle threshold; IPF, idiopathic pulmonary fibrosis; LAS, lung allocation score; LLL, left lower lobe; LRT, lower respiratory tract; LUL, left upper lobe; MVA, motor vehicle accident; NP, nasopharyngeal; NSIP, nonspecific interstitial pneumonia; PF, Pulmonary fibrosis; PH, pulmonary hypertension; RLL, right lower lobe; RUL, right upper lobe.

**Table 2** Outcomes After Lung Transplant

Case	Surgery	COVID-19 transmission	PGD at 72 h	ACR	Postoperative			Status
					ICU LOS	Hospital LOS	Days To date	
1	Bilateral	N	1	A1	11	13	330	Alive
2	Bilateral	N	0	N	3	12	205	Alive
3	Bilateral	N	0	N	4	26	176	Alive
4	Bilateral	N	0	N	7	12	146	Alive
5	Bilateral	N	3	N	11	49	120	Alive
6	Bilateral	N	0	N	30	53	95	Alive
7	Bilateral	N	1	N	6	12	64	Alive
8	Bilateral	N	1	N	14	21	225	Alive

Abbreviations: ACR, acute cellular rejection; ICU, intensive care unit; LOS, length of stay; PGD, primary graft dysfunction.

8 potential donors were evaluated. We believe that performing LRT COVID-19 RT-PCR to rule out infection in appropriate donors, such as those with incidental positive NP COVID-19 positive RT-PCR with a Ct greater than 30, normal P/F ratio and benign chest imaging, could potentially increase the donor pool even further. While most (7 of 8) tested positive by NP RT-PCR alone with negative LRT testing, it should be noted that 1 donor had negative NP testing and subsequent LRT positivity with Ct value above 35. We thus did not make a distinction between NP or LRT source if Ct value threshold >35 was met and did not decline donors due to lack of prior COVID testing data if initial RT-PCR positivity was within 20 days of procurement. We observed that the donors' causes of death are attributed to circumstances that often pose a practical challenge to ensuring adequate time from initial positive testing to organ procurement as proposed under current OPTN guidelines. Ct may therefore represent a surrogate for consideration for donor organ risk stratification in case of incidental COVID-19 positive RT-PCR, as proposed in Figure 1. Since positive RT-PCR by LRT with negative NP testing was represented by only 1 donor during the study period, the donor selection algorithm we put forth in Figure 1 utilizes positive NP RT-PCR alone (Ct value >35) as initial criteria.

Our study has limitations. First, our experience is small with only 8 LTs. Second, donor clinical information was limited to data obtained by organ procurement organizations. However, there were no cases of COVID-19 donor transmission and no mortality to date. Moreover, we noted similar rate of PGD to what is reported in literature.<sup>10</sup> These results should be interpreted cautiously but they support a reassessment of current recommendations for donor lung acceptance to maximize donor utilization as incidental COVID-19 positive testing is expected to increase.

## Disclosure statement

The authors of this publication have no conflicts of interest or financial considerations to disclose.

J.H., A.Y., L.Z., and R.R. contributed to the analysis and drafted the manuscript. All other authors revised the manuscript and approved the final version. R.R., P.Z., P.D. and D.J.M. contributed to the planning of the study.

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