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CASE REPORT

Lung donation following SARS-CoV-2 infection

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There have been over 177 million cases of COVID-19 worldwide, many of whom could be organ donors. Concomitantly, there is an anticipated increase in the need for donor lungs due to expanding indications. Given that the respiratory tract is most commonly affected by COVID-19, there is an urgent need to develop donor assessment criteria while demonstrating safety and "efficacy" of lung donation following COVID-19 infection. Accordingly, we report an intentional transplant using lungs from a donor with recent, microbiologically confirmed, COVID-19 infection into a recipient suffering from COVID-19 induced ARDS and pulmonary fibrosis. In addition to the standard clinical assays, both donor and recipient lungs were analyzed using RNAscope, which confirmed that tissues were negative for SARS-CoV-2. Immunohistochemistry demonstrated colocalized *KRT17*+ basaloid-like epithelium and *COL1A1*+ fibroblasts, a marker suggestive of lung fibrosis in COVID-19 associated lung disease, in the explanted recipient lungs but absent in the donor lungs. We demonstrate that following a thorough assessment, lung donation following resolved COVID-19 infection is safe and feasible.

KEYWORDS
clinical research/practice, donors and donation, lung transplantation/pulmonology, lung transplantation: living donor

1 | INTRODUCTION

The COVID-19 pandemic has led to concerns related to lung donation following SARS-CoV-2 infection. Here, we describe an intentional lung transplant from a donor with resolved COVID-19 infection into a recipient suffering from severe COVID-19.

2 | CASE PRESENTATION

2.1 | Recipient

A 65-year-old man with severe COVID-19 acute respiratory distress syndrome (ARDS) in May 2020 required mechanical ventilation and extracorporeal membrane oxygenation (ECMO) but was weaned after a protracted medical course and discharged to a long-term care hospital. At 6 months following the original diagnosis, he developed combined hypoxemic and hypercapnic respiratory failure requiring readmission. He was unable to be weaned from the ventilator due to poor lung compliance from progressive pulmonary fibrosis (Figure 1A–D). The patient was referred for lung transplantation approximately 9 months after illness onset and underwent two negative COVID-19 PCRs from bronchoalveolar fluid (BAL), 24 h as part of the transplant evaluation. He was awake, interactive, and participating in physical therapy at the time of listing, while being supported on the mechanical ventilator, consistent with our recent publications.[1,2]

2.2 | Donor

The donor was a woman in her 40s who was a social smoker and who sustained brain death due to a drug overdose. She had developed mild

Abbreviations: ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar LAVAGE; ECMO, extra corporeal membrane oxygenation; PCR, polymerase chain reaction.

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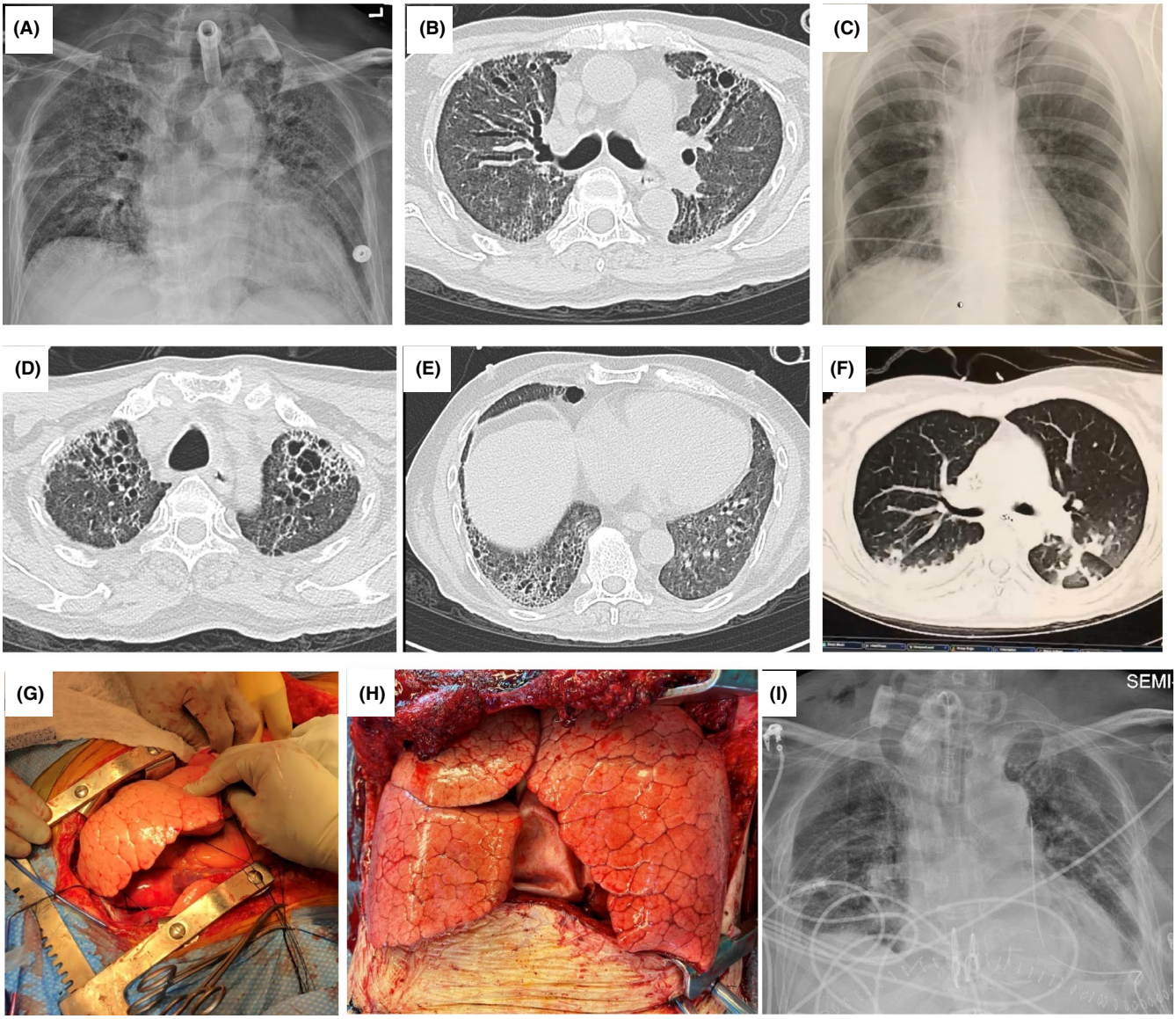

FIGURE 1 Assessment of recipient and donor lungs. (A–D) Pre-transplant chest radiograph and computed tomography of the recipient demonstrating honeycombing and pulmonary fibrosis. (E, F) Donor lung images showing normal radiograph and mild bibasilar atelectasis with signs of aspiration in left lung. (G) Intraoperative donor lung assessment demonstrating normal compliance and no gross fibrosis. (H) Normal lung compliance and gross appearance of donor allograft following implantation. (I) Chest radiograph of the donor allografts a week following implantation

COVID-19 with cough and fevers, confirmed positive by PCR of nasopharyngeal swab 7 weeks prior to the donation. At the time of donation, bronchoscopy revealed petechial airway hemorrhage and airway cultures were positive for *Staphylococcus aureus* (100 000 colonies/ml). Chest radiograph was clear and computed tomography showed mucous plugging, bibasilar atelectasis, and patchy opacities, concerning for aspiration (Figure 1E,F). No evidence of pulmonary fibrosis or interstitial lung disease was noted. The PaO2/FiO2 ranged from 280 to 474. Both nasopharyngeal swab and BAL tested negative for SARS-CoV-2 by PCR.

2.3 | Intraoperative donor assessment

Donor lung pulmonary compliance was normal. On manual palpation, there was no scarring noted on the parietal pleura (Figure 1G). Selective venous sampling revealed a PaO2/FiO2 ratio of greater than 300 in all four pulmonary veins. Lungs were procured in a standard manner using Perfadex solution (Xvivo) and transported over ice.

2.4 | Transplant procedure

The recipient underwent standard consent process then underwent sequential double lung transplantation using clamshell thoracotomy. Central veno-arterial ECMO was performed using atrial and aortic cannulation. The procedure was technically challenging due to extensive pleural scarring and bulky hilar lymphadenopathy. The recipient had severe pulmonary hypertension (88/64 mm Hg) with moderate right ventricular dysfunction. Total ischemic time was 245 min for the left lung and 340 min for the right. The patient received 6 units of

packed red blood cells. Upon completion of the procedure, the patient was successfully weaned off ECMO and demonstrated good allograft function (Figure 1H,I). There was no evidence of primary graft dysfunction, however, he was empirically treated with three cycles of plasmapheresis, three doses of eculizumab (1200 mg after 1st cycle of plasmapheresis, 900 mg after 2nd cycle, and 600 mg after 3rd cycle), and one dose of rituximab (600 mg) for a positive retrospective crossmatch for HLA B7 (PRA 9% for class I and 0% for class II). Standard induction therapy was administered: basiliximab (20 mg) at post-operative day 0 and 4 and intravenous methylprednisolone (1000 mg) prior to reperfusion of the allograft. Additionally, the patient received three-drug immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone. His post-operative course was complicated by the development of bilateral pleural effusions necessitating image-guided chest tube placement at 3 weeks post-operative. By post-operative day 27, he was weaned off the ventilator and decannulated. On day 40, he was awaiting placement to an inpatient rehabilitation center and breathing room air. On multiple bronchoscopic sampling on days 1, 3, 7, 14, 21, 30, and 35, there was no recurrence of SARS-CoV-2 or other nosocomial pathogens in the allografts.

2.5 | Histological assessment

While donor lungs were normal, explanted native lungs revealed interstitial fibrosis (Figure 2A–E), microcysts with histiocytic reaction (Figure 2F), honeycombing (Figure 2G), with acute and chronic inflammation (Figure 2H,I). Using RNAscope,[2] we found no evidence of SARS-CoV-2 in the donor lungs (Figure 3). We performed immunohistochemistry for the presence of colocalized *KRT17*+ basaloid-like epithelium and *COL1A1*+ fibroblasts[2] in the distal lung parenchyma. While the explanted lungs showed extensive KRT17/COL1A1 colocalization, the donor lungs did not (Figure 3).

3 | DISCUSSION

As of June 2021, over 34 million cases of COVID-19 have been documented in the United States. Additionally, thousands of new cases are diagnosed daily. While non-pulmonary transplants have been performed from COVID-19 positive donors,[3–5] given the uncertainties pertaining to lung damage and risk of transmission, there are

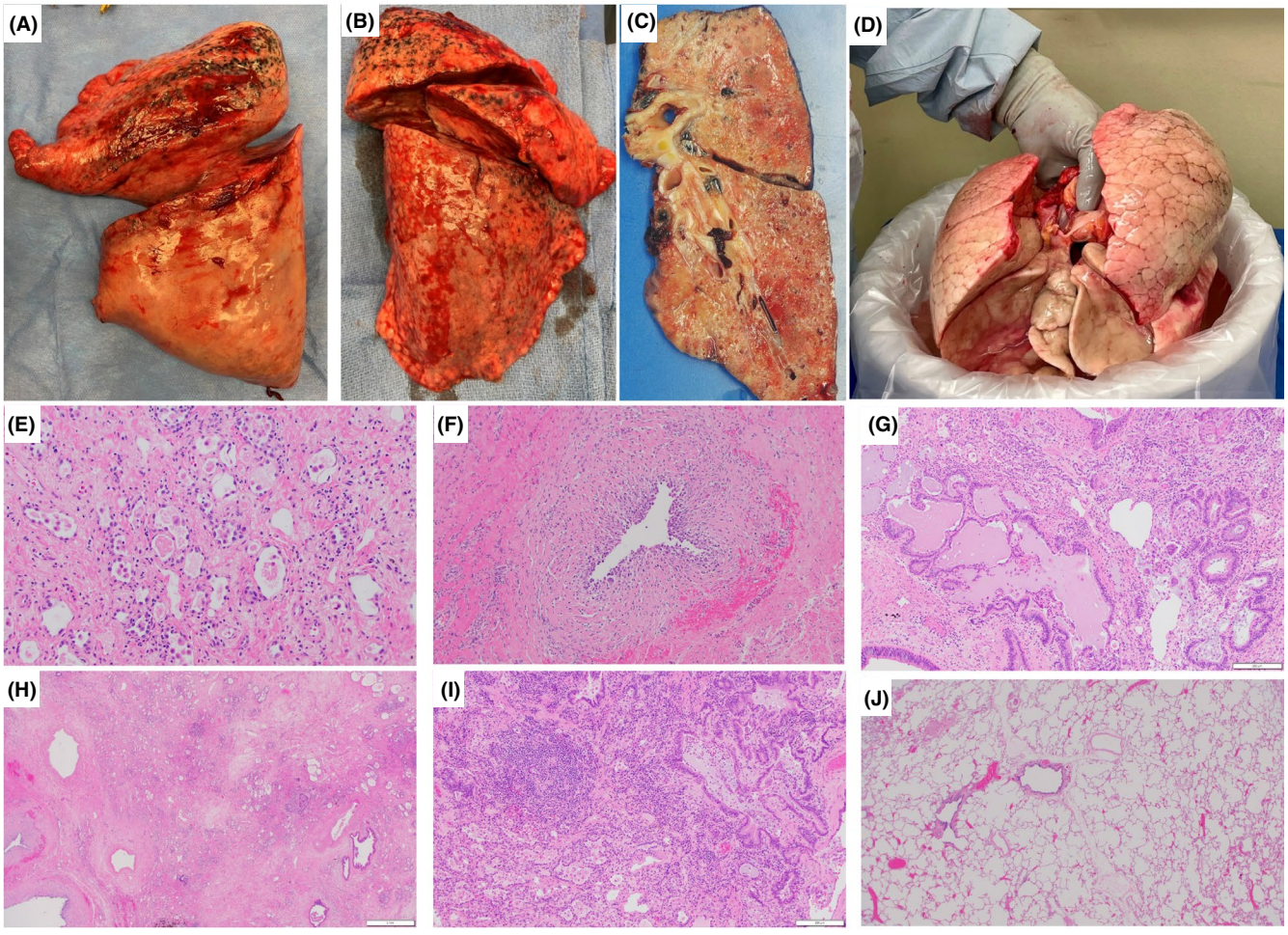

FIGURE 2 Pathological examination of native and donor lungs. (A–C) Gross appearance of the explanted native lungs showing fibrosis and honeycombing. (D) Normal appearance donor lung allografts prior to cold storage. Histological assessment of the explanted lungs showed (E) interstitial fibrosis (200x), (F) microcysts with histiocytic reaction (100x), (G) microscopic honey comb changes (100x), (H) diffuse interstitial fibrosis (20x), (I) acute and chronic inflammation (100x), while the donor lung was normal (J)

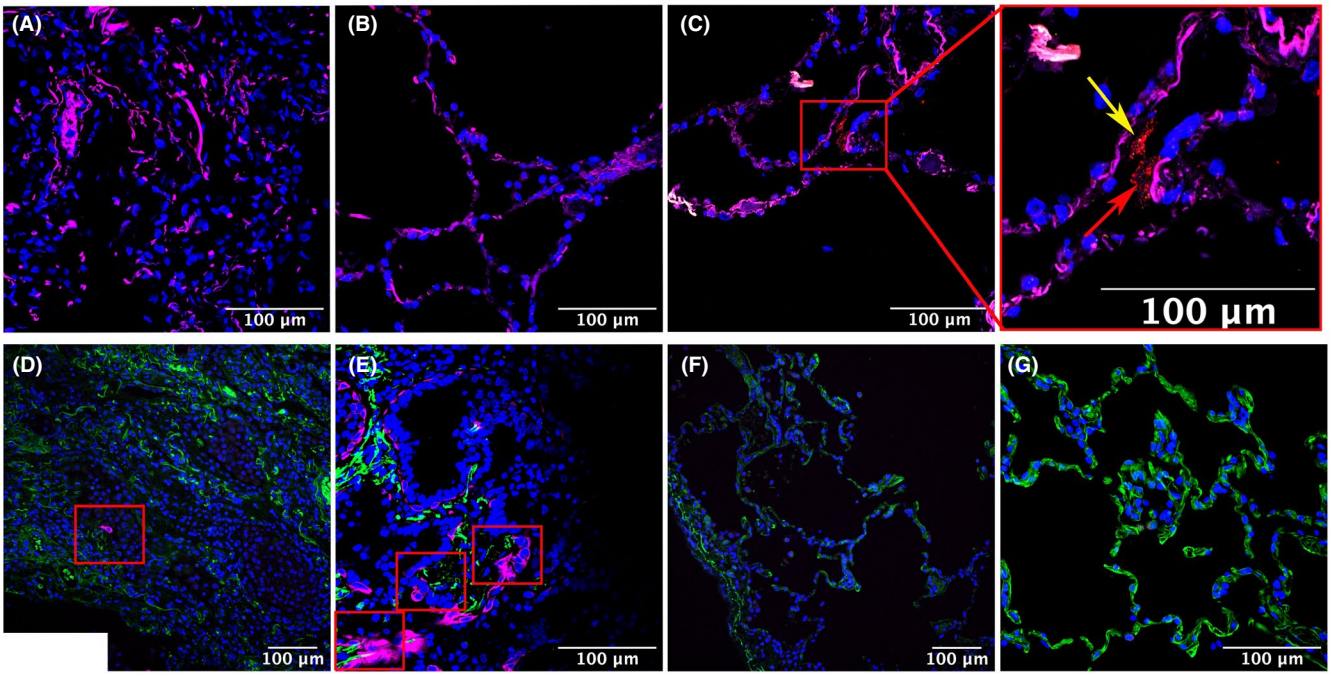

FIGURE 3 RNAScope and IHC of native and donor lung tissue. (A–C) RNAScope of the explanted native lung (A) and implanted donor lung (B) in comparison to autopsy lung tissue from a patient who died of COVID-19 as a positive control (C). Nuclear staining (blue), positive strand SARS-CoV-2 RNA (red), negative strand SARS-CoV-2 RNA (yellow). Positive strand SARS-CoV-2 RNA was detected in the positive control denoted by a red arrow with rare negative strand SARS-CoV-2 RNA denoted by a yellow arrow in epithelial cells. Neither positive or negative RNA was found in the implanted or explanted lung tissues. (D–G) Immunofluorescence microscopy of KRT17 (magenta) and COL1A1 (green) of the explanted lung (D and E) and implanted donor lung (F and G). Immunofluorescence microscopy revealed Krt17+ cells colocalized with Col1a1+ fibroblasts in the distal parenchyma of the explanted lung tissue without normal airway architecture (red box). KRT17 staining was absent in the donor lung tissue

concerns amongst transplant centers with regard to the utilization of lungs from patients with history of COVID-19. In particular, since the respiratory tract presumably carries the highest viral burden of SARS-CoV-2, lung donation is considered to have increased risk for transmission. Indeed, the concerns about donor to recipient transmission during lung transplantation are highlighted in recent reports where an adverse outcome occurred with the use of lungs from a donor who was tested negative for SARS-CoV-2 by nasopharyngeal swab but later found positive in the bronchoalveolar lavage fluid.[4,6] The seriousness of donor-derived SARS-CoV-2 transmission during lung transplant was manifested not only in the risk to the recipient but also to the transplanting team since the surgeon in one of the reports also contracted COVID-19.[4]

Considering the wait-list mortality of lung transplant recipients combined with such a large burden of COVID-19 disease, it is impractical to exclude donors with previous COVID-19 infections from donation. Furthermore, there is an anticipated increase in need for donor lungs as more cases of COVID-19 associated lung injury and ARDS are being considered for lung transplant across the globe. Hence, it is important to develop a thoughtful approach for the utilization of lungs from COVID-19 donors. To date, there are no known reports of intentional lung transplantation using lungs from donors with prior COVID-19 infection in the United States, although there was a recent report from Belgium proposing that this approach may be safe.[7] In that report, lungs from a donor reported to have exposure to SARS-CoV-2 three months prior to organ procurement, along with positive serology one day prior to organ procurement, were successfully utilized.[7] While donor nasopharyngeal PCR was negative the authors reported a positive donor SARS-CoV-2 PCR from a peripheral lung biopsy obtained at the time of transplant, approximately 3 months after exposure. Concomitant viral culture was negative. In our donor, there was both microbial as well as symptomatic confirmation of COVID-19 and our recipient showed no recurrence of SARS-CoV-2. Together, these reports support the safety and feasibility of such lung donations. At our institution, recipients of such lungs undergo the same consent process as those receiving lungs from COVID-naïve donors. Additionally, we do not restrict the use of lung donation after COVID-19 only to recipients with severe COVID-19.

The UNOS/OPTN has summarized current evidence for SARS-CoV-2 testing for lung donors (https://optn.transplant.hrsa.gov/media/4424/sars-cov-2-summary-of-evidence.pdf) which suggests that lower respiratory fluid assessment is important to reduce donor to recipient transmission of SARS-CoV-2. SARS-CoV-2 replication and shedding in the upper respiratory tract is found in the early stages of COVID-19, however, the vast majority of the viral receptor ACE2 is found in the lower respiratory tract and peripheral lung.[8] Studies have shown that the lower respiratory tract can test positive for a much longer duration compared to upper respiratory tract which could explain the discordance of a negative nasopharyngeal

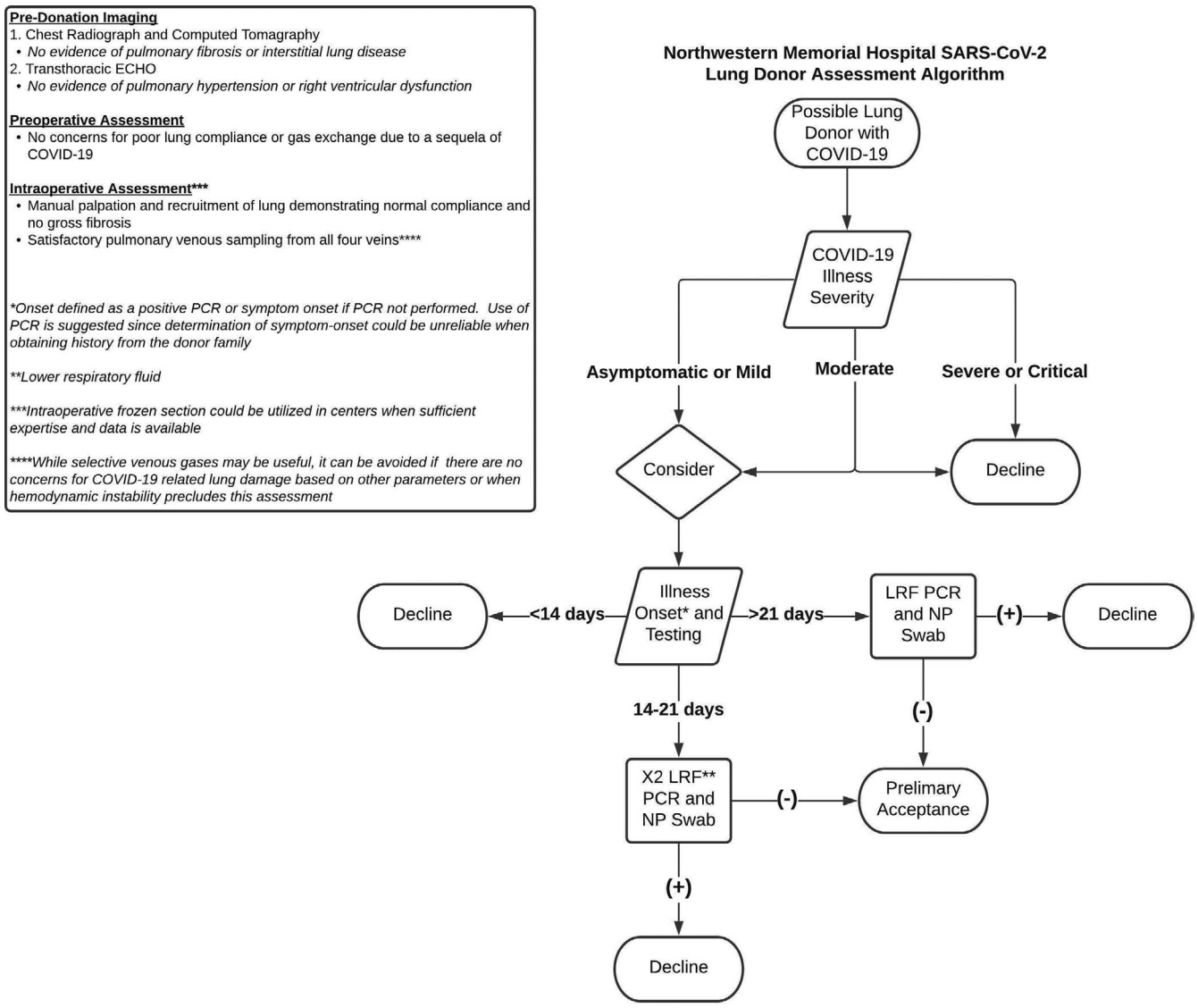

FIGURE 4 Institutional practice for assessment of lungs from donor with historic COVID-19

swab with a positive BAL fluid.[4] These findings support the importance of a lower respiratory tract testing for lung donors. Such testing can certainly lead to unnecessary discard of the organ if the test is falsely positive. Hence, in the circumstances of a positive test when pre-test probability of transmissible COVID-19 infection in the donor is low or when the cycle threshold (Ct), a value inversely proportionate to the amount of target nucleic acids in the samples, is high, our institutional practice is to repeat the test to reduce the likelihood of false positivity and mitigate organ discard.

Our donor had mild COVID-19 infection seven weeks prior but was subsequently tested negative for SARS-CoV-2 using the nasopharyngeal swab. However, viral shedding has been reported for extended durations.[8,9] Since the nasopharyngeal swab may not exclude replication-competent virus in the lungs, as evident by recent report,[4] we performed bronchoscopic sampling for SARS-CoV-2 prior to acceptance of donor lungs, consistent with the recent (UNOS/OPTN policy https://optn.transplant.hrsa.gov/media/4576/policy_notice_lunglowerrespiratorytesting_20210426.pdf). Indeed, testing the lower respiratory fluid for donors with prior COVID-19 infection remains our approach for all cases, regardless of the time frame of infection. For this case, we additionally confirmed viral clearance using RNAscope analysis of lung allograft.[2] RNAscope is a highly sensitive in-situ method to detect RNA transcripts down to the single cell level as a post-transplant confirmation but would not serve well as a rapid detection system for donor assessment.

Based on the current evidence, the UNOS/OPTN document suggests that the donor to recipient transmission is unlikely when a previously infected donor is between 21–90 days of symptom onset. Whether to accept lungs from donors who test positive for SARS-CoV-2 PCR after 21 days remains debatable. Since viral cultures are currently unavailable at our center and conclusive evidence of infectivity in the setting of positive lower respiratory culture viral culture is lacking, we do not accept donor lungs if the lower respiratory fluid COVID-19 PCR remains positive on repeat testing. Nevertheless, we recognize that medical urgency of recipients might compel centers to use lungs in the setting of positive COVID-19 PCR if the clinical judgement suggests

that the transmission risk is negligible. Furthermore, these suggestions might not be applicable to non-pulmonary transplants where the risk of transmission of COVID-19 is much lower.

It is known that SARS-CoV-2 causes lung damage.[2,10,11] While lung injury might improve, respiratory impairment and diffusion restriction can persist.[12–15] In general, the SARS-CoV-2 induced lung injury is associated with pulmonary findings of fibrosis on computed tomography. Accordingly, our donor assessment included computed tomography, determination of lung compliance, and blood gases prior to the organ acceptance (Figure 4). At the donor site, we also performed manual palpation of the organs, selective venous sampling of all four veins, and assessment of lung compliance. We also performed intraoperative frozen section analysis of lung tissue. This was analyzed by both the pathologist of the donor hospital and our institution, confirming normal architecture. Nevertheless, we have found that such a frozen section analysis can be conflicting as inconsequential and frequently observed mild non-specific interstitial pneumonitis may be confused by resolving or active COVID-19 related lung injury resulting in the unnecessary discard of the organs (data not shown). Hence, we suggest that the assessment of donor lung quality be made using non-histological criteria. We recently found that presence of an intermediate basaloid-like epithelial cell, characterized by *KRT17*+, when colocalized next to *COL1A1*+ fibroblasts in the distal lung parenchyma can suggest irreversible pulmonary fibrosis.[2] This colocalization signifies aberrant and irreversible epithelial repair after lung damage such as COVID-19 pneumonia. While the explanted donor lungs were replete with *KRT17*+ cells, the donor lungs were negative (Figure 2). This, combined with histological assessment of the allograft, confirms that carefully selected donor lungs with prior COVID-19 infection can have normal architecture. We have summarized our institutional guidelines (Figure 4), based on literature review, UNOS/OPTN guidelines, and our center-specific practices, which are used to assess lungs from select donors with prior, mild COVID-19 infection. We acknowledge that practices will change as more data becomes available.

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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 from the corresponding author upon reasonable request.

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