

ORIGINAL ARTICLE

Current precautions and future directions in lung transplantation during the COVID-19 pandemic – a single center cohort study

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SUMMARY

The unprecedented public health emergency caused by the acute viral respiratory coronavirus disease (COVID-19) has drastically changed current practices in solid organ transplantation, markedly so for transplantation of the lungs, the major target of the virus. Although national and state authorities do not recommend postponing transplant procedures, most specialists are reluctant to proceed due to substantial uncertainty and increased risks in the midst of the pandemic. There is an urgent need for evidence-based directions to move forward. Here, we offer our insights as specialists at a high-volume center located in a geographical area with high infection rates.

Transplant International 2020; 33: 1453–1457

Key words

computed tomography, COVID-19, donor selection, health personnel, infectious disease transmission, lung transplantation, pandemic, recipients selection

Received: 29 April 2020; Revision requested: 25 May 2020; Accepted: 29 June 2020; Published online: 22 September 2020

Introduction

The unprecedented public health emergency of the novel coronavirus disease COVID-19 has drastically changed clinical practice in solid organ transplantation, markedly more so for transplantation of the lungs, the major target of the virus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). On March 18, 2020, the Centers for Medicare and Medicaid Services (CMS), a division of the United States Department of Health and Human Services, announced that all elective surgeries, nonessential medical procedures, and nonessential surgical procedures should be delayed during this COVID-19 outbreak, but the CMS identified

transplants as Tier 3b procedures that should not be postponed [1]. Nonetheless, most specialists are reluctant to proceed due to substantial uncertainty and increased risks in the midst of the pandemic.

There are significant limitations both in available treatments when patients suffer from COVID-19 and in the fundamental transplant selection and screening processes established to optimize patient safety and transplant outcomes during the COVID-19 epidemic. Validation of screening processes and decisions to proceed to transplant have been deferred to transplant programs, which must quickly adapt. There is an urgent need for evidence-based recommendations to move forward. Here, we offer our insights as specialists at a

high-volume center located in a geographical area with high COVID-19 infection rates.

Initial experiences in patients with lung transplantation complicated by COVID-19 at Temple University Hospital

Philadelphia, the largest city in the state of Pennsylvania, is a hotspot of COVID-19 infection in the United States with >6000 confirmed cases and ~500 deaths attributed to COVID-19 as of April 14, 2020, when there were ~614 000 cases and ~26 000 deaths nationwide in the United States. Temple University Hospital (TUH) is located in the heart of Philadelphia and is treating the more patients with COVID-19 than any other hospital in the region.

As of April 14, 2020, TUH had performed 43 lung transplants in 2020, consistent with the fact that we have done more lung transplants than any other transplant center in the United States for the past 3 years [2]. In March 2020, when the number of reported diagnosed cases of COVID-19 started to soar nationally, we transplanted lungs into 17 patients at TUH. Serious complications and death due to transmission of COVID-19 occurred in 2 of the 17 patients (11%). A 75-year-old, single-lung transplantation recipient tested positive for COVID-19 by nasal-swab testing on post-transplant day 6 after he became progressively hypoxic with a low grade fever. A chest computed tomography (CT) scan demonstrated multifocal ground-glass opacities (GGOs) in his transplanted lung. His clinical condition improved after reduction of immunosuppressant therapy and administration of anti-viral medications (Remdesivir: enrolled in a clinical trial) coupled with pulse-dose steroids; however, he developed acutely decompensating sepsis and died on post-transplant day 11. A 73-year-old single-lung transplant recipient with concurrent coronary artery bypass grafting surgery complained of acute abdominal pain and was diagnosed with acute pancreatitis after he was discharged from the intensive care unit. A chest CT scan, which was performed concurrently with an abdominal CT to diagnose his pain, showed GGOs in his native lung although he was asymptomatic from a respiratory standpoint. Nasal-swab testing was positive for COVID-19 on post-transplant day 13. Subsequently, he became hypoxic. He responded well to Remdesivir coupled with pulse-dose steroids and improved significantly from respiratory standpoints back on the baseline with a nasal cannula with 2 l oxygen maintaining oxygen saturation of 96–98%. However, his acute pancreatitis recurred,

developed progressively, and eventually died of extensive necrotizing pancreatitis on post-transplant day 30.

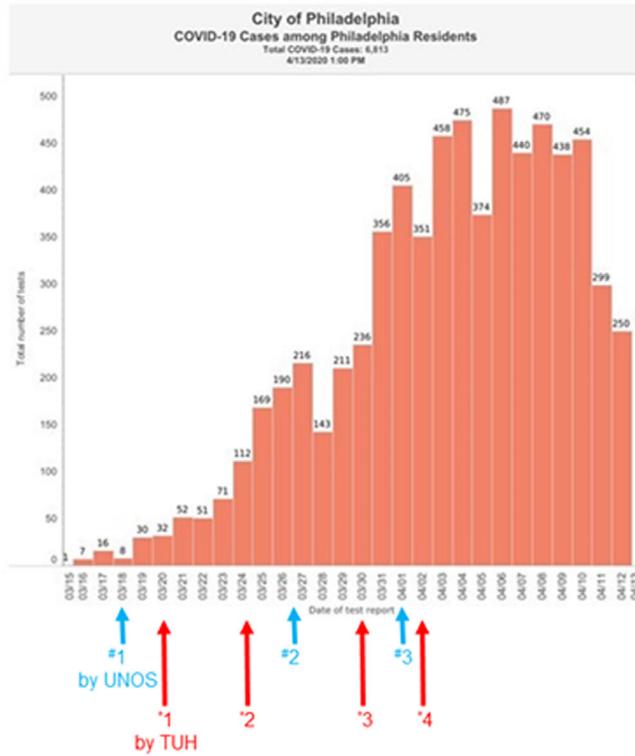
Three additional patients who underwent transplantation in March 2020 were readmitted to TUH due to respiratory symptoms suspicious for COVID-19 but were negative in nasal-swab testing. One demonstrated significant GGO in high-resolution CT (HRCT) imaging. After observation, he was eventually discharged without treatment because his pulmonary function did not decline.

How to safely proceed with transplants: selection of donor and recipient

Given the soaring number of COVID-19 cases locally and nationally, and after encountering the two mortalities due to the COVID-19 discussed above, we have recently become more cautious of proceeding with lung transplantation. The United Network for Organ Sharing (UNOS) has continued to provide recommendations for safely continuing with the clinical practice of solid organ transplantation [3]. We have taken the UNOS updates into consideration and modified our programmatic directions in hopes of safely allowing patients to proceed to transplantation (Fig. 1). We are selecting donors and recipients on a case-by-case basis and limiting travel of our procurement teams.

Although COVID-19 nasal-swab nucleic acid tests currently play an important role in screening patients with suspicious viral infection, they have evident limitations that have been well demonstrated [4,5]. Testing limitations limit our ability to identify recipients and donors who have not been exposed to COVID-19 recently and who are not actively infected. We stress the importance of imaging via HRCT to screen for GGO. This is supported by recently published reports from China [6,7]. Imaging to identify GGOs should be performed to achieve a comprehensive diagnosis of COVID-19 when combined with the currently available testing, clinical symptoms, and epidemiological history, which includes direct or indirect exposure to viral transmission. Of note, while small patchy GGO and consolidations are the main HRCT signs of COVID-19 infection, one report alluded to the differences in HRCT imaging features in patients of different ages. Imaging in younger patients with COVID-19, such as adolescents, yielded fewer and smaller GGO lesions as compared with those in middle-aged and older patients with COVID-19 [8]. We should keep this in mind when evaluating lungs from young donors even in the presence of excellent lung function.

Local, confirmed cases with Action Plans for Transplants



UNOS

- March 18 (#1)
Code and status changes for the candidates
Inactivating transplant programs
- March 20
Referred to CMS guidelines for transplant surgery
- March 24 (#2)
Patient safety reporting
- March 28 (#3)
Recommended surgical recovery of organs by local teams

Temple University Hospital Lung Transplant Program

- March 19 (*1)
 - Limited the organ offers to locally and selected import OPOs
 - Included GGO evaluation with HRCT for donor assessment
- March 24 (*2)
 - Included confirmed PCR test result in donor assessment
 (March 25, the 1st COVID-positive patient posttransplant)
- March 30 (*3)
 - Required both PCR test result and stat HRCT for candidates when admitted for transplants
 (April 1, the 2nd COVID-positive patient posttransplant)
- April 2 (*4)
 - Classified stable patients older than 70 as temporarily inactive

Figure 1 Timeline of cases and actions.

We propose the following screening process based on our recent experiences (Fig. 2). For donors, a thorough clearance of epidemiological history including direct or

indirect exposure to individuals suspicious for COVID-19 is crucial. This should include evaluation of their possible exposure to other patients as well as to medical

Proposed Screening/Evaluation Process when proceeding to transplant

Donors

- Clinical backgrounds and epidemiological history free of COVID-19 exposure
- Confirmed negative PCR from a nasal swab +/- BAL within 48 hours
- Negative GGO evaluation in HRCT within 24–48 hours

Recipients

- Clinical backgrounds and epidemiological history free of COVID-19 exposure
- Confirmed negative nasal swab PCR at the time of admission*
- Confirmed negative GGO in HRCT after admission

*will need earlier admission +/- possible request for delay for cross clamp

Figure 2 Screening process for donors and recipients.

professionals after the hospital admission when they become a donor. Ideally, a nasal-swab nucleic acid test result that is negative for COVID-19 should be confirmed or updated 24–48 h prior to organ offers. Lower respiratory tract specimens, in particular bronchoalveolar lavage (BAL) samples, are advocated by some experts to have higher yield, and thus, the diagnostic value may be higher; however, due to high viral load, the aerosol-generating procedure may carry a higher risk to staff. Therefore, BAL sample collection should be determined with careful consideration and not included in the mandatory screening process at this point in time. The absence of GGO lesions in HRCT also should be confirmed through imaging updated 24–48 h prior to offering donated organs. For recipients, we advocate the importance of a dual-screening process with the PCR diagnostic panel and HRCT imaging. The timing is more involved and sensitive for recipient screening as compared with donor screening. Recipient screening needs to be completed after their admission for a possible transplant and completed by the time of organ procurement. Although ambitious, this can be achieved with well-coordinated institutional multidisciplinary collaboration and has been proven through our recent experiences at TUH. Currently, HRCT for lung transplant screening can be done within one hour of admission, and the PCR test results are to be confirmed within 3 h at most when a special request is made for transplant screening.

Among transplant programs, there has been ongoing debate regarding the appropriate selection of the recipients on the current waiting list who should proceed to transplant during the COVID-19 pandemic. However, in our view, this is not the primary issue to be determined programmatically. It should be discussed after establishing a solid and reliable screening process as is detailed above. We are continuing to prioritize by lung

allocation score (LAS). We have heard through personal communications that some lung transplant programs are using an LAS-cutoff, for example LAS >45 or 50, to decide when to proceed with lung transplant given the risk-benefits balance during the current pandemic. We have not implemented a cutoff based on LAS.

How to care for patients who suffer from COVID-19 post-transplant

Despite the large number of lung transplants we performed in March 2020, we have not experienced any donor-derived COVID-19 complications to date. Acquired COVID-19 complications, including clinically suspicious infection based on HRCT imaging, occurred in 3 of our patients (3/17, 16%) with two mortality cases (11%). Currently, multiple treatment options for COVID-19 patients are available at our institution as one of the leading lung centers participating in clinical trials sponsored by the National Institutes of Health (NIH). While further experience is warranted to determine the effectiveness of these treatments, promising treatment options coupled with our multidisciplinary COVID specialists' expertise is needed if a lung transplant recipient acquires COVID-19 while they are heavily immunosuppressed. These strengths encourage us to safely proceed with lung transplantation under the tremendous challenges currently imparted by the COVID-19 pandemic.

Future directions: moving lung transplantation forward during the pandemic

Many questions remain unanswered, particularly regarding effective and timely testing and treatments including a COVID-19-specific vaccination, anti-viral therapies, and inhibition of potentially deadly cytokine storm

inflammatory cascades in the patients with heavily suppressed immune system. We must ask whether there are differences in COVID-19 incidence or response to potential treatments between lung transplant recipients with GGO in the transplanted lung versus native lung or among recipients with specific characteristics such as older age or comorbidities. Additionally, we reiterate the need to better understand the importance of diagnostic imaging. There is a potential downside of overvaluing the role of GGO findings in HRCT in determining donor or recipient suitability, as this may decrease the number of lung transplants performed during the epidemic. Currently, virus-related GGO cannot be differentiated from GGO due to benign pathologies that were not contraindications for lung donation prior to the pandemic. Evolving imaging techniques should facilitate more accurate stratification of GGO lesions by COVID-19 status leading to appropriate selection of the donor lungs.

During this unprecedented medical emergency of COVID-19 infection, it is important to keep abreast daily of all available updates regarding the pandemic toll and scientific advancements to fight the virus. However, we should also be cautious of being trapped in this flood of information, some of which are flawed and misleading causing an irrational fear of the virus. We believe by proactively implementing a multidisciplinary approach to patient care informed by scientific, translational, programmatic, and administrative insights we can overcome this unprecedented challenge.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have no conflicts of interest to declare.

REFERENCES

- Centers for Medicare and Medicaid Services. <https://www.cms.gov/newsroom/press-releases/cms-releases-recommendations-adult-elective-surgery-non-essential-medical-surgical-and-dental>. Last Modified March 18, 2020; Accessed April 17, 2020.
- Shigemura N, Toyoda Y. Elderly patients with multiple comorbidities: insights from the bedside to the bench and programmatic directions for this new challenge in lung transplantation. *Transplant Int* 2020; **33**: 347.
- COVID-19 and solid organ transplant. <https://unos.org/covid/>. Accessed April 17, 2020.
- Wang W, Xu Y, Gao R, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; **323**: 1843.
- To KK, Tsang OT, Leung WS, *et al*. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020; **20**: 565.
- Han R, Huang L, Jiang H, *et al*. Early clinical and CT manifestations of coronavirus disease (COVID-19) pneumonia. *AJR Am J Roentgenol* 2020; 1.
- Pan F, Ye T, Sun P, *et al*. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology* 2020; **295**: 715.
- Chen Z, Fan H, Cai J, *et al*. High-resolution computed tomography manifestations of COVID-19 infections in patients of different ages. *Eur J Radiol* 2020; **126**: 108972.