Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Published study, we note, first, that exclusion criteria might have been significant confounding factor for a number of reasons. In our study, we did not aim to assess clinical outcomes other than the passing comment in another brief correspondence. We do not believe asymptomatic COVID-19 was a significant confounding factor for a number of reasons. In our published study, we note, first, that exclusion criteria included “SARS-CoV-2 infection (presence of a positive polymerase-chain reaction assay result for SARS-CoV-2, and a history of suspected clinical SARS-CoV-2 infection.” Second, the issue of a potential confounding effect from asymptomatic COVID-19 is highlighted and discussed in our study limitations: “We did not longitudinally routinely perform polymerase-chain-reaction testing for SARS-CoV-2, which could have resulted in underdiagnosis of SARS-CoV-2 infection.” Third, our cohort is unique in that the patients undergo close monitoring and are in continuous and active close contact with the medical team. Transplant patients undergo active screening more often than the general population due to the need for in patient screening procedures such as endomyocardial biopsies, coronary angiography or stress testing. Therefore, the contribution of asymptomatic SARS-CoV-2 infection as a confounding factor is estimated to be minimal. Patients are instructed to proactively report exposure or on any event suspected of being a “symptom.” Fourth, longitudinally assessed, none of the patients demonstrated an elevation in levels of antibodies, arguing against an etiology of an asymptomatic infection. Finally, our manuscript did not aim to assess clinical outcomes. At present, we are following the clinical outcomes of our cohort as the pandemic continues, and, to date, our current data support the findings presented in our article. We have also additionally observed that neutralization titers post COVID-19 are much higher and on an entirely different scale from the postvaccination response (to be submitted for publication).

In conclusion, as the pandemic continues, assessment of clinical presentation and severity of COVID-19 disease demand further research to better define the role of immunization status, time from transplant, immune response, optimal serological and neutralization correlates that confer clinical immunity, era and variants of concern. Until more evidence becomes available, extra precautions must be taken for transplant patients, including the endorsement of vaccinations and optimization of immunogenicity alongside alternative strategies to effectively protect such patients from COVID-19 given the increased mortality associated with this condition in the heart transplant population.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

References

1. JHLT-D-22-00472
2. Peled Y, Afek A, Kreiss Y, et al. Kinetics of cellular and humoral responses to third BNT162B2 COVID-19 vaccine over six months in heart transplant recipients - implications for the omicron variant. J Heart Lung Transpl 2022;41:1526-7.
3. Rivinius R, Kaya Z, Schramm R, et al. COVID-19 among heart transplant recipients in Germany: a multicenter survey. Clin Res Cardiol 2020 Dec;109:1531-9.
4. Akalin E, Azzi Y, Bartash R, et al. COVID-19 and kidney transplantation. N Engl J Med 2020;382:2475-7.
5. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transpl 2020;20:1800-8.
6. Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. JAMA Cardiol 2020;5:202159.
7. Havlin J, Svorcova M, Dvorackova E, et al. Immunogenicity of BNT162b2 mRNA COVID-19 vaccine and SARS-CoV-2 infection in lung transplant recipients. J Heart Lung Transpl 2021;40:754-8. https://doi.org/10.1016/j.healun.2021.05.004. Epub 2021 May 21. PMID: 34120839; PMCID: PMC8139179.
8. Aslam S, Danziger-Isakov L, Mehra MR. COVID-19 vaccination immune paresis in heart and lung transplantation. J Heart Lung Transpl 2021;40:763-6.
9. Orner EP, Rodgers MA, Hock K, et al. Comparison of SARS-CoV-2 IgM and IgG serocconversion profiles among hospitalized patients in two US cities. Diagn Microbiol Infect Dis 2021;99:115300.
10. Joob B, Wiwanitkit V. Letter to the editor: coronavirus disease 2019 (COVID-19), infectivity, and the incubation period. J Prev Med Public Health 2020;53:70.
11. Aslam S, Ison MG. SARS-CoV-2 vaccination in heart transplantation: what we do and do not know. J Heart Lung Transpl 2022 Feb;41:158-60. https://doi.org/10.1016/j.healun.2021.10.017. Epub 2021 Nov 4. PMID: 34876356; PMCID: PMC8566197.

Tackling the paradox of orthotopic heart transplantation from SARS-CoV-2 positive donors: A single center experience

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The ongoing COVID-19 pandemic has profoundly impacted many aspects of patient care, including heart transplantation (HTx). Early in the pandemic, several transplant societies, recommended against transplanting grafts from SARS-CoV-2-positive (SARS-CoV-2+) donors given the potential risk for transmission of the virus and risk of allograft dysfunction. However, multiple recent case reports in solid organ transplants have noted nontransmission of the virus.

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We report our single-center outcomes experience of eight HTx recipients of SARS-CoV-2+ donors as well as our proposed protocol for donor evaluation and recipient monitoring. (Figure 1A: donor selection, 1B: recipient workflow). Data points for donors include cause of death, current or prior symptoms of COVID-19, sample source (nasal swab versus sputum versus bronchial alveolar lavage), type of test (polymerase chain reaction or PCR test vs antigen test), cycle threshold (CT) value and radiographic review. Albeit conservatively, we tended to decline the offer if the CT value was <20, while unknown or higher values would trigger further, multidisciplinary discussion. For recipients, the key considerations are assessment of the risk-benefit ratio of accepting a SARS-CoV-2+ donor, vaccination status, informed consent, adjustment of immunosuppression (if applicable) and post-transplant monitoring. Lastly, a protocol for the procurement team, implanting surgical team, and the post-operative team were developed. Post-transplant, patients are isolated for 3 days and a nasopharyngeal PCR test for SARS-CoV-2 is performed on day 4.

Table 1 lists information about our recipients who received a SARS-CoV-2+ donor including the UNOS listing status, immunosuppression strategy, and outcomes. All our recipients were vaccinated at the time of HTx, as per our institution policy. Post HTx, they were tested with a nasopharyngeal swab for SARS-CoV-2 on day 4 and were negative. Four of 8 patients received basiliximab, in addition to the standard triple regimen of tacrolimus, mycophenolate and prednisone but these decisions were made to account for their individual risk of rejection/infection or need to delay tacrolimus, unrelated to the donor being SARS-CoV-2+. At 90 days post-HTx, all recipients were doing well, with no evidence of viral transmission, clinically significant graft dysfunction, rejection, or other major adverse events. Median duration of follow-up is 204 days. There was no transmission of the virus to any member of the procurement or implanting surgical team. All patients receive 1 dose of tixagevimab and cilgavimab (Evushield, AstraZeneca Pharmaceuticals LP, Wilmington, DE) before hospital discharge. Table 2 lists donor information. COVID-19 was diagnosed as part of routine testing at the donor centers but was not the admitting/clinical diagnosis or cause of death for any of them. The vaccination status of these donors was often unknown.
### Table 1  Recipient Information

| Case number | UNOS status | SARS COV-2 antibody level (> 80 = positive) | Immunosuppression | Clinically significant rejection at any period (> Grade 1R ACR or any AMR) | Graft function - 90 days | Outcome till date |
|-------------|-------------|--------------------------------------------|-------------------|-------------------------------------------------------------------------|--------------------------|------------------|
| 1           | 3           | Basiliximab, Tacrolimus, prednisone         | No                | Normal LV, RV dysfunction                                               | Normal                   | Alive at 1 year  |
| 2           | 6           | Basiliximab, Tacrolimus, mycophenolate, prednisone | No                | Normal                                                                  | Normal                   | Alive at 1 year  |
| 3           | 4           | Tacrolimus, mycophenolate, prednisone       | No                | Alive at 9 months                                                      | Alive at 6 months        |
| 4           | 2           | Basiliximab, Tacrolimus, mycophenolate, prednisone | No                | Alive at 9 months                                                      | Alive at 6 months        |
| 5           | 1           | Basiliximab, Tacrolimus, mycophenolate, prednisone | No                | Alive at 9 months                                                      | Alive at 6 months        |
| 6           | 3           | Tacrolimus, mycophenolate, prednisone       | No                | Alive at 9 months                                                      | Alive at 6 months        |
| 7           | 6           | >250 Tacrolimus, mycophenolate, prednisone  | No                | Alive at 9 months                                                      | Alive at 6 months        |
| 8           | 3           | >250 Tacrolimus, mycophenolate, prednisone  | No                | Alive at 9 months                                                      | Alive at 6 months        |

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; BAL: Bronchoalveolar lavage COVID-19 PCR test; CT, PCR cycle threshold number; NP: nasopharyngeal COVID-19 PCR test; TA, Tracheal Aspirate COVID 19 PCR Test.

### Table 2  Donor Information

| Donor number | History of vaccination | Symptoms of COVID | Clinical context | Cause of death related to COVID? | Donor testing | LVEF of donor heart >55% |
|--------------|------------------------|-------------------|-----------------|----------------------------------|---------------|--------------------------|
| 1            | N/A                    | Yes - fever and cough | Lower lobe consolidation related to bacterial pneumonia | No | NP + (D-2; CT 40), TA - (D-2), NP - (D-2) | Yes |
| 2            | N/A                    | No                | Bilateral consolidations, repeat bronchoscopy negative | No | BAL - (D-5), BAL + (D-3), NP - (D-3), BAL - (D-3) | Yes |
| 3            | N/A                    | No                | Bilateral perihilar ground-glass opacities, 2 negative bronchoscopies | No | NP - (D-3), BAL - (D-3), NP - (D-2), BAL - (D-2), BAL - right lung (D-1), BAL + left lung (D-1) | Yes |
| 4            | Yes                    | No                | No              | No | NP- (D-4), NP + (D-3) (CT 30.8 and 33.3), BAL - (D-2) | Yes |
| 5            | N/A                    | No                | No              | No | NP Antigen - (D-4), NP + (D-4), NP - (D-3), BAL - (D-3) | Yes |
| 6            | N/A                    | No                | Bilateral multilobar consolidation; likely aspiration, negative bronchoscopy | No | NP + (D-1), BAL - (D-1) | Yes |
| 7            | N/A                    | No                | Bilateral patchy, lower lobe consolidation, likely aspiration | No | NP (D-2) (CT 27.1), BAL (D-1) (CT 27.7) | Yes |
| 8            | Yes                    | No                | No              | No | NP + (CT 36), NP + (CT 36) | Yes |

Abbreviations: BAL, bronchoalveolar lavage; CT, cycle threshold; D, day of transplantation; N/A, not available; NP, nasopharyngeal swab; TA, tracheal aspirate.
Although recommendations from transplant societies are evolving, data regarding outcomes is sparse and recommendations are largely driven by expert recommendations. While there are reports of viral detection in the myocardium based on autopsy studies, there are no reported cases of SARS-CoV-2 infection transmission from a donor to HTx recipients to our knowledge. There is no data regarding the usage of CT values to guide clinical decision making, however, lower CT values are considered to reflect a higher viral load and vice versa and should be used as one of many data points when considering donors. We did not have the information of donor vaccination status in all cases but did not feel strongly that it would preclude our decision to consider those donors.

Understanding the safety and feasibility of SARS-CoV-2 + donors for HTx at individual centers will allow us to develop appropriate best practices and selection strategies, as the pandemic rages on. We propose that the use of hearts from asymptomatic SARS-CoV-2+ donors could be safe and effective and that such donors should be carefully evaluated in a multidisciplinary fashion. Our small sample-size results and proposed algorithm should be considered with caution, especially as new variants continue to mutate. Ongoing experience and evaluation of long-term outcomes will determine future best-practices in considering such donors.

**Disclosure statement**

The authors have no conflicts of interest to declare.

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**References**

1. Weiss MJ, Hornby L, Foroutan F, et al. Clinical practice guideline for solid organ donation and transplantation during the COVID-19 pandemic. Transpl Direct 2021;7:e755. https://doi.org/10.1097/txd.00000000000001199.
2. article C4. C4 article: implications of COVID-19 in transplantation. Am J Transpl 2021;21:1801-15. https://doi.org/10.1111/aht.16346.
3. Eichenberger EM, Coniglio AC, Milano C, et al. Transplanting thoracic COVID-19 positive donors: an institutional protocol and report of the first 14 cases. J Heart Lung Transpl 2022. https://doi.org/10.1016/j.healun.2022.06.018. 2022/06/30.
4. Weiss MJ, Lalani J, Patriniq-Stoner C, et al. Summary of international recommendations for donation and transplantation programs during the coronavirus disease pandemic. Transplantation 2021;105:14-7. https://doi.org/10.1097/tp.0000000000003520.
5. Gauksen 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;105:1405-22. https://doi.org/10.1097/tp.0000000000003744.

**A rare case of late onset tacrolimus-induced leukoencephalopathy and coma after pediatric orthotopic heart transplantation**

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A 3-year-old male with heterotaxy, complete atrioventricular canal, pulmonary atresia, total anomalous pulmonary venous return, bilateral superior vena cava, major aorto-pulmonary collateral arteries, orthotopic heart transplantation complicated by renal failure requiring peritoneal dialysis and tracheostomy with ventilatory dependence presented with acute altered mental status 7 months post-transplant. He was obtunded and progressed to coma within 24 hours. Tacrolimus level was within goal (10.8 ng/ml). He had pre-existing hypertension but was normotensive. Immunosuppressant regimen included mycophenolate and prednisone; the latter was being weaned slowly after early cellular rejection 1-month post-transplant (grade 2R, donor specific antigen [DSA] negative). Cerebrospinal fluid was negative for bacteria and viruses. Brain MRI revealed confluent symmetric hypointense signal on T2-weighted sequences with significant associated restricted diffusion within the bilateral deep and periventricular white matter, predominantly sparing subcortical white matter (Figure 1), which can occur in toxic leukoencephalopathies. This pattern of white matter involvement is different from subcortical and posterior predominant posterior reversible encephalopathy syndrome. T2 signal abnormality, without restricted diffusion, was also noted within the peripheral cerebellar hemispheres. Continuous electroencephalogram (EEG) was hyparrhythmia-like with epileptiform discharges (Figure 2). He developed myoclonic jerks with EEG confirming myoclonic seizures. Seizures were refractory to multiple medications. Clobazam was initiated with seizure cessation and EEG improvement. Tacrolimus was discontinued 1 day after symptom onset with transition to sirolimus. Four days after symptom onset, mental status improved with return to neurologic baseline by 6 days. Brain MRI after 1 week was unchanged. Sirolimus was continued in lieu of

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