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Early Mortality for Children on Extracorporeal Membrane Oxygenation at Lung Transplant: True or Due to Confounding Variables?

To the Editor:

A recent publication in *AnnalsATS* by Thompson and colleagues reported the outcomes of children who were on extracorporeal membrane oxygenation (ECMO) or mechanical ventilation at the time of lung transplant (LTx) from January 2004 to August 2019 (1). In the same issue of *AnnalsATS*, Barbaro and colleagues provided an editorial on the results and limitations of any analysis using data from the United Network for Organ Sharing (UNOS) Registry (2). In their retrospective analysis, Thompson and colleagues (1) identified an increased trend in the use of ECMO as a means to bridge children to LTx but found an increased hazard risk for mortality at 1 month and 1 year post-LTx for children on mechanical ventilation alone or ECMO, but this difference in risk dissipated at 5 years, as detailed in Table 3 of their article. The authors concluded that, despite the increased use of ECMO as a bridge to LTx, it is associated with increased in-hospital mortality compared with mechanical ventilation alone or no mechanical support at the time of LTx. Although Thompson and colleagues (1) included hospital volume in their analysis, LTx center factors could be influencing their early post-LTx findings that were not explored.

Thompson and colleagues (1) performed an analysis of contemporary data from the same registry that builds upon similar work in children on ECMO at the time of LTx published in 2015 (3), but with a stark difference. This previous study from 2015 limited their study cohort to patients under 18 years of age who underwent LTx at pediatric-majority programs, whereas Thompson and colleagues' 2022 study (1) included patients between 18 and 21 years of age in their analysis, with no designation of whether patients underwent LTx at programs that predominately perform pediatric or adult LTx. Inclusion of this older age group could possibly influence early post-LTx outcome findings, especially with 43% (29/68) of their study cohort having cystic fibrosis (CF). Here, I explore possible confounding factors.

In the United States, patients with CF are disproportionately transplanted at pediatric and low-volume majority-adult LTx centers, so center expertise in LTx for CF is discordant with total center LTx volume (4). A study demonstrated that annual CF LTx volume by a center and not annual total LTx volume was associated with improved survival among adolescents and adults with CF undergoing LTx (4). Furthermore, this survival advantage for patients with CF who received LTx was not present early at 1 year post-LTx but occurred later for those patients with CF who received LTx and lived more than 1 year after transplant (4). On the basis of these findings, the investigators theorized that centers with higher CF LTx volume had developed specific strategies not captured in the UNOS Registry that optimized long-term rather than short-term outcomes. Additionally, another study found that children with CF under 18 years of age who underwent LTx at majority-adult centers had inferior early outcomes, with a third of pediatric CF LTxs in the United States being performed at majority-adult centers at that time (5). Both of these studies using UNOS Registry data identified inferior early post-LTx outcomes for the CF LTx population when undergoing LTx at a center with a low CF LTx volume and for pediatric CF patients who underwent LTx at majority-adult centers, regardless of their respiratory support. It is unclear to me whether these confounding factors were addressed by Thompson and colleagues (1).

As discussed by both Thompson and colleagues (1) and Barbaro and colleagues (2), further research is needed with more granular data

to help answer key questions on how to best care for children on ECMO and/or mechanical ventilation who require LTx. If the aforementioned confounding factors were not addressed, I would recommend further exploration of the UNOS Registry focused on children under 18 years of age on ECMO and/or mechanical ventilation at pediatric LTx programs. If there truly are inferior outcomes earlier in the post-LTx course for children on ECMO and/or mechanical ventilation that were not present in the previous work from 2015 (3), that is suggestive of management issues during the postoperative course or treatment of early LTx complications, so pediatric LTx programs in the United States should address that. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply: Early Mortality for Children on Extracorporeal Membrane Oxygenation at Lung Transplant: True or Due to Confounding Variables?

From the Authors:

We thank Dr. Hayes for the thoughtful comments in his letter in response to our recent publication entitled, "Early Mortality for Children on Extracorporeal Membrane Oxygenation at Lung Transplant" (1). Before discussing these further, we would like to clarify our findings regarding the mortality trends. In our study, we found that mechanical support, which included use of both pretransplant extracorporeal membrane oxygenation (ECMO) and/or mechanical ventilation (MV), was associated with an increase in mortality at the time of hospital discharge. This was an increase in mortality for both ECMO and MV and not simply ECMO alone. However, at both 1 year and 5 years after transplantation, there was no difference in pretransplant mechanical support (ECMO and/or MV) and no mechanical support. This suggests that if patients survive to hospital discharge, the need for and use of pretransplant mechanical support, including ECMO, has no long-term survival impact but does impact the initial survival.

As Dr. Hayes has pointed out, many confounding factors may have impacted our results, the first being transplant center. We included pediatric lung transplant volume and transplant center as a random effect in our mixed-effect logistic regression analysis to adjust for center characteristics. We did not, however, control specifically for centers by annual cystic fibrosis lung transplant volume. Lastly, the decision to include transplants up to but not including 21 years of age is different than the prior studies by Hayes. Because many patients continue to receive lung transplants at pediatric transplant centers beyond the age of 18, we found it important to include those <21 years of age. We cannot rule out residual confounding from these specific center characteristics, despite adjusting for random variability by center in our analyses. The limitations of the dataset and our analyses are discussed in detail in our manuscript.

The issues related to confounding raised by Dr. Hayes illustrate a greater need to look at data beyond what is available through the United Network for Organ Sharing (UNOS) database, especially data on ECMO support, to further understand outcomes of children bridged to lung transplantation with ECMO. In addition, in the editorial that accompanied our manuscript, Barbaro and colleagues highlight the need for evaluating those listed for lung transplant during ECMO support, with a more comprehensive view of ECMO use in this population (2). This would provide mortality data on not only those who survived the pretransplant period and went on to receive a transplant but also those who died before transplant. This was done with pediatric heart transplant patients and would be important information for lung transplant patients (2, 3). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Supported by Callaghan Family Chair in Cardiac Intensive Care, Boston Children's Hospital (R.T.).

Author Contributions: K.T. and R.T.: Conception and design and drafting and approval of the manuscript.