Age at Lung Transplant Impacts Post-Transplant Survival in Cystic Fibrosis; Why?

Emily S. Clausen, M.D., and Denis Hadjiliadis, M.D., Ph.D.

Department of Pulmonary, Allergy and Critical Care, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

ORCID ID: 0000-0002-8602-9503 (D.H.).

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Cystic fibrosis (CF) remains a prevalent but still incurable disease despite multiple advances in therapy, with lung transplantation remaining the ultimate life-extending treatment for end-stage CF. Ongoing gains in median life expectancy for those living with CF have continued to occur and are expected to accelerate with development of Cystic Fibrosis Transmembrane Regulator–modulating therapies, but many patients will still go on to develop severe respiratory failure necessitating lung transplant. Previous studies have established adult recipients with CF have a significant survival benefit from lung transplantation (1). Other studies have attempted to understand the nuances of factors influencing lung transplant outcomes in this specific disease population (2). In this issue of *AnnalsATS*, Sethi and colleagues (pp. 44–50) describe survival difference among adult recipients with CF over 30 years of age compared with those less than 30 years of age after lung transplantation by review of the United Network of Organ Sharing (UNOS) Registry (3).

Updated CF foundation guidelines recommend lung transplant referral for any patient with CF with forced expiratory volume in 1 second (FEV_1) < 50% predicted with evidence of rapid decline (considered >20% drop in FEV_1 within 12 mo), FEV_1 < 40% with other evidence of advanced disease (6-minute-walk test [6MWT] distance <400 m, hypoxia, hypercarbia, pulmonary hypertension, and underweight as examples), or any patient with CF with FEV_1 < 30% (4). The most recent guidelines regarding indications for lung transplant evaluation list chronic infection with highly resistant and/or virulent bacterial organisms, which cannot be controlled before transplant as an absolute contraindication to lung transplant (5). Given the financial costs, scarcity of donors, and morbidity associated with lung transplantation, more data to improve our ability to predict outcomes with transplant are critically needed. Existing data on the benefits of lung transplant in CF are positive (1), and improvements in survival without transplant (6) suggest that this population in particular is one in which more guidance would improve our abilities to counsel patients on this important treatment option.

This study by Sethi and colleagues included age, body mass index, sex, serum albumin, serum creatinine, human leukocyte antigen (HLA) mismatch, insurance, diabetes, pulmonary hemodynamics, lung allocation score (LAS), and graft ischemic time in the final analysis model (3). Significant survival difference between the two different age groups persisted in both the unadjusted and adjusted model. Secondary analyses also examined cause of death and found significant differences between the two age groups, with those in the younger cohort more likely to die from graft failure or infection (3). As may be expected, the older cohort had a higher incidence of malignancy, but interestingly, the younger cohort had a higher incidence of post-transplant lymphoproliferative disorder (3).

Comparable to this study, Stephenson and colleagues described an association of extremes of age with worse survival, such that those that were youngest and oldest had shorter survival benefit when compared with median age distribution around 28 years after lung transplantation (2). On an international level, registry data has also found that adults with CF >40 years of age have better survival than young adults (7). Further study to understand the mechanisms of this observed improvement would be an interesting addition to the field. One hypothesis could be that older recipients have phenotypically milder CF, despite similar genotypes, that coincides with their ability to delay transplant to an older age that goes on to also affect their transplant outcome. Despite controlling for other characteristics, uncontrolled biases can still exist (possibly milder gastrointestinal disease, sinus disease, diabetes mellitus, or pulmonary inflammation). One of the most interesting issues uncovered by Sethi and colleagues is the effect of having public insurance and its impact on survival, which transcends age at transplant (3). In addition, public insurance was more common in the younger cohort, possibly explaining some of the worse survival. It comes after a series of manuscripts that have brought up socioeconomic status as a barrier to improved outcomes and access to care in patients with CF (8, 9).

Specific to CF transplant recipients, Stephenson and colleagues found that more recent year of transplant was associated with improving survival after lung transplant (2). An interesting finding by Sethi and colleagues was that the survival difference between those over age 30 compared with those under persisted when adjustments were made for pre-LAS and post-LAS period (3). However, the analysis was not granular

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enough to assess trends in smaller age groups and tighter transplant eras. The true inflection point of where age starts making a difference in survival, if there is one, cannot be assessed by the current study.

Other potential variables of interest that were not included in this study include transplant center volume, patient status at time of transplant (being an outpatient, in the hospital, or in the intensive care), and cytomegalovirus (CMV) donor and recipient status. Even if some of these variables were not complete, bias might have been introduced by their omission. The UNOS registry collects information on patient status at time of transplant and describes whether surgery occurred from an outpatient, inpatient, or intensive care unit setting. This variable has been associated with mortality (10). Hayes and colleagues have previously examined the UNOS registry and found that, unlike the general lung transplant population, overall lung transplant center volume was not associated with improved post-transplant survival, but a center's specific experience with annual lung transplant volume for those with CF (hazard ratio per 10 lung transplants, 0.66; 95% confidence interval, 0.49–0.89; $P = 0.006$) did correlate with improved survival outcomes (11). CMV donor and recipient status, specifically CMV mismatch (donor positive/recipient negative), significantly affects post–lung transplant morbidity and mortality for all lung transplants (10). In addition, CMV recipient negative status is likely more common in younger patients, therefore making more common a higher risk status (CMV donor positive/recipient negative) in the younger age group (12). Same is true for Epstein-Barr virus mismatch, which can lead to increased risk for post-transplant lymphoproliferative disorder (12).

In summary, the current manuscript by Sethi and colleagues provides new data on the effect of age at lung transplant for patients with CF and post–lung transplant survival, with some insight into reasons for the difference. The current study can provide useful information for transplant programs, CF programs, and patients, as they apply the new guidelines for transplant referral in patients with CF. However, future studies need to further refine the reasons behind the disparities in survival, whether they are physiologic or socioeconomic, and attempt to address them. ■

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

References

1 Thabut G, Christie JD, Mal H, Fournier M, Brugière O, Leseche G, *et al*. Survival benefit of lung transplant for cystic fibrosis since lung allocation score implementation. *Am J Respir Crit Care Med* 2013; 187:1335–1340.

2 Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, *et al*. Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. *J Heart Lung Transplant* 2015;34:1139–1145.

3 Sethi J, Bugajski A, Patel KN, Davis NM, Wille KM, Qureshi MR, *et al*. Recipient age impacts long-term survival in adult subjects with cystic fibrosis after lung transplantation. *Ann Am Thorac Soc* 2021;18: 44–50.

4 Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, *et al*.; CF Lung Transplant Referral Guidelines Committee. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. *J Cyst Fibros* 2019;18:321–333.

5 Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, *et al*. A consensus document for the selection of lung transplant candidates: 2014--an update from the pulmonary transplantation council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015;34:1–15.

6 Ramos KJ, Quon BS, Heltshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, *et al*. Heterogeneity in survival in adult patients with cystic fibrosis with $FEV_1 < 30\%$ of predicted in the United States. *Chest* 2017;151: 1320–1328.

7 Benden C, Goldfarb SB, Stehlik J. An aging population of patients with cystic fibrosis undergoes lung transplantation: an analysis of the ISHLT Thoracic Transplant Registry. *J Heart Lung Transplant* 2019;38: 1162–1169.

8 Schechter MS, McColley SA, Silva S, Haselkorn T, Konstan MW, Wagener JS; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis; North American Scientific Advisory Group for ESCF. Association of socioeconomic status with the use of chronic therapies and healthcare utilization in children with cystic fibrosis. *J Pediatr* 2009;155:634–639, e1–e4.

9 Lehr CJ, Fink AK, Skeans M, Faro A, Fernandez G, Dasenbrook E, *et al*. Impact of socioeconomic position on access to the US lung transplant waiting list in a matched cystic fibrosis cohort. *Ann Am Thorac Soc* [online ahead of print] 10 Jul 2020; DOI: 10.1513/AnnalsATS.202001-030OC.

10 Chambers DC, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, *et al*.; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult lung and heart-lung transplantation report-2019; focus theme. Donor and recipient size match. *J Heart Lung Transplant* 2019;38:1042–1055.

11 Hayes D Jr, Sweet SC, Benden C, Kopp BT, Goldfarb SB, Visner GA, *et al*. Transplant center volume and outcomes in lung transplantation for cystic fibrosis. *Transpl Int* 2017;30:371–377.

12 Lowery EM, Adams W, Grim SA, Clark NM, Edwards L, Layden JE. Increased risk of PTLD in lung transplant recipients with cystic fibrosis. *J Cyst Fibros* 2017;16:727–734.