Which Shall I Choose? Lung Transplantation Listing Preference for Individuals with Interstitial Lung Disease and Chronic Obstructive Pulmonary Disease

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Single or double lung transplantation is a therapeutic option for individuals with end-stage chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) (1). Since the new lung allocation system was implemented in the United States in 2005, the number of lung transplants has increased almost every year (2). However, there are still more individuals on the waitlist for lung transplantation than there are lung donors available. As a result, death without a transplant is an unfortunate outcome for some patients on the waitlist. The likelihood of dying on the waitlist (or waitlist removal for clinical deterioration) is approximately 15% per year for individuals with ILD (2). As nearly 75% of transplants are bilateral (two lungs to one recipient), one potential strategy to increase the number of lung transplant recipients is to promote single lung transplantation (two recipients receiving a single lung from a single donor pair) when clinically feasible (2).

There is an important distinction between listing preference and the surgical procedure that a patient undergoes (Figure 1). Providers may, and often do, list their patients with a preference for bilateral lung transplantation only (restricted) versus any other procedure preference (unrestricted). The procedure options available to a particular patient will depend to a large extent on the patient's underlying diagnosis, presence of anatomical abnormalities in the chest, degree of pulmonary hypertension, disease severity, and other patient-related factors (e.g., age). Local and regional circumstances may also dictate a transplant center's approach to listing because of the dynamics of interacting with the Organ Procurement Organizations. Donor characteristics, including donor size, suitability of one or both lungs for transplant, and "marginal" viability of the available lung or lungs, will also affect the procedure a matched recipient will undergo. However, a reflexive approach to "restricted" listing by some centers can limit the opportunities for eventual (and timely) transplantation. Individuals with an "unrestricted" listing preference have more opportunities to receive transplant offers. Accordingly, an investigation of the net effect of listing practices is both interesting and important at the individual and societal levels.

In this month's issue of the *AnnalsATS*, Anderson and colleagues (pp. 231–239) provide evidence contrasting the outcomes of patients by their listing preference (3). Using the US transplant registry, with information for 13,988 patients with COPD or ILD (2005–2014), the authors leverage a number of new empirical strategies to address this question. The composite ("intention to treat") outcome of the study was the number of days from listing until death, removal from waitlist for deterioration, or

re-transplantation. This novel patient-centered outcome is of unique interest to both patients and their providers because at the time of listing, a patient cannot know whether waitlist mortality or posttransplant survival will be the more relevant statistic in his/her case. The fully adjusted primary analysis revealed no significant association of unrestricted listing with the composite outcome. The authors identified a decreased risk for death on the waitlist (and an increase in transplantation) for patients with COPD or ILD with an unrestricted listing preference. Short-term (1-year) and medium-term (5-year) graft survival appears comparable for patients with restricted or unrestricted listing preferences. However, there was a trend toward worsened 5-year graft survival for patients with COPD with unrestricted preference. Survival posttransplant for individuals who received single versus double lung transplantation was not assessed in this cohort, but prior studies have shown superior survival for recipients of double lung transplants (4–6), most notably in those individuals with the highest lung allocation scores (7).

The analytic approach taken by the authors provides a new model for outcomes research in transplantation more broadly in at least two ways. First, the composite outcome jointly examining pre- and posttransplant metrics, although previously used by the authors (8), now provides a second practical application of the novel framework. The overwhelming majority of published transplantation research, both on clinical outcomes and social disparities, focus on either waitlist or posttransplant outcomes. Although such a focus is informative, it provides an incomplete portrayal of the patient experience, and by extension provides limited empirical guidance for policy development.

Second, the authors demonstrate the utility of the E-value for observational

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Figure 1. Waitlist outcomes for individuals with chronic obstructive pulmonary disease (COPD) and (A) restricted listing preference or (B) unrestricted listing preference, and individuals with interstitial lung disease (ILD) and (C) restricted listing preference or (D) unrestricted listing preference. Data were abstracted from Figure 1 and Table 2 in the manuscript by Anderson and colleagues (3). For example, panel A shows 2,634 individuals with restricted listing preference (Table 1, Figure 1), of whom 1,875 (71%) underwent bilateral transplant and 112 (4%) underwent single transplant; Table 2 describes 322 (12%) of individuals with COPD and restricted preference died or deteriorated on the waitlist. The remaining 325 (12%) of patients in panel A were either alive at the end of follow-up or lost to follow-up, based on Figure 2 and supporting text.

transplantation research (9). In the study by Anderson and colleagues, there is a potential indication bias present in the restricted listing preference exposure (3). Specifically, younger patients and those with higher lung allocation score (LAS) or severe pulmonary hypertension for COPD or any pulmonary hypertension for ILD, were more likely to be listed with a restricted preference. Thus, the patients who remained eligible for an unrestricted listing were comparatively healthier, and thus more likely to have more favorable (waitlist and posttransplant) outcomes. Thus, unmeasured confounding between patients listed for a restricted versus an unrestricted preference is a threat to the estimated associations of this study. As the authors note, “unmeasured clinical indications for a restricted preference could

have suppressed a true effect, thereby biasing toward the (largely) null effects” observed in their study. The E-value provides an understandable approach to assess how strong such a confounder would need to be to reverse this effect. Although no statistical method can remove the potential biases inherent in observational research, providing bounds of the extent to which such concerns could manifest supports a balanced interpretation of new research studies. To our knowledge, this is the first study in lung transplantation to apply the E-value to assess the robustness of their results.

In addition, this research can inform lung transplant selection committee decision-making. First, increasing the proportion of candidates with COPD or ILD with an unrestricted listing preference may

increase their opportunity to undergo transplantation. More than a quarter of individuals with unrestricted listing preference underwent bilateral lung transplantation, but the advantage of the unrestricted preference appears to be manifested by the shorter time to transplant for individuals who receive single lung transplantation. For the patient, there is a benefit of decreasing time spent on the waitlist without a clinically relevant loss of time spent with an improved quality of life posttransplant. Second, listing more individuals with an “unrestricted” preference may also increase the rates of single lung transplantation, thereby improving the societal utilization of a scarce medical resource in the absence of an expanded donor population. However, it is important to note that the surgical procedure choice remains at the individual patient level. This study did not address the composite pre- and posttransplant survival outcomes for individuals who underwent single versus double lung transplantation, and it cannot be stated that the procedure choice of single lung transplantation yields equivalent survival to double lung transplantation based on these data.

In summary, this study identified a decreased risk for death on the waitlist when patients with COPD or ILD were listed with a single lung option without a substantive compromise in short- or medium-term posttransplant survival outcomes. Choosing to list lung transplant candidates for all options opens the door to either single or double lung transplantation. Undergoing single lung transplantation is, on average, a trade-off, potentially placing more of the mortality risk in the posttransplant period (10). With the new geographic system for lung distribution (11–13), patients with COPD (and lower LAS) will need to consider the longer wait times and may get substantial benefit in their quality of life with the option of receiving a single lung transplant. With high rates of death on the waitlist, patients with ILD may also stand to benefit from a shift toward increased rates of single lung transplantation. Regardless of surgical procedure choice, an unrestricted listing preference appears clinically beneficial for individuals with COPD or ILD, and clinical decision-making can be informed by these observational results. ■

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

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Altitude, Adaptation, and Ancestry and the Interpretation of Lung Function Tests

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The need for population-specific lung function reference values is well recognized. The American Thoracic Society/European Respiratory Society (ATS/ERS) advises pulmonary function testing units to select appropriate lung function predicted values that are representative of characteristics (age, height, ethnicity, location) to the patients being referred for testing (1). Without a matched, appropriate population reference, there is potential for misinterpretation of lung function results causing erroneous clinical outcomes. The Global Lung Function Initiative (GLI) was formed with the goal of broadening the quality and representativeness of lung function reference equations and increasing the accuracy of the interpretation of lung function tests. Since its conception, the GLI has published all-ages, multiethnic spirometry reference values (2) and, more recently, reference equations for the single-

breath transfer factor of the lung for carbon monoxide (T_{LCO}) (3).

Despite the global call for submission of T_{LCO} data from healthy participants across all ethnic groups, more than 85% of submissions to GLI were from individuals identifying as Caucasian (3). These data only provide validated predictions in a Caucasian population, and hence a significant evidence gap for those patients of non-Caucasian ancestry. The GLI called for additional T_{LCO} data across other non-Caucasian populations to expand the generalizability of T_{LCO} prediction equations (3).

In this month's issue of the *AnnalsATS*, Gochicoa-Rangel and colleagues (pp. 240–247) responded to this need and offer an important contribution to our understanding of T_{LCO} in Mexican/Latino children, adolescents, and young adults living at a moderate altitude (2,240 m above sea level) (4). The authors obtained T_{LCO} results from 420 participants (aged 4–20 years) of Mexican/Latino nationality and aimed first

to assess the effect of the latest ATS/ERS T_{LCO} methodology guidelines (5), and second to develop normal T_{LCO} values in this population. This study reported 60% of participants in the 4- to 6-year age range were able to complete a T_{LCO} manoeuvre rated as an A or B grade according to the 2017 T_{LCO} guidelines (5). This success rate increased to 90% in those older than 13 years, thus providing evidence that T_{LCO} testing is feasible and should not be overlooked in the clinical decision-making process for young children and adolescents. Gochicoa-Rangel and colleagues subsequently compared T_{LCO} outcomes from Mexican/Latino children and young people with those of the GLI T_{LCO} reference equations and found a poor fit, which persisted after adjustment of T_{LCO} outcomes for hemoglobin and atmospheric pressure, with reported T_{LCO} differences being 2.46 ± 1.22 z-scores higher for males and 1.72 ± 1.08 z-scores higher for females (4). Alveolar volume (V_A) and the transfer coefficient of

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