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Defining Transplantation and Listing Benefit in Patients with Chronic Obstructive Pulmonary Disease

Many chronic lung diseases demonstrate a progressive course with severe pulmonary dysfunction heralding high short-term mortality. Alternatively, patients with advanced chronic obstructive pulmonary disease (COPD) may suffer for years with significant symptoms, making it difficult to discriminate severely affected patients with COPD who have a high short-term risk of death from those with lower risk. Accordingly, it is challenging to appropriately time listing and performance of lung transplantation, which has its own risks, to significantly prolong life in these patients. In 2006, 31% of lung transplants in the United States were for COPD, and 371 patients with COPD (36% of those on a waitlist) were left waiting for a lung allograft (1, 2). The decision when to list and transplant patients with COPD affects organ utilization and therefore all lung transplant candidates.

Thabut and colleagues (3) provide important insights in this issue of the *Journal* (pp. 1156–1163). They develop models based on individual risk factors to predict median survival with and without transplant for patients with COPD. They then simulate these along with organ offer times to estimate survival gains or losses from time of listing. Although some have suggested that risk with transplantation always exceeds risk without transplantation for COPD (4, 5), Thabut and colleagues argue that listing for lung transplantation prolongs life for approximately 50% of patients under a waiting time–based allocation system.

Proper interpretation of Thabut and colleagues' results requires careful consideration of their definition of benefit. These investigators address a two-part question: If waitlisted under the former waiting time–based allocation system in the United States, would a patient with COPD (*1*) live until offered a lung allograft and (*2*) upon transplantation, have a longer, shorter, or similar survival than if never waitlisted? If a patient dies during the simulated wait time, then listing was futile. If a patient survives long enough to be transplanted in the simulation, overall survival may be better, worse, or no different than the natural history of that individual's disease.

Patient 2 in Figure E4 of the online supplement conceptualizes this idea. This patient has an estimated 2-year waitlist survival time but a 3-year waiting time. Their algorithm therefore assigns a benefit of zero, because Patient 2 did not survive long enough to be impacted positively or negatively by transplant. If,

however, this same patient had been transplanted a few days after listing, he would have lived 1 year post-transplant, but lost a year of life overall. Therefore, Thabut and colleagues' ascribed "transplant benefit" may more accurately be described as "listing benefit," because some simulated patients don't survive to see a transplant benefit (or risk).

Although calculated using many common variables, Thabut and coworkers' estimated listing benefit should not be confused with transplant benefit, as defined in the Lung Allocation Score (LAS) (6), which is used to prioritize patients for lung transplantation in the United States. First, as opposed to median survival gains due to listing, the LAS estimates patient-days gained or lost over the year after a lung transplant. In contrast to Thabut and colleagues' simulations, the LAS does not consider wait times, the probability of surviving until an offer, or outcomes after 1 year, but it does estimate transplant benefit for all listed patients. LAS benefit projections recorded for patients with emphysema/COPD transplanted from May 2005 to June 2007 had 12.7% of transplanted patients with positive 1-year transplant benefit and, using a longer projection, 22.0% with positive 3-year benefit (7).

Another difference between Thabut and colleagues' listing benefit and LAS transplant benefit centers on those simulated patients who live long enough to get transplanted in the model. Because better waitlist survival is likely correlated with both living until being offered an allograft and post-transplant outcomes, Thabut and coworkers' simulation results may be weighted toward healthier patients. As fewer patients with poor waitlist survival get the opportunity for transplant in the simulation, the listing benefit calculations may be less applicable to patients ordered by LAS. Sicker patients actually get a better chance at allocation under the LAS system, potentially resulting in worse post-transplant outcomes, although this is yet to be determined.

Some take a broader view of benefit than is reflected in the relatively simplistic estimates of both Thabut and colleagues and the LAS. Although prolonging survival is an important goal, impact on quality of life is another crucial consideration. Many patients would gladly trade years of life burdened with severe COPD for the same or smaller number of years of an active post-transplant lifestyle. Although controversial, our fiduciary responsibility to patients may warrant listing and transplanting such individuals despite a lack of survival benefit.

Thabut and coworkers observed that double-lung transplantation had a lower estimated risk than single-lung transplantation. The inclusion of procedure type in modeling post-transplant outcomes poses some difficulty. Often, a patient with COPD may be eligible for either a single- or double-lung transplant and accept whichever is offered first. At listing, it may be unclear which procedure the patient will eventually receive, making it impossible to divine what the listing benefit will actually be. Of course, whether procedure choice itself confers a survival benefit is controversial and will unlikely be answered in an entirely unbiased fashion by nonrandomized studies.

Thabut and colleagues aim to help a clinician decide if a patient with COPD should be listed for transplant, based on the historical wait times and experience in the United Network for Organ Sharing. As advised by the authors, this model should not be used clinically until externally validated. The dramatic alteration in wait times and organ allocation from the LAS score might affect the accuracy of this system based on the older system and purely on time waiting. In addition, patients with COPD who did not necessarily need immediate transplantation were often waitlisted to accrue time under the old system. This means that patients whom we might consider to waitlist for transplant in 2008 may be an entirely different subset (or at a different point in their disease course) from those used to derive both Thabut and colleagues' models and the LAS. Therefore, we await further studies in the United States and around the world to help decide when "to transplant or not to transplant" patients with COPD.

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Predicting Tuberculosis
Does the IGRA Tell the Tale?

The tuberculin skin test (TST) has been used to diagnose infection with *Mycobacterium tuberculosis* for close to 100 years. This longevity reflects the TST's low cost and ease of administration, as well as the numerous longitudinal studies correlating