Pro/Con Debate: Lung Allocation Should Be Based on Medical Urgency and Transplant Survival and Not on Waiting Time*

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Key Words: lung transplantation; organ allocation; resource allocation

Abbreviations: CF = cystic fibrosis; DHHS = Department of Health and Human Services; LAS = lung allocation score; MELD = Model for End-Stage Liver Disease; OPTN = Organ Procurement and Tissue Network; QOL = quality of life; UNOS = United Network for Organ Sharing

Pro

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Lung transplantation is an acceptable therapy with which to palliate patients with a variety of end-stage lung diseases, but there is a severe shortage of suitable donor lungs to meet the demand (Fig 1), which hinders broad application. In the last 5 years, approximately 2,500 potential lung recipients have died while on the UNOS lung transplant waiting list.1 Because of the shortage of lungs for transplantation, strict listing criteria have been espoused2; thus, the deaths of patients on the waiting list underrepresent the extent of the donor shortage. The discrepancy between the supply of organs and the demand for them as lifesaving therapies has resulted in the intense scrutiny of organ distribution systems and algorithms.

In 1999, the US Department of Health and Human Services (DHHS) published “the Final Rule” a directive to UNOS, the Organ Procurement and Tissue Network (OPTN) contractor, to examine organ distribution policies and make changes that would direct organs to patients who were most in need, minimizing effects of geography.3 A report was commissioned by the Institute of Medicine4 to respond to the publication of the final rule. Although the Institute of Medicine report4 focused on liver transplantation, it was the directive of the DHHS that the OPTN review all organ distribution algorithms and report to the DHHS on alterations to distribution algorithms or provide justification that the system met the objectives espoused in the rule. This resulted in the creation of the Lung Allocation Subcommittee of the UNOS Thoracic Organ Committee to make recommendations to UNOS and the transplant community at large concerning policies for the distribution of donated lungs. After several years of analyses, discussion, public comment, and forums, in June 2004 the UNOS Board of Directors accepted the recommendation of the subcommittee to replace the existing lung distribution system with an entirely new algorithm.

The current system, based primarily on the allocation of lungs by waiting time, gave way in the spring of 2005 to a system that allocates lungs by calculating a lung allocation score (LAS) [defined below] for each candidate.

How Should Lungs Be Allocated?

At the center of any discussion of how organs should be allocated is the controversial issue of how any scarce resource should be allocated. For most commercial items, market forces come into play, but this is arguably unacceptable for transplantation, and in the United States it is illegal under the provisions of the National Organ Transplant Act. The notion of “waiting in line” is a frequently employed method to...
access goods and services, and is easy to understand. Waiting in line for medical services is common practice but when life is at stake, triage is a generally accepted way to apportion medical care. For example, surgery for a ruptured aneurysm “bumps” an electively scheduled operation. Indeed, a heart transplant bumps an elective coronary bypass. But who should get the heart? The patient who has waited the longest time? Or the one who cannot wait any longer? And what if the patient is so sick that recovery from surgery is unlikely or compromised? Or what if one patient is more likely to survive than another?5

Given the current shortage of lungs for transplantation, another fundamentally important issue is whether lung transplants should be performed strictly to increase survival or to improve health, and to what extent either of these should be a priority for allocation. A provocative analysis by Hosenpud and colleagues6 demonstrated that for a large cohort of transplant patients dying while waiting for transplantation (black bars) by year. From OPTN and the Scientific Registry of Transplant Recipients.21

patients who are “well enough” to wait the longest. A corollary is that patients with seniority in the current allocation scheme may have a better chance of longer survival time without undergoing transplantation, which was a finding both in the study by Hosenpud et al6 and in analyses performed by the Lung Allocation Subcommittee. Thus, the method of using waiting time as the sole criterion for distribution is not equitable and, in fact, may give advantage to patients who might benefit the least from transplantation.

Most people cannot stand idly by when an individual person’s life is threatened if effective rescue measures are available.7 This “rule of rescue” describes the human imperative to rescue life and the ethical construct of distributive justice (what we owe each other).7 The rule of rescue was echoed in a survey9 of 1,752 transplant candidates, recipients, and members of the general public commissioned by UNOS to sample attitudes concerning organ allocation. Approximately half of recipients and candidates thought that the top priority should be given to patients with the least amount of time to live. Making waiting time about the same for all recipients was considered a top priority for allocation among only a minority of those surveyed.

However, to allocate lungs solely on the basis of risk of death without a transplant would lead to large numbers of lung transplants being performed in critically ill individuals who would proceed to die despite receiving a transplant. This is ethically untenable. A federal government Task Force on Organ Transplantation10 held that “donated organs belong to the community, as public resources, whose effective transfer is in the hands of transplant teams, which hold the organs as trustees and stewards on behalf of the community.” As stewards of this scarce community resource, transplant professionals must recommend policies for the fair distribution of organs; to promote a policy that would waste organs would be irresponsible. Thus, the subcommittee concluded that some measure of posttransplant survival probability should be incorporated into the algorithm. In two separate analyses, it was possible to predict posttransplant survival from pretransplant data among listed patients.11,12 Because pretransplant factors likely only have an influence on early posttransplant survival, it was decided to utilize the 1-year survival rate as a measure of utility. Additional analyses performed for the subcommittee identified the same pretransplant factors when 2-year survival rate was used instead of the 1-year rate.

THE NEW ALLOCATION SYSTEM

The new lung allocation system is outlined in detail on the OPTN web site.13 Briefly, candidates
listed for lung transplantation are assigned a lung allocation score (LAS) (Fig 2).

The new system continues to offer lungs to children < 12 years of age based on waiting time, because it was not possible to identify the factors associated with risk of death on the waiting list or posttransplant survival for this small cohort of patients with a diverse group of diagnoses. Because of the demonstrated disparity of lungs offered to pediatric patients under the age of 18 years, lungs from donors under the age of 18 years will first be offered to potential candidates under the age of 18 years. This will make the lung allocation policy consistent with other organ distribution policies that preferentially direct adolescent organs to adolescent recipients before adult recipients.

The LAS is calculated for each patient as a function of waitlist survival probability without a transplant and the transplant benefit. Transplant benefit is defined as the difference between the area under a calculated 1-year survival probability curve post-lung transplantation and the area under a calculated 1-year survival probability curve without a transplant (ie, waitlist survival probability). The score is normalized on a scale from 0 to 100. The estimated survival curves are determined from clinical variables provided for each patient at the time of listing and are outlined in Table 1. These can be updated as often as desired as a patient’s clinical condition changes, but all variables except heart catheterization data must be updated every 6 months. These variables were identified as significant predictors of death on the waiting list and/or were significantly associated with survival or death within 1 year of transplantation by several analyses of two different large cohorts of waitlist candidates and lung recipients encompassing different time periods. The second analysis identified the same risk factors (with slightly different hazard ratios) and served as a validation of the algorithm. Additional variables may be added to the algorithm on the completion of a UNOS audit of > 2,000 patient records examining certain variables that were not available in the OPTN database at the time of the analyses by the subcommittee.

There were some surprises regarding variables
that were not identified as significant predictors of waitlist mortality. For example, analyses of risk factors for death among patients with CF routinely identify FEV1 as a strong predictor of outcome. Similarly, central venous pressure and other determinants of right heart function are strong predictors of survival among patients with pulmonary hypertension. However, patients with these disorders who are listed for transplant likely represent the preliminary end of the spectrum of all patients with these diagnoses. Among CF patients who are listed for lung transplantation, the range of percent predicted FEV1 values is relatively narrow, and thus, in this subset of CF patients, FEV1 is no longer a strong predictor of survival to transplant. Similarly, most patients with pulmonary hypertension who are listed for lung transplantation already have evidence of severely elevated right heart filling pressures, rendering these variables statistically insignificant as predictors of mortality in the subset of patients of interest (ie, those listed for lung transplant), as opposed to the entire population of US patients with pulmonary hypertension or CF.

A seminal feature of the algorithm is that it will be modified every 6 months by updated analyses of the most current 3-year cohort of candidates on the waiting list and lung transplant recipients. New factors that have been determined to be important predictors of death while on the waitlist or after transplant survival can be incorporated into the algorithm, and the hazard ratios for established variables can be modified based on these analyses. It is anticipated that the collection of serial data will provide additional important information that will allow refinement of the algorithm. For example, changes in specific pulmonary function parameters over time may be more important than an absolute value provided at the time of listing. As newer information accrues, the algorithm can be modified to include it.

Dr. Kotloff will make the argument that the new lung allocation system requires prospective validation, but the means to do so is currently lacking. Indeed, prospective validation has never been applied to any changes in organ allocation policy since the OPTN came into existence. Computer simulation of organ allocation models is based on historical “turn-down” rates, which are generally higher for lungs than for other organs transplanted, in part due to a higher rate of lung dysfunction among brain-dead organ donors, but also in large measure due to the former allocation system, which offers the lung first to those who have experienced a longer waiting time who may not be sick enough to justify the risk of transplantation. Thus, computer models simulating lung allocation currently suffer from a lack of credibility. By continually reanalyzing 3-year patient cohorts and adjusting the algorithm accordingly, inequities and shortcomings should be identified relatively quickly.

**Advantages and Disadvantages of the New Algorithm**

With waiting time removed from allocation consideration, there will be no reason to actively list candidates until they are ready to be transplanted. Currently, there are many patients listed to “accrue waiting time” even though their listing centers have no intention to perform transplants in them, resulting in a large number of wasted hours by transplant coordinators trying to place lungs. The turn-down rate for lung offers is higher than that for any other solid organ. Using risk of death on the waiting list as a criterion for distribution should increase the efficiency of organ allocation logistics and should reduce the number of deaths while patients are on the waiting list. The allocation system only defines the order in which offers are made; it does not require centers to accept organs for patients in whom they do not wish to perform transplants. Thus, patients who wish to be transplanted who remain active on the list will have opportunities to receive organ offers, even if their net transplant benefit is minimal or negative.

It was a deliberate strategy of the subcommittee to attempt to remove subjectivity and “gameable” factors from the algorithm to enhance fairness. Factors that determine the LAS are in large part objectively measured, and would be difficult to manipulate without some degree of conspiracy with other health-care professionals (eg, patients who are coaxed to perform poorly on pulmonary function tests should be recognized by respiratory technologists). A lung review board will review special cases
and possibly to adjust LASs in unusual circumstances when clinicians may feel that the assigned LAS does not accurately reflect a candidate’s status.

The system is admittedly complex and difficult to understand, both for patients and for transplant professionals. An LAS will not predict when a given patient will be offered an organ, although individual centers will have access to their patient list and their LASs. But new patients who are added to the list at any time may have a higher score and thus may be more likely to receive a lung offer than patients who have been waiting longer. Because of confidence intervals for waitlist and posttransplant survival predictions, there is a legitimate statistical argument that the LAS does not necessarily discriminate accurately between two individuals with similar but different scores. However, two individuals with scores that are high and are close to each other should both receive offers before individuals who are much more likely to survive without a transplant. Some patients have expressed concern that they might “wait forever” for a lung offer. If they are well enough to do so, then perhaps there are more suitable candidates!

Concern has been expressed that the new allocation system favors patients with some particular diagnoses over those with other diagnoses. However, the point of the new system is to direct lungs to those patients who are at risk of death on the waiting list irrespective of their diagnosis. It turns out that diagnosis is an important factor (but definitely not the only factor) predicting both waitlist survival and posttransplant outcome. No patient with any diagnosis is precluded from having a high LAS, depending on the patient’s individual clinical characteristics.

The new lung allocation system does not address the geographic disparities among organ offers that, it may be argued, are inherent in the current allocation system. Currently, the lung allocation system requires that lungs be offered first to potential candidates within the local organ procurement organization of the donor hospital, and then to potential candidates in concentric 500-nautical-mile circles. However, once the new system is in place, it may be possible to accurately simulate the impact of altering this geographic distribution method. Finally, if the new system is successful at substantially reducing deaths on the waiting list, then this will reduce the power of subsequent analyses. However, this is a problem that the Lung Allocation Subcommittee would relish.

**The Future**

A key feature of the new algorithm is the requirement to perform new analyses every 6 months to continually improve the algorithm. Thus, the algorithm is not “fixed in stone” but is intended to be dynamic and to adapt to the population of patients currently being listed and undergoing transplantation. A long-term goal is the ability to incorporate data on QOL into the algorithm, but reliable QOL data on lung transplant candidates and recipients were not available for analyses. The relative value of QOL vs the importance of improving survival should be the subject of public discussion and debate.

It has been argued that changing the organ distribution algorithm only changes the postal codes of individuals who die because of the shortage of organs. The supply of suitable lungs for transplantation is woefully inadequate, and any change to the distribution algorithm does not address this fundamental problem. However, the new lung distribution algorithm should reduce waiting list deaths while avoiding futile transplantations in individuals who are unlikely to survive in any case. Some individuals may wait even longer for lungs for transplant than under the current system, but if they can survive longer without a transplant, this may be a fairer alternative for all. In the not-too-distant future, the use of lungs from non-heart beating donors may alleviate the lung donor shortage, ultimately making future arguments about fair distribution moot.

**Con**

**Robert M. Kotloff, MD, FCCP**

Prediction is very difficult, especially about the future.

Niels Bohr (Nobel Laureate in Physics)

For the past 15 years, lung allocation in the United States was based on a seniority system that prioritized candidates on the basis of the amount of time they had accrued on the waiting list. The system was easily understood, based on a simple and objective parameter (time), and was relatively resistant to manipulation. However, the system was called into question because it failed to accommodate those patients with a more rapidly progressive course who often could not tolerate the prolonged waiting times to transplantation and who were likely to die prior to receiving a lung. Indeed, excessive wait list mortality has been documented among certain patient populations, such as those patients with idiopathic pulmonary fibrosis and cystic fibrosis (CF), compared to patients with COPD, which is a disorder with a more protracted natural history even in the advanced stages. In response to the perceived ineq-
utilities of the time-based system, and under mandate of the federal government, a new system was recently implemented that allocates lungs on the basis of both waitlist urgency (ie, risk of death without a transplant) and net transplant benefit (ie, the difference between predicted posttransplant survival and survival with continued waiting). By incorporating this latter concept, the system attempts to avoid the pitfall of preferentially allocating the scarce donor organ pool to desperately ill patients with an unacceptably high posttransplantation mortality rate. While ethically appealing in its intended goals, this new system is potentially flawed in its attempt to make an exact science out of the imperfect art of predicting the natural history of lung disease.

THE NEED FOR VALIDATION

The new model, which is derived from a multivariate analysis of data from the comprehensive United Network for Organ Sharing (UNOS) national database, identifies 10 factors that are independently predictive of death on the wait list and seven factors that are predictive of death following transplantation. For each patient, these factors are utilized in a complex set of computations that result in a prediction of the exact number of days the patient is expected to live during an additional year of waiting and during the first year posttransplantation. The following hypothetical calculation that is provided in the official UNOS policy illustrates this: "Patient Y is expected to live 69.2 days during the following year on the waitlist and 262.9 days posttransplant during the following year." This degree of exactitude is necessary for a system that is intended to differentially rank a large number of patients for the purposes of organ allocation. However, Braitman and Davidoff, in an essay entitled "Predicting Clinical States in Individual Patients," caution that the use of such exact point estimates of the probability of clinical events "may lead users to underestimate the actual uncertainty hidden in those predicted probabilities." From a statistical perspective, we have no information on the actual confidence intervals (ie, degree of uncertainty) associated with the survival figures generated by the model nor do we know how closely the predicted survival estimates conform to actual outcomes. A first approximation of this can be obtained by internal validation techniques utilizing the data set from which the model was derived to test the reproducibility of the predictions. However, a common pitfall of prognostic models is that their accuracy degrades when they are subsequently applied to a new sample of patients (ie, they are not generalizable). Because of this, caution must be exercised in utilizing a predictive model until it is externally validated in populations that are distinct from the original one, ideally in a prospective fashion. In the case of the lung allocation model, neither internal nor external validation has been performed, and therefore the wisdom of implementing this model must be seriously questioned. In the words of the Evidence-Based Medicine Working Group: "Clinical decision rules that investigators have derived but not validated should not be considered ready for clinical application." The complex and unvalidated predictive model for lung allocation stands in stark contrast to the Model for End-Stage Liver Disease (MELD) that serves as the basis for liver allocation. MELD employs only the following three variables to predict mortality: bilirubin level; international normalized ratio for prothrombin time; and creatinine level. It was originally derived from a database composed of patients with advanced liver disease who were undergoing transjugular intrahepatic portosystemic shunt procedures at four medical centers within the United States and was immediately validated in a discrete set of patients undergoing transjugular intrahepatic portosystemic shunt procedures in the Netherlands. Prior to its adoption by UNOS in 2002, MELD was further validated utilizing four independent databases of adult patients, confirming its generalizability across a broad spectrum of liver diseases of varying severity. Given the methodological rigor with which MELD was developed and validated, it is not surprising that some studies have confirmed its predictive abilities when applied specifically to candidates on the waitlist for liver transplantation.

PREVIOUS EXPERIENCE WITH PREDICTIVE MODELS OF LUNG DISEASE

Based on the experience to date with prognostic models for predicting the natural history of various lung diseases, there is every reason to be skeptical about the validity of the lung allocation model. Space limitations preclude a full review of the literature for each disease; CF will be discussed as an example. Analyzing a cohort of 673 CF patients from the Hospital for Sick Children in Toronto, Kerem and colleagues published a landmark study in 1992 that identified FEV_{1} as the single most significant predictor of mortality. These investigators noted that an FEV_{1} of < 30% predicted was associated with a 2-year mortality rate of 50%, and they suggested using this FEV_{1} value as a threshold for lung transplant referral, a recommendation that was subse-
quently incorporated into published international guidelines for the selection of lung transplant candidates. Other single-center studies that followed offered discrepant findings, with median survival times of 3.9 to 4.6 years associated with an FEV1 of < 30%. In 2001, Liou and colleagues published a 5-year survivorship model that was derived from data on 5,800 patients in the multicenter Cystic Fibrosis Foundation Patient Registry and validated using data from an additional 5,800 registry patients. Nine parameters, including FEV1, were identified as independent predictors of mortality by multivariate analysis and were incorporated into the model. When applied to the validation cohort, this complex model performed in a superior fashion to the simpler model proposed by Kerem et al utilizing FEV1 alone. More recently, Mayer-Hamblett and colleagues developed and validated a 2-year mortality model utilizing methods identical to those of Liou et al in conjunction with a more current and larger cohort of patients (n = 14,572) from the Cystic Fibrosis Foundation Patient Registry. In contrast to the findings of Liou et al, this well-fitting model derived from the largest collection of data available on patients with CF provided no better diagnostic accuracy than the simpler FEV1 criterion. Both the multivariate model and the FEV1 alone were far better at identifying patients who would survive for 2 years than those who would die. Given the conflicting data generated by these studies, are we not justified in questioning the ability of the new lung allocation model, which was derived from a smaller cohort of CF patients and lacks validation, to predict mortality?

The challenge of predicting mortality in the subset of patients who are on a lung transplant waiting list is rendered even more problematic by the fact that this is a more homogeneous population of patients with many shared clinical characteristics and a much narrower spectrum of physiologic abnormalities. Vizza and colleagues highlighted this concern in an analysis of 146 CF patients awaiting transplantation at Washington University. A shorter 6-min walk distance, the presence of diabetes mellitus, and higher pulmonary artery systolic pressure, factors that are common to the UNOS lung allocation model, were predictive of mortality on the waiting list. However, the authors noted that there was no threshold for any of these factors that reliably separated the patients who died from those who were still alive, underscoring “the difficulties and limitations that will be encountered in trying to devise legitimate medical urgency criteria for allocating donor lungs.”

**Dealing With Uncommon Diseases: Should We Lump or Split?**

Another aspect of the lung allocation model that engenders concern is the method chosen to handle patient populations with less common lung diseases. Having identified underlying diagnosis as a major predictor of waitlist survival, an observation that has been corroborated by multiple previous studies, the model creates four major disease groups based on the leading indications for lung transplantation, as follows: COPD; primary pulmonary hypertension; CF; and idiopathic pulmonary fibrosis. In a highly unorthodox and seemingly unsubstantiated fashion, the model assigns all of the less common disease entities to one of these four major groups. For example, Eisenmengers syndrome is grouped with primary pulmonary hypertension despite available evidence suggesting that Eisenmengers syndrome is associated with a far more indolent and unpredictable natural history than primary pulmonary hypertension. Similar concerns can be raised about the arbitrary clustering of lymphangioleiomyomatosis and non-CF bronchiectasis with COPD, and obliterative bronchiolitis (unrelated to previous lung transplant) with idiopathic pulmonary fibrosis.

**Defining Transplant Benefit**

Finally, one must question the manner in which “transplant benefit” is defined in this model. The use of 1-year posttransplant survival is too heavily influenced by differences in disease-specific perioperative mortality rates and overlooks the fact that ultimately transplantation becomes the “great equalizer,” with all disease populations facing a similar set of long-term complications. As noted in the 2004 Report of the Registry of the International Society for Heart and Lung Transplantation, “there is some separation by diagnosis during the first year, but the survival ranking among the diagnoses shifts over the long-term” such that by 5 years most of the diseases share a similar outcome. Thus, 1-year survival cannot be used as a surrogate marker for long-term survival and should not, therefore, be employed in a calculation of transplant benefit. More fundamentally, is the net number of days of life gained through transplantation the exclusive and most appropriate measure of transplant benefit? Offering a median survival time of only 4.4 years, lung transplantation in its current state falls conspicuously short of the goal of meaningfully extending life for the majority of recipients. The greatest benefit of lung transplantation, in my opinion, is reflected in its impact on the quality of life (QOL) rather than on its duration. As such, I would argue that a COPD patient who
achieves 5 years of quality life with transplantation in place of 5 years of misery without it has realized immeasurable benefit from the procedure even if there is no net benefit in absolute number of days lived. Yet, as currently conceived, the new allocation system would recognize no transplant benefit for this type of patient and would consequently assign a very low priority score.

CONCLUSIONS

Dr. Tom Egan and his colleagues on the UNOS Lung Allocation Subcommittee are to be commended for their groundbreaking efforts in developing this first iteration of a risk-stratified allocation system for lung transplantation. Unfortunately, due to pressures arising from the federal mandate to implement the new system, a step that is considered to be essential before any predictive model is considered ready for widespread clinical use has been bypassed: statistical validation.26 In the absence of validation, we cannot assume that this more sophisticated allocation system is any less flawed than the straightforward seniority system that it is replacing. If we have learned anything from past efforts to devise prognostic models of lung disease, it is that the accurate prediction of the future is an elusive goal.

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