

Development of the New Lung Allocation System in the United States

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This article reviews the development of the new U.S. lung allocation system that took effect in spring 2005. In 1998, the Health Resources and Services Administration of the U.S. Department of Health and Human Services published the Organ Procurement and Transplantation Network (OPTN) Final Rule. Under the rule, which became effective in 2000, the OPTN had to demonstrate that existing allocation policies met certain conditions or change the policies to meet a range of criteria, including broader geographic sharing of organs, reducing the use of waiting time as an allocation criterion and creating equitable organ allocation systems using objective medical criteria and medical urgency to allocate donor organs for transplant. This mandate resulted in reviews of all organ allocation policies, and led to the creation of the Lung Allocation Subcommittee of the OPTN Thoracic Organ Transplantation Committee. This paper reviews the deliberations of the Subcommittee in identifying priorities for a new lung allocation system, the analyses under-

taken by the OPTN and the Scientific Registry for Transplant Recipients and the evolution of a new lung allocation system that ranks candidates for lungs based on a Lung Allocation Score, incorporating waiting list and posttransplant survival probabilities.

Key words: Lung transplantation, organ allocation, modeling, OPTN, SRTR, transplant benefit, waiting list

Introduction

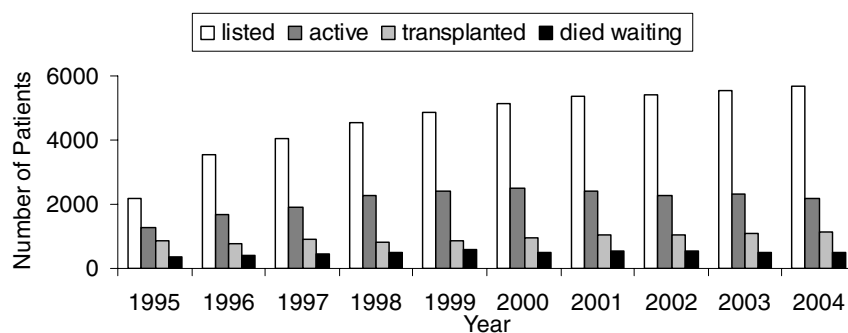
In May 2005, the policy for lung allocation for transplantation in the United States was changed by the Organ Procurement and Transplantation Network (OPTN),¹ from a system that allocated donor lungs based primarily on waiting time to a system that allocated lungs based primarily on a Lung Allocation Score (LAS). The LAS for potential lung recipients is calculated from estimates of survival probability while on the lung transplant waiting list and following transplantation. This article reviews the history of lung allocation in the United States, the rationale for making sweeping changes to the system, and the analyses that were performed by the OPTN and the Scientific Registry of Transplant Recipients (SRTR) that were the basis for the new system. It also describes the new system and its effects.

Unless otherwise noted, the statistics in this article are drawn from the reference tables in the *2005 OPTN/SRTR Annual Report*. A companion article in this report, 'Analytical Methods and Database Design: Implications for Transplant Researchers, 2005', explains the methods of data collection, organization and analysis that serve as the

¹The Organ Procurement and Transplantation Network is the network that links the organizations of the solid organ donation and transplantation system in the United States, including transplant centers, organ procurement organizations and histocompatibility laboratories. The United Network for Organ Sharing (UNOS) is a private nonprofit membership organization that has operated the OPTN under contract with the Health Resources and Services Administration (HRSA), part of the U.S. Department of Health and Human Services, since 1986. The SRTR, administered under contract to HRSA by the University Renal Research and Education Association with the University of Michigan, supports the ongoing evaluation of the scientific and clinical status of solid organ transplantation in the United States.

*Note on sources: The articles in this report are based on the reference tables in the *2005 OPTN/SRTR Annual Report*, which are not included in this publication. Many relevant data appear in the tables figures included here; other tables from the *Annual Report* that serve as the basis for this article include the following: Tables 12.2, 12.3 and 13.4. All of these tables may be found online at <http://www.ustransplant.org>.

Figure 1: Number of potential recipients listed (open bars), and listed in active status (dark gray bars) for isolated lung transplants, number of isolated lung transplants performed by year (light gray bars), and number of patients dying on the lung transplant list (black bars) by year.



Source: 2005 OPTN/SRTR Annual Report, Tables 12.1b, 12.3, 12.4.

basis for this article (1). Additional detail on the methods of analysis employed herein may be found in the reference tables themselves or in the technical notes of the *OPTN/SRTR Annual Report*, both available online at <http://www.ustransplant.org>.

History of Lung Allocation and Lung Allocation Policy

In the last 15 years, lung transplantation has emerged as a reasonable therapy for patients with a variety of end-stage lung diseases. The number of lung transplant programs has grown, but the relative scarcity of suitable lung donors among the pool of conventional brain-dead organ donors has resulted in increasing numbers of patients listed for lung transplant, and development of relatively strict criteria for candidacy (2). Under the previous system that allocated organs to transplant candidates based on their waiting time, the number of deaths on the waiting list increased, and approximately 1000 lung transplants were performed annually (Figure 1).

In 1990, OPTN thoracic organ allocation policies were amended to include provisions for the allocation of donor lungs to isolated lung transplant candidates. Before this, the policies had provided for the allocation of donor hearts and heart-lung combinations, but not for isolated single or double lungs. The initial policy requirements were basic. Donor lungs were allocated based on ABO match and the amount of time that candidates had accumulated on the waiting list. Offers were made first to candidates within the local organ procurement organization (OPO) donor service area of the hospital where the donor was located, then within expanding 500-nautical-mile concentric zones around the donor hospital. Until the recent implementation of the new lung allocation system, these original lung allocation policies remained largely unchanged, with one notable exception: In 1995, an additional 90 days of waiting time were provided to candidates with idiopathic pul-

monary fibrosis (IPF) to address the increased waiting list mortality among this group.

In 1998, the Final Rule on organ allocation was published by the Department of Health and Human Services (3). The Final Rule, which went into effect in March 2000, set forth requirements for the OPTN that emphasized the broader sharing of organs, reducing the use of waiting time as an allocation criterion, and the creation of equitable organ allocation systems that focus on the use of objective medical criteria and medical urgency for allocation. A report was commissioned from the Institute of Medicine (IOM) to respond to publication of the Final Rule (4). The IOM report agreed that organ allocation should be based on measures of medical urgency while avoiding futile transplants, should minimize the effect of waiting time, and should employ broader geographic sharing in organ allocation.

The OPTN Thoracic Organ Transplantation Committee responded to the requirements for organ allocation published in the OPTN Final Rule by agreeing to study the feasibility of developing a system for lung allocation based primarily on medical urgency criteria rather than waiting time.² The Committee agreed that waiting time was an ineffective measure of equity in organ allocation, and should be considered only as a part of a framework of organ allocation that includes other relevant factors such as medical urgency and cold ischemic time.³

The following year, the Thoracic Committee formed the Thoracic Organ Allocation Modeling Subcommittee (later called the Lung Allocation Subcommittee) to study the possibility of prioritizing lung candidates according to clinical criteria or urgency status, to design equity and

²Report of the OPTN Thoracic Organ Transplantation Committee to the Board of Directors, June 1998.

³Report of the OPTN Thoracic Organ Transplantation Committee to the Board of Directors, November 1998.

performance measures for evaluating the effectiveness of alternative lung allocation methods, and to recommend a specific alternative lung allocation system to be modeled.⁴ The Subcommittee, in keeping with the goals of the Final Rule, announced the following general goals for the future lung allocation system: (1) reduction of mortality on the lung waiting list; (2) prioritization of candidates based on urgency while avoiding futile transplants; and (3) 'de-emphasizing the role of waiting time and geography in lung allocation within the limits of ischemic time'.⁵ The Subcommittee outlined a methodology that would use multi-variable modeling to determine waiting list survival based on data collected from transplant candidates at the time of listing, with the intent to update clinical variables for candidates as their conditions changed.

The Subcommittee continued its review of data and analyses over the next 2 years until an early version of the lung allocation system was developed. This early model generated a distribution algorithm score based on candidates' predicted waiting list and posttransplant survival, described in more detail below. This preliminary version of the new lung allocation system was presented at the OPTN/UNOS Conference on Lung Allocation Policy in March 2003. In large part, the members of the transplant community attending that forum expressed support for the Subcommittee's goal of designing a system that departed from waiting time as a primary allocation factor. However, much of the input from the community suggested that the Subcommittee should continue the development of a new system with a more substantial and more current data set. Following the conference, the Subcommittee worked to incorporate many of the suggestions it had received, and in August 2003, a proposed lung allocation system was released for public comment.

The transplant community at large did not favor this initial proposal, expressing concerns that the cohort of candidates used in the analyses was not current enough to sufficiently represent recent survival rates among all diagnoses. The notion that the allocation system would be based on the most current cohort of patients was apparently not articulated well enough and was not widely understood.

There were also concerns that the diagnostic factors used to predict survival did not include all of the factors that clinicians had found to be predictive of survival among end-stage lung disease patients. For example, analyses of wait-listed patients failed to identify forced expiratory volume in 1 s (FEV-1) with increased risk of death for patients with cystic fibrosis (CF), although FEV-1 has been recog-

nized as a major predictor of mortality among CF patients in the CF registry (5). Also, no parameter of right heart function was associated with an increased risk of mortality among patients waitlisted with primary pulmonary hypertension (PPH), despite the documented association of parameters of right heart function, including central venous pressure and pulmonary artery (PA) pressure, with survival among patients with PPH (6). However, neither central venous pressure nor right atrial pressure was collected by the OPTN, and thus these data were not available for analysis. In addition, closer scrutiny suggested that only patients with end-stage CF and pulmonary hypertension were on the U.S. lung transplant waiting list, and the relatively narrow range of FEV-1 values in CF patients and PA pressure values in PPH patients reduced the power of these parameters to identify patients at an increased risk of death.

Patient advocacy groups voiced concern that the use of separate survival models for major diagnoses drew prejudicial distinctions among candidates with different illnesses. Further, the pediatric lung transplant community contended that the proposed system did not provide for allocation preferences to pediatric candidates to address the special urgency needs among that population. In response to input from the public, the OPTN Thoracic Organ Transplantation Committee and the Lung Allocation Subcommittee returned to the drawing board to address these concerns.

In June 2004, the OPTN Board of Directors unanimously approved the revised lung allocation policies proposed by the Thoracic Committee. The goals of the new policies, as stated by the Committee in its proposal, are to: '(1) reduce the number of deaths on the lung transplant list; (2) increase transplant benefit for lung recipients and (3) ensure the efficient and equitable allocation of lungs to active transplant candidates'.⁶ The allocation system assigns priority for donor offers by calculating a LAS for each active registered lung candidate aged 12 years and older. The LAS is an adjusted scale from 0 to 100 that represents a weighted combination of each candidate's predicted survival during the following year on the waiting list and his or her predicted survival during the first year following a transplant. In short, the LAS features the net benefit of the transplant to the candidate as well as clinical urgency, and it is calculated using a series of pretransplant clinical diagnostic data that analyses revealed to be predictive of both pre- and posttransplant outcomes. In addition, the system continues to use geographic proximity to the donor hospital (geographic zones), ABO match and individual candidate screening criteria (size, serology) as allocation factors. As always, the treating physician and the patient have the discretion to accept or decline a lung offer.

⁴Report of the OPTN Thoracic Organ Transplantation Committee to the Board of Directors, November 1999.

⁵Report of the OPTN Thoracic Organ Transplantation Committee to the Board of Directors, June 2000.

⁶Report of the OPTN Thoracic Organ Transplantation Committee to the Board of Directors, June 2004, Exhibit A.

A Lung Review Board was also created to review situations in which a treating physician has a reason to believe a LAS may not adequately reflect the needs of a particular candidate or where diagnostic data needed to calculate a score are not available for a particular candidate. Finally, as a part of the proposal, and in response to earlier concerns by the transplant community, the OPTN completed a national project to collect extensive clinical data on a large sample of transplant candidates and recipients from centers across the country to acquire additional data for survival analyses and help make future revisions to the lung allocation system.

Following programming on the UNetsm system (an Internet-based program for collecting transplant data), the LAS system was implemented and began allocating donor lungs on May 4, 2005. Additional detail and clarification on the existing policies were also made when the new system began operating. These late changes addressed policy provisions related to providing and updating candidates' clinical data, resolving situations in which multiple candidates have equal priority for an organ offer, and operating the Lung Review Board. In addition, a provision was added to the system to allow transplant programs to override adverse decisions of the Lung Review Board, subject to peer review.

Ethical Issues Considered by the Lung Subcommittee

The members of the Lung Allocation Subcommittee realized that the task of designing and implementing a new system for organ allocation was a serious responsibility, representing an opportunity to modify a system that many believed was outdated and was no longer serving the best interests of patients with end-stage lung disease. The ethical issues considered and discussed by members of the Subcommittee have been reviewed elsewhere (7).

Briefly, four major ethical principles were considered from the outset. *Equity*, a sense of fairness or impartiality, demands that there should be no bias or discrimination in selecting a recipient for a potential donor. *Justice* is the principle of rendering to each individual what is due to him or her. *Beneficence*, the requirement that physicians and surgeons act in ways reliably expected to result in a greater balance of clinical good over harm for their patients, implies that the patient should experience a net benefit from transplant. *Utility*, the principle of making the best use of a scarce resource, is always a consideration in questions of organ allocation. The IOM report emphasized that it was critical to balance justice with utility so as not to waste the precious resource of donor organs in short supply (4). Finally, the new system needed to be fair and transparently so, and ideally it would be based on objective, evidence-based data.

Goal of the Algorithm

Members of the Subcommittee believed that the principal goal of the new allocation system should be to reduce the number of deaths among potential and actual lung transplant candidates. Although it was recognized that lung transplantation offers an opportunity to substantially improve quality of life among survivors, this benefit is notoriously difficult to quantify, and reliable objective data on quality of life for wait-listed and transplanted patients in the United States were simply not available.

The current liver allocation system (Model for End-stage Liver Disease/Pediatric End-stage Liver Disease, or MELD/PELD) is based solely on waiting list survival as a measure of urgency, as is the status system for heart allocation. In the case of lung candidates, however, to focus solely on waiting list mortality ran the risk of promoting futile transplants: More deaths might occur as a result of lung transplant procedures being performed on critically ill candidates with a high probability of posttransplant death. Thus, it was the goal of the Subcommittee to design a system that would offer organs first to patients at the highest risk of mortality on the waiting list, balanced somehow with the probability of posttransplant survival. That is, if two patients had a similarly high risk of dying on the waiting list, then the lung or lungs available should be directed first to the patient with the best chance of posttransplant survival.

It was the intent of the Subcommittee to base the allocation system on objective clinical data elements that could predict risk of waiting list or posttransplant death, rather than relying on subjective parameters of illness severity. As much as possible, the Subcommittee wished to exclude from the algorithm any factors that might be easily manipulated by patients or physicians. The Subcommittee also wanted to design a system that could adapt to changes in clinical practice and to changes in characteristics of populations of lung transplant candidates. With these as the specified goals of the design of the new allocation system, analyses were undertaken to determine if indeed there were objective factors associated with increased or decreased risk of death either on the waiting list or after lung transplantation.

Initial Subcommittee Analyses

The Lung Allocation Subcommittee recommended that the first step in the development of a lung allocation system be to determine if it was possible to develop meaningful multi-variable models for waiting list mortality by disease. As four diagnoses accounted for approximately 80% of the waiting list registrations, the initial analyses focused on these groups: emphysema/COPD, including alpha-1 antitrypsin deficiency (COPD), IPF, CF and PPH. The initial analyses were limited to adult patients, defined as age 18 years and older. Because it was anticipated that factors would vary

Table 1: Results of multivariable diagnosis-specific models for waiting list mortality

COPD	CF	IPF	PPH
In ICU/hospital	In ICU/hospital	In ICU/hospital	In ICU/hospital
Steroid dependency ≥ 5 mg/day	Steroid dependency ≥ 5 mg/day	On ventilator	On ventilator
2 or more i.v.-treated pulmonary sepsis episodes within last 12 months	Diabetes	6-minute walk distance < 150 ft	Steroid dependency ≥ 5 mg/day
Alpha-1 vs. other COPD	Wedge pressure	Wedge pressure	Wedge pressure
FEV1 % predicted	FVC % predicted	FVC % predicted	
O ₂ requirement at rest	Cardiac output	PA systolic	
BMI	BMI	Weight	
Age		Age	

Source: OPTN.

by disease, analyses were performed separately based on diagnosis for waiting list mortality and for posttransplant mortality. The plan was to examine the disease-specific models as a first step and then to combine them all into one overall model at a later date, if possible, perhaps using interactions to account for differential effects by diagnosis. The Subcommittee decided to focus the analyses on outcomes within 1 year, which allowed for the use of a recent cohort and reduced the impact of posttransplant factors beyond a year. It was reasoned that the impact of pretransplant factors would diminish with time after transplantation, and that other factors would affect later post-transplant survival.

Waiting list mortality

Mortality on the waiting list was examined using a Cox proportional hazards model. Candidates removed from the waiting list for transplant or reasons other than death were censored at the time of removal from the waiting list. The chronologic time from listing was used, regardless of whether a patient was inactive on the waiting list at any point during this period, as candidates could have died while inactive. Initially, all factors collected on the OPTN Transplant Candidate Registration (TCR) form at the time of listing were considered as potential predictors of waiting list mortality. This included a wide variety of demographic, medical and social history, clinical, hemodynamic, and pulmonary function factors. After further discussion, the Lung Subcommittee chose to exclude factors from consideration that could be considered easily manipulated or that would not be appropriate for the use in prioritizing candidates for donor lungs within the allocation system, such as ABO or race/ethnicity.

The cohort for this analysis included all patients added to the lung transplant waiting list between January 1, 1997 and December 31, 1998, with COPD (n = 1461), CF (n = 708), IPF (n = 608) and between January 1, 1995 and December 31, 1998, for patients with PPH, in order to analyze a cohort of sufficient size (n = 636 PPH patients). There were no exclusions based on candidate age or previous transplant. A p-value of < 0.05 was considered statistically significant.

There was a dramatic effect of diagnosis on waiting list mortality risk (8). The *percentage* of wait-listed patients dying by the time of analysis was 13.8% for COPD patients, 33% for IPF patients, 28% for CF patients and 30% for patients with PPH. For each of these four diagnoses, risk factors that were significant predictors of increased or decreased hazard of death on the waiting list were identified; they are listed in Table 1.

Posttransplant mortality

To examine the impact of candidate characteristics on post-transplant mortality within 1 year, a multivariable logistic regression analysis was performed. For patients with known status at 1 year (alive or dead), a weight of 1 was used. For patients reported as alive but with incomplete follow-up at 1 year, a weight was used that corresponded to the proportion of the 365-day interval for which the patient's status was known. All factors collected on the OPTN TCR and Transplant Recipient Registration forms that were not considered manipulable and were deemed appropriate for the use in an allocation system were considered as potential predictors for posttransplant mortality. This included a wide variety of demographic, clinical, hemodynamic, and pulmonary function factors.

The cohort for this analysis included all deceased donor lung-only transplants performed between January 1, 1996 and June 30, 1999, with COPD (n = 1422), CF (n = 498), IPF (n = 463) or PPH (n = 146). There were no exclusions for recipient age or previous transplant. A p-value of < 0.05 was considered statistically significant. Once again, diagnosis was a significant factor in posttransplant survival. Kaplan-Meier survival at 1 year for each of these diagnoses was 79.7%, 80.2%, 66.0% and 64.0%, respectively (9). Other factors identified by the multivariable analysis are shown in Table 2.

History of Diagnosis Grouping

Once it was established that data available at the time of listing and transplant could predict waiting list and post-transplant mortality for the four most common diagnoses,

Table 2: Results of multivariable diagnosis-specific models for posttransplant mortality within 1 year

COPD	CF	IPF	PPH
In ICU/hospital at transplant	Drug-treated peptic ulcer disease prior to listing	On mechanical support at transplant	In ICU at transplant
Older age		History of coronary artery disease at listing	Single lung transplant
Center volume		pCO ₂ at transplant	Higher weight

Source: OPTN.

attention was directed toward predicting survival probabilities for the remaining (less common) diagnoses that together constituted 20% of the patients listed for lung transplantation. However, the numbers of patients with these less common diagnoses did not constitute sample sizes large enough to build reliable diagnosis-specific mortality models. It was decided that those less common diagnoses would borrow strength from one of the above four main diagnoses with similar clinical and statistical features, if they could be grouped together. In this way, risk factors found to be important in predicting survival for one of the main diagnoses might also assist in predicting survival for the less common diagnoses grouped with them. Because of the convincing data showing that diagnosis was a significant predictor of mortality, diagnoses with sufficient data would retain a diagnosis-specific hazard to better capture their survival probabilities.

Thus, the Subcommittee reviewed data for other diagnoses with relatively small numbers for waiting list survival and observed posttransplant survival. Figures 2 and 3 show waiting list and posttransplant survival rates, respectively, for each of the four main diagnoses, as well as for less common diagnoses with sufficient data to statistically inform grouping decisions. Based on these survival probabilities and the pathophysiology of the underlying disease (i.e. primary obstructive, restrictive, vascular or infectious), patients with other diagnoses listed for lung transplantation were assigned to one of the four diagnosis groups designated by letter (Table 3). Diagnoses that did not have enough statistical information upon which to base a grouping decision were assigned to one of the four groups entirely on clinical grounds.

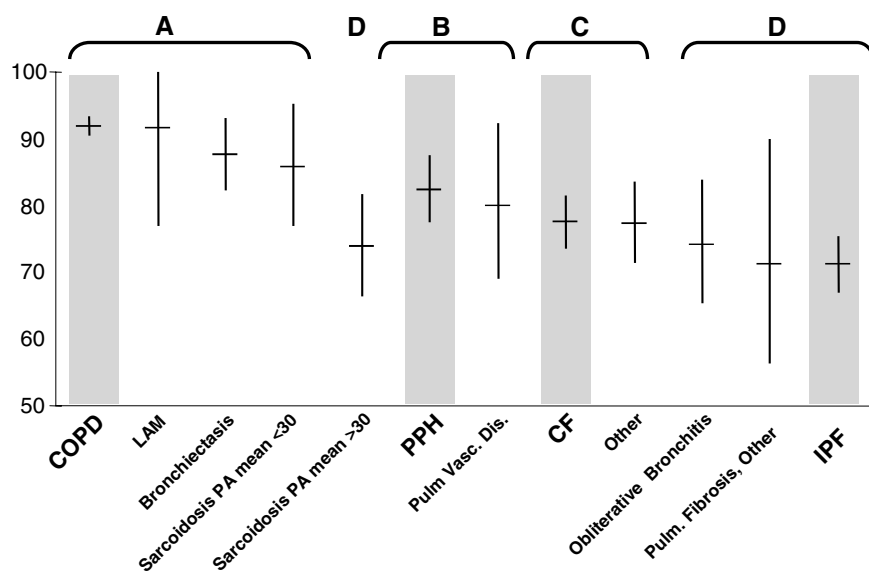
Additional analyses were performed to test whether the hazards for each of the less common diagnoses in Table 3 were statistically different from the more common diagnoses in the group to which they had been assigned. The results from these analyses showed that, except for sarcoidosis, all the less common diagnoses were statistically similar with respect to mortality to those in their assigned diagnosis group ($p > 0.05$). The pathophysiology of sarcoidosis is variable; some patients with sarcoidosis have mainly restrictive disease, while others have mainly obstructive disease and frequently pulmonary hypertension develops. When patients with sarcoidosis were stratified based on their mean PA blood pressure, it appeared that

pulmonary hypertension was associated with a lower waiting list survival comparable to that of IPF patients. Patients with sarcoidosis who had normal mean PA pressure (≤ 30 mmHg) had waiting list survival rates similar to rates of those with COPD (see Figure 2). Therefore, patients with sarcoidosis with a mean PA pressure ≤ 30 mmHg were assigned to Group A, while those with sarcoidosis and a mean PA pressure > 30 mmHg were assigned to Group D.

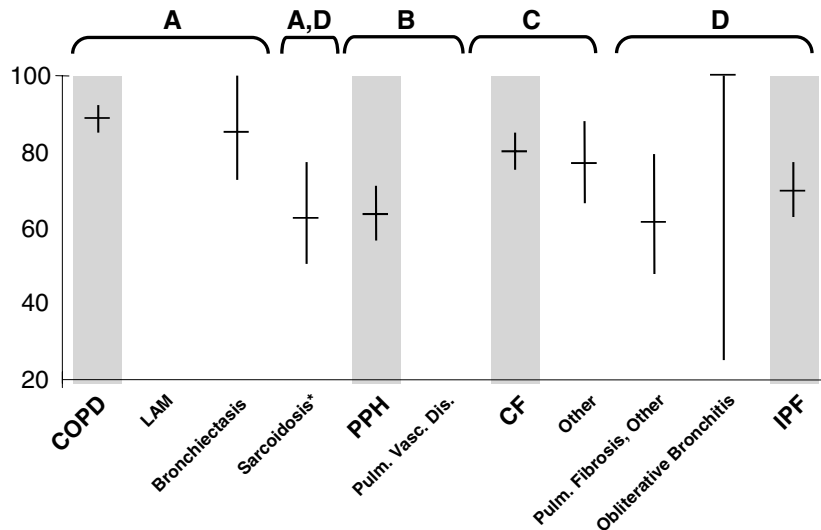
Incorporation of Pediatric Candidates

Pediatric candidates for lung transplantation pose vexing challenges. In young patients, there are serious size constraints for thoracic organs in general and lungs in particular, because of the effect of age and height on the volume of the chest cavity that must accommodate the graft. Fortunately, the incidence of life-limiting lung disease in very young patients is quite low, making the demand for pediatric lungs much less than that seen for adults with end-stage lung diseases. However, the number of sudden deaths leading to organ donation in children is also low, making the number of potential lung donors in this segment of the population also low, and inadequate to meet the demands of lung transplant programs.

Based on analysis of the distribution of diagnoses of wait-listed and transplanted pediatric candidates and recipients, it appeared that there was a difference in diagnosis patterns and incidence of diagnoses among children younger than 10 or 11 years, and among teenagers, whose incidence of certain diagnoses for end-stage lung disease resembled that of a cohort of adults in the third decade of life. Additional analyses of waiting list and posttransplant survival by age for patients younger than 18 years (summarized partially in data tables of the *OPTN/SRTR Annual Report*) led the Subcommittee to conclude that there appeared to be a 'break point' at the age of 12 years. Adolescent and teenage lung transplant recipients aged 12 years and older had similar incidence of diagnoses and waiting list and posttransplant survival to young adults, while children younger than 12 years old had different diagnoses and survival probabilities. Thus, the Subcommittee decided to group all potential recipients younger than 12 years together as a separate group (Group E), place all patients aged 12 years and older in Groups A through D, and re-



Survival rates are represented by the short horizontal lines; 95% CIs are represented by the vertical lines. LAM=lymphangioleiomyomatosis. *All patients transplanted with sarcoidosis and PA pressure <30 mm Hg died within one year of transplant. Source: SRTR Analysis, 2002.



Survival rates are represented by the short horizontal lines; 95% CIs are represented by the vertical lines. LAM=lymphangioleiomyomatosis. *All patients transplanted with sarcoidosis and PA pressure <30 mm Hg died within one year of transplant. Source: SRTR Analysis, 2002.

Figures 2 and 3: One-year adjusted survival by diagnosis, based on a multivariable mortality model for patients in the group. The survival rates are represented by the short horizontal lines, and the 95% confidence intervals are represented by the vertical lines. LAM = lymphangioleiomyomatosis. (A) Survival on the waiting list. (B) Survival posttransplant. *All patients transplanted with sarcoidosis and PA pressure <30 mmHg died within 1 year of transplant.

peat the analyses to identify predictors of waiting list and posttransplant survival.

Because of the small number of potential recipients younger than 12 years, risk factors for death cannot be reliably calculated with the available data. After consultation with large-volume pediatric lung transplant programs at Children’s Hospital of Philadelphia and St. Louis Children’s Hospital, Washington University, it was decided that, until sufficient data become available, time on the waiting list remained the most appropriate way to allocate lungs to this small group of patients.

Analyses with All Patients

Group-specific Cox proportional hazards models for both waiting list and posttransplant survival were developed which now included patients aged 12 years and older as well as patients with all diagnoses. Groups A, C and D included patients listed for a first transplant between January 1, 1997 and December 31, 1998, and Group B included those listed between January 1, 1995 and December 31, 1998; for all groups, patients who received a first transplant in the same time period were included in the analyses. Cox models were chosen in preference to logistic

Table 3: Diagnosis groups and their constituent diagnoses

Group A	Group B	Group C	Group D
Chronic obstructive pulmonary disease (COPD)	Primary pulmonary hypertension (PPH)	Cystic fibrosis (CF)	Idiopathic pulmonary fibrosis (IPF)
Emphysema	Eisenmenger's syndrome	Immune deficiency syndromes, e.g. IgG deficiency	All other restrictive lung diseases, including hemosiderosis
Alpha-one antitrypsin deficiency emphysema	All specific pulmonary vascular diseases, including pulmonary venous obstructive disease, chronic pulmonary thromboembolic disease		Eosinophilic granulomatosis
Bronchiectasis, including primary ciliary dyskinesia			Sarcoidosis with mean PA pressure >30 mmHg
Lymphangioleiomyomatosis (LAM)			Scleroderma/CREST
Sarcoidosis with mean PA pressure \leq 30 mmHg			Bronchoalveolar carcinoma (BAC)
			Bronchiolitis obliterans syndrome (BOS) following lung transplant
			Primary graft failure following lung transplant

Source: SRTR.

regression analysis for posttransplant survival because of improved handling of censored patient histories and flexibility to study areas under patient-specific survival curves during the first year after transplantation. Again, diagnosis group was a significant predictor of survival, and statistically significant predictors of mortality on the waiting list and posttransplant for the four groups were similar to those identified in earlier analyses of the four main diagnoses. Inclusion of the additional diagnoses and the younger patients did not materially affect the magnitude or direction of estimated hazards in these models (10,11). For Group E, the small number of patients ($n = 131$) and waiting list deaths ($n = 43$) made interpretation of the data unreliable.

Development of Mechanics of the Algorithm

From early deliberations of the Lung Allocation Subcommittee, the concept of survival with or without a transplant was identified as central to the idea of transplant benefit. Translating this concept into a numerical score required several key insights and decision points.

The first key insight is that a patient's probability of survival changes over time, so that any assessment of risk or benefit should allow updates based on changes in risk. This posed a challenge for those developing the first iteration of the lung allocation system algorithm, because the OPTN did not then collect serial data on lung transplant candidates. The only indirectly measured time-dependent predictor available for modeling waiting list survival at the time of a potential organ offer was the amount of time that a patient had survived since listing, which to some extent captured additional information regarding current patient risk. The continually changing probability of surviving over a fixed period after an organ offer knowing that a patient had survived since listing was developed as a theoretical method called prosper function analysis and was used in early iterations of algorithm development (12,13). The Lung Allocation Subcommittee eventually decided to simplify the method so that it corresponded to

more standard calculations of survival that were computationally quick at producing ranks in real time and completely removed dependence on waiting time from the algorithm.

The original goal of allowing estimates of patient risk to change over time is currently accomplished more directly by frequent collection of data for updating a patient's score. This approach has potential for improvement in the long term since current waiting list and posttransplant models are restricted to data collected at listing or transplant only. In the course of applying the algorithm, as patient outcome data are prospectively collected, changes in key predictors over time will also be evaluated and potentially included in future iterations of the algorithm. A lung data audit conducted by the OPTN and funded by HRSA is being used to identify additional useful predictors currently not used in the allocation algorithm.

Another decision point in developing the algorithm was whether to summarize patients' waiting list and posttransplant prognosis—either by using their probability of survival after a certain window of time, for instance their 1-year survival probability, or by taking into account the risk of death along the way by using their expected lifetime over the same period. This latter measure translates into area under a survival curve during the time window of interest. These different methods of summarizing survival using a single number are demonstrated in Figure 4 (14). Two candidates might have the same 1-year survival probability, based on their individual risk factors, while their expected survival times over the same 1-year period would differ. The Subcommittee felt that expected survival time with or without an organ, estimated using an area under a patient's relevant posttransplant or waiting list survival curve, respectively, better captured the gain to be made from receiving a transplant.

Figure 5 (14) shows how a measure of waiting list urgency and posttransplant survival (expected survival over a 1-year period) is used to calculate transplant benefit. A candidate's expected 1-year transplant benefit is calculated

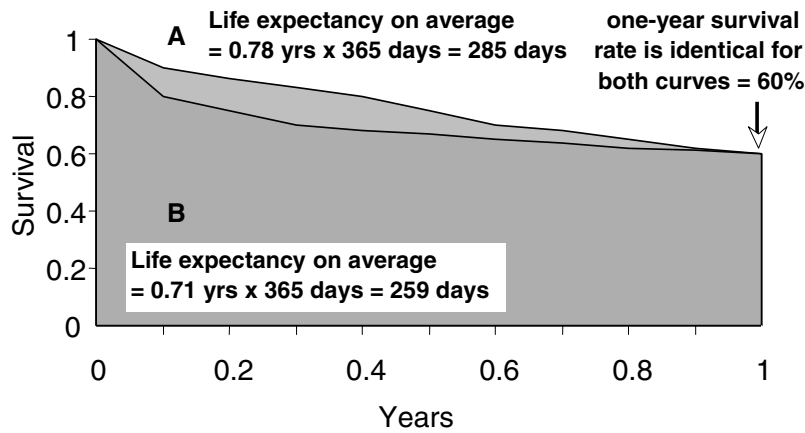


Figure 4: Two hypothetical patients can have similar *interval 1-year survival*, but Patient A (top line) experiences more days of survival on average than Patient B (lower line). If interval 1 year survival is compared, these patients are indistinguishable. If area under the curve (representing average days of survival) is compared, the difference between the two patients is clear. Patient A has more expected days of survival than patient B.

Source: SRTR Analysis, 2003.

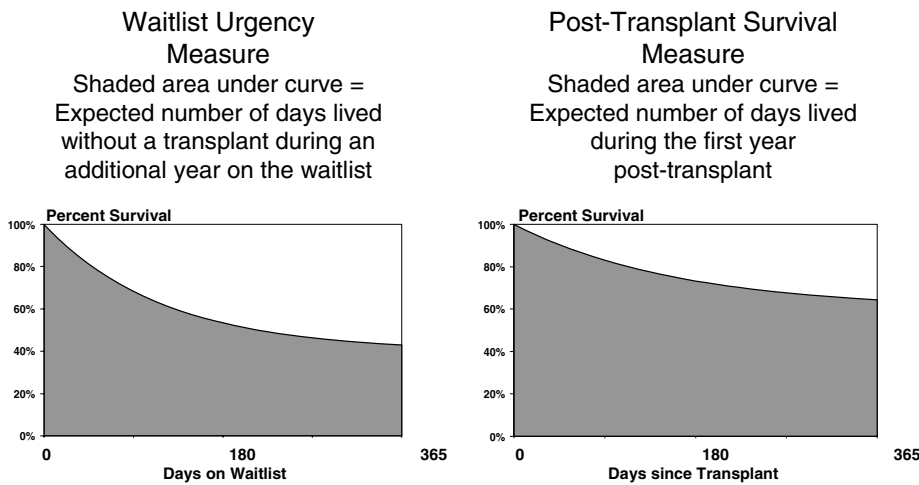


Figure 5: Example of a waiting list survival curve (left) and posttransplant survival curve (right) for a hypothetical patient. Area under the waiting list curve is a measure of transplant urgency, while area under the posttransplant survival curve is a measure of projected first-year posttransplant survival. The difference between the two is a measure of transplant benefit. Reproduced with permission from Marcel Dekker, Inc. (14)

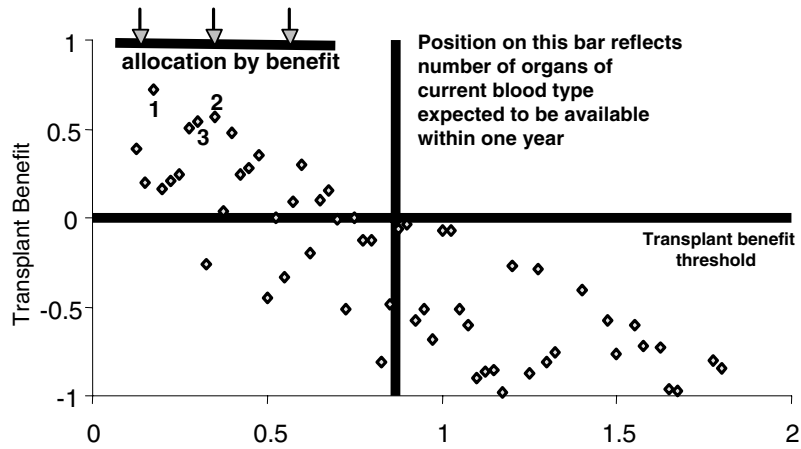
Source: SRTR Analysis, 2004.

by subtracting the waiting list urgency measure from the posttransplant survival measure. Candidates represented by Figure 5 would have a positive transplant benefit since they have a longer expected lifetime with a transplant than they would have if they were to remain on the waiting list. However, it is possible for some candidates to have a negative benefit—that is, their expectation of posttransplant lifetime would be less than if they continued to remain on the waiting list without a transplant.

Another key decision was how to combine the numerical summaries of the waiting list urgency measure and transplant benefit measure into a single allocation score. Options for selecting the relative importance of urgency versus transplant benefit are depicted in Figures 6–8. Prioritizing based on benefit alone (Figure 6) might allocate organs to patients with a high chance of survival on the waiting list over the short term; candidates who could afford to

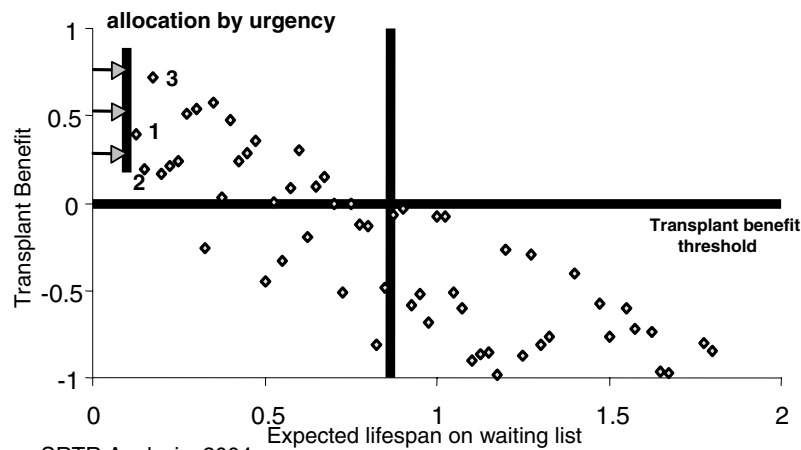
wait longer for a lung and in some cases might elect to do so upon being offered an organ. Prioritizing by urgency alone (Figure 7) might allocate organs to patients with poor posttransplant outcomes, resulting in a small expected lifetime from the transplanted lung. After considerable deliberation, and some mathematical modeling by the SRTR with the Thoracic Simulated Allocation Model (TSAM), the Subcommittee decided that the 45° bar descending through the points on the scatter plot representing listed patients depicted in Figure 8 was an attractive option that captured patients with high benefit while allowing for patients with high urgency quicker placement than an algorithm based on benefit alone.

Transplant benefit over different time periods was explored and it was determined that allocation ranks were essentially the same whether a 1- or 2-year horizon was used in calculating transplant benefit that determined



Source: SRTR Analysis, 2004.

Figure 6: Scatterplots of expected waiting list survival and calculated transplant benefit for a hypothetical population of patients of a particular blood type (transplant benefit = expected posttransplant survival minus expected waiting list survival) allocated by benefit alone. Patients below the ‘transplant benefit threshold’ have a negative transplant benefit. Only so many organs will become available within a year for this blood group, so not all listed patients can be transplanted. As time progresses, more patients can be added to the scatterplot; patients are removed if they are transplanted or if they die or are removed from the waiting list. If organs were offered solely based on *transplant benefit*, the allocation order is depicted as a horizontal bar descending through the patient points on the scatterplot, with the allocation order as shown (1–3). Reproduced with permission from Marcel Dekker Inc. (14).



Source: SRTR Analysis, 2004.

Figure 7: Scatterplots of expected waiting list survival and calculated transplant benefit for a hypothetical population of patients of a particular blood type (transplant benefit = expected posttransplant survival minus expected waiting list survival) allocated by urgency alone. Patients below the ‘transplant benefit threshold’ have a negative transplant benefit. Only so many organs will become available within a year for this blood group, so not all listed patients can be transplanted. As time progresses, more patients can be added to the scatterplot; patients are removed if they are transplanted or if they die or are removed from the waiting list. If organs were offered solely based on *urgency*, the allocation order is depicted as a vertical bar crossing through the patient points on the scatterplot, with the allocation order as shown (1–3). Reproduced with permission from Marcel Dekker Inc. (14).

allocation scores. Because the shorter time horizon allows the algorithm to be updated based on the most recent clinical outcome data, a 1-year time horizon was selected. One-year survival was also preferred by the members of the Subcommittee because of the belief, alluded to above, that pretransplant factors that played a role in posttransplant

survival would have a diminishing impact as time went on after transplantation.

The definitions and formulas used to calculate the LAS are summarized in Table 4. The raw allocation score that captures the 45° angle used in allocation is equal

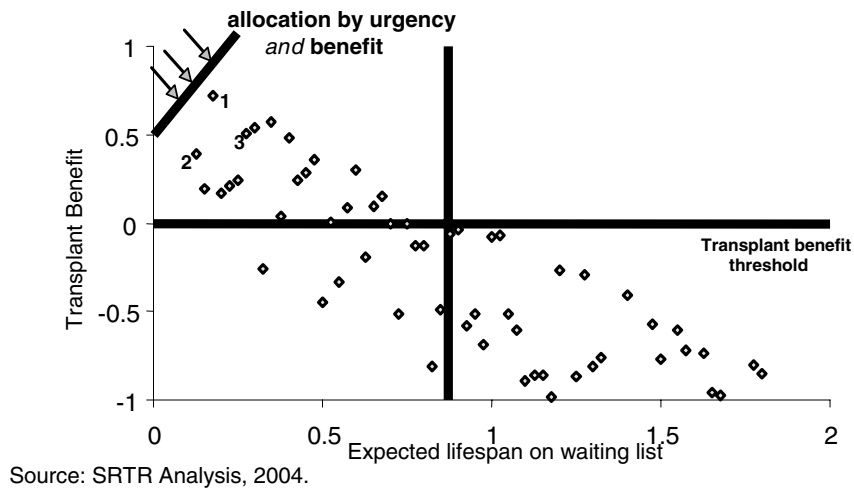


Figure 8: Scatterplots of expected waiting list survival and calculated transplant benefit for a hypothetical population of patients of a particular blood type (transplant benefit = expected posttransplant survival minus expected waiting list survival) allocated by urgency and benefit together. Patients below the ‘transplant benefit threshold’ have a negative transplant benefit. Only so many organs will become available within a year for this blood group, so not all listed patients can be transplanted. As time progresses, more patients can be added to the scatterplot; patients are removed if they are transplanted or if they die or are removed from the waiting list. If organs are offered based on a combination of transplant benefit and urgency, giving equal weight to both, then the allocation order is depicted as a 45° bar descending through the patient points on the scatterplot as depicted with the allocation order as shown (1–3). Different angles of this bar would give different weight to urgency or benefit. The Lung Allocation Subcommittee reviewed TSAM analyses performed by SRTR that modeled the number of total deaths (waiting list and posttransplant) for different angles: 0° (Figure 6), 30°, 60° and 90° (Figure 7). There was only a modest difference between the 0°, 30° and 45° angles, but there were clearly more deaths predicted for 60° and 90°. After considerable deliberation, the members of the Lung Allocation Subcommittee felt that balancing urgency and benefit *equally* was the most appropriate way to design the algorithm, resulting in adopting the 45° angle. Reproduced with permission from Marcel Dekker Inc. (14).

Table 4: Definitions and formulas to calculate Lung Allocation Score (LAS)

LAS components	Definition or formula
Waiting list urgency measure	= Expected number of days lived without a transplant during an additional year on the waiting list (area under the 1-year waiting list survival curve)
Posttransplant survival measure	= Expected number of days lived during the first year following transplantation (area under the 1-year posttransplant survival curve)
Transplant benefit	= Posttransplant survival measure – waiting list urgency measure, i.e. the number of expected additional days of life over the next year if a particular candidate received a transplant rather than remaining on the waiting list
Raw allocation score	= Transplant benefit measure – waiting list urgency measure = (posttransplant survival measure – waiting list urgency measure) – waiting list urgency measure = posttransplant survival measure – 2 × (waiting list urgency measure)
Normalized lung allocation score	= $100 \times (\text{raw score} + 2 \times 365) / 3 \times 365$

The possible range of values for the raw allocation score would be from +365 to –730 (the two extremes of 100% survival posttransplant but dying today without a transplant to a 100% chance of living for a year on the waiting list but a 100% probability of dying before the first day after a transplant). Because the Lung Allocation Subcommittee felt that negative allocation scores would be difficult to understand, it was decided to ‘normalize’ the score and produce a range from 0 to 100 according to the following formula: $100 \times (\text{raw score} + 2 \times 365) / 3 \times 365$

Source: SRTR.

to the transplant benefit measure minus the waiting list urgency measure, that is, the posttransplant survival measure minus twice the waiting list urgency measure. This calculation results in raw allocation scores ranging from +365 to –730. This score is then normalized so

that it ranges instead from 0 to 100 as described in Table 4.

During the public comment period, and in response to feedback from the OPTN/UNOS Conference on Lung Allocation

Policy in March 2003, the SRTR began structuring overall waiting list and posttransplant models that would consolidate estimated hazard ratios for predictive factors that had similar risk profiles in all separate diagnosis group models while still estimating hazards differently across diagnosis groups when the data supported doing so. In particular, diagnosis groups were included as predictors in the overall model, while interaction terms of other predictors were used to model hazards for risk factors that varied according to diagnosis group.

Because hazard patterns over time were allowed to have different shapes according to diagnosis group in each of the previous survival models,⁷ the assumption of proportional hazards was explored to see if this simplification in assumptions would materially affect allocation. Upon determination that similar allocation ranks were produced using either proportional or stratified hazards, proportional hazards models were chosen for simplicity.

At the time the lung allocation algorithm was submitted to the OPTN Board of Directors for approval, the waiting list models were based on 5109 candidates aged 12 years and older first listed for a lung transplant between 1999 and 2001. The transplant models were based on 2700 recipients aged 12 years and older of first lung transplants performed between 1999 and 2001. Heart-lung transplant candidates were not included in these models. The factors identified in these models and used for the initial iteration of calculating LAS are listed in Table 5.

The policy passed by the OPTN Board of Directors includes a plan to update the models every 6 months to include the most recent data with at least 3 years of follow-up. The intent is to identify, as accurately as possible, risk factors that are current, in order to include the impact of changes in clinical practice and changes among the characteristics of patients being listed for lung transplantation. Pre- and post-transplant mortality data are cross-referenced with data from the Social Security Death Master File to improve data capture in this process.

The policy requires that transplant centers must update variables used to calculate LAS every 6 months, with the exception of right heart catheterization data, which can be updated at the discretion of the center (to reduce risk to pa-

⁷When each diagnostic group was modeled separately using Cox proportional hazards models, the data specific to each group were used to estimate hazards and survival curves. There was no assumption of proportional hazards linking these different survival models to one another. The respective proportional hazards assumptions applied to the risk factors in each of these models separately. Upon combining all diagnosis groups together, diagnosis group indicators become risk factors as well, and the assumption of proportional hazards of these group indicators in relation to one another was assessed as described.

Table 5: Factors used to calculate LAS when the allocation system was implemented

Factors used to predict waiting list survival	Factors used to predict posttransplant survival
FVC (% predicted)	FVC (% predicted)
PA systolic pressure	PCW mean pressure \geq 20 mmHg
O ₂ required at rest (L/min)	Continuous mechanical ventilation
Age at offer	Age at transplant
Body mass index (BMI)	Serum creatinine (mg/dL)
NYHA functional status	NYHA functional status
Diagnosis	Diagnosis
Six-minute walk distance < 150 feet	
Continuous mechanical ventilation	
Diabetes	

Source: SRTR.

tients) if there is no indication that right heart hemodynamics have changed. Centers may update data on candidates at more frequent intervals if they wish to reflect changes in clinical status, and allocation scores will change as a result. It is anticipated that serial changes in some variables (like FVC or FEV-1) over time may prove to be important predictors of waiting list death or posttransplant outcome and may influence future revisions to the lung allocation system.

Allocation scores were calculated for the population of 2233 candidates aged 12 years or older and listed as active on the lung transplant list on January 1, 2003. Higher allocation scores correspond to a higher priority for receiving a lung offer. The distribution of scores when the system came into effect is expected to differ, because individual candidates may have clinical data elements updated. Nevertheless, there appeared to be reasonable access to lungs across diagnoses (Figure 9) and age (Figure 10), with high scores in all diagnoses and age groups. There was no difference in scores seen based on racial identity of candidates or gender (data not shown). Although certain factors receive more weight than others in calculating the score, no single factor dominated the calculations.

Allocation of Lungs to Pediatric Patients

The Subcommittee learned that pediatric recipients were most often assigned lungs from donors of a similar age, but that lungs from adolescent donors were often allocated to adults on the waiting list. The Subcommittee reviewed data that showed that intended lung recipients who were adolescents had a disproportionately higher risk of death on the waiting list under the old allocation system than adults. Because of concerns about the impact of end-stage organ failure on growth and development, OPTN allocation

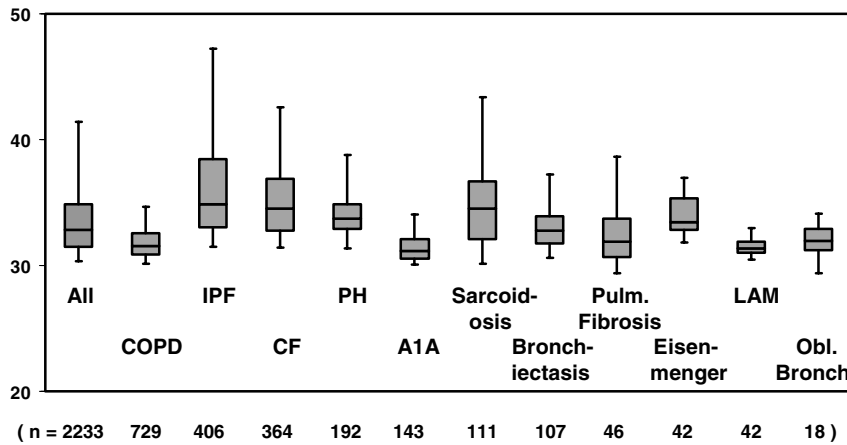


Figure 9: Distribution of calculated allocation scores for a 'snapshot' of patients listed in active status on the U.S. lung transplant list on January 1, 2003, by diagnosis. The horizontal line represents the median score for the designated group, the box contains 75% of the scores, the vertical bars indicate 95% of the scores. A1A = alpha-one antitrypsin deficiency emphysema.

Source: SRTR Analysis, 2004.

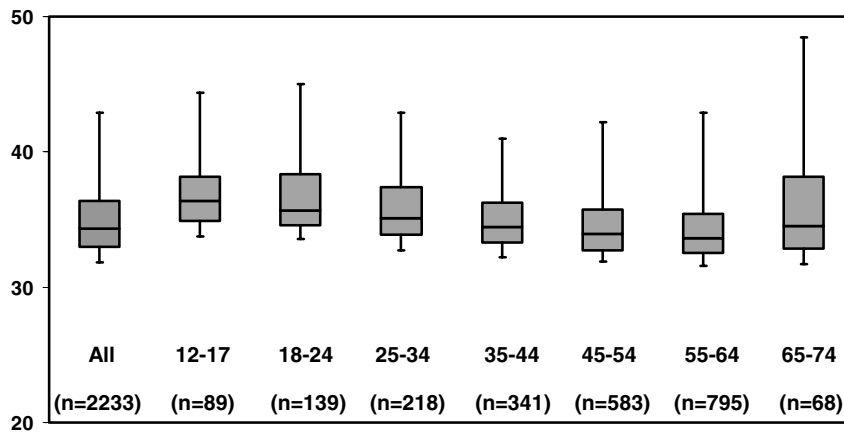


Figure 10: Distribution of calculated allocation scores for a 'snapshot' of patients listed in active status on the U.S. lung transplant list on January 1, 2003, by age. The horizontal line represents the median score for the designated group, the box contains 75% of the scores, the vertical bars indicate 95% of the scores.

Source: SRTR Analysis, 2004.

policy for other organs directs organs from pediatric donors preferentially to pediatric recipients. Thus, after consulting with representatives from the OPTN Pediatric Transplantation Committee, the Subcommittee recommended that lungs from pediatric donors be allocated according to the schema represented in Table 6. TSAM modeling of this schema predicted 50% more pediatric transplants than the original proposal with minimal impact on adult transplants or waiting list mortality. Lungs from donors younger than 12 years are offered first to candidates younger than 12 years based on time waiting, and then to pediatric candidates aged 12–17 years based on LAS, before being offered to adults (based on LAS). The rationale for this pediatric preference is the likelihood that these donor lungs would be too small for most adult candidates. Lungs from donors aged 12–17 years are offered first to candidates the same age according to LAS, and then to candidates younger than 12 years by waiting time, before being offered to adults according to LAS.

Table 6: Schema for allocation of lungs by donor age

Allocation order	Donor age <12 years	Donor age 12–17 years	Donor age ≥18 years
Prioritized by	Time waiting	LAS	LAS
1st	<12	12–17	12+
2nd	12–17	<12	<12
3rd	≥18	≥18	

Intended recipient age for lung offers from donors younger than 12 years, between age 12 and 17 years and aged 18 years and older. Intended recipients younger than 12 years are prioritized by time waiting, while intended recipients aged 12 years and older are prioritized by LAS.

Source: SRTR.

Allocation of Organs to Heart-Lung Recipients

Heart-lung transplants, already a relatively rare procedure, are becoming increasingly uncommon in the United States:

Only 175 procedures were performed between 2000 and 2004, compared to 268 between 1995 and 1999. Potential recipients of a heart-lung transplant appear on both the heart and lung match lists. When either organ is offered to them, based on status and waiting time for hearts, or on LAS (age ≥ 12 years) or waiting time (age < 12 years) for lungs, the other organ is supposed to default to the heart-lung recipient. This is complicated by circumstances when one organ is offered to and accepted by a program for another recipient. Increasing numbers of Status 1 heart transplants are being performed at the 'expense' of Status 2 recipients, making the prospect for 'elective' heart-lung transplantation even more rare. This is a problem that will require additional study and refinement by the Thoracic Organ Transplantation Committee in the future.

Consequences of the New System

While the lung transplant community agreed that waiting time was less than ideal for allocation of scarce donor lungs, there was no consensus on how to improve it. Difficulty in placement of lungs was one side effect of the old system based exclusively on waiting time. OPOs often spent inordinate amounts of time contacting centers with lung offers, only to be turned down for a wide variety of reasons, with turndown rates in actual match run data much higher for lungs than for hearts and livers. Part of this problem may have been due to the survivor effect of those on the waiting list, by which those who can wait longer do so, while more urgent cases may succumb to disease. Indeed, two earlier analyses (15,16) and analyses performed for the Subcommittee with a more recent cohort of patients showed that a survival benefit of the procedure could not be demonstrated for a substantial number of lung recipients during the first year of follow-up, although these analyses did not examine the potential for a quality of life benefit. A further analysis by Liou et al. showed that certain patients with CF do not benefit from transplantation, and suggested that others ought to receive higher priority (17).

It is hoped that the new allocation system will improve the efficiency of offers by limiting OPO calls and ensuring frustrations, and by ensuring overall survival benefit from lung transplantation. It is anticipated that the new system will lead to a shorter active waiting list, with patients deemed too well for transplantation consigned to inactive status until their diseases progress enough to require operation. In fact, in the first few weeks of implementation of the new lung allocation system, the total number of active waitlisted patients declined from nearly 1700 to fewer than 1500, while lung placement occurred within a median of five offers, compared with 12 offers 1 year earlier.⁸ It is hoped that this enhanced efficiency will con-

tribute to ease of balancing utility with outcome by the new approach.

Future Directions and Challenges

There will likely be future iterations of the new system that will reexamine allocation, particularly to patients with pulmonary hypertension, for whom few predictors of outcome could be identified in the analyses undertaken using the data available in the OPTN database. Mandating submission of data for candidates to remain active on the waiting list will result in a more complete data set, which will more accurately identify predictors of survival in subsequent analyses every 6 months. It is also anticipated that serial data collection will identify that changes in certain clinical variables will be important predictors of survival on the waiting list and perhaps following transplantation.

It is likely that the new system will result in behavioral changes among transplant programs. Programs may choose to delay listing potential recipients who have a low LAS; conversely, programs may choose to list critically ill patients who might not have been listed before because of a low chance of receiving an offer of a suitable lung under the old waiting time system. This adjustment of the waiting list population will naturally affect future iterations of the algorithm, and will provide challenges for assessing the impact of the change. For example, if more critically ill patients are listed as a result of the policy change, a paradoxical effect may be an increase in the number of waiting list deaths.

There are additional factors that affect waiting list and post-transplant survival that were not identified by analyses performed for the Subcommittee, but these analyses were limited by data availability in the OPTN/SRTR database. Data on some factors known to affect posttransplant survival, such as colonization of CF patients with *Burkholderia cepacia* species (18,19), are not currently collected by the OPTN. A multi-institutional chart review undertaken by the OPTN before the new allocation system was implemented may identify important data elements to include in future iterations of the distribution algorithm.

Preliminary analyses of this data collection effort suggest that serial changes in pulmonary function parameters may be important predictors of waiting list mortality. This information will be available with no further reporting requirements. However, there has been little enthusiasm for more data collection on the part of transplant programs, which cited additional costs and reporting requirements as problems when the request for more data elements was submitted for public comment. As new elements are identified, their inclusion as required data elements is anticipated by mandate by the OPTN Board of Directors after recommendation by the Thoracic Organ Transplantation Committee.

⁸Report to the UNOS Board of Directors, June 23, 2005.

A controversial area in which no consensus could be achieved was the role of geography in lung allocation. There is a substantial disparity in the size of OPOs, both by geographic area and by population, and in the number of thoracic transplant programs within each OPO and the populations it serves. Other confounding issues are the presence of exceptions to the standard geographic allocation sequence in the form of alternate listing units and statewide sharing agreements. While a national list may not be practical because of time and distances involved, the rationale for offering organs first within the arbitrary boundary of an OPO is unclear, and, some may argue, inconsistent with the intent of the Final Rule. In the future, such geographic restrictions may not be justifiable, particularly if TSAM modeling of the new system predicts a significant reduction in deaths with wider geographic distribution of lungs beyond the local OPO.

The OPTN Pediatric Committee remains interested in pursuing the possibility that lung allocation to pediatric candidates younger than 12 years can be based on a similar approach—that is, balancing urgency with utility in allocation, rather than allocating organs by waiting time. Additional analyses may facilitate identification of suitable risk factors for this small and diverse group of candidates.

If the goal of the new algorithm—a reduction in overall numbers of deaths—is achieved, it will paradoxically reduce the power of future analyses to identify risk factors for death to incorporate into the algorithm. Indeed, if the algorithm eliminated *all* deaths, then it would not be possible to identify any new factors, or to verify the validity of factors currently in the algorithm, although this would be a dilemma relished by the Thoracic Organ Committee and the lung transplant community as a whole. In the absence of major changes in public opinion or policy to change the number of conventional organ donors, it is unlikely that the number of lungs available for transplantation will grow considerably. It is conceivable that using lungs from donors after cardiac death may increase the size of the lung donor pool, but there are substantial logistical hurdles to overcome before this practice becomes widespread (21–24).

Summary

The development of the new system for lung allocation in the United States has been a complex and at times controversial process (20). Lung allocation is no longer based on waiting time; it now balances a measure of waiting list urgency (expected lifetime without a transplant) and a measure of transplant benefit (the difference between expected lifetime with versus without a transplant). The urgency and benefit measures are estimated from clinical measurements and demographic data. When potential recipients' clinical condition changes, their data can be updated and their score will change accordingly. Because the population of patients waiting and the risks of waiting

list mortality and posttransplant mortality may change with time, the system is intended to be modified as often as every 6 months, based on analysis of the most recent 3-year cohort of patients. Any new risk factors identified by these analyses can be incorporated into future iterations of the allocation system. In addition to regular reviews, the Lung Subcommittee has recommended that the system be reviewed at a forum with the lung transplant community at a suitable time after implementation for feedback and suggestions for refinement.

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This study was approved by HRSA's SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the "Public Benefit and Service Program" provisions of 45 CFR 46.101(b)(5) and HRSA Circular 03.

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