The societal impact of single versus bilateral lung transplantation for chronic obstructive pulmonary disease

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ONLINE DATA SUPPLEMENT

Appendix

Methods

Model Design

Figure E-1 is a conceptual representation of the full model. The model consisted of two main branches: one branch in which all patients with COPD were assigned to receive bilateral lung transplantation (BLT strategy), and a second branch in which all patients with COPD were assigned to receive single lung transplantation (SLT strategy). Within each branch, Markov chains were used to simulate the experience of a population of patients listed for lung transplantation. Simulated patients were assigned initial Markov states corresponding to different positions on the transplant waitlist with a listing diagnosis assigned based on the distribution of listing diagnoses in our study cohort. We considered patients with IPF to be eligible for SLT,(E1) whereas patients with cystic fibrosis, pulmonary hypertension, and sarcoidosis were considered to require BLT. Patients listed with COPD all were assigned to receive either SLT or BLT depending on the modeled allocation strategy.

Once on the waitlist, patients remained in their waitlist position for one Markov cycle, defined as the number of days between eligible donors. At the end of the Markov cycle, patients assigned to the top position on the waitlist could experience one of two transitions: transplantation or removal from the waitlist prior to transplantation. Patients whose listing diagnosis required a bilateral lung transplant and who were listed below the top position could also undergo two possible transitions: advance to a higher position on the waitlist or removal from the waitlist prior to transplantation. Patients whose listing diagnosis would allow a single lung transplant and who were assigned to positions below the top position could experience one of three transitions: change to a higher waitlist position, transplantation, or removal from the waitlist prior to transplantation. Transition probabilities at the end of each Markov cycle were dependent upon the patient's position on the waitlist at the beginning of the Markov cycle, listing

diagnosis, probability of being removed from the waitlist during the interval between donors, the transplant requirements of patients listed in higher positions (BLT or SLT), and the allocation strategy for COPD patients.

Terminal Markov states were defined as death; survival after BLT for pulmonary hypertension, cystic fibrosis, sarcoidosis and COPD (in the BLT strategy arm); and survival after SLT for idiopathic pulmonary fibrosis (IPF) and COPD (in the SLT strategy arm).

Waitlist size

To determine the correct size of the waitlist, we quantified the extent of competition for donor organs in the post-LAS era using data from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) files.(E2) We examined the wait lists for each of the 11 UNOS donor regions and 4 blood types on one randomly selected day in each two week period from September 1, 2005 through January 31, 2008 to generate a total of 63 sampled waitlists for each region and blood type combination. We then varied the height of a hypothetical donor for each sampled wait list and recorded the number of patients whose listing height was within four inches above or below that of the hypothetical donor. These patients were considered to be in competition for that donor's organs. We repeated this process, modifying the donor's height in one inch increments, until the maximum number of patients in competition for a donor organ was achieved. We then averaged this maximum number of potential recipients across all 63 sampled waitlists to generate an estimate of the maximum competition for donor organs for each region and blood type combination. Because competition was substantially higher among blood types A and O, and because these blood types are the most common, we used the mean across all regions of the maximum competition for blood types A and O as our baseline waitlist size.

Interval between donors

The length of the Markov cycle was defined as the duration between available donors. To calculate this interval, we used the UNOS database to determine the total number of donors that became available in each region when a compatible recipient was actively listed from September 2005 through February 2008. We then separated these donors by blood type and quintile of height to determine the average number of days between donors for each of the 220 possible combinations of blood type, region and height quintile. The median donor interval for blood types A and O was used for the base case. Sensitivity analyses were then conducted varying the donor interval from the 5^{th} to 95^{th} percentile of observed donor intervals for blood types A and O (Table E-1).

Probability of death awaiting transplant

Using UNOS data in the post-LAS period, we created separate survival curves for each of the five most common transplant diagnoses using the date of listing as "day 0" and censoring observations at the time of transplantation. We used removal from the list for any reason other than transplantation as the outcome of these survival analyses. In each case, the survival curves appeared linear. We therefore calculated the daily probability of being removed from the list prior to transplantation for each listing diagnosis as the total number of observed waitlist removals divided by the duration of waitlist time. We derived 95% confidence intervals around these estimates assuming a Poisson distribution. The daily probability of being removed from the waitlist was then included in the decision model as a beta distribution to allow sampling in Monte Carlo simulations. The daily probability of waitlist removal was then converted to the probability of being removed during a specified donor interval using the equation $1\text{-}e^{-(\text{daily probability of removal})(\text{donor interval})}$.(E3)

To determine the number of deaths that occurred prior to transplantation, we identified all patients in our UNOS sample that were removed from the waitlist for any reason other than

transplantation. Among this group, we calculated the proportion of patients that had a listed reason for removal of either "died" or "candidate condition deteriorated, too sick to transplant." We presumed that this latter category also died prior to transplantation. We applied this proportion (85.0%) to the number of patients in our model that were removed prior to transplantation to arrive at our final estimates of the number of patients who died prior to transplantation under each modeled allocation strategy.

Post-transplant survival

Separate terminal Markov states were created for each listing diagnosis. To define the post-transplant survival value assigned to each of the terminal Markov states for the baseline model, we used the International Society of Heart and Lung Transplantation registry data to derive unadjusted estimates of median survival after SLT for IPF and BLT for cystic fibrosis, pulmonary hypertension, sarcoidosis, and COPD. These values measured in days of post-transplant survival were assigned to the terminal Markov states specific to each listing diagnosis. The terminal state "death" was assigned a value of zero.

To determine the expected post-transplant survival following SLT for COPD while taking into account confounding factors that influence the selection of SLT vs. BLT procedures in clinical practice, we first divided the cohort of patients in the UNOS database with a listing diagnosis of COPD into age categories as follows: <50, 50-55, 56-60 and >60 years of age. These age categories are the same as those used by Thabut and colleagues to show that the relative survival of SLT compared to BLT varies by recipient age.(E4) We then used the adjusted hazard ratios published by Thabut and colleagues for each of these age categories to calculate a weighted average of the adjusted hazard ratio for SLT compared to BLT.(E4) This weighted average was used to calculate the expected median survival following SLT compared to BLT for our base case analysis.

Primary Analyses

We first analyzed our baseline model to calculate the expected values under each allocation strategy for the number of patients receiving a transplant, the number of deaths prior to transplantation, and total post-transplant survival. To generate 95% confidence intervals around the estimated differences in expected values between each strategy, we used Monte Carlo simulations. In these simulations, 10,000 samples were taken from the beta distributions used to model the probability of waitlist removal while awaiting a transplant for each listing diagnosis. The differences between the expected values for each outcome under each strategy were then calculated for each of the 10,000 iterations. The 95% confidence intervals were defined as the range between the 2.5^{th} and 97.5^{th} percentile of these sampled estimates.

Sensitivity Analyses

After analyzing our model under baseline assumptions, we ran sensitivity analyses varying the donor interval, the comparative survival benefit of BLT compared to SLT, and the number of patients on the waitlist. The ranges of values used in these analyses are included in Table E-1. For the donor interval, we varied the value from the 5^{th} percentile to the 95^{th} percentile of observed donor intervals for the 110 combinations of height quintile, region, and the two most common blood types (A and O). We varied the survival benefit of BLT compared to SLT from the unadjusted difference in observed median survivals (HR 0.75) through the adjusted hazard ratio reported by Thabut and colleagues for the benefit of BLT compared to SLT in recipients over the age of 60 (HR 0.95).(E4) We then tested our model using waitlist lengths of 10 and 5 patients respectively.

References cited

E1. Thabut G, Christie JD, Ravaud P, Castier Y, Dauriat G, Jebrak G, Fournier M, Leseche G, Porcher R, Mal H. Survival after bilateral versus single-lung transplantation for idiopathic pulmonary fibrosis. *Ann Intern Med* 2009;151:767-774.

E2. Munson JC, Crowley EM, Christie JD, Halpern SD. Level of competition for donor lungs in the period following implementation of the lung allocation score. *Am J Respir Crit Care Med* 2009;179:A4593.

E3. Collett D. Modelling survival data in medical research. Boca Raton: Chapman and Hall/CRC; 2003.

E4. Thabut G, Christie JD, Ravaud P, Castier Y, Brugière O, Fournier M, Mal H, Lesèche G, Porcher R. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: A retrospective analysis of registry data. *The Lancet* 2008;371:744-751.

Table E-1 – Range of values used in sensitivity analyses

Variable	Value Range	Rationale
Interval between donors	20 days – 270 days	5^{th} to 95^{th} percentile of observed donor intervals for blood types O and A across all donor regions and height quintiles
Ratio of median survival for SLT compared to BLT	0.75 – 0.95	Unadjusted ratio of median survivals in ISHLT registry data (0.75) to the HR for BLT compared to SLT for recipients with COPD > 60 years of age (0.95)
Waitlist size	20/10/5 patients	20 patients represents the average maximal competition for blood types A and O across donor regions; shorter waitlists chosen to account for smaller regions or less common height groups

Figure Legend:

Figure E-1 – Conceptual model of decision tree showing possible transitions from each waitlist position according to listing diagnosis among a waitlist of three patients

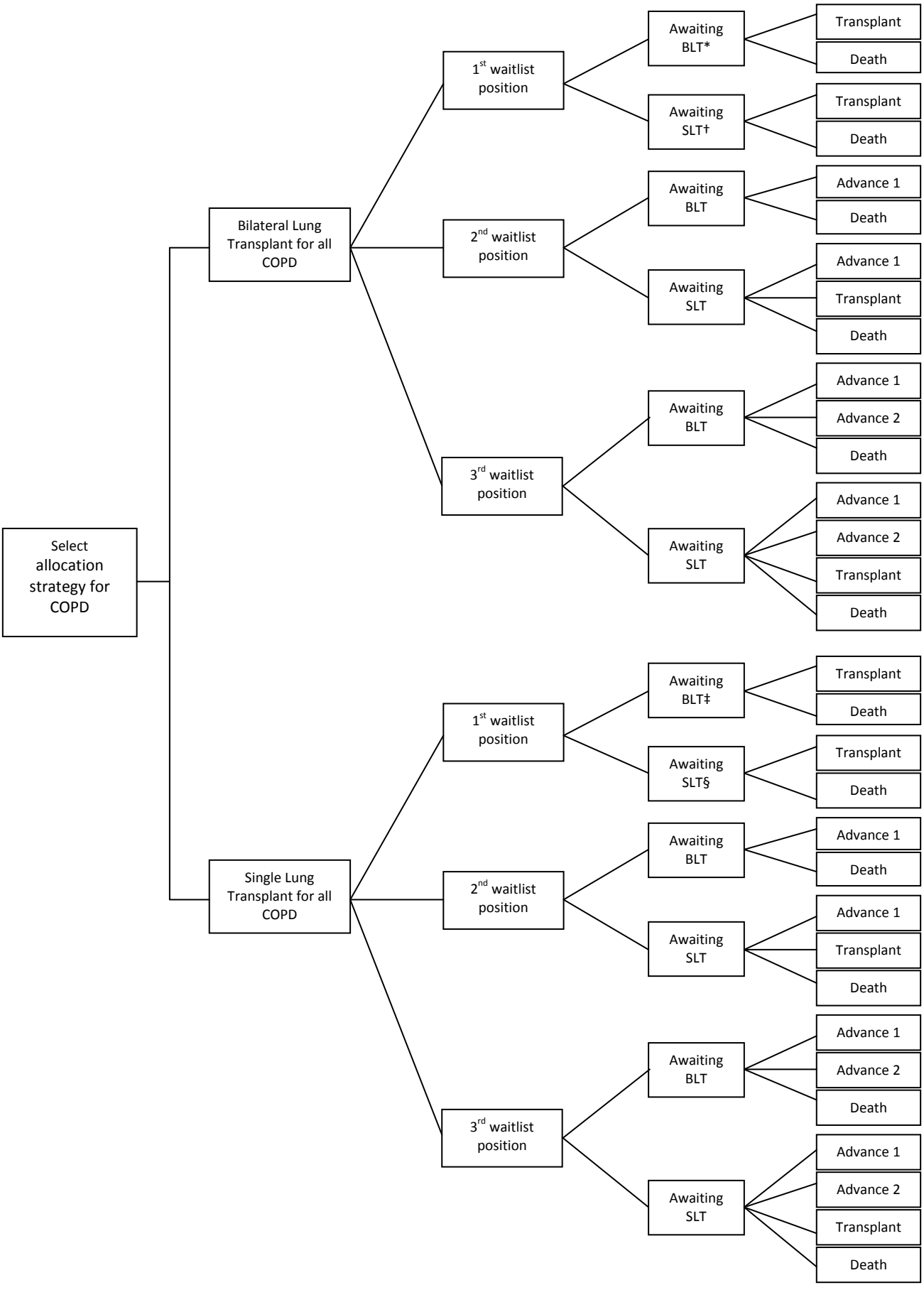
* includes cystic fibrosis, pulmonary hypertension, sarcoidosis and COPD

† includes only idiopathic pulmonary fibrosis

‡includes cystic fibrosis, pulmonary hypertension and sarcoidosis

§includes idiopathic pulmonary fibrosis and COPD

Figure E-1


Select allocation strategy for COPD
Bilateral Lung Transplant for all COPD
Single Lung Transplant for all COPD
1st waitlist position
2nd waitlist position
3rd waitlist position
Awaiting BLT*
Awaiting SLT†
Awaiting BLT
Awaiting SLT
Awaiting BLT‡
Awaiting SLT§
Transplant
Death
Advance 1
Advance 2