Short Stature and Access to Lung Transplantation in the United States

A Cohort Study

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Abstract

Rationale: Anecdotally, short lung transplant candidates suffer from long waiting times and higher rates of death on the waiting list compared with taller candidates.

Objectives: To examine the relationship between lung transplant candidate height and waiting list outcomes.

Methods: We conducted a retrospective cohort study of 13,346 adults placed on the lung transplant waiting list in the United States between 2005 and 2011. Multivariable-adjusted competing risk survival models were used to examine associations between candidate height and outcomes of interest. The primary outcome was the time until lung transplantation censored at 1 year.

Measurements and Main Results: The unadjusted rate of lung transplantation was 94.5 per 100 person-years among candidates of short stature (<162 cm) and 202.0 per 100 person-years among

candidates of average stature (170–176.5 cm). After controlling for potential confounders, short stature was associated with a 34% (95% confidence interval [CI], 29–39%) lower rate of transplantation compared with average stature. Short stature was also associated with a 62% (95% CI, 24–96%) higher rate of death or removal because of clinical deterioration and a 42% (95% CI, 10–85%) higher rate of respiratory failure while awaiting lung transplantation.

Conclusions: Short stature is associated with a lower rate of lung transplantation and higher rates of death and respiratory failure while awaiting transplantation. Efforts to ameliorate this disparity could include earlier referral and listing of shorter candidates, surgical downsizing of substantially oversized allografts for shorter candidates, and/or changes to allocation policy that account for candidate height.

Keywords: healthcare disparity; body height; health services accessibility; outcome assessment

Deceased donor lungs are a scarce resource that can prolong life and improve health-related quality of life when transplanted into carefully selected adults and children with advanced lung diseases (1–3). In 2014, a total of 1,880 adults and 45 children underwent lung transplantation in the United States, yet 2,584 persons were added to the waiting list, and as of April 11, 2015,

there were 1,613 candidates awaiting lung transplantation. To equitably allocate deceased donor organs in the setting of a long-standing imbalance between donor organ supply and demand, the U.S. Department of Health and Human Services created the “Final Rule” in March 2000. The Final Rule was intended “to avoid wasting organs, to avoid futile transplants,

to promote patient access to transplantation, and to promote the efficient management of organ placement.” (4) In response, the Organ Procurement and Transplantation Network (OPTN) replaced the United States’ waiting time-based lung allocation policy with a priority-based allocation policy in May 2005 (5). This system has led to a decrease

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At a Glance Commentary

Scientific Knowledge on the

Subject: Shorter stature is associated with higher mortality rates in pediatric lung transplant candidates.

What This Study Adds to the

Field: In the United States, adult lung transplant candidates of short stature experience a lower rate of lung transplantation and higher rates of death and respiratory failure while awaiting transplantation independent of their priority for lung transplantation, sex, or center volume.

in the number of deaths on the waiting list; an increase in the number of transplants performed; and, to date, no decrement in 1-year post-transplant survival rates (6).

Priority-based lung allocation seems to have ameliorated racial differences in access to lung transplantation (7, 8), but may have led to an unexplained difference by sex, with women facing lower transplant rates than men (7). We have anecdotally noted that short lung transplant candidates seem to have longer waiting times than taller candidates, perhaps related to the common practice of attempting to find donor lungs of similar size to the candidate. Recently, shorter height was found to be a predictor of higher waiting list mortality in pediatric lung transplant candidates (9). In this study, we tested the hypothesis that short adult lung transplant candidates have lower transplantation rates and higher mortality rates than taller candidates. Some of the results in this study have been previously reported in the form of an abstract (10).

Methods

Study Design, Participants, and Data Sources

We performed a retrospective cohort study of adults aged 18 years or older, placed on the lung transplant waiting list in the United States between May 4, 2005 and December 31, 2011 with follow-up through June 2013 using data provided by the OPTN. We also examined post-transplant survival in adults who underwent lung transplantation between May 4, 2005 and January 1, 2012.

The study was approved by the Columbia University Medical Center Institutional Review Board with a waiver of informed consent (CUMC IRB #AAAB5142).

Measurements

The primary exposure variable was standing height measured in centimeters by clinical personnel at each transplant center. We analyzed height both as a continuous variable (per 5-cm decrement) and as a categorical variable, arbitrarily divided into quartiles: less than or equal to 162 cm, greater than 162–170 cm, greater than 170–176.5 cm, and greater than 176.5 cm. The third height quartile was selected as a reference group in all analyses because it includes the average height of adults in the United States (11).

The primary outcome was the number of days between placement on the lung transplant waiting list and transplantation censored at 1 year. Secondary outcomes were the number of days from listing until death or removal because of clinical deterioration (“too sick for transplantation”), removal from the waiting list because of other reasons, and respiratory failure (first instance of mechanical ventilation or use of extracorporeal life support [ECLS]). All analyses were censored at 1 year. Reasons for removal other than clinical deterioration included medical unsuitability, refusal of transplantation, improved condition, inability to contact candidate, removal by error, and other unknown reasons. Waiting list candidates on a mechanical ventilator or ECLS at the time of listing were excluded from the respiratory failure analysis. We also examined survival during the first year after lung transplantation.

Analysis Approach

We constructed competing risk regression models to examine associations between height and waiting list outcomes (12). Competing risk models are appropriate when the occurrence of one outcome prevents the occurrence of another outcome. For example, the time to transplantation cannot be measured for those who die on the waiting list. Neither can the time to death on the waiting list be determined for those who undergo lung transplantation. We therefore chose to use competing risk regression models in lieu of Cox proportional hazards model to

account for competing outcomes on the waiting list.

The following variables were purposefully selected for inclusion in the models based on plausible associations with height and waiting list outcomes (i.e., potential confounders) or with waiting list outcomes alone (i.e., precision variables): age, sex, race, diagnosis, mechanical ventilation or ECLS at listing, initial oxygen requirement, blood type, lung allocation score (LAS) at listing, body mass index (BMI) at listing, double lung preference, listed with prospective crossmatch requirement, or with unacceptable antigens (virtual crossmatch requirement). We also performed analyses stratified by age, sex, diagnosis, LAS, blood type, bilateral transplant requirement, prospective or virtual crossmatch requirement, and listing center. We used stratified Cox proportional hazards models to examine the association between candidate height and respiratory failure while awaiting transplantation. The models were adjusted for the covariates previously listed, excluding ventilation or ECLS at listing. Diagnosis and blood type were included in the model as stratification variables. We also performed analyses stratified by the factors listed previously.

We used stratified Cox proportional hazards models to examine the association between recipient height and survival after transplantation with adjustment for recipient, donor, and procedural factors. Recipient factors included age, sex, height, previous cardiac surgery, LAS, transplant center diagnosis, previous lung transplantation, and mechanical ventilation. Donor factors included age, sex, BMI, height, arterial partial pressure of oxygen, alcohol use, smoking history, pulmonary infection, cause of death, diabetes, and donor-recipient sex interaction. Procedural factors were ischemic time and procedure type (bilateral vs. single lung transplantation). Region, diagnosis, and mechanical ventilation were included in the model as stratification variables. We performed analyses stratified by age, sex, LAS, BMI, ventilation or ECLS at transplant, diagnosis, procedure type, and transplant center.

Predicted cumulative incidence function curves were generated by height quartile using mean covariate values. We used multiple imputation by chained

equations to account for missing covariate data (13). We checked the proportional hazards assumption by examining covariate effects over time in the competing risks models and by regressing Schoenfeld residuals over time in Cox models. Analyses were performed using Stata version 13.1 (StataCorp, College Station, TX) and

R version 2.15.2 (R Foundation, Vienna, Austria).

Results

There were 13,346 lung transplant candidates included in the study (*see*

Figure E1 in the online supplement). Most candidates were white (83%), male (54%), and listed for bilateral transplantation (54%). The median age was 57 years (interquartile range, 47–63 yr), the median height was 170 cm (interquartile range, 162–176.5 cm), and 516 (3.9%) were mechanically ventilated or on ECLS at

Table 1. Baseline Characteristics of 13,346 Lung Transplant Candidates at the Time of Placement on the Lung Transplant Waiting List

Characteristic	Height Quartiles			
	≤162 cm	>162–170 cm	>170–176.5 cm	>176.5 cm
Number of candidates	3,358	3,369	3,289	3,330
Age, yr	55.0 (42.0–64.0)	56.0 (45.0–62.0)	59.0 (49.0–64.0)	59.0 (51.0–64.0)
Female, %	93.4	66.6	19.1	2.4
Race/ethnicity, %				
White	78.0	79.3	85.1	88.2
Black	8.7	10.9	7.9	8.7
Hispanic	9.3	7.2	4.8	2.4
Other	4.0	2.6	2.1	0.7
Weight, kg	59.2 (49.2–69.4)	67.6 (56.2–78.0)	77.1 (65.3–86.8)	86.8 (75.8–97.5)
Body mass index	24.1 (20.1–28.3)	24.6 (20.6–28.5)	25.8 (21.9–29.0)	26.3 (23.0–29.5)
Body mass index classification, %				
Underweight	13.9	11.6	8.2	5.6
Normal	41.0	41.0	35.7	34.4
Overweight	30.5	31.7	38.3	39.8
Obese	14.6	15.6	17.9	20.3
Diagnosis, %				
Obstructive pulmonary disease	36.8	35.7	32.4	29.4
Pulmonary vascular disease	6.5	4.8	3.9	2.9
Cystic fibrosis	14.4	13.8	9.9	6.5
Interstitial lung disease	42.4	45.8	53.8	61.2
Lung Allocation Score, %				
<35	46.2	42.5	42.0	36.5
>35–45	35.9	37.6	36.4	38.9
>45–55	8.9	9.3	9.8	10.9
>55	9.1	10.6	11.8	13.7
Initial oxygen requirement, L/min	3 (2–4)	3 (2–4)	3 (2–5)	3 (2–5)
Mechanical ventilation or extracorporeal life support at listing, %	3.5	4.2	3.4	4.9
Bilateral transplant required	58.0	52.0	52.1	50.0
ABO blood type, %				
O	46.8	45.4	45.0	45.7
A	38.7	39.6	40.1	40.0
B	10.9	11.1	10.8	11.2
AB	3.5	4.0	4.1	3.1
Prospective crossmatch required, %	12.4	10.2	7.0	5.7
Virtual crossmatch required, %	19.0	17.4	12.5	10.9
Region, %				
1	2.5	2.8	3.0	2.5
2	16.9	16.4	15.3	14.9
3	11.5	12.3	13.4	13.8
4	10.8	9.3	11.3	10.6
5	15.7	14.9	13.4	14.4
6	3.1	3.5	2.8	3.2
7	7.9	8.6	8.5	8.8
8	5.5	5.6	5.8	6.5
9	4.4	3.9	4.0	2.7
10	12.7	14.1	12.7	11.5
11	9.1	8.7	9.8	11.0

Data are median (interquartile range) and percentage. Complete data were available for all variables except oxygen requirement, which was only available for $n = 13,100$.

listing. Compared with those in the third height quartile (170–176.5 cm), the shortest quartile (<162 cm) contained a higher proportion of women (93% vs. 19%), Hispanics (9% vs. 5%), and those that required a prospective crossmatch (12% vs. 7%) (Table 1). Those in the first quartile also weighed less (mean weight, 59 vs. 77 kg), but had similar BMI compared with those in the third height quartile. Other baseline characteristics were similar across height quartiles. Candidate and donor height distributions are shown in Figure 1.

Height and Waiting List Outcomes

The unadjusted transplantation rates were 94.5, 146.9, 202.0, and 251.0 per 100 person-years within each height quartile, respectively (Table 2). The multivariable adjusted rate of transplantation decreased by 8% for each 5-cm decrement in height (subhazard ratio [SHR], 0.92; 95% confidence interval [CI], 0.90–0.93). Candidates less than 162 cm tall had a 34% relatively lower multivariable-adjusted rate of transplantation compared with candidates 170–176.5 cm tall (SHR, 0.66; 95% CI, 0.61–0.71) (Table 2, Figure 2A).

The unadjusted rates of death or removal because of clinical deterioration were 28.7, 26.6, 28.2, and 34.3 per

100 person-years within each quartile of height, respectively (Table 2). The adjusted rate of death or removal because of clinical deterioration increased by 12% for each 5-cm decrement in height (SHR, 1.12; 95% CI, 1.08–1.17). Candidates less than 162 cm tall had a 62% increase in the multivariable-adjusted rate of death or removal because of clinical deterioration compared with candidates 170–176.5 cm tall (SHR, 1.62; 95% CI, 1.24–1.96) (Table 2, Figure 2B).

The unadjusted rates of respiratory failure were 14.1, 13.6, 13.4, and 15.6 per 100 person-years for each height quartile, respectively (Table 2). The multivariable adjusted rate of respiratory failure increased by 6% for each 5-cm decrement in height (hazard ratio, 1.06; 95% CI, 1.001–1.11) (Table 2, Figure 2C). Candidates less than 162 cm tall had a 42% relative increase in the multivariable-adjusted rate of respiratory failure compared with candidates 170–176.5 cm tall (SHR, 1.42; 95% CI, 1.10–1.85).

Height and Survival after Lung Transplantation

Of the 13,346 candidates analyzed for waiting list outcomes, 9,103 underwent transplantation before January 1, 2012 (see Figure E1). The LAS at transplantation was similar across height

quartiles, with no trend of greater disease severity across height quartiles (see Table E1; *P* for trend = 0.11). The unadjusted post-transplant 1-year mortality rates were 13.5, 15.2, 16.0, and 18.5 per 100 person-years for each height quartile, respectively (Table 2; see Figure E2). There was a nonsignificant association between shorter stature and a lower mortality rate after lung transplantation (SHR, 0.96 per 5-cm decrement in height; 95% CI, 0.91–1.00; *P* = 0.07) (Table 2).

Stratified Analyses

Stratified analyses are shown in Figure 3 and Figure E3. The associations of height with both the rate of transplantation and the rate of death or removal because of clinical deterioration were somewhat stronger among women compared with men (*P* values for interaction < 0.001 and 0.06, respectively) (Figure 3). Among women, the rate of transplantation decreased by 16% per 5-cm decrement in height (SHR, 0.84; 95% CI, 0.82–0.87), whereas among men, the rate decreased by only 5% per 5-cm decrement in height (SHR, 0.95; 95% CI, 0.93–0.97). Among women, the rate of death or removal for clinical deterioration increased by 18% per 5-cm decrement in height (SHR, 1.18; 95% CI, 1.12–1.25). Among men, the rate increased by 10% per 5-cm decrement in height (SHR, 1.10; 95% CI, 1.04–1.16). Similarly, the associations between height and the rate of transplantation were particularly strong among those with pulmonary vascular disease and those requiring a prospective crossmatch (*P* values for interaction were 0.01 and 0.004, respectively). The association between height and transplantation rate was consistent across centers (see Figure E3).

Sex Disparity

As previously reported by others (7), female sex was associated with a lower rate of transplantation (SHR, 0.63; 95% CI, 0.60–0.65) and a higher rate of rate of death or removal because of clinical deterioration (SHR, 1.22; 95% CI, 1.10–1.36) in our study in a model adjusting for the variables included in the fully adjusted model described in Table 2, excluding height as a covariate. Addition of height to the fully adjusted model led to a 54% reduction in the size of the beta coefficient estimate for sex in the transplantation model (SHR, 0.81; 95% CI, 0.76–0.86) and completely

Figure 1. Distributions of donor and candidate heights.

Table 2. Associations between Height and Waiting List Outcomes and Survival after Lung Transplantation

Outcome	Height Quartile				P Value for Trend	Subhazard Ratio per 5-cm Decrement in Height	P Value
	≤162 cm	>162–170 cm	>170–176.5 cm	>176.5 cm			
Transplantation							
No. transplanted	1,653	2,104	2,324	2,495			
Transplant rate per 100 person-years (95% CI)	94.5 (90.0–99.2)	146.9 (140.7–153.3)	202.0 (194.0–210.4)	251.0 (241.4–261.1)			
Subhazard ratios (95% CI)							
Unadjusted	0.53 (0.50–0.57)	0.78 (0.74–0.83)	1	1.14 (1.08–1.21)	<0.001	0.87 (0.86–0.88)	<0.001
Fully adjusted*	0.66 (0.61–0.71)	0.90 (0.84–0.96)	1	1.09 (1.03–1.16)	<0.001	0.92 (0.90–0.93)	<0.001
Death or removal for clinical deterioration							
No. of decedents/removals	502	381	325	341			
Rate of death or removal per 100 person-years (95% CI)	28.7 (25.3–31.3)	26.6 (24.1–29.4)	28.2 (25.3–31.5)	34.3 (30.9–38.1)			
Subhazard ratios (95% CI)							
Unadjusted	1.53 (1.22–1.76)	1.15 (0.99–1.33)	1	1.04 (0.90–1.22)	<0.001	1.09 (1.06–1.12)	<0.001
Fully adjusted*	1.62 (1.24–1.96)	1.17 (0.98–1.39)	1	0.94 (0.80–1.11)	<0.001	1.12 (1.08–1.17)	<0.001
Respiratory failure							
No. respiratory failure	241	190	152	151			
Respiratory failure rate per 100 person-years	14.1 (12.5–16.0)	13.6 (11.8–15.7)	13.4 (11.5–15.8)	15.6 (13.3–18.2)			
Hazard ratios (95% CI)							
Unadjusted	1.28 (1.04–1.56)	1.12 (0.90–1.38)	1	1.07 (0.85–1.56)	0.04	1.04 (1.00–1.08)	0.05
Fully adjusted*	1.42 (1.10–1.85)	1.19 (0.931–1.50)	1	1.00 (0.80–1.26)	0.01	1.06 (1.001–1.11)	0.04
Death 1 yr after transplantation							
No. decedents	229	308	347	410			
Mortality rate per 100 person-years	13.5 (11.9–15.4)	15.2 (14.4–17.8)	16.0 (14.4–17.8)	18.5 (16.8–20.4)			
Hazard ratios (95% CI)							
Unadjusted	0.84 (0.72–1.00)	0.95 (0.82–1.11)	1	1.15 (1.00–1.33)	<0.001	0.95 (0.92–0.97)	<0.001
Fully adjusted†	0.90 (0.72–1.14)	1.03 (0.86–1.22)	1	1.13 (0.97–1.31)	0.06	0.96 (0.91–1.00)	0.07

Definition of abbreviation: CI = confidence interval.

*Adjusted for confounders and precision variables (age, sex, race, diagnosis, mechanical ventilation or extracorporeal life support at listing, initial oxygen requirement, blood type, lung allocation score at listing, body mass index at listing, double lung preference, and prospective crossmatch requirement).

†Adjusted for recipient factors (age, sex, height, previous cardiac surgery, lung allocation score, transplant center diagnosis, previous lung transplantation, and mechanical ventilation), donor factors (age, sex, body mass index, height, arterial partial pressure of oxygen, alcohol use, smoking history, pulmonary infection, cause of death, diabetes, and donor–recipient sex interaction), and procedural factors (bilateral transplant and ischemic time).

eliminated any meaningful association between female sex and the rate of death or removal because of sickness (SHR, 0.88; 95% CI, 0.76–1.03).

Discussion

We found that shorter stature is independently associated with a lower rate of transplantation and a higher rate of death or removal because of clinical deterioration among adults listed for lung transplantation in the United States since 2005. Shorter stature was also associated with a higher rate of respiratory failure while awaiting lung transplantation, but was not associated with a higher rate of death early after lung transplantation.

In our study, 25% of candidates and 16% of donors were less than 162 cm tall. Because many transplant centers attempt to match donors to waiting list candidates of similar height or total lung capacity, shorter

candidates have a relatively small pool of available donor lungs, leading to the lower rate of lung transplantation we observed among shorter transplant candidates. Consequently, shorter lung transplant candidates are more likely to develop respiratory failure from their underlying disease, die while awaiting transplantation, or be removed from the waiting list because of clinical deterioration. As expected, there was no signal that shorter lung transplant candidates have worse outcomes after lung transplantation. Together these data suggest that the differences in outcomes we observed between short and taller adults are a disparity, which the World Health Organization defines as a “differences in health that are not only unnecessary and avoidable, but in addition, are considered unfair and unjust.” (14, 15)

Although shorter height has been previously shown to be associated with a higher rate of death among pediatric lung

transplant candidates (9), there has been little formal examination of the impact of candidate height on outcomes before and after lung transplantation. Registry reports from the International Society for Heart and Lung Transplantation do not examine waiting list outcomes, and therefore have not identified short stature as a risk factor for poor outcomes (16). For the first time, the 2013 report from the Scientific Registry of Transplant Recipients noted that taller candidates have had higher transplantation rates than shorter candidates in the 4 years preceding the report (6). Our results extend these prior studies by demonstrating the magnitude of the disparity among adults while controlling for potential confounding factors.

Transplant center personnel can begin ameliorating this disparity by introducing changes to donor–recipient matching practices. In recent years, improved post-transplant survival has been observed among recipients who have received lungs

Figure 2. Predicted cumulative incidences of (A) transplantation (P for trend < 0.001), (B) death or removal because of clinical deterioration (P for trend < 0.001), and (C) respiratory failure (P for trend = 0.01) by height quartile. Mean values for covariates in fully adjusted models from Table 2 were used to generate these predicted values.

from donors whose predicted total lung capacity is larger than the recipient's (i.e., "oversizing") (17). This practice is also associated with a reduced risk of primary graft dysfunction after lung transplantation (18). It is common for transplant surgeons to reduce the volume of the allograft during transplant surgery, and lobar transplantation is an accepted transplant procedure (19–22). Together these data suggest that it may be reasonable to perform lobar transplantation or surgically downsize substantially oversized allografts for shorter transplant candidates and expect that outcomes would be no worse, and perhaps better, than a strategy that includes an extended waiting period until a small allograft is available. In addition, earlier referral and listing of shorter candidates should be encouraged to give each candidate the greatest chance of undergoing transplantation.

Transplant policymakers should also address this disparity by altering lung allocation policy in the United States. Height is currently not included in the calculation of the LAS, perhaps as a result of the use of methods that do not account for the competing event of transplantation in the development of the waiting list urgency score component of the LAS (5). Commensurate with their higher waiting list mortality rates and lower transplantation rates, shorter lung transplant candidates should receive higher priority for lung transplantation than they currently experience in the United States. This change could be implemented either through reestimation of the beta coefficient estimates in the waiting list urgency score model using competing risk methods, through the development of a sliding scale that assigns additional LAS prioritization points according to candidate height similar to that developed for kidney transplant candidates with a high calculated panel reactive antibody score in the United States (23), and/or through a standardized LAS appeal process similar to that already in place for those with pulmonary arterial hypertension (24).

We found that women seem to suffer disproportionately from this disparity, with stronger associations between short stature and poor waiting list outcomes among women compared with men. This finding may be caused by the shorter height range among women, resulting in an even smaller pool of available donors for women. The

Figure 3. Forest plots of multivariable-adjusted associations between height and transplantation rate, death or removal because of clinical deterioration, and respiratory failure rate stratified on selected clinical and demographic variables. Boxes represent point estimates. Whiskers are 95% confidence intervals. Interaction *P* values are shown. CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; PVD = pulmonary vascular disease.

height and sex disparities may also be attributable to higher rates of allosensitization among women. However, our analyses found an association between height and waiting list outcomes, independent of the need for a prospective or virtual crossmatch. Our data suggest that addressing the height disparity might also address the previously identified sex disparity in waiting list outcomes (7).

Our study has several limitations. First, all measurements were recorded and reported to OPTN by clinical personnel and are therefore subject to missingness and

misclassification. Second, our findings are not generalizable to non-LAS-based organ allocation systems. Third, we have not demonstrated that implementation of changes in allocation policy or transplant center practices would result in improved outcomes for those of shorter stature. Finally, we did not include pediatric lung transplant candidates in our study because they have been examined previously (9).

In conclusion, we found shorter lung transplant candidates suffer from an unfair disparity in access to lung transplantation in the United States as evidenced by an

acceptably low rate of lung transplantation resulting in higher rates of respiratory failure, death, and removal from the waiting list. Earlier referral and listing of short candidates, and further refinements of the U.S. LAS-based allocation system and in donor-recipient matching practices by transplant center personnel may help to ameliorate this disparity and equalize access to lung transplantation services for children and shorter adults. ■

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

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