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Significantly reduced patient and graft survival for left vs right donor lungs for lung transplant recipients

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KEYWORDS:
single lung transplant;
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graft failure;
laterality

BACKGROUND: To evaluate the association of right vs left single lung transplants (SLT) from split lung donors with long-term post-transplant recipient outcomes.
METHODS: We performed a retrospective review of the Scientific Registry of Transplant Recipients data of split SLT adult recipients comparing right and left lung grafts between 2005 and 2021. We used a paired donor model to account for underlying differences between donors and evaluated post-transplant patient and graft survival with Cox proportional hazard models with robust variance estimates adjusted for recipient characteristics. We also used Wilcoxon signed-rank, McNemar's, and Bowker's tests to evaluate complication rates between donor pairs.
RESULTS: There were 5,180 recipients with 2,590 right and left split allografts. Left SLT had higher rates of mortality (hazards ratio [HR] = 1.17, 95% confidence interval [CI]: 1.08, 1.27) and graft failure (HR = 1.16, 95% CI: 1.06, 1.26) compared to right SLT in adjusted models. There were more early deaths (< 13 days post-transplant) among left vs right SLT (n = 52 vs 31, p = 0.018). Estimated 5-year graft survival was 47.1% (95% CI: 45.1, 49.3) and 51.4% (95% CI: 49.4, 53.5) for left and right SLT, respectively. Right SLT was associated with longer length of stay (median 14 days vs 13 days, p = 0.016) and more prolonged ventilation (> 5 days) (n = 319, 12.6% vs n = 270, 10.6%; p = 0.030).
CONCLUSIONS: Left SLT was associated with significantly worse mortality and graft failure while right SLT was associated with more short-term complications from split lung donors. Organ listing and acceptance decisions should consider donor lung laterality.

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Background

Since the 1980s, lung transplantation has been an acceptable palliative therapy for end-stage lung disease refractory to medical management.[1,2] The lung allocation system (LAS), implemented in May 2005, introduced a paradigm shift basing lung transplant allocation on waitlist and post-transplantation survival rather than waitlist time to prioritize organ allocation to those with the greatest medical urgency.[2-4] Since LAS implementation, there have been more transplantations performed despite no increase in the donor pool. Despite an increase in mean recipient age to greater than 50 years old, and a shift in recipients with a diagnosis of fibrotic lung disease, implementation of the LAS has also been associated with reductions in mortality while on the waitlist and 1-year post-transplant mortality. This change may have reflected a decreased median waitlist time from 792 days in 2004 to less than 200 days in the more recent era.[3,4] While double lung transplantation has been associated with equivalent or improved survival rates, single lung transplantation (SLT) remains an acceptable alternative to increase the number of potential lung donors while reducing preoperative complications in selected lung transplant recipients.[5-11]

Survival after lung transplantation has improved due to changes in donor selection, organ preservation, and perioperative management. However, many risk factors for poor outcomes have been identified including age, body mass index, race mismatch, center volume, ischemic time, kidney function, liver function, hospitalization at time of transplant, extracorporeal membrane oxygenation before transplant, and mechanical ventilation before transplant.[11] The lung laterality chosen for transplant is often based on multiple baseline recipient factors. However, donor lung laterality in isolation has not been as thoroughly analyzed as a factor affecting post-transplant outcomes. Small series have evaluated donor laterality on post-transplant outcomes; however, these have not used a paired model to account for donor characteristics.[9,12] Additionally, of the paired or split SLT studies published, none included an analysis of modern-day outcomes in the era of the lung allocation score.[13-15]

Herein, we present a retrospective database review using the Scientific Registry of Transplant Recipients (SRTR) data to identify differences in right and left SLT outcomes from split lung donors.[16] Our primary outcomes were post-transplant survival and graft failure within 5 years after transplantation.

Materials and methods

This study used data from the SRTR. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources & Services Administration, US Department of Health and Human Services provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. The data reported here have been supplied by the Hennepin Healthcare Research Institute as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government.

This study was approved by the Colorado Multiple Institutional Review Board and exempt from informed consent. SRTR data was received in September 2022 including all split SLT performed in adult recipients between May 1, 2005 and December 1, 2021. Multiorgan recipients and patients younger than 18 years of age were excluded. Only paired SLT records were included in the study, meaning that both right and left donor lungs were used, and both sides were eligible for inclusion in the current study. This study was performed in compliance with the International Society for Heart and Lung Transplantation Ethics statement.

Baseline characteristics for donors and recipients as well as center volume were evaluated overall and by lung transplant laterality and were compared using Wilcoxon signed-rank test on the difference for continuous variables, McNemar's test for categorical variables with 2 levels, and Bowker's test of symmetry for categorical variables with more than 2 levels.

Post-transplant length of stay, in-hospital acute rejection, and ventilator support were tabulated by lung laterality. Right and left SLT were compared using Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Sensitivity analyses were also performed, excluding patients who died within 5 days for the 5-day ventilator measure and excluding patients who died before the median hospital length of stay for the acute rejection measure. Lung transplant laterality was also compared to readmission rate, need for long-term dialysis, and presence of bronchial stricture and bronchial obliterans syndrome (BOS) during the first year of follow-up.

The main outcomes were post-transplant survival and post-transplant graft failure. Graft failure was defined as graft failure or death before the reporting time point. Mortality was censored using TFL_ENDTXFU, and graft failure was censored using TFL_ENDTXFU and TFL_LAFUDATE. All follow-up was censored at 5 years. The Cox proportional hazards model was used to compare transplanted lung laterality with a robust sandwich estimator to account for the paired donation by donor identifier. Unadjusted survival estimates were obtained, and the estimated survival was graphed by laterality. Unadjusted survival graphs were also obtained for split lungs going to both recipients with obstructive and restrictive diagnoses, respectively. Cox models were also adjusted including the following variables: recipient age, sex, race/ethnicity, blood type, LAS at time of transplantation, diagnosis group, and prior transplant. A sensitivity analysis was used to evaluate separately split lungs transplanted at the same center and lung pairs transplanted at different centers. Additional sensitivity analyses were performed to evaluate separately split lungs going to recipients with obstructive disease, restrictive disease, donor-recipient predicted total lung capacity (D/R PTLC) 0.8 to 1.2, D/R PTLC > 1.2, and by donor chest X-ray. Only lungs with both sides going to the same subset category were included in sensitivity analyses. We also evaluated whether the effect of laterality was different across centers with different transplant volumes by categorizing centers into tertiles of volume based on the volume of lung transplants and testing the interaction between volume and lung laterality. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

We included 5,180 records for 2,590 right and 2,590 left split lungs (Figure 1). Table 1 shows recipient characteristics for left vs right SLT as well as center volume within the study period. The median ages for recipients of right and left SLT were 65 and 64 years, respectively. The percentage of male recipients was 64.6% and 62.3%, respectively. There were no significant differences in recipient cardiac output or prior lung surgery between right and left SLT. Donor characteristics were identical on left and right sides and are depicted in Table 2. Lung preference at listing demonstrated a slight preference toward right SLT over left SLT. Of the 3,135 patients listed for single lungs, 900 were listed for only right SLT whereas 776 were listed for only left SLT. Conversely, among the 2,045 patients listed for bilateral or single lungs, 287 listed preference for left lungs only, whereas 213 listed preference for right lungs only. There was greater D/R size mismatch associated with right SLT regarding D/R pTLC ratios < 0.8 but there were no other differences noted among the other D/R pTLC ratios.

The median post-transplant length of stay was 14 and 13 days for right and left SLT, respectively (Table 3a). The sensitivity analysis that excluded patients with early in-hospital mortality demonstrated similar results as compared to the main analysis (Table 3b).

We observed 2,224 deaths during a median follow-up of 3.4 years. There were no appreciable differences in cardiovascular, cerebrovascular, graft failure, or pulmonary causes of death between right and left SLT. Majority of deaths were due to pulmonary causes (19.7% right SLT, 21.7% left SLT), graft failure (17.6% right SLT, 18.6% left SLT), infectious causes (21.3% right SLT, 19.4% left SLT), and malignancy (14.7% right SLT, 13.2% left SLT). Overall, survival was significantly lower for single left lung recipients. Estimated survival at 5 years was 48.5% for SLT and 53% for the single right transplant (Figure 2 and Table 4). Table 5 shows results from unadjusted and adjusted models. In the adjusted model, left lungs had 17% higher hazard of death compared to right lungs (HR = 1.17, 95% CI: 1.08, 1.27, $p < 0.001$). Left SLT was also associated with more early deaths (within 13 days after transplant, $p = 0.018$) than right lungs, with 52 early deaths following left SLT in comparison to 13 early deaths after right SLT (Table 3b).

Graft survival was also significantly lower for left lung recipients. Estimated 5-year graft survival was 47.1% and 51.4% for left and right SLT, respectively (Figure 3 and Table 4). In the adjusted model, left lungs had 16% higher hazard of graft failure compared to right lungs (HR = 1.16, 95% confidence interval: 1.06, 1.26, $p < 0.001$) (Table 5). Among the 2,274 patients with graft failure, 131 (6%) underwent retransplantation, of which 63 were left SLT and 68 were right SLT. Among all SLTs included, there were higher rates of right single lung retransplantations ($n = 139$, 5.4%) compared to left single lung retransplantations ($n = 107$, 4.1%, $p = 0.038$). Single lung retransplantation following heart-lung transplant was rare. Among the retransplantations, there were higher rates of right SLT retransplants following prior left SLT ($n = 75$, 54%) compared to the left SLT retransplants following prior right SLT ($n = 50$, 47%). There were similar rates of right SLT retransplants following prior right SLT ($n = 17$, 12%) and left SLT retransplants following prior left SLT ($n = 11$, 10%). There were also similar numbers of right and left SLT retransplants following bilateral sequential lung transplants ($n = 41$, 29% vs $n = 42$, 39%).

Unadjusted patient and graft survival curves for right and left SLT within obstructive diagnosis (group A) showed similar results to the overall analysis, but did not reach statistical significance within restrictive diagnosis (group D) (Supplemental Figure 1). Adjusted results were consistent with the main analysis and statistically significant for both obstructive and restrictive diagnosis groups for patient survival (HR = 1.30, 95% CI: 1.01, 1.66, and HR = 1.14, 95% CI: 1.01, 1.29, respectively) and graft survival (HR = 1.28, 95% CI: 1.01, 1.63, and HR = 1.13, 95% CI: 1.01, 1.27, respectively) (Supplemental Table 1). We also performed sensitivity analyses on lungs that were split and received at the same center ($n = 1{,}152$ pairs, 44.5%), and on lungs that went to different centers (n = 1438 pairs, 55.5%).

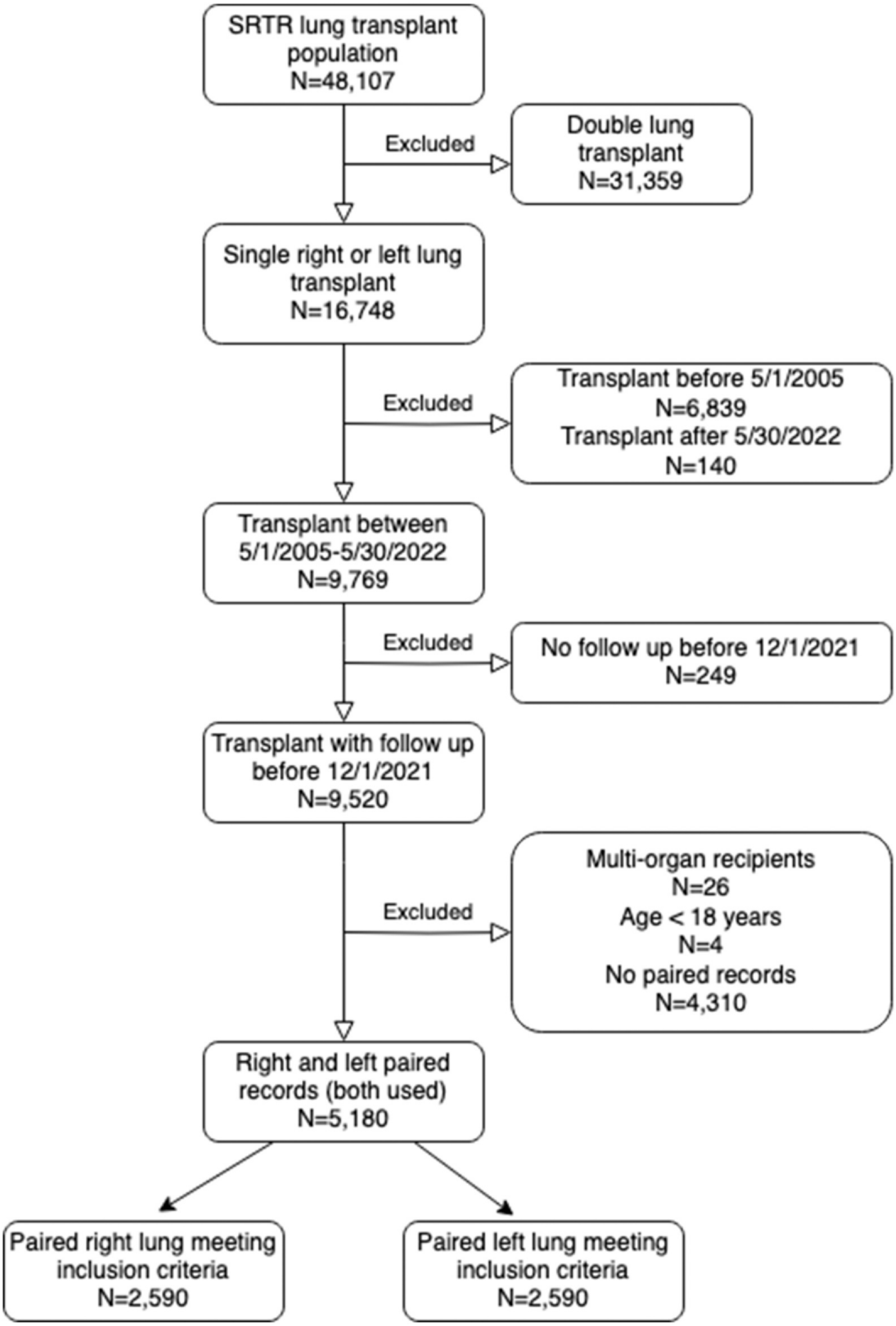

Figure 1 Flowchart depicting inclusion and exclusion criteria. SRTR, Scientific Registry of Transplant Recipients.

When evaluating only split lungs that were received at the same center, results were consistent with the main analysis. The mortality HR for left vs right lungs was 1.20 (1.06, 1.37) and graft failure HR was 1.17 (1.04, 1.33). Results were also consistent when evaluating lungs going to different centers. Our sensitivity analyses showed consistent results across DR PTLC 0.8 to 1.2, and DR PTLC > 1.2. When evaluating laterality within categories of donor X-ray results, we found consistent results when split lungs were both normal on X-ray (mortality HR 1.17, 95% CI: 1.04, 1.31, and graft loss HR 1.15, 95% CI: 1.03, 1.29). However, analyses on laterality for subsets with abnormal left only, right only, or both did not reach statistical significance. Centers were grouped based on volume and evaluated for an association with mortality and graft failure based on lung laterality with no significant differences ($p = 0.48$, $p = 0.76$, respectively).

Table 1 Baseline Paired Lung Transplant Recipient Characteristics Comparing Right and Left Lung Graft Recipients

Factor	N missing	Total (N = 5,180)	Right (N = 2,590)	Left (N = 2,590)	*p*-value
Age at transplant (years)		64.0 [60.0, 68.0]	65.0 [60.0, 69.0]	64.0 [60.0, 68.0]	0.010[a]
Sex					
Female		1,893 (36.5)	917 (35.4)	976 (37.7)	0.06[b]
Male		3,287 (63.5)	1,673 (64.6)	1,614 (62.3)	
Recipient race/ethnicity					0.11[c]
Black		318 (6.1)	152 (5.9)	166 (6.4)	
Hispanic		346 (6.7)	165 (6.4)	181 (7.0)	
Other		124 (2.4)	50 (1.9)	74 (2.9)	
White		4,392 (84.8)	2,223 (85.8)	2,169 (83.7)	
BMI (kg/m^2)	10	26.6 [23.5, 29.3]	26.3 [23.3, 29.2]	26.8 [23.6, 29.4]	0.001[a]
BMI category	10				0.16[c]
13-20		394 (7.6)	215 (8.3)	179 (6.9)	
> 20-25		1,496 (28.9)	769 (29.7)	727 (28.1)	
> 25-30		2,298 (44.4)	1,132 (43.7)	1,166 (45.0)	
> 30-35		924 (17.8)	448 (17.3)	476 (18.4)	
35-50		58 (1.1)	21 (0.8)	37 (1.4)	
Missing		10 (0.2)	5 (0.2)	5 (0.2)	
A B O blood group					0.91[c]
O		2,432 (46.9)	1,214 (46.9)	1,218 (47.0)	
B		450 (8.7)	221 (8.5)	229 (8.8)	
A		2,164 (41.8)	1,085 (41.9)	1,079 (41.7)	
AB		134 (2.6)	70 (2.7)	64 (2.5)	
Lung allocation score	2	39.2 [34.5, 47.5]	39.4 [34.5, 48.4]	39.0 [34.5, 46.9]	0.028[a]
Oxygen requirement at rest (liter/min)	2,462	4.0 [2.0, 6.0]	3.3 [2.0, 6.0]	4.0 [2.0, 5.0]	0.73[a]
Preoperative ECMO					0.56[b]
No		5,132 (99.1)	2,564 (99.0)	2,568 (99.2)	
Yes		48 (0.93)	26 (1.00)	22 (0.85)	
Main pulmonary artery pressure ≥40 mm Hg*	293				0.35[b]
No		4,696 (90.7)	2,348 (90.7)	2,348 (90.7)	
Yes		191 (3.7)	103 (4.0)	88 (3.4)	
Missing		293 (5.7)	139 (5.4)	154 (5.9)	
Preoperative ventilator					0.72[b]
No		5,048 (97.5)	2,522 (97.4)	2,526 (97.5)	
Yes		132 (2.5)	68 (2.6)	64 (2.5)	
Six-minute walk distance (feet)	2,444	800 [467.5, 1100]	764.5 [431, 1076.5]	850 [500,1120]	< 0.001[a]
Forced expiratory volume in the first second (FEV1)% predicted	83	43.0 [26.0, 57.0]	42.0 [24.0, 58.0]	43.0 [27.0, 57.0]	0.24[a]
Forced vital capacity (FVC) % predicted	69	48.0 [38.0, 59.0]	48.0 [38.0, 60.0]	47.0 [38.0, 59.0]	0.54[a]
Most recent serum creatinine (mg/dl)	10	0.83 [0.70, 1.00]	0.82 [0.70, 1.00]	0.83 [0.70, 1.00]	0.22[a]
Recipient diagnosis group					0.009[c]
Obstructive (group "A")		1,542 (29.8)	816 (31.5)	726 (28.0)	
Pulmonary vascular disease (group "B")		87 (1.7)	45 (1.7)	42 (1.6)	
Cystic fibrosis (group "C")		24 (0.46)			
Restrictive (group "D")		3,527 (68.1)	1,721 (66.4)	1,806 (69.7)	
Previous lung transplant					0.038[b]
No		4,934 (95.3)	2,451 (94.6)	2,483 (95.9)	
Yes		246 (4.7)	139 (5.4)	107 (4.1)	
Average center volume per year (in study period)		39.0 [25.0, 63.8]	37.9 [24.8, 63.8]	39.6 [25.2, 63.8]	< 0.001[a]
Recipient total ischemic time (hours)	143	4.2 [3.5, 5.1]	4.3 [3.5, 5.1]	4.2 [3.4, 5.0]	0.001[a]
Recipient CO liter/min	387	5.2 [4.4, 6.0]	5.2 [4.4, 6.0]	5.2 [4.4, 6.1]	0.58[a]
Prior lung surgery (nontransplant)					0.18[c]
No		4,793 (92.5)	2,404 (92.8)	2,389 (92.2)	
Unknown		42 (0.81)	21 (0.81)	21 (0.81)	
Yes		345 (6.7)	165 (6.4)	180 (6.9)	

(*continued on next page*)

Table 1 ? ? ? (*Continued*)

Factor	N missing	Total (N = 5,180)	Right (N = 2,590)	Left (N = 2,590)	*p*-value
Prior lung surgery—left thoracotomy		46 (0.89)	22 (0.85)	24 (0.93)	0.76[b]
Prior lung surgery—right thoracotomy		74 (1.4)	37 (1.4)	37 (1.4)	0.99[b]
Recipient PTLC		6.7 [5.3, 7.4]	6.7 [5.3, 7.4]	6.7 [5.2, 7.4]	0.009[a]

Abbreviations: BMI, body mass index, ECMO, extracorporeal membrane oxygenation.
Cystic fibrosis N by side not reported due to small N.
Statistics are presented as median [P25, P75], N (column %).
[a]Wilcoxon signed-rank test on the paired difference.
[b]McNemar's test.
[c]Bowker's test of symmetry.

Table 2 Baseline Paired Lung Transplant Donor Characteristics

Factor	Total (N = 5,180)	Right (N = 2,590)	Left (N = 2,590)	*p*-value
Donor age (years)	34.0 [23.0, 47.0]			
Donor sex				
Female	1,894 (36.6)			
Male	3,286 (63.4)			
Donor race/ethnicity				
Black	1,046 (20.2)			
Hispanic	862 (16.6)			
Other	152 (2.9)			
White	3,120 (60.2)			
Donor cause of death				
Anoxia	1,046 (20.2)			
Cerebrovascular/stroke	1,734 (33.5)			
Head trauma	2,242 (43.3)			
Central nervous system tumor	30 (0.58)			
Other	128 (2.5)			
Cigarette use > 20 pack years ever				
No	4,640 (89.6)			
Unknown	76 (1.5)			
Yes	464 (9.0)			
Donor left ventricular ejection fraction	60 [55, 65]			
Donor chest X-ray				
No chest X-ray	42 (0.81)			
Normal	2,562 (49.5)			
Abnormal-left	490 (9.5)			
Abnormal-right	578 (11.2)			
Abnormal-both	1,490 (28.8)			
Results unknown	14 (0.27)			
Nonheart beating donor	82 (1.6)			
Donor PTLC/recipient PTLC	1.03 [0.93, 1.2]	1.03 [0.91, 1.1]	1.03 [0.94, 1.2]	0.014[a]
Donor/recipient PTLC group				0.032[b]
DR PTLC < 0.8	402 (7.8)	224 (8.6)	178 (6.9)	
DR PTLC 0.8-1.2	3,783 (73.0)	1,873 (72.3)	1,910 (73.7)	
DR PTLC > 1.2	995 (19.2)	493 (19.0)	502 (19.4)	
Donor recipient sex mismatch				< 0.001[c]
No	3,527 (68.1)	1,706 (65.9)	1,821 (70.3)	
Yes	1,653 (31.9)	884 (34.1)	769 (29.7)	

Statistics are presented as median [P25, P75], N (column %).
Four recipients received lungs from donors from whom it was unknown if chest X-ray was performed.
[a]Wilcoxon signed-rank test on the paired difference.
[b]Bowker's test of symmetry.
[c]McNemar's test.

Table 3a Postoperative Length of Stay and Complications Comparing Right and Left Single Lung Transplantation Within 1 Year After Transplantation

Factor	N missing	Overall	Right (N = 2,590)	Left (N = 2,590)	*p*-value
In-hospital					
Post-transplant length of stay (LOS) (days)	4	13.0 [10.0, 21.0]	14.0 [10.0, 22.0]	13.0 [10.0, 21.0]	0.016[a]
Any acute rejection episodes between transplant and discharge	0				0.96[b]
No		4,751 (91.7)	2,376 (91.7)	2,375 (91.7)	
Yes		429 (8.3)	214 (8.3)	215 (8.3)	
Post-transplant (Tx) ventilator ≥5 days	110				0.030[b]
No		4,481 (88.4)	2,212 (87.4)	2,269 (89.4)	
Yes		589 (11.6)	319 (12.6)	270 (10.6)	
During 1-year follow-up					
Hospitalization first year	935				0.70[b]
No		2,030 (47.8)	1,022 (47.7)	1,008 (47.9)	
Yes		2,215 (52.2)	1,120 (52.3)	1,095 (52.1)	
Hospitalized for infection first year	988				0.51[b]
No		3,149 (75.1)	1,578 (74.5)	1,571 (75.7)	
Yes		1,043 (24.9)	539 (25.5)	504 (24.3)	
Chronic dialysis first year	911				0.83[b]
No		4,244 (99.4)	2,137 (99.3)	2,107 (99.5)	
Yes		25 (0.59)	15 (0.70)	10 (0.47)	
Bronchial stricture first year	1,560				0.006[b]
No		3,446 (95.2)	1,754 (96.1)	1,692 (94.3)	
Yes		174 (4.8)	71 (3.9)	103 (5.7)	
BOS of any degree first year	1,645				0.14[b]
No		3,216 (91.0)	1,608 (90.4)	1,608 (91.6)	
Yes		319 (9.0)	171 (9.6)	148 (8.4)	

Abbreviation: SRTR, Scientific Registry of Transplant Recipients.

Year 1 variables not available when data missing, or patient has no follow-up form (due to death, not seen yet, or loss to follow-up). Seven hundred and twenty-three died within year 1 (355 R, 368 L).

Bronchial stricture and BOS stopped data collection in SRTR sometime in 2020.

[a]Wilcoxon signed-rank test.

[b]McNemar's test.

Table 3b Sensitivity Analysis: Postoperative Length of Stay and Complications Comparing Right and Left Single Lung Transplantation Excluding Patients Who Died Within the Time Period Examined

Factor	Overall	Right	Left	*p*-value
Post-transplant LOS (days) excluding deaths before 13th day	13.0 [10.0, 21.0]	14.0 [10.0, 22.0]	13.0 [10,21]	0.038[a]
Post-transplant LOS (days) for patients discharged alive without graft loss	13.0 [10.0, 20.0]	13.0 [10.0, 21.0]	13.0 [9.5, 20.0]	0.023[a]
Any acute rejection episodes between transplant and discharge[b]				
No	4,675 (91.7)	2,347 (91.7)	2,328 (91.7)	0.92[c]
Yes	422 (8.3)	212 (8.3)	210 (8.3)	
Post-Tx ventilator ≥5 days[d]				0.029[c]
No	4,451 (88.3)	2,199 (87.3)	2,252 (89.4)	
Yes	587 (11.7)	319 (12.7)	268 (10.6)	

For length of stay among patients discharged alive without graft loss, 226 patients were excluded due to graft loss/death within hospitalization. An additional 4 patients lacked date of discharge and were excluded. Of these, 3 had early graft losses (before 1.5 months). Among the total 230 excluded, there were 108 right and 122 left sides.

[a]Wilcoxon signed-rank test.

[b]For acute rejection and length of stay, data excluded if recipients died before median length of stay (13 days). Eighty-three patients died within 13 days post-transplant (31 right and 52 left sides). Additionally, 3 patients were missing LOS.

[c]McNemar's test.

[d]For ventilator ≥5 days, data excluded if recipients died within 5 days of transplant. Thirty-six patients died within 5 days post-transplant (15 right and 21 left sides). An additional 106 were missing post-transplant ventilator data.

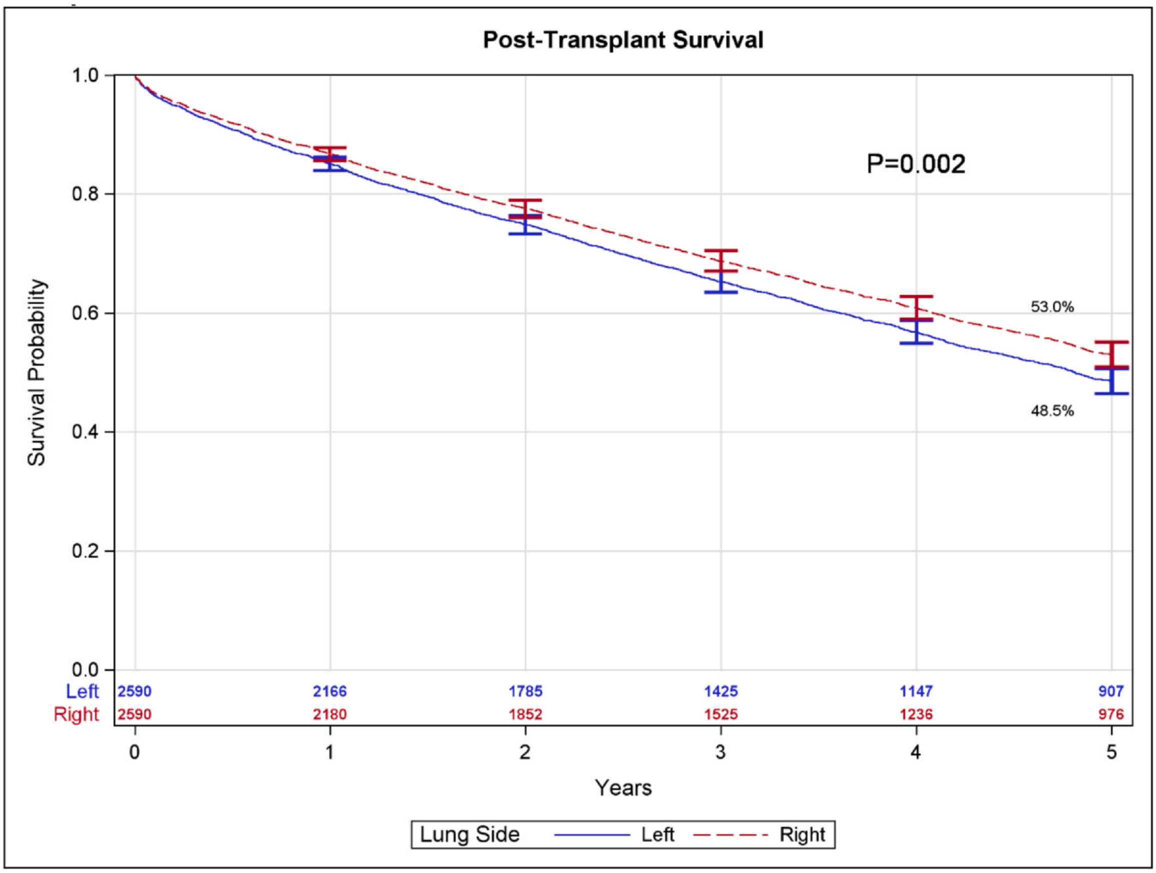

Figure 2 Post-transplant recipient survival following right vs left split single lung transplants. Estimates obtained from Cox model with robust sandwich estimator to account for donor observations.

Table 4 Unadjusted Recipient Survival Estimates for Left vs Right Single Lung Transplant Recipients

	Left		Right	
Year post-Tx	*Number at risk*	*Survival estimate (95% CI)*	*Number at risk*	*Survival estimate (95% CI)*
1	2,166	85.1 (83.9, 86.2)	2,180	86.8 (85.7, 87.8)
3	1,425	65.3 (63.5, 67.0)	1,525	68.7 (67.1, 70.5)
5	907	48.5 (46.4, 50.6)	976	53.0 (50.9, 55.1)
Year post-Tx		*Graft survival estimate (95% CI)*		*Graft survival estimate (95% CI)*
1	2,087	84.3 (83.1, 85.5)	2,127	86.0 (84.9, 87.1)
3	1,326	63.9 (62.1, 65.7)	1,427	67.2 (65.5, 69.0)
5	838	47.1 (45.1, 49.3)	899	51.4 (49.4, 53.5)

Abbreviation: CI, confidence interval.

Table 5 Cox Proportional Hazards Ratio for Mortality and Allograft Failure in Left vs Right Single Lung Transplantation

Model	Mortality HR (95% CI)	*p*-value	Graft failure HR (95% CI)	*p*-value
Unadjusted model left vs right	1.14 (1.05,1.24)	0.002	1.13 (1.04,1.23)	0.003
Adjusted model left vs right[a]	1.17 (1.08, 1.27)	< 0.001	1.16 (1.06, 1.26)	< 0.001

Abbreviation: CI, confidence interval.
[a]Adjusted for recipient age, sex, race/ethnicity, blood type, LAS at time of transplantation, diagnosis group, and prior transplant. For adjusted model N = 5,178 due to a pair of lungs from early May 2005 missing LAS score.

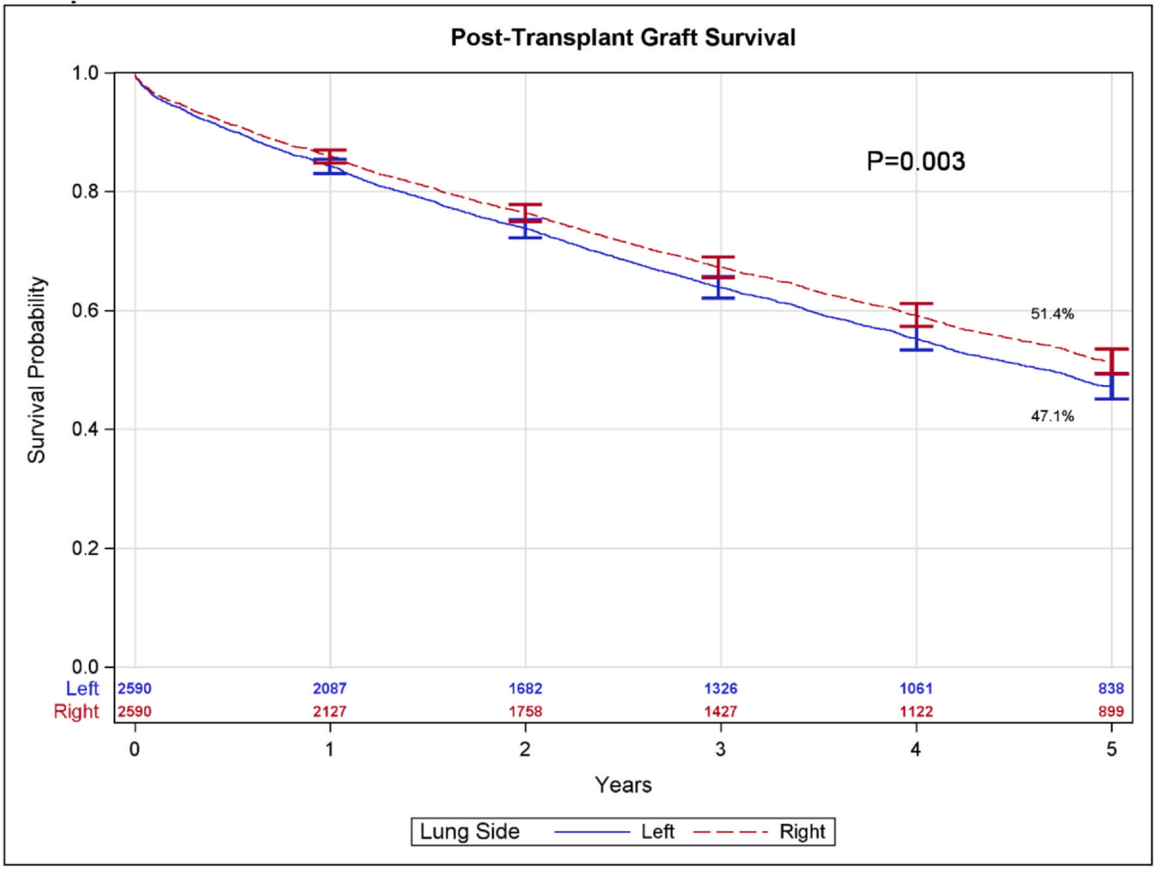

Figure 3 Post-transplant allograft survival for right vs left split single lung transplants. Estimates obtained from Cox model with robust sandwich estimator to account for donor observations.

Discussion

Our study demonstrated significantly worse overall lung transplant recipient survival and lung allograft survival in recipients of left SLTs compared to recipients of right SLT split from the same donors. The increased mortality and graft failure risks of left SLT remained after adjustment for age, gender, race, blood type, lung allocation score, recipient diagnosis group, and history of prior transplant. Left SLT also notably had higher rates of postoperative bronchial stricture in the first year after transplantation than right SLTs, which is consistent with published literature.[12] However, bronchial stricture was not collected for all years included in our study, and we should be careful with the interpretation of this finding. There were no other statistically significant differences in 1-year postoperative complications. Centers where both lungs transplants were performed did not significantly impact mortality or graft failure. Interestingly, left SLT was associated with significantly shorter median length of stay following transplantation and lower rates of prolonged post-transplantation ventilation requirement in comparison to right SLT. We demonstrate 1-, 3-, and 5-year overall survival of 85.1%, 65.3%, and 48.5% associated with left SLT and 86.8%, 68.7%, and 53.0% associated with right SLT. These survival rates are improved compared to Tsagkaropoulos et al who demonstrated 1- and 5-year overall survival of 76%, 78.3% and 41.8%, 44.8% associated with left and right SLT performed from July 1991 to July 2009, respectively. This finding is consistent with the overall trend of improved survival over time with advances in surgical techniques, medical management post-transplant, and lung protective ventilation.[3,15]

Our findings of worse outcomes associated with left SLT were consistent with the findings of Snell et al, which had a smaller sample size of 76 paired SLT performed in Australia. Their group found significantly higher rates of 6-month, 1-year, and 2-year mortality and bronchial anastomotic complications associated with left SLT.[13] Smits et al also had a smaller sample size of 90 paired SLT performed in 16 centers in Europe and demonstrated higher 1-year mortality associated with left SLT (62% left vs 92% right) but, interestingly, found higher rates of bronchiolitis obliterans syndrome associated with right SLT.[14] There have been significant advances in lung transplantation in the last 2 decades, as demonstrated in the improvement in survival demonstrated in our study and others published recently in comparison to the 50% to 60% 5-year survival shared by Snell et al in 1998.[13] Other SLT studies comparing right and left lung grafts that were not split from the same donor also had smaller sample sizes and demonstrated no significant differences in early or late survival, rejection, infection, time to extubation, hospital length of stay, or native lung complications.[9,12,15] Importantly, these studies were carried out before the implementation of LAS or were biased by a heterogeneous group of allografts from nonsplit donors.

The reasons for worse left SLT overall and graft survival in this study were not clear but have been attributed in the literature to anatomical differences. The right lung contains more lung volume than the left which has been associated with improved postoperative outcomes, as seen in the literature on pneumonectomies for lung cancer which has demonstrated 2% to 7% worse short- and long-term survival associated with right pneumonectomy in comparison to left pneumonectomy, although there was no significant difference in 5-year survival.[17,18] We were not able to assess the effect of lung volume in our study as it is not included in the SRTR. The left bronchial anastomosis is also more technically difficult to perform as the left hemithorax is smaller and obstructed by the cardiac silhouette.[8,9,12,13] However, there is a higher aspiration risk associated with the shorter, more vertical right bronchus. Similar studies performed examining paired single renal transplantations report worse early delayed right renal graft function attributed to anatomic differences that make the right renal transplantation more technically difficult, such as the shorter right renal vein potentially requiring an interposition graft and longer right renal artery at risk of kinking.[19,20] These studies do not demonstrate differences in long-term graft function or graft survival, supporting that their early differences in outcomes are less attributed to intrinsic differences in the grafts such as the smaller size of the right kidney.[19-21] In contrast, our study demonstrates more pronounced differences in graft and overall survival over time associated with left SLT in comparison to right SLT, rather than a significant difference early on that stabilizes over time, suggesting that there are likely other contributing intrinsic differences at play rather than simply a more technically difficult left lung implantation, which future studies should examine.

There was a slight predisposition toward right SLT among patients who underwent retransplantation. There are only a few studies examining single lung retransplantation given its rarity and no studies comparing paired single lung retransplantation to our knowledge. A survival analysis of the United Network for Organ Sharing (UNOS) registry demonstrated worse survival with single lung retransplantation when compared only to double lung retransplantation, but they found no difference in survival when all variations of single or double lung retransplantations were compared.[10] Another analysis of the International Society for Heart and Lung Transplantation registry did not find variation in single or double lung transplantation and retransplantation to be a strong predictor of mortality after retransplantation, although they reported a 7% increased risk of 1-year mortality associated with consecutive single lung retransplants (69%) in comparison to consecutive double lung retransplants (76%).[22] In contrast, a UNOS dataset analysis of staged contralateral SLTs demonstrated comparable rates of acute rejection, airway dehiscence, stroke, length of hospital stay, 30-day mortality, and overall survival with double lung transplantation, suggesting that contralateral SLTs may be appropriate options for patients who have had prior SLT in consideration of retransplantation.[23] Future studies should further elucidate any additional risk factors associated with worse outcomes after single lung retransplantation including lung laterality.

As this is a retrospective database study, limitations of this study include inability to provide details on donor warm ischemia time due to high missingness, specific center volume, and the potential for selection bias due to institution-specific practice patterns. Additionally, as our study spanned 16 years, it did not account for changes in preoperative, intraoperative, or postoperative patient management practices that have evolved over time. The definition of graft failure per the SRTR is nonspecific for any documented "graft failure" or mortality, which may contribute to a wide variation and inconsistency in reporting graft failure and subsequent failure to capture all patients. Last, the SRTR registry also lacks granular details regarding a transplant center's reason for choosing a recipient's transplant laterality. This decision may include information derived from preoperative ventilation/perfusion scan and computed tomography scan and may more precisely identify the SLT recipient's risk of post-transplant complications related to the remaining native lung. Inability to control for native lung disease severity and its risk of post-transplant disease progression further bias our results since this factor may account for some of the excess post-transplant mortality noted in recipients of left SLT noted in this study.

Conclusion

This study is the largest paired lung study utilizing nationally collected data of right vs left SLT to date. Because this study spans the era post-LAS implementation, we have provided an avenue to compare lung allograft function and post-transplant survival by laterality while naturally controlling for donor characteristics, thereby allowing a more precise analysis of recipient factors associated with post-transplant graft failure and survival. As our results demonstrate a small but significant improvement in survival and graft survival with right SLT in comparison to left SLT, we recommend that donor selection and transplant listing should preferentially list and select patients for right SLT in comparison to left SLT when possible.

Author contribution

Concept and design: J.R.H.H., J.D.S. Acquisition and analysis of data: S.A., E.A.P., J.S. Interpretation of data: all authors. Drafting of the manuscript: S.Y.P., E.B., J.S., N.V., J.R.H.H. Critical revision of the manuscript: all authors. Statistical analysis: J.S., S.A. Obtained funding: none. Supervision: J.R.R.H., J.D.S.

Disclosure statement

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relationship with TFF Pharmaceuticals Inc. that includes board membership, consulting or advisory, and travel reimbursement. Elizabeth Pomfret, MD, PhD, reports a relationship with American Society of Transplant Surgeons that includes board membership. John D. Mitchell, MD, reports a relationship with The American Board of Thoracic Surgery Inc. that includes board membership. John D. Mitchell, MD, reports a relationship with The American Board of Surgery that includes board membership. John D. Mitchell, MD, reports a relationship with The Society of Thoracic Surgeons that includes board membership. Robert A. Meguid, MD, MPH, reports a relationship with Medtronic Inc. that includes consulting or advisory. Jordan R.H. Hoffman, MD, MPH, reports a relationship with Donor Alliance Inc. that includes board membership. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The data reported here have been supplied by the Hennepin Healthcare Research Institute as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100148.

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