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Gender differences in long-term survival posttransplant: a single-institution analysis in the lung allocation score (LAS) era

Gabriel Loor, MD¹, Roland Brown², Rosemary F. Kelly, MD¹, Kyle D. Rudser, PhD², Sara J. Shumway, MD¹, Irena Cich¹, Christopher T. Holley, MD¹, Colleen Quinlan¹, and Marshall I. Hertz, MD³

¹University of Minnesota Department of Surgery, Minneapolis, MN

²University of Minnesota School of Public Health, Minneapolis, MN

³University of Minnesota Department of Medicine, Minneapolis, MN

Abstract

Purpose—To clarify the significance of recipient gender status on lung transplant outcomes in a large single institution experience spanning three decades.

Methods—We analyzed data from all lung transplants performed in our institution since 1986. Kaplan-Meier curves and Cox proportional hazard models were used to evaluate the effect of recipient characteristics on survival and BOS score 1-free survival. Logistic regression analysis was used to explore the association of gender with short term graft function.

Results—876 lung transplants were performed between 1986 and 2016. Kaplan-Meier survival estimates at 5 years post-transplant for females versus males in the LAS era were 71% versus 58%. In the LAS era females showed greater unadjusted BOS 1-free survival than males (35% vs 25%, $P=0.02$) over 5 years. Female gender was the only factor in the LAS era significantly associated with improved adjusted 5 year survival [HR 0.56 (95% CI 0.33, 0.95) $P=0.03$]. Conversely, in the pre-LAS era female gender was not associated with improved survival.

Conclusion—Female recipients showed significantly improved survival over 5 years compared to males in the LAS era. A prospective analysis of biologic and immunologic differences is warranted.

INTRODUCTION

Understanding factors associated with reduced long-term survival after lung transplants is important for predicting, and potentially improving, outcomes. Currently, the average unadjusted 5-year survival rate remains low: 56%.¹ Several factors have been implicated in reduced long-term survival, such as primary graft dysfunction (PGD), certain primary diagnoses, older recipient age, frailty, donor-recipient human leukocyte antigen (HLA) mismatches, elevated body mass index (BMI), and single-lung transplants.^{1–5} The biologic and psychosocial differences between the genders can also uniquely affect outcomes posttransplant.

Several studies have demonstrated improved survival rates for female (as compared with male) recipients. Roberts and colleagues showed a 5-year survival of 65% for female recipients, as compared with 40% for male recipients.⁶ In a single-center cohort analysis, Demir and colleagues observed a similar difference between female and male recipients.⁷ In contrast, in their review of a large International Society for Heart and Lung Transplantation (ISHLT) registry of 18,702 patients, mostly in the pre-LAS era, Gries and colleagues found no overall gender differences in survival.⁸ Some have advocated that a donor-recipient gender mismatch is more important than the recipient gender alone. Demir and colleagues showed that poor survival was associated with a female-to-male mismatch (i.e., a female donor and a male recipient).⁷ Likewise, in a multivariate analysis of the ISHLT registry, Sato and colleagues showed that a female-to-male mismatch was associated with a strong negative effect on long-term survival.⁹ One reason might be that female donor organs, on average, have a lower functional mass than male donor organs. Thus, for improving outcomes and preventing PGD, appropriate donor-recipient size matching might be more relevant than donor-recipient gender matching per se.^{10,11}

The initiation of the lung allocation score (LAS) in the United States—by the United Network for Organ Sharing (UNOS) through the Organ Procurement and Transplantation Network (OPTN)—has changed the dynamics of the field, giving priority to higher-risk transplant candidates. Since the beginning of the LAS era, a disproportionate number of lung recipients have been male.¹ Thus, the effect of male gender might be amplified by other characteristics that make recipients higher-risk, per the LAS. Moreover, female recipients might have protective mechanisms against long-term graft dysfunction. In our current study, we analyzed the differences in characteristics and outcomes, particularly long-term survival posttransplant, between male and female recipients in the LAS era.

MATERIALS AND METHODS

Study Design

For our retrospective analysis, we used the Transplant Information Services (TIS) database at the University of Minnesota, which includes prospectively collected information on all lung transplants at our institution from January 1986 through January 2016. For our study period, we intentionally spanned both the pre-LAS era (January 1986 through April 2005) and the LAS era (May 2005 through January 2016). Our study was approved by the University of Minnesota institutional review board, which waived the need for consent from individual patients.

Outcomes

Certain outcomes—such as the bronchiolitis obliterans score (BOS), peak PGD score, re-exploration for bleeding posttransplant, number of ventilator days posttransplant, intensive care unit (ICU) length of stay (LOS)—were available only in the LAS era. For all recipients in the LAS era, an observer blinded to gender calculated the PGD scores (at Time 0 and at 24, 48, and 72 hours), in accordance with the suggested ISHLT definition (PGD 3 = $\text{PaO}_2:\text{FiO}_2 < 200$).³ The primary outcome was overall survival; the secondary outcomes

included development of bronchiolitis obliterans, peak PGD score in the first 72 hours, number of ventilator days posttransplant, ICU LOS, and hospital LOS.

Statistical Analysis

We tabulated overall descriptive statistics, by LAS era and by recipient gender. For continuous variables, we calculated the mean and standard deviation; for categorical variables, the frequency and percentage. Over a period of 10 years posttransplant, we analyzed overall survival, comparing male and female recipients. We summarized *unadjusted* differences in survival with a hazard ratio (HR), a 95% confidence interval, and a *P* value, using a Cox proportional hazards model with only a single term for gender.

Then, we performed an *adjusted* analysis, using a Cox model with additional terms for transplant laterality (single vs. bilateral), recipient age, donor age, and primary diagnosis, i.e., chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), or “other” primary disease. For this adjusted analysis, we included all recipients with no missing values for any variables.

We also conducted an additional analysis, restricted to patients in the LAS era (on or after May 4, 2005). For this adjusted analysis, we included these additional variables: LAS, peak PGD score in the first 72 hours, BMI and estimated glomerular filtration rate (eGFR) at the time of the transplant. For all our adjusted analysis, we used an *a priori* constructed set of covariates (influenced by level of missingness).

We analyzed secondary time-to-event outcomes in a similar fashion as overall survival. For categorical secondary outcomes, we used logistic regression for our adjusted analyses and summarized our results with odds ratios, 95% confidence intervals, and *P* values. For continuous secondary outcomes, we used generalized linear regression with either an identity test (for an additive interpretation of covariate effects) or a log-rank test (for a multiplicative interpretation). Confidence intervals and *P* values throughout were 2-sided, based on a type I error level of 0.05 and on robust variance estimation. For all analyses, we used R Foundation for Statistical Computing software, version 3.1.1.¹²

RESULTS

Patient Characteristics

Of the 876 lung transplants we analyzed, 501 were in the pre-LAS era; 375, in the LAS era.

In the pre-LAS era, 55.6% of the recipients were female. Of the 501 recipients in this era, 62.7% of the females and 57.2% of the males underwent single-lung transplants; 16.1% of the females and 20.7% of the males were at least 60 years old at the time of their transplant (Table 1). The primary diagnosis was IPF for 9.3% of the females and 16.7% of the males. And 10% of the females and 7.2% of the males had evidence of pulmonary hypertension. Of note, 25.2% of the males had a female donor (i.e., a female-to-male mismatch).

In the LAS era, the proportion of female recipients decreased to 47.7%. Of the 375 recipients in this era, 52% of the females and 46.9% of the males underwent single-lung

transplants; 30.7% of the females and 38.8% of the males were at least 60 years old at the time of their transplant. The primary diagnosis was IPF for 25.7% of the females and 42.9% of the males. And 4.5% of the females and 7.1% of the males had evidence of pulmonary hypertension. Of note, 17.8% of the males had a female donor (i.e., a female-to-male mismatch). Again, certain outcomes were available only in the LAS era. Of the 375 recipients in this era, 10.1% of the females and 13.3% of the males had a BMI > 30. Conversely, 26.8% of the females and 16.3% of the males had a BMI < 20. There were 81 short stature women (< 162cm) (~45% of LAS era women) compared to 4 short stature men (~2% of LAS era men). We saw no qualitative differences in patient characteristics between short females and normal height females.

Only 14.5% of the females, as compared with 19.9% of the males, had an LAS 50. Similar percentages received a lung from a smoker: 32.4% of the females and 31.6% of the males. Ischemic times were slightly shorter for the females (mean, 292 minutes) than for the males (mean, 314 minutes). But we observed no significant gender differences related to socioeconomic status, although males were more likely to pursue graduate-level education than females and were less likely to have been on disability at the time of the transplant (Table 2).

Unadjusted Survival

Overall, for both eras, the 5- and 10-year survival rates were similar by gender: 59% and 33% for females, as compared with 56% and 33% for males (Figure 1). In the pre-LAS era, the 1- and 5-year survival rates were nearly identical by gender: 77% and 52%, as compared with 77% and 54% for males (Figure 2).

But in the LAS era, the 1- and 5-year survival rates diverged: 90% and 71% for females, as compared with 86% and 58% for males ($P = 0.011$) (Figure 3). And donor-recipient gender mismatches widened the gap in the 5-year survival rates even further: 61% for male-to-male matches and 43% for female-to-male mismatches ($P = 0.02$) (Figure 4).

In the LAS era, 11.2% of the females, as compared with 17.9% of the males, underwent re-exploration for bleeding posttransplant (Table 3). The peak PGD score in the first 72 hours was 3 for 16.8% of the females, as compared with 13.3% of the males. The mean number of ventilator days posttransplant was 6.7 for females, as compared with 8.7 for males; only 26.3% of the females required 5 ventilator days, as compared with 28.6% of the males. Females spent a mean of only 8.7 days in the ICU, as compared with 16.5 days for males.

Adjusted Survival

Among the 876 recipients in our entire cohort (covering both eras), only 2 risk factors were independently associated with lower 5-year survival rates: a single-lung (vs. bilateral) transplant (HR 1.55, $P = 0.004$) and a diagnosis of “other” primary disease (vs. COPD) (HR 1.72, $P = 0.005$) (Table 4). (In that analysis, we adjusted for transplant laterality, recipient age, donor age, and primary diagnosis.)

However, the HR for 5-year survival in female recipients went from 1.04 ($P = 0.75$) in the pre-LAS era to 0.56 ($P = 0.03$) in the LAS era. In the LAS era, male recipient gender was

the only independent predictor of lower 5-year survival rates. In our analysis of the LAS era, we also adjusted for LAS score, peak PGD score in the first 72 hours of 3, BMI and eGFR 60 at the time of the transplant. In our analysis adjusting for female-to-male mismatches, the HR was 1.88 for female-to-male (vs. male-to-male) mismatches ($P = 0.06$). Recipient female gender remained the only independent predictor of improved long-term survival (Table 5). Short stature females (<162 cm) had worse survival than normal size females after transplant in our adjusted analysis but both survived longer than males.

In the LAS era, the adjusted odds ratio for re-exploration for bleeding posttransplant was 2.63 for male (vs. female) recipients ($P = 0.042$); 0.34 for single-lung (vs. bilateral) transplants ($P = 0.034$); and 4.98 for peak PGD score of 3 (vs. < 3) ($P < 0.001$). The adjusted odds ratio for peak PGD score of 3 was 1.03 for male (vs. female) recipients ($P = 0.94$). The adjusted odds ratio for mean number of ventilator days ≥ 2 was 0.96 for male (vs. female) recipients ($P = 0.899$). Only LAS (HR 1.22, $P = 0.004$) and a peak PGD score of 3 (HR 4.37, $P < 0.001$) predicted mean number of ventilator days ≥ 2 . The adjusted odds ratio for ICU LOS > 7 days was 1.21 ($P = 0.56$) for male (vs. female) recipients, 0.41 for single-lung (vs. bilateral) transplants ($P = 0.019$), 1.20 for an LAS increase ≥ 10 ($P = 0.009$), and 5.13 for a peak PGD score of 3 ($P < 0.001$).

Gender Effects on Bronchiolitis Obliterans-free Survival

In the LAS era, the 1- and 5-year rates of bronchiolitis obliterans-free survival were 75% and 35% for female recipients, as compared with 65% and 25% for male recipients ($P = 0.02$) (Figure 5). In our unadjusted analysis, the HR was 1.4 for male (vs. female) recipients ($P = 0.013$) and 1.35 for single-lung (vs. bilateral) transplants ($P = 0.039$). In our adjusted analysis, the only 2 factors associated with improved bronchiolitis obliterans-free survival that neared statistical significance were female gender and higher LAS. The HR for male (vs. female) recipients was 1.43 ($P = 0.07$) and for an LAS increase ≥ 10 was 1.08 ($P = 0.074$).

DISCUSSION

Female lung transplant recipients might have a significant advantage in long-term survival, as compared with male recipients. In our single-institution analysis spanning 3 decades (January 1986 through January 2016) and including 876 lung transplants, male recipient gender was among the most important independent predictors of decreased long-term survival and decreased bronchiolitis obliterans-free survival in the LAS era. This difference was not driven by comorbidities, donor-recipient gender mismatches, or socioeconomic factors captured in the transplant registry.

The phenomenon of a gender advantage in transplants has been observed in several solid-organ scenarios. Female kidney transplant recipients have a higher (by 8%) cumulative survival rate, and a lower (by 75%) incidence of severe graft rejection, as compared with male recipients.¹³ In female recipients of a heart transplant or a lung transplant, a survival advantage over male recipients has been noted (although that advantage is largely accounted for by the negative influence of female-to-male mismatches).^{14,15} In the field of lung transplantation, several, but not all, authors have observed a survival advantage for female

recipients.^{6,7,16} As noted above, Gries and colleagues—in their review of a large ISHLT registry of 18,072 patients, mostly in the pre-LAS era—found no overall gender differences in survival.⁸ Their finding is consistent with ours: we observed a similar survival rate between male and female recipients in the pre-LAS era and in both eras combined. Our study adds to the growing body of evidence showing improved outcomes in female lung transplant recipients, but highlights an important transition that occurred in the LAS era.

Since the beginning of the LAS era, national waitlist deaths have decreased from 500 per year to 300 per year, and the number of lung transplants performed annually has doubled.¹⁷ Those improvements have come with the change in the makeup of lung transplant recipients: they are now more likely to be male, to be more seriously ill, and to be older than they were in the pre-LAS era.^{1,18} In the LAS era, the national 1-year survival rate has seen a small but statistically significant increase; however, the 5-year survival rate continues to be low, with an unadjusted average of 56%.¹ Our institution's data parallel those findings: we, too, noted an increased proportion of sicker and older male recipients in the LAS era, as compared with the pre-LAS era. Thus, although we adjusted for that demographic change, our findings might simply reflect a higher proportion of sicker and older male recipients in our cohort in the LAS era.

Several theoretical reasons could help explain why female recipients might have better long-term outcomes. One reason has to do with donor-recipient gender mismatches. As noted above, Demir and colleagues showed that poor survival was associated with a female-to-male mismatch.⁷ A similar negative impact of female-to-male mismatches has also been shown in liver and heart transplant recipients.^{14,15} In our study, we also saw a negative impact on survival associated with female-to-male mismatches. Female donors tend to be smaller in size than male donors; this size discrepancy can contribute to PGD.^{10,11,19} Conversely, female recipients can do well no matter what size graft they receive; their slightly lower metabolic demand accommodates smaller grafts, and larger grafts can reduce PGD.¹¹ There may also be a selection bias for females who survive to transplant. Sell and colleagues demonstrated that patients (often females) with shorter stature have a 62% higher death or removal rate on the waitlist due to clinical deterioration²⁰. Those of short stature that make it to transplant may be better recipients. However, in our LAS cohort, short stature females actually did worse after transplant, not better, than females of normal size. Both short stature and normal size females did better than males.

In our study, female recipients had a higher rate of bronchiolitis obliterans-free survival than male recipients. That alone could certainly explain their overall survival benefit. During pregnancy, females demonstrate tolerance for alloantigens. The underlying mechanism is unclear, but it may contribute to improved tolerance after solid-organ transplants. Elevated estrogen levels might be protective against long-term rejection. In experimental studies, rats treated with high-dose estradiol were resistant to chronic rejection after orthotopic kidney transplants.²¹

Interestingly, we saw a greater rate of re-exploration for bleeding posttransplant in male recipients than in female recipients. We did not record data on the indications for re-exploration, but in general, the vast majority is due to hemothorax and wound revisions. In

cardiac surgery patients, re-exploration for bleeding has been shown to be a significant factor in reducing long-term survival.²² Thus, after lung transplants, it may be especially important in male recipients to be meticulous about hemostasis.

Despite improved long-term outcomes in female lung transplant recipients, several authors have documented an increased incidence of PGD and worse long-term quality of life. Diamond and colleagues noted a trend toward an increased incidence of PGD in female lung transplant recipients with more than 2 pregnancies.²³ A meta-analysis by Lanuza and colleagues found an odds ratio of 1.38 ($P = 0.008$) for PGD in female lung transplant recipients, who accounted for the majority (55%) of PGD events. In our study, female recipients (despite their lower mean number of ventilator days posttransplant) also had a higher incidence of a peak PGD score of 3 in the first 72 hours, as compared with male recipients. Conceivably, hormonal differences account for the differences in PGD, while other factors such as size and reoperations accounted for the differences in ventilator days. Moreover, quality of life studies of lung transplant recipients suggest that males have lower stress levels posttransplant and decreased mood disturbances than females.²⁴ Rodriguez and colleagues reported worse health-related quality of life gains in females than in males, but better long-term spirometry results in females than in males.²⁵ In our study, we attempted to explore socioeconomic factors that might be different between the genders at baseline in the LAS era, but found no differences.

Study Limitations

Our study is subject to the biases and confounding factors inherent in a retrospective cohort design. Nonetheless, those limitations are counterbalanced by our single-institution analysis, with consistent perioperative practices around surgical technique, postoperative care, and immunosuppression.

Like most lung transplant programs, we did refine our protocols over time, but they have stayed very consistent in the LAS era. We did not collect blood transfusion records in this study. It is conceivable that our male lung transplant recipients (given their higher re-exploration rate) received more blood products, which could account for differences in long-term survival. Also, controlling for the LAS score causes a dilemma. On the one hand, it provides a helpful and simple description of the degree of illness prior to transplant. There were greater comorbidities in the male cohort in the LAS era and no other factor could describe this difference better than the LAS. On the other hand, adjusting for LAS also counts certain variables such as age and diagnosis twice which could unfairly penalize the male cohort. Without adjusting for LAS the hazard ratio becomes even greater for the males in the latter era.

CONCLUSION

In our large single-institution study spanning 3 decades, male recipient gender was significantly associated with decreased long-term survival and increased bronchiolitis obliterans-free survival after lung transplants. Those findings were most evident in the LAS era. The negative effect of male recipient gender might have been exacerbated by increased comorbidity in the LAS era and/or by the positive (but not clearly understood) effect of

female recipient gender. The commendably high long-term survival for female lung transplant recipients at 5 years merits additional investigation. A prospective analysis of biologic and immunologic characteristics of male and female lung transplant recipients is warranted. Furthermore, considerable attention to pretransplant optimization and selection of male lung transplant recipients, as well as to operative hemostasis, could improve their long-term outcomes.

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References

1. Valapour M, Skeans MA, Heubner BM, et al. OPTN/SRTR 2013 Annual Data Report: lung. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015; 15(Suppl 2):1–28.
2. Allen JG, Arnaoutakis GJ, Weiss ES, Merlo CA, Conte JV, Shah AS. The impact of recipient body mass index on survival after lung transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2010; 29(9):1026–1033.
3. Suzuki Y, Cantu E, Christie JD. Primary graft dysfunction. Seminars in respiratory and critical care medicine. 2013; 34(3):305–319. [PubMed: 23821506]
4. Wilson ME, Vakil AP, Kandel P, Undavalli C, Dunlay SM, Kennedy CC. Pretransplant frailty is associated with decreased survival after lung transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2016; 35(2):173–178.
5. Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. Jama. 2015; 313(9):936–948. [PubMed: 25734735]
6. Roberts DH, Wain JC, Chang Y, Ginns LC. Donor-recipient gender mismatch in lung transplantation: impact on obliterative bronchiolitis and survival. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2004; 23(11):1252–1259.
7. Demir, A., Coosemans, W., Decaluwe, H., et al. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2014. Donor-recipient matching in lung transplantation: which variables are important?dagger.
8. Gries CJ, Rue TC, Heagerty PJ, Edelman JD, Mulligan MS, Goss CH. Development of a predictive model for long-term survival after lung transplantation and implications for the lung allocation score. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2010; 29(7):731–738.
9. Sato M, Gutierrez C, Waddell TK, Liu M, Keshavjee S. Donor-recipient gender mismatch in lung transplantation: Impact on obliterative bronchiolitis and survival. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2005; 24(11):2000–2001.
10. Mason DP, Batizy LH, Wu J, et al. Matching donor to recipient in lung transplantation: How much does size matter? The Journal of thoracic and cardiovascular surgery. 2009; 137(5):1234–1240. e1231. [PubMed: 19379997]
11. Eberlein M, Reed RM, Bolukbas S, et al. Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2015; 34(2):233–240.

12. team R. A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria:
13. Inoue S, Yamada Y, Kuzuhara K, Ubara Y, Hara S, Ootubo O. Are women privileged organ recipients? Transplantation proceedings. 2002; 34(7):2775–2776. [PubMed: 12431606]
14. Rustgi VK, Marino G, Halpern MT, Johnson LB, Umana WO, Tolleris C. Role of gender and race mismatch and graft failure in patients undergoing liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2002; 8(6):514–518.
15. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report--2012. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2012; 31(10):1052–1064.
16. Alvarez A, Moreno P, Illana J, et al. Influence of donor-recipient gender mismatch on graft function and survival following lung transplantation. Interactive cardiovascular and thoracic surgery. 2013; 16(4):426–435. [PubMed: 23322094]
17. Egan TM, Edwards LB. Effect of the lung allocation score on lung transplantation in the United States. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2016; 35(4):433–439.
18. Maxwell BG, Levitt JE, Goldstein BA, et al. Impact of the lung allocation score on survival beyond 1 year. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2014; 14(10):2288–2294.
19. Marshall MB, Kohman LJ. Gender and lung transplantation: size matters, does sex? The Journal of thoracic and cardiovascular surgery. 2004; 128(3):352–353. [PubMed: 15354090]
20. Sell JL, Bacchetta M, Goldfarb SB, et al. Short Stature and Access to Lung Transplantation in the United States. A Cohort Study. American journal of respiratory and critical care medicine. 2016; 193(6):681–688. [PubMed: 26554631]
21. Muller V, Szabo A, Viklicky O, et al. Sex hormones and gender-related differences: their influence on chronic renal allograft rejection. Kidney Int. 1999; 55(5):2011–2020. [PubMed: 10231466]
22. Vivacqua A, Koch CG, Yousuf AM, et al. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? The Annals of thoracic surgery. 2011; 91(6):1780–1790. [PubMed: 21619974]
23. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. American journal of respiratory and critical care medicine. 2013; 187(5):527–534. [PubMed: 23306540]
24. Lanuza DM, McCabe M, Norton-Rosko M, Corliss JW, Garrity E. Symptom experiences of lung transplant recipients: comparisons across gender, pretransplantation diagnosis, and type of transplantation. Heart Lung. 1999; 28(6):429–437. [PubMed: 10580217]
25. Rodrigue JR, Baz MA. Are there sex differences in health-related quality of life after lung transplantation for chronic obstructive pulmonary disease? The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2006; 25(1):120–125.

Figure 1.
 Patient Survival, Both Eras, by Recipient Gender
 yr = years posttransplant

Figure 2.
 Patient Survival, Pre-LAS Era, by Recipient Gender
 yr = years posttransplant

Figure 3.
Patient Survival, LAS Era, by Recipient Gender
yr = years posttransplant

Figure 4.
Patient Survival, LAS Era, by 3 Groups
yr = years posttransplant

Figure 5.
Bronchiolitis Obliterans-free Patient Survival, LAS Era
yr = years posttransplant]

TABLE 1

Patient Characteristics

Covariate	Overall (N = 876)	Pre-LAS Era Female (n = 279)	Pre-LAS Era Male (n = 222)	LAS Era Female (n = 179)	LAS Era Male (n = 196)
Male	418 (47.7%)	0 (0.0%)	222 (100.0%)	0 (0.0%)	196 (100.0%)
Single-lung tx	487 (55.6%)	175 (62.7%)	127 (57.2%)	93 (52.0%)	92 (46.9%)
Recip age, years, by subgroup					
- 40	184 (21.0%)	74 (26.5%)	47 (21.2%)	37 (20.7%)	26 (13.3%)
- > 40 but < 55	288 (32.9%)	110 (39.4%)	84 (37.8%)	42 (23.5%)	52 (26.5%)
- 55 but < 60	182 (20.8%)	50 (17.9%)	45 (20.3%)	45 (25.1%)	42 (21.4%)
60	222 (25.3%)	45 (16.1%)	46 (20.7%)	55 (30.7%)	76 (38.8%)
Age at tx, years	50.4 (13.0)*	47.4 (13.6)*	49.6 (12.0)*	51.8 (13.3)*	54.1 (11.8)*
Primary diagnosis					
- COPD/alpha ₁	401 (45.8%)	149 (53.4%)	120 (54.1%)	70 (39.1%)	62 (31.6%)
- Cystic fibrosis	120 (13.7%)	28 (10.0%)	28 (12.6%)	35 (19.6%)	29 (14.8%)
- IPF/ILD	193 (22.0%)	26 (9.3%)	37 (16.7%)	46 (25.7%)	84 (42.9%)
- Other	162 (18.5%)	76 (27.2%)	37 (16.7%)	28 (15.6%)	21 (10.7%)
Recip smoked: yes	--	--	--	107 (59.8%)	120 (61.2%)
- Missing data or no	--	--	--	5 (2.8%)	4 (2.0%)
Mean PA BP 40	66 (7.5%)	28 (10.0%)	16 (7.2%)	8 (4.5%)	14 (7.1%)
- Missing data	175 (20.0%)	80 (28.7%)	60 (27.0%)	18 (10.1%)	17 (8.7%)
PA BP	27.1 (13.5)*	28.1 (16.6)*	27.7 (15.1)*	25.8 (11.0)*	26.5 (9.43)*
- Missing data	175 (20.0%)	80 (28.7%)	60 (27.0%)	18 (10.1%)	17 (8.67%)
Recip BMI	--	--	--	23.6 (4.76)*	24.9 (4.67)*
- Missing data	--	--	--	13 (7.26%)	16 (8.16%)
LAS	--	--	--	40.8 (17.1)*	44.5 (20.8)*
- Missing data	--	--	--	4 (2.23%)	2 (1.02%)
LAS 50	--	--	--	26 (14.5%)	39 (19.9%)
- Missing data	--	--	--	4 (2.2%)	2 (1.0%)
eGFR	--	--	--	86.6 (54.6)*	95.1 (36.9)*
- Missing data	--	--	--	41 (22.9%)	56 (28.6%)
Donor male gender	529 (60.4%)	110 (39.4%)	166 (74.8%)	92 (51.4%)	161 (82.1%)

Covariate	Overall (N = 876)	Pre-LAS Era Female (n = 279)	Pre-LAS Era Male (n = 222)	LAS Era Female (n = 179)	LAS Era Male (n = 196)
Donor age, years, by subgroup					
- 40	543 (62.0%)	173 (62.0%)	152 (68.5%)	96 (53.6%)	122 (62.2%)
- > 40 but < 50	176 (20.1%)	61 (21.9%)	36 (16.2%)	38 (21.2%)	41 (20.9%)
50	140 (16.0%)	35 (12.5%)	27 (12.2%)	45 (25.1%)	33 (16.8%)
- unknown	17 (1.9%)	10 (3.6%)	7 (3.2%)	0 (0.0%)	0 (0.0%)
Donor smoked: yes					
-	--	--	--	58 (32.4%)	62 (31.6%)
Missing data or no					
-	--	--	--	120 (67.0%)	134 (68.4%)
Longest isch time					
-	--	--	--	292 (136.4)*	314 (148.4)*
- Missing data	--	--	--	52 (29.1%)	57 (29.1%)

Values presented as N or n (%), except * = mean (standard deviation)

(-) indicates excluded entries due to excessive missing values (> 50%); alpha1 = alpha1-antitrypsin deficiency; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; isch = ischemic; LAS = lung allocation score; PA BP = pulmonary artery blood pressure; Recip = recipient; tx = transplant

TABLE 2

Socioeconomic Differences, by Gender (2010–2015 Transplants)

Covariate	Overall (N = 217)	Female (n = 104)	Male (n = 113)	Female - Male (95% CI)	P
Private insurance	99 (45.6%)	43 (41.3%)	56 (49.6%)	-8.21% (-22.4 to 5.92)	0.282
Not working for pay*	169 (77.9%)	82 (78.8%)	87 (77.0%)	1.86% (-10.1 to 13.8)	0.869
Unwillingly not working**	129 (59.4%)	65 (62.5%)	64 (56.6%)	5.86% (-8.1 to 19.8)	0.459
Education level					0.073
- High school or lower	82 (37.8%)	42 (40.4%)	40 (35.4%)		
- Attended/Completed college	113 (52.1%)	56 (53.8%)	57 (50.4%)		
- Graduate degree	18 (8.3%)	4 (3.8%)	14 (12.4%)		
Work status					
- Not working (disability)	116 (53.5%)	60 (57.7%)	56 (49.6%)		
- Not working (treatment)	3 (1.4%)	1 (1.0%)	2 (1.8%)		
- Not working for pay (homemaker)	2 (0.9%)	2 (1.9%)	0 (0.0%)		
- Not working (retiree)	38 (17.5%)	15 (14.4%)	23 (20.4%)		
- Not applicable (hospitalized)	8 (3.7%)	2 (1.9%)	6 (5.3%)		
- Not working for pay (other)	2 (0.9%)	2 (1.9%)	0 (0.0%)		
- Working for pay	33 (15.2%)	15 (14.4%)	18 (15.9%)		

Values presented as N or n (%). Difference in proportion tests were performed on binary variables; chi-square test, on the 3-level education variable

* Includes retirees and homemakers

** Excludes retirees and homemakers

CI = confidence interval

TABLE 3

Patient outcomes

Covariate	LAS Era Female (n = 179)	LAS Era Male (n = 196)
Reexploration: yes	20 (11.2%)	35 (17.9%)
- Missing data	1 (0.6%)	2 (1.0%)
Peak PGD score = 3	30 (16.8%)	26 (13.3%)
- Missing data	9 (5.0%)	14 (7.1%)
Ventilator days, by subgroup		
- 2	94 (52.5%)	109 (55.6%)
- > 2 but < 5	36 (20.1%)	30 (15.3%)
- 5	47 (26.3%)	56 (28.6%)
- Missing data	2 (1.1%)	1 (0.5%)
No. of ventilator days	6.66 (13.1)*	8.7 (18.2)*
- Missing data	2 (1.12%)	0 (0.0%)
ICU LOS, days	8.69 (10.2)*	11.5 (16.5)*
- Missing data	3 (1.68%)	0 (0.0%)
Hospital LOS	20.8 (18.1)*	23.2 (23.3)*
- Missing data	2 (1.12%)	0 (0.0%)

Values presented as N or n (%), except * = mean (standard deviation)

LAS = lung allocation score; PGD = primary graft dysfunction; ICU = intensive care unit; LOS = length of stay; No. = number

TABLE 4

Variables Affecting 5-year Patient Survival

Covariate	Overall			Pre-LAS Era			LAS Era		
	HR (95% CI)	P		HR (95% CI)	P		HR (95% CI)	P	
Unadjusted Cox results									
Female (vs. male) recip	0.91 (0.74 to 1.13)	0.398		1.03 (0.80 to 1.34)	0.807		0.60 (0.40 to 0.90)	0.013	
Single-lung (vs. bilateral) tx	1.31 (1.05 to 1.64)	0.017		1.55 (1.17 to 2.05)	0.002		0.81 (0.55 to 1.20)	0.297	
Adjusted Cox results									
Female (vs. male) recip	0.87 (0.69 to 1.08)	0.210		1.04 (0.80 to 1.36)	0.752		0.56 (0.33 to 0.95)	0.030	
Single-lung (vs. bilateral) tx	1.55 (1.15 to 2.07)	0.004		1.59 (1.10 to 2.30)	0.014		0.88 (0.47 to 1.66)	0.698	
Recip age 10 years	0.99 (0.88 to 1.13)	0.933		1.05 (0.89 to 1.23)	0.581		1.06 (0.81 to 1.39)	0.656	
Donor age 10 years	1.06 (0.98 to 1.14)	0.138		1.11 (1.01 to 1.22)	0.032		0.91 (0.75 to 1.10)	0.313	
CF (vs. COPD)	1.28 (0.81 to 2.04)	0.294		1.41 (0.76 to 2.59)	0.274		0.96 (0.39 to 2.35)	0.926	
IPF (vs. COPD)	1.13 (0.86 to 1.49)	0.381		2.08 (1.50 to 2.87)	<0.001		0.76 (0.39 to 1.47)	0.412	
Other (vs. COPD)	1.72 (1.18 to 2.51)	0.005		1.81 (1.16 to 2.81)	0.008		1.38 (0.54 to 3.52)	0.500	
LAS 10							1.08 (0.96 to 1.23)	0.195	
Peak PGD score = 3							1.54 (0.80 to 2.97)	0.199	
eGFR 60							0.91 (0.44 to 1.90)	0.812	
		n = 859			n = 484			n = 251	

CF = cystic fibrosis; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; LAS = lung allocation score; PGD = primary graft dysfunction; recip = recipient; tx = transplant

TABLE 5

Variables Affecting 5-year Patient Survival, including Gender Mismatches

Covariate	Overall			Pre-LAS Era			LAS Era		
	HR (95% CI)	P		HR (95% CI)	P		HR (95% CI)	P	
Unadjusted Cox results									
Female recip (vs. male-to-male match)	0.99 (0.78 to 1.25)	0.932		1.10 (0.83 to 1.46)	0.496		0.66 (0.43 to 1.02)	0.059	
Female-to-male mismatch (vs. male-to-male match)	1.37 (0.96 to 1.96)	0.085		1.20 (0.76 to 1.89)	0.434		1.70 (0.95 to 3.04)	0.075	
Adjusted Cox results									
Female recip (vs. male-to-male match)	0.94 (0.74 to 1.19)	0.610		1.10 (0.83 to 1.45)	0.524		0.60 (0.39 to 0.94)	0.026	
Female-to-male mismatch (vs. male-to-male match)	1.37 (0.95 to 1.98)	0.091		1.16 (0.74 to 1.83)	0.524		1.88 (0.97 to 3.66)	0.061	
Single-lung (vs. bilateral) tx	1.58 (1.18 to 2.12)	0.002		1.67 (1.15 to 2.42)	0.007		0.99 (0.59 to 1.64)	0.955	
Recip age 10 years	1.01 (0.89 to 1.15)	0.841		1.07 (0.92 to 1.25)	0.392		1.10 (0.88 to 1.39)	0.395	
CF (vs. COPD)	1.28 (0.80 to 2.03)	0.300		1.46 (0.80 to 2.70)	0.220		1.24 (0.59 to 2.60)	0.566	
IPF (vs. COPD)	1.11 (0.84 to 1.46)	0.453		2.07 (1.51 to 2.84)	<0.001		0.67 (0.40 to 1.11)	0.121	
Other (vs. COPD)	1.65 (1.13 to 2.40)	0.009		1.73 (1.12 to 2.68)	0.014		1.83 (0.90 to 3.72)	0.097	

CF = cystic fibrosis; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; LAS = lung allocation score; PGD = primary graft dysfunction; recip = recipient; tx = transplant