Age-dependent Gender Disparities in Post Lung Transplant Survival Among Patients With Idiopathic Pulmonary Fibrosis

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Background. **The influence of age and gender on survival after lung transplant in patients with idiopathic pulmonary fibrosis (IPF) is not well defined.**

Methods. **The United Network for Organ Sharing database was queried to identify IPF patients receiving lung transplant between 2005 and 2015.**

Results. **There were 6,677 patients receiving lung transplant between May 2015 and June 2015 who met the inclusion criteria, predominantly males (n = 4,769, 71%). Within 1 year posttransplant, the survival curves of male and female recipients diverged, with male recipients having significantly worse survival (log-rank test p = 0.008). Univariate Cox proportional hazards regressions demonstrated no gender difference in survival below age 65 years (HR = 1.051; 95% CI = 0.945, 1.168; p = 0.362) but a significant increase in mortality hazard associated with male gender among patients age 65 years and older (HR = 1.161; 95% CI = 1.000, 1.347; p = 0.049). Multivariable Cox regression accounting for age modulation of the gender effect further demonstrated the emergence of a male disadvantage in post-transplant survival above age 65 years at transplantation.**

Conclusions. **In patients with IPF receiving lung transplant at greater than 65 years of age, male gender is associated with significantly increased risk for death, so referral for lung transplant in IPF should be considered early in the disease course.**

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Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown etiology presenting with progressive cough, dyspnea, and hypoxemia, and is fatal [1–6]. Both the prevalence and incidence of IPF appear to be increasing due to an aging population, increased public awareness, and improved diagnostic capabilities of computed tomography imaging [1, 7]. In the United States, prevalence of IPF is 14 to 42.7 per 100,000 and incidence is 6.8 to 16.3 per 100,000 per year. There is no proven medical therapy, with median survival remaining at 2 to 3 years. Early diagnosis is helpful and lung transplantation (LTx) can improve survival. Male gender has long been noted as a predictor of increased mortality hazard in IPF [8], and recent studies have developed and applied a staging system for IPF incorporating gender, age, and lung physiology (GAP) characteristics as predictors of survival [9, 10]. In this staging system, male gender and older age are considered as additive risk factors for early mortality in IPF [9]. It is unclear, however, if previously reported gender disparities in survival among IPF patients with end-stage lung disease are consistent across the range of ages at which IPF is diagnosed. Because of the increasing numbers of lung transplants being performed in patients with IPF, we conducted this study to evaluate the influence of age on gender disparities in posttransplant survival in the IPF population with data from an available registry in the United States.

Materials and Methods

Data Collection

Secondary analysis of a deidentified transplant registry was approved by the institutional review board at Nationwide Children's Hospital (IRB14-00716) with a waiver of individual consent. The United Network for Organ Sharing Standard registry was used as the source of data for analysis [11]. The registry was queried for lung transplants performed in adult patients diagnosed with IPF. The cohort was limited to May 2005 and onward in order to focus on the lung allocation score (LAS) era. The analytic sample was limited to first-time recipients of single or double LTx from a cadaveric donor. Patients with complete data on covariates in the analysis were used for multivariable analysis.

Statistical Methods

Characteristics of male and female LTx recipients diagnosed with IPF were compared using *t* tests for

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continuous variables (presented as means and standard deviations) and χ^2 tests for categorical variables (presented as counts with percentages). The primary endpoint was patient survival in days since the date of the transplant. Patients with 0 days at risk were assigned an arbitrarily short duration of survival time (<1 day). Kaplan-Meier curves with a log-rank test were used to compare survival by gender in the overall sample and in subsamples defined by age at transplantation. Multivariable Cox proportional hazards models were used to estimate the interaction between recipient age at transplantation and recipient gender. Prior to including this interaction in the Cox model, the Grambsch-Therneau test was used to assess potential violations of the proportional hazards assumption by the gender or age covariates [12]. Based on the model interacting gender with age, the hazard ratio (HR) associated with male (as compared with female) gender was plotted over age at transplantation to identify the age at which a gender disparity in survival emerged. The multivariable models were adjusted for donor gender and age, recipient and donor race, type of transplant, the year of the transplant, the final LAS, allograft ischemic time, and recipient creatinine and body mass index at transplantation. The analysis was performed using Stata/IC, version 13.0 (StataCorp LP College Station, Texas), and p less than 0.05 was considered statistically significant.

Results

There were 6,677 patients receiving LTx between May 2005 and June 2015 who met the inclusion criteria, with this cohort being predominantly male (n = 4,769, 71%). Gender differences in covariates are described in Table 1. Male LTx recipients diagnosed with IPF were significantly more likely to be white compared with female recipients. Although males were, on average, older than female recipients, they tended to receive allografts from younger donors. Despite differences in body mass index and creatinine between males and females, no gender difference in transplant urgency was identified, based on the final LAS. Other significant differences included male patients receiving allografts with longer ischemic time and male patients being more likely to receive an allograft from a white donor.

All 6,677 patients were included in univariate survival analysis, with a gender difference in survival emerging in the overall cohort (Fig 1). Within less than 1 year posttransplant, the survival curves of male and female recipients diverged, with male recipients having significantly worse survival as indicated by a log-rank test ($p = 0.008$). An age threshold of 65 years was arbitrarily selected to examine differences in this gender disparity across age at transplant. Among 4,336 patients aged less than 65 years at transplantation, no gender differences in survival were identified (Fig 2; $p = 0.362$), whereas the male survival disadvantage was evident in a subanalysis of 2,341 patients aged 65 years and greater at transplantation (Fig 3; $p = 0.049$). Univariate Cox proportional hazards regressions further demonstrated no gender difference below age 65 years (HR = 1.051; 95% confidence interval [CI] = 0.945, 1.168; $p = 0.362$) but a significant increase in mortality hazard associated with male gender among patients age 65 years and older (HR = 1.161; 95% CI = 1.000, 1.347; $p = 0.049$).

Multivariable Cox proportional hazards models were fitted to test for a gender difference in survival net of potential confounders and to test whether this gender difference depended on age at transplantation as suggested by Figures 2 and 3. Results from the multivariable analyses are summarized in Table 2, where model 1 presents the adjusted hazard ratio of gender and model 2 considers how this adjusted hazard ratio varies by age at transplant. Recipients' age at transplant was centered at 65 years, meaning that in model 2, containing an interaction term between age and gender, the main effect of gender represents the gender disparity in survival as estimated for patients age 65 years at transplantation.

Model 1 of Table 2 demonstrates that in the overall cohort of IPF patients, male gender was no longer significantly associated with survival when adjusting for patient, donor, and transplant characteristics (HR = 1.059; 95% CI = 0.961, 1.167; $p = 0.245$), whereas older age remained associated with increased mortality hazard (HR = 1.024; 95% CI: 1.018, 1.029; $p < 0.001$). The Grambsch-Therneau test determined that neither gender ($p = 0.551$) nor age ($p = 0.243$) violated the proportional hazards assumption. Allowing the hazard ratio of gender to vary by patient age in model 2 revealed that for patients aged 65 years, there was a significantly greater mortality hazard associated with male gender (HR = 1.121; 95% CI = 1.004, 1.252; $p = 0.042$), and, at older ages, this disparity increased, as indicated by a statistically significant interaction term between age and gender (HR = 1.012; 95% CI = 1.002, 1.022; $p = 0.024$). For example, at age 70 years, model 2 estimated that males had 19% greater hazard of posttransplant mortality than females (HR = 1.189; 95% CI: 1.033, 1.370; $p = 0.016$).

Based on the significant interaction between gender and age at transplantation in model 2 of Table 2, hazard ratios associated with male as compared with female gender were calculated for select ages from 30 to 75 years of age at transplantation. These ages represent the 1st and 99th percentiles of the age distribution in the study cohort, respectively. The hazard ratios of gender are presented with 95% confidence intervals in Figure 4. Below age 65 years, the final multivariable model estimated no significant gender disparities in survival (confidence intervals including 1), whereas above age 65 years, a survival disadvantage (HR > 1, $p < 0.05$) emerged for male recipients. Among other covariates entered in the final multivariable model, older age, black donor race, older donor age, and higher final LAS were associated with increased mortality hazard, whereas bilateral LTx was protective.

Comment

Efforts to better define mortality risk in IPF have led to the identification of male gender and older age as independent predictors of increased mortality hazard [8, 9]. The main finding of our study was that, among IPF patients