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Short Report

Impact of Sex and Age at Lung Transplantation on Long-Term Survival of Patients with Cystic Fibrosis

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Abstract

Careful selection of lung transplant (LT) recipients with cystic fibrosis (CF) may improve outcomes; therefore, we studied the impact of sex and age at the time of LT on long-term survival of patients with CF. LT recipients with CF who received post-LT care at our center between July 1, 2007 and April 30, 2021 were included. The primary outcome was death or retransplantation. Cox proportional hazard analysis and the Kaplan-Meier method were used. Of 59 included LT recipients, the median age at first LT was 28 (22, 36) years, 36 (61%) patients were ≥25 years old, and 30 (51%) were male. At the end of the study, 21 (36%) had died and 17 (29%) had required retransplantation, with a median lung allograft survival of 33.4 (16.1, 66.4) months. The remaining 21 patients (36%) were alive at a median of 68 (28, 112) months after primary LT. The probability of survival of male patients trended higher than that of female patients (66.7% vs 44.8%, p = 0.069). Compared to age < 25 years at LT, age ≥ 25 years was associated with a significantly higher probability of survival (63.9% vs 43.5%, p = 0.047). LT recipients with CF aged ≥ 25 years at LT had significantly higher survival than younger patients, and survival trended higher for male recipients compared to female recipients. These

results identify an at-risk population of LT recipients who may warrant closer attention after LT. Large multicenter trials with adequate power are needed.

Keywords
Lung transplant; cystic fibrosis; age; sex

1. Introduction

Cystic fibrosis (CF) is caused by mutations in the CF transmembrane conductance regulator gene; these mutations impair chloride conduction, which reduces water on the cell surface and leads to an accumulation of viscous mucous in the lungs. Accumulated mucous drives chronic infections, bronchiectasis, and eventually, respiratory failure requiring lung transplantation (LT) [1]. LT is a standard of care for carefully selected candidates with end-stage CF [2]; however, whether LT improves long-term survival among patients with CF remains somewhat controversial [3]. Despite higher survival rates in adult lung recipients with CF compared to those with alternative pulmonary diagnoses [4], this cohort has unique post-LT risk factors. CF-specific pre-LT risk factors for post-LT mortality have been described, such as certain underlying infections, including strains of *Burkholderia cenocepacia* and *B. gladioli*, mechanical ventilation, hypoalbuminemia, reduced renal function, malnutrition, poor socioeconomic status, lack of private insurance in the United States, and nonadherence in adolescents [2, 5, 6]. Female sex and young age at the time of LT for CF have also been associated with suboptimal post-LT survival [7-10]. Post-LT mortality risk stratification will decrease barriers to LT referral, improve candidate selection, and facilitate mitigation strategies in recipients with modifiable risk factors. We aimed to study the impact of sex and age at the time of LT on long-term survival of LT recipients with CF at our institution.

2. Methods

We accessed our prospectively maintained database to identify LT recipients with CF who received posttransplant care at our center between July 1, 2007 and April 30, 2021. Demographic characteristics at primary LT, referral centers, and survival data for included subjects were reviewed. The primary outcome was death or retransplant, as the need for retransplant was considered death of the allograft. The Institutional Review Board of St. Joseph's Hospital and Medical Center, Norton Thoracic Institute, Phoenix, Arizona approved this retrospective cohort study with a waiver of written patient consent (IRB PHXU-21-500-137-73-18 dated 3/31/2021), and this study conforms to the standards of the US Federal Policy for the Protection of Human Subjects.

3. Statistical Analysis

Data are expressed as count (percentage) or median (interquartile range). Nonparametric Kruskal-Wallis test was used to compare continuous variables. Lung allograft survival was computed from the date of primary LT to the date of death, retransplant, or last follow-up. Cox proportional hazard analysis and Kaplan-Meier method were used to study the risk of death and survival, respectively, in the groups stratified by sex and age at LT. All tests were two-sided with a significance

level of 0.05. Analyses were performed with Stata Statistical Software, Release 13 (Stata Corp College Station, TX).

4. Results

A total of 952 candidates underwent LT at our center during the study period, and 59 met the study inclusion criteria. The median age of included subjects at the time of primary LT was 28 (22, 36) years, and 8 candidates were ≤18 years of age at the time of primary LT. The median lung allocation score, body mass index, and length of post-LT hospital stay for the recipients who underwent primary LT at our center (n = 35) were 43.33 (37.08, 60.34), 18.55 (16.97, 21.27) kg/m^2, and 14 (10, 23) days, respectively; the remaining study subjects either underwent a redo LT at our center (n = 17) or only received posttransplant care with us after LT at another center (n = 7). At the end of the study period, 21 (36%) LT recipients had died and 17 (29%) had required redo LT with a median lung allograft survival of 33.4 (16.1, 66.4) months. The remaining 21 patients (36%) were alive at a median of 68 (28, 112) months after primary LT.

5. Impact of Sex

Of the included subjects, 30 (51%) were male. The median (IQR) lung allocation scores of male and female recipients at the time of LT were comparable (43.21 [37.06, 57.29] vs 44.96 [38.32, 74.69], p = 0.317). The Cox proportional hazard analysis showed that the risk of death of male patients trended lower than that of female patients (HR: 0.487 [95% CI: 0.221-1.075], p = 0.075). The Kaplan-Meier analysis showed that the probability of survival of male patients trended higher than that of female patients (66.7% vs 44.8%, p = 0.069, Figure 1).

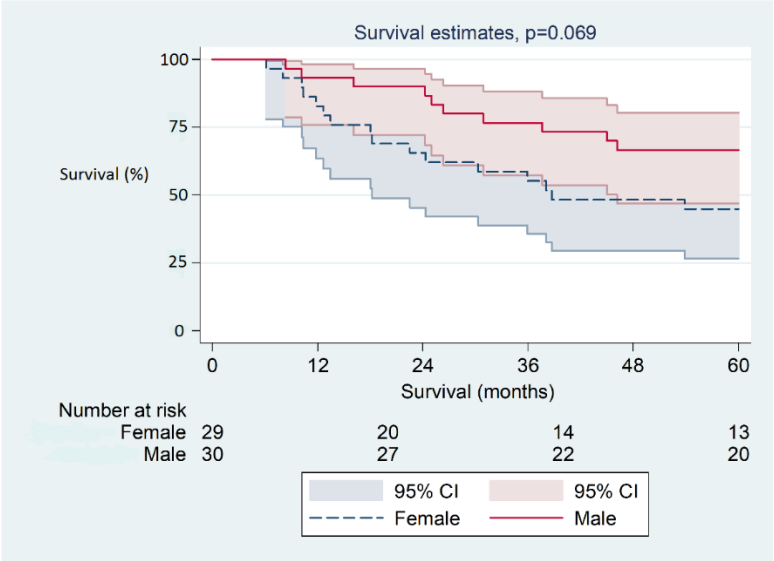

Figure 1 Survival estimates in lung transplant recipients with cystic fibrosis stratified by sex.

6. Impact of Age at Lung Transplantation

Of the included subjects, 36 (61%) candidates were ≥25 years old at the time of primary LT for

CF. The median (IQR) lung allocation scores of candidates aged ≥ 25 years and those aged < 25 years at the time of LT were comparable (44.84 [37.05, 59.64] vs 44.17 [38.29, 61.83], p = 0.729). The Cox proportional hazard analysis showed that the risk of death of patients aged ≥ 25 years trended lower than that of patients aged < 25 years (HR: 0.466 [95% CI: 0.215-1.007], p = 0.052). The Kaplan-Meier analysis showed that age ≥ 25 years was associated with a significantly higher probability of survival than age < 25 years (63.9% vs 43.5%, p = 0.047, Figure 2).

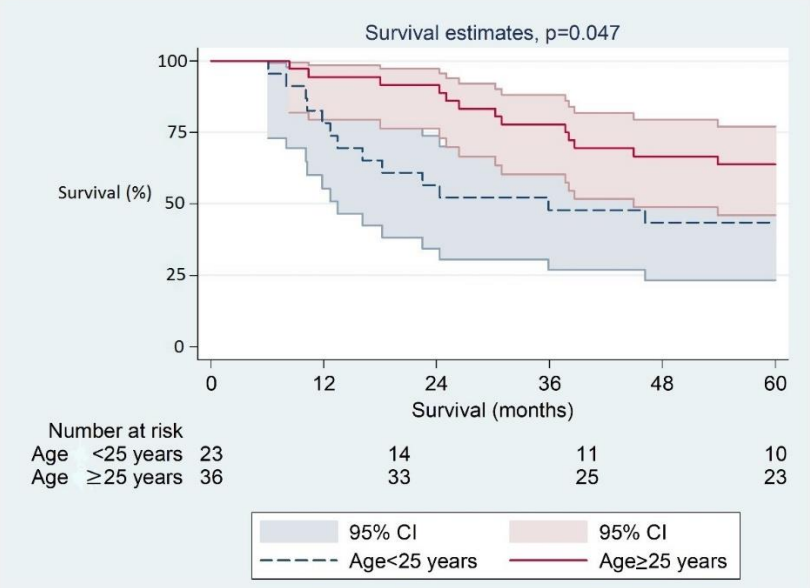

Figure 2 Survival estimates in lung transplant recipients with cystic fibrosis stratified by age.

7. Discussion

Sex disparities among children and adults with CF have been described [11]. The overall life expectancy of female patients with cystic fibrosis is shorter than that of male patients with CF, without accounting for LT recipients [11]. In addition, female patients with CF undergo LT at a younger age and die at an earlier overall age than male patients with CF [8]. Various hypotheses have been proposed to explain sex disparities among patients with CF. Harness-Brumley et al [11] examined airway microbiology in 32,766 patients with CF and found that female patients developed airway infections at a younger age and that earlier acquisition of *Pseudomonas aeruginosa*, methicillin resistant *Staphylococcus aureus, Achromobacter xylosoxidans, Burkholderia cepacia, Aspergillus* spp., and nontuberculous mycobacterium was associated with higher mortality in female patients compared to male patients. The distinct post-puberty increases in CF exacerbations among female patients in their study were attributed to the differences in sex hormones. Estrogen-mediated interrelated factors result in aggravation of CF, as circulating estradiol correlates with infectious exacerbations, facilitates *P. aeruginosa* biofilm formation, increases bacterial burden, alters respiratory transepithelial ion transport, and has a proinflammatory effect through stimulation of T-cell–dependent immune responses and T_H17 activity [12]. Furthermore, Stephenson et al [13] found that women with CF had a higher prevalence of CF-related diabetes

than men with CF (30% vs 17%, $p < 0.001$), and the risk of death for women with CF-related diabetes was higher than that for men with CF-related diabetes ($p = 0.004$). Differences in socioeconomic status, airway diameter, and immune responses between women and men may also contribute to the "gender" gap in patients with CF [14].

Although differential pre-LT outcomes of male and female patients with CF have been widely acknowledged, there are limited data on post-LT survival differences. Raghavan et al [8] studied 4971 lung recipients with CF between January 2000 and December 2012 from the International Thoracic Transplant Registry and found similar 10-year survival rates between 2593 male and 2378 female patients (median survival 8.293 years vs 8.027 years, respectively, $p = 0.464$). Savi et al [15] from Italy followed 123 recipients with CF (61 male, 62 female) for 20 years and also found that sex did not influence survival ($p = 0.22$). Similarly, we did not find a statistically significant difference in survival rates; however, there was a strong trend toward lower survival of female patients. In contrast, using the International Thoracic Transplant Registry, Gries et al [16] demonstrated that male sex was associated with a significantly lower 5-year survival than female sex among LT recipients with CF ($n = 2912$).

Age-related survival disparities among LT recipients with CF have been described. Adult LT recipients with CF (≥18 years) have better survival than pediatric (<18 years) recipients, and older adults (≥40 years) have better survival than younger adults (18-39 years) [7]. These age-related survival disparities have been attributed to underweight body habitus in young LT recipients, young age of referral in female patients, psychosocial instability and nonadherence in adolescent patients, limited pediatric-specific transplant center expertise, and transition of care from a pediatric to an adult care transplant program [5, 7]. Similar to our study, Sethi et al [10] compared post-LT survival of 2002 CF transplant recipients aged 18 to 29 years with that of 1879 CF transplant recipients aged ≥ 30 years between 1992 and 2016 and reported that older adults had significantly higher overall survival (9.47 years vs 5.21 years) and lower mortality due to allograft failure (28% vs 36.5%) than younger adults. On the other hand, Paraskeva et al [6] reported that adolescent LT recipients aged 15 to 19 years had the lowest 3-year survival when compared with those aged 10 to 14 years and those aged 20 to 24 years (59% vs 73% and 66%, respectively, $p < 0.0001$). Our finding of lower survival among LT recipients <25 years old, along with those of the supporting literature, reiterate the importance of careful candidate selection, a detailed psychosocial assessment, and thorough transplant education for at-risk adolescent and young adult LT candidates with CF.

Our study has limitations besides its non-randomized, single-center, retrospective design with a small sample size. The study cohort included 8 CF transplant recipients aged < 18 years (5 female and 3 male patients). Of these, 5 patients had undergone primary LT at our center, 1 underwent retransplant at age 26 at our center, and the remaining 2 patients received posttransplant care at our center after LT elsewhere. It has been reported that pediatric LT performed in a pediatric LT center has a survival benefit over pediatric LT performed in an adult LT center [5]; however, we are a large-volume center with extensive experience.

In our study, LT recipients with CF older than 25 years at the time of LT had significantly higher survival than younger patients, and survival trended higher for male recipients compared to female recipients. These results identify an at-risk population of LT recipients who may warrant closer attention after LT. Large multicenter trials with adequate power are needed.

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Author Contributions

All authors have made substantial contributions to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, and final approval of the version to be published in accordance with ICMJE guidelines. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests

The authors have declared that no competing interests exist.

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