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Changing demographics and outcomes of lung transplantation recipients with cystic fibrosis

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lung transplantation;
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BACKGROUND: Cystic fibrosis (CF) is one of the most common diagnoses in adult and pediatric patients undergoing lung transplantation (LTx). A changing pattern of indications for LTx among patients with CF has been noted. This study analyzes the prevalence and characteristics of patients with CF who underwent LTx in the current era.

METHODS: A retrospective analysis was performed using data from the United Network of Organ Sharing database of all LTx performed from 1999 to 2013 ($N = 20{,}345$). Sub-analyses focused on children (<18 years old). Patients with CF who underwent LTx were assigned to early (1999–2003), mid (2004–2008), and current (2009–2013) eras based on the date of the procedure as well as before and after implementation of the new lung allocation score system in 2005.

RESULTS: CF was the indication for LTx in 14% (2,877) of who patients underwent LTx, a decrease from >17% in the early era to <13% in the current era ($p < 0.001$). In the pediatric cohort, CF was the indication for LTx in 383 (53%) patients, a proportion that also decreased across eras (early, 60%; mid, 53%; current, 47%; $p = 0.009$). The mean age of patients with CF undergoing LTx increased across the eras (early, 28 years ± 10; mid. 28 years ± 10; current, 30 years ± 11; $p < 0.001$). Pre-transplant ventilator use and incidence of pan-resistant infections also increased ($p < 0.001$), whereas pre-transplant forced expiratory volume in 1 second and waitlist times decreased ($p < 0.001$) in patients with CF. Graft survival across the eras remained similar ($p > 0.05$) at 5.1 years overall.

CONCLUSIONS: The proportion of LTx performed for CF has significantly decreased over time, a trend especially pronounced in pediatric patients. The change in pre-transplant characteristics across eras indicates a trend to perform LTx in more clinically ill and older patients with CF. The overall post-LTx survival has not changed.

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Cystic fibrosis (CF) is the most common lethal genetic disorder in populations of northern European descent, among whom the disease occurs in approximately 1 in 3,000 births. Patients with CF often experience symptoms involving multiple organs; among these, pulmonary disease leading to respiratory failure is the most frequent cause of death. The life expectancy for patients with CF has improved to 37 years.[1] Also new therapies continue to be developed, such as the promising new medical therapy ivacaftor (VX-770), a CF transmembrane conductance

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regulator potentiator.[2] However, lung transplantation (LTx) remains a final option for patients with end-stage pulmonary disease.

Historically, CF is one of the most common diagnoses among adult patients undergoing LTx, accounting for 16% of all LTx performed in adults from January 1995 through June 2013.[3] Chronic obstructive pulmonary disease (38%) and interstitial lung disease (24%) are the 2 most common indications in adults. In contrast, CF is the most common indication for LTx in children worldwide. At least 50% of all children undergoing LTx have a diagnosis of CF.[4] The indications for pediatric LTx typically depend on the age of the recipient. The primary indications for children from infancy to 5 years of age include idiopathic pulmonary arterial hypertension and interstitial lung disease. However, CF is the primary indication for LTx in children >6 years old, and almost 70% of adolescents undergo LTx for CF.[4]

The number of patients waiting for LTx remains large because of the shortage of donor lungs, similar to the situation for other solid organs. In May 2005, the Organ Procurement and Transplant Network (OPTN) modified the policy of lung allocation for transplantation in the United States from a system that allocated donor lungs based primarily on waiting time to a system based primarily on a new lung allocation score (LAS) that reflected not only disease severity[5,6] but also post-LTx outcomes.[7,8] A higher LAS is typically associated with increased survival benefit of LTx.[9] Since implementation of the LAS-based donor allocation system, decreased number of patients on the active waiting list, waiting times for LTx, and waitlist mortality have been reported.[10] In this context, we analyzed the prevalence and characteristics of patients with CF undergoing LTx over 15 years and assessed current trends in these patients as well as the impact of era and LAS implementation on their LTx outcomes.

Methods

This was a retrospective analysis of the United Network of Organ Sharing (UNOS) database for all patients including pediatric patients who underwent LTx in the United States from January 1999 to September 2013. The UNOS is a private, non-profit organization that administers the OPTN. The OPTN is a unified transplant network established by the US Congress under the National Organ Transplant Act of 1987.

Study cohort and variables

Data were analyzed for all age populations and sub-analyzed for pediatric populations (<18 years old). Patients were divided into CF in all age populations, idiopathic pulmonary fibrosis in all age populations, primary pulmonary hypertension in pediatric populations, and other patient groups. CF groups were further divided into 3 cohorts based on year of LTx to analyze trends across 5-year periods, defined as the early (1999–2003), mid (2004–2008), and current (2009–2013) eras. The patients with CF were also divided into 2 cohorts that had undergone LTx before and after the 2005 implementation of the new LAS (pre-LAS, 1999 to May 2005; post-LAS, June 2005 to 2013). The variables collected for this study included age and height at LTx, sex, race, diagnosis, time on the waitlist, ischemic time, pre-transplant use of ventilator, pre-transplant use of steroid therapy, pre-transplant forced expiratory volume in 1 second (FEV_1), pre-transplant pan-resistant bacterial infection, pre-transplant extracorporeal membrane oxygenation (ECMO) at listing and at transplant, mean LAS, and lung graft survival time.

Statistical analysis

Values are presented as means with SDs for continuous variables or numbers (percentages) for categorical variables. For baseline characteristics, continuous data were compared using *t*-tests. Categorical variables were compared using chi-square tests. Graft survival analysis was estimated using the Kaplan-Meier method, and the equality of survival curves were tested using log-rank tests. A *p*-value of <0.05 was considered statistically significant.

Results

During the study period, 20,345 adult and pediatric patients underwent LTx, with the annual number of transplant patients increasing from <900 in 1999 to approximately 1,800 per year in recent years (Figure 1). The indication for LTx was CF in 2,877 (14%) patients. The proportion of LTx for CF decreased from >17% in 1999 to <13% in 2013 (early, 17%; mid, 14%; current, 13%; $p < 0.001$). The proportion of LTx for idiopathic pulmonary fibrosis significantly increased from 16% to 38%. There was also a significant change between pre-LAS and post-LAS eras (16% vs 13%, $p < 0.001$). Of 716 pediatric patients who underwent LTx, 383 (53%) had CF (Figure 2). The proportion of LTx performed for CF in pediatric patients decreased across eras (early, 60%; mid, 53%; current, 47%; $p = 0.009$). The proportion of LTx for primary pulmonary hypertension also decreased from 13% to 7%. There was also a significant change between pre-LAS and post-LAS eras (59% vs 50%, $p = 0.024$).

Patient characteristics

All patients with CF

Patient baseline characteristics according to era are summarized in Table 1 (for all patients with CF) and Table 2 (for pediatric patients with CF). The mean ages (28 years vs 28 years vs 30 years; $p < 0.001$) and heights (163 cm vs 164 cm vs 165 cm; $p = 0.013$) of all patients with CF undergoing LTx increased across eras. The proportion of patients with CF undergoing LTx shifted even further to adults over the past 15 years; adults now constitute 90% of all patients with CF undergoing LTx compared with 84% in the earlier era. The mean ischemic time (5.3 hours vs 5.7 hours vs 5.6 hours; $p < 0.001$), pre-transplant ventilator use (5% vs 6% vs 11%; $p < 0.001$), incidence of pre-transplant pan-resistant bacterial infections (10% vs 20% vs 22%; $p < 0.001$), pre-transplant ECMO at listing (0% vs 0.4% vs 1.8%; $p < 0.001$) and at transplant (0.5% vs 0.4% vs 4.1%; $p < 0.001$), and mean LAS (43 vs 49; $p < 0.001$)