

# Changing demographics and outcomes of lung transplantation recipients with cystic fibrosis



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## KEYWORDS:

lung transplantation;  
cystic fibrosis;  
demographics;  
lung allocation score  
system;  
transplant candidacy;  
mechanical ventilation

**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  $\pm 10$ ; mid, 28 years  $\pm 10$ ; current, 30 years  $\pm 11$ ;  $p < 0.001$ ). 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>4</sup>

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<sup>5,6</sup> but also post-LTx outcomes.<sup>7,8</sup> A higher LAS is typically associated with increased survival benefit of LTx.<sup>9</sup> 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.<sup>10</sup> 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<sub>1</sub>), 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.

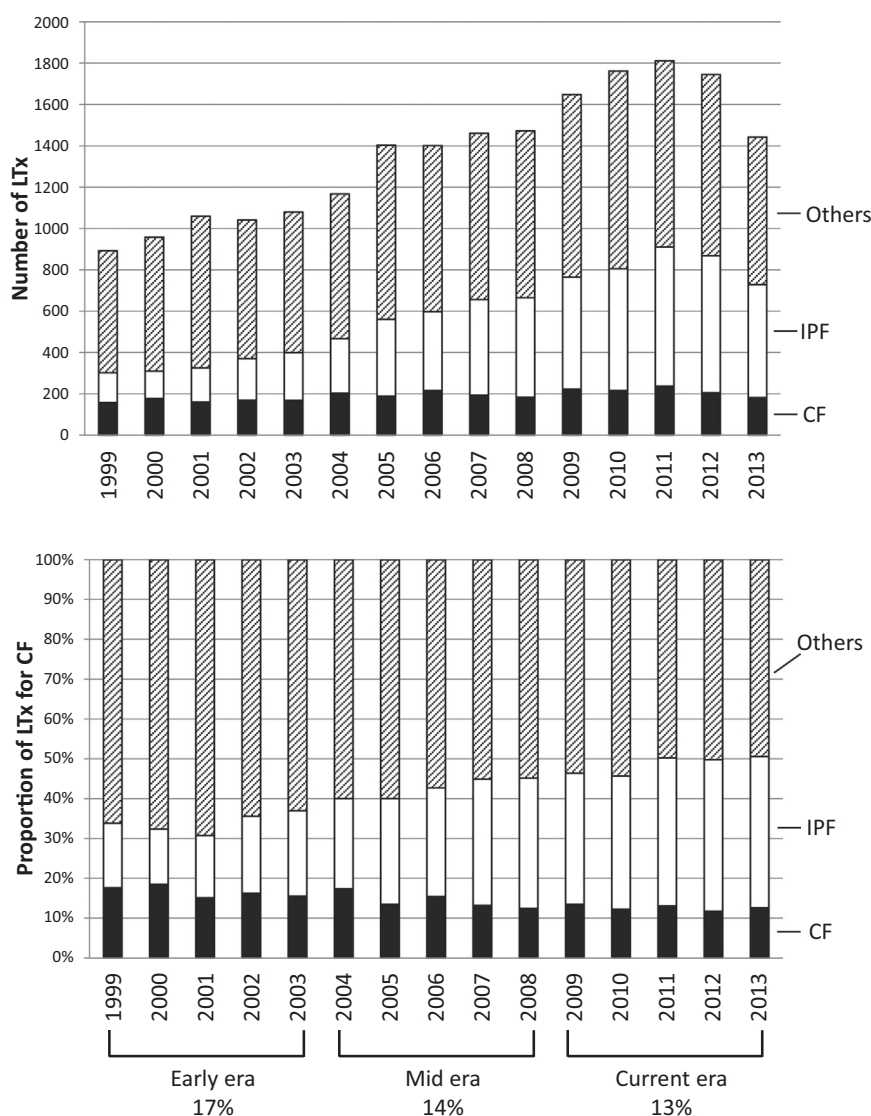
## Results

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)



**Figure 1** Overall trends in LTx from 1999 to 2013 in all age populations. Number and proportion of patients with CF who underwent LTx in all age populations across eras. The trend for idiopathic pulmonary fibrosis (IPF) was also examined for comparison.

also increased across eras; pre-transplant FEV<sub>1</sub> (28% vs 27% vs 25%) decreased ( $p < 0.001$ ) in patients with CF.

### LAS eligible patients

Comparison of pre-LAS and post-LAS eras revealed that all LAS eligible patients in the post-LAS era were significantly older (28 years vs 29 years;  $p = 0.001$ ) and taller (163 cm vs 165 cm;  $p = 0.002$ ). Mean ischemic time (5.4 hours vs 5.7 hours), pre-transplant ventilator use (4% vs 10%), incidence of pre-transplant pan-resistant bacterial infections (11% vs 21%), and pre-transplant ECMO at listing (0% vs 1.1%;  $p < 0.001$ ) and at transplant (0.4% vs 2.7%;  $p < 0.001$ ) increased ( $p < 0.001$ ), whereas pre-transplant FEV<sub>1</sub> (28% vs 26%) decreased ( $p < 0.001$ ) in patients with CF (Table 1).

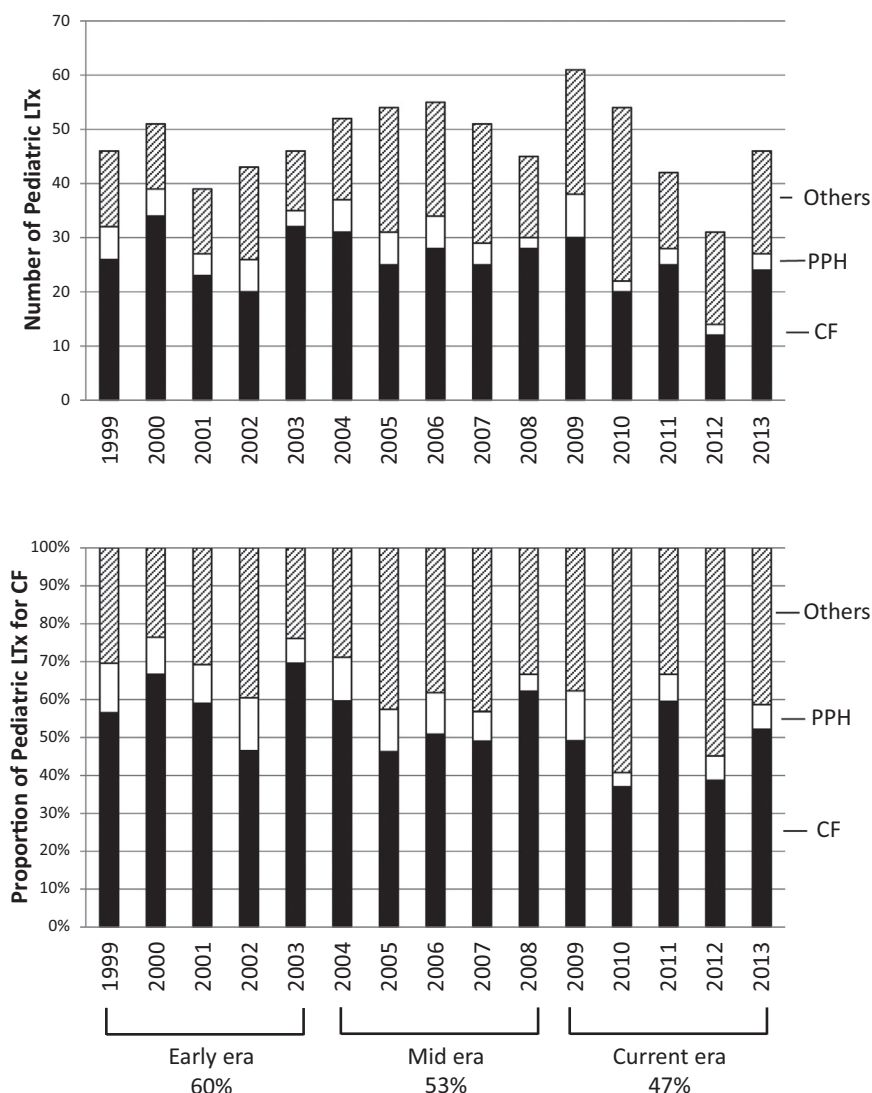
### Pediatric patients

Among pediatric patients with CF, there were statistically significant differences in race (Caucasians, 93% vs 80% vs

79%;  $p = 0.004$ ), pre-transplant steroid use (25% vs 36% vs 22%;  $p = 0.003$ ), and incidence of pre-transplant pan-resistant bacterial infections (11% vs 26% vs 27%;  $p = 0.013$ ) over the eras. Comparison of pre-LAS and post-LAS eras in this cohort revealed that mean ischemic time (4.4 hours vs 5.5 hours), pre-transplant FEV<sub>1</sub> (29% vs 32%), and incidence of pre-transplant pan-resistant bacterial infections (14% vs 26%) increased significantly in the post-LAS era, whereas only proportion of Caucasian patients had decreased (91% vs 79%;  $p = 0.003$ ) (Table 2).

### Waitlist time

The waitlist time for patients with CF who underwent LTx was significantly shorter in the current era for all patients in the adult and pediatric sub-groups (from 468 to 86 days, from 503 to 84 days, and from 337 to 80 days;  $p < 0.001$ ). The waitlist times were also significantly decreased in the post-LAS era compared with the pre-LAS era ( $p < 0.001$ ), from 261 to 70 days (all patients), from



**Figure 2** Overall trends in LTx from 1999 to 2013 in pediatric populations. Number and proportion of pediatric patients with CF who underwent LTx across eras. The trend for primary pulmonary hypertension (PPH) was also examined for comparison.

447 to 101 days (adult patients), and from 320 to 105 days (pediatric patients).

### Graft survival in patients with CF undergoing LTx

Overall median survival was 5.1 years in all patients with CF and 3.6 years in pediatric patients with CF. There were no significant differences in graft survival across 5-year periods for adult and pediatric patients with CF ( $p > 0.05$ ) (Figure 3A and B). There was a tendency for better graft survival in the post-LAS era than in the pre-LAS era, although these results did not reach statistical significance ( $p > 0.05$ ) (Figure 4A and B).

### Discussion

This study demonstrates the changing demographics of adult and pediatric patients with CF undergoing LTx over 15 years. Overall, the proportion of patients with CF as an indication for LTx has been decreasing, with older and more clinically ill patients with CF undergoing LTx in the current

era. The number of patients undergoing LTx has been increasing dramatically in the past 15 years. The reasons for this increase are likely multifactorial and include advances in diagnostics and management for lung diseases, development of donor lung management protocols,<sup>11</sup> more liberal use of marginal donors, and reduced death rates among patients on waitlists.<sup>10</sup> The number of patients with CF undergoing LTx has also increased over the years, although the rate of increase has been low, and the relative proportion of adult patients with CF undergoing LTx has been decreasing steadily. One reason for this is that the number of successful transplants among patients with lung diseases other than CF who could not previously receive LTx has rapidly increased because of increasing success and better outcomes in LTx. Indications for LTx appear to be expanding in the current era. We demonstrated a significant increase in the number and proportion of patients with idiopathic pulmonary fibrosis who underwent LTx compared with patients with CF. Another reason for this trend would be that the improvement in management (medical as well as supportive) for CF may have made LTx a more

**Table 1** Characteristics of CF Patients With CF Before LTx in Different Eras

Variables	Early era (1999–2003), <i>n</i> = 831	Mid era (2004–2008), <i>n</i> = 984	Current era (2009–2013), <i>n</i> = 1,062	<i>p</i> -value	Pre-LAS (Jan 1999–May 2005), <i>n</i> = 1,109	Post-LAS (Jun 2005–Sep 2013), <i>n</i> = 1,768	<i>p</i> -value
Age (y)	28 ± 10	28 ± 10	30 ± 11	<0.001	28 ± 10	29 ± 11	0.001
Height (cm)	163 ± 14	164 ± 12	165 ± 12	0.013	163 ± 13	165 ± 12	0.002
Age group							
Children (1–10 y)	27 (3%)	15 (2%)	17 (2%)	0.001	33 (3%)	26 (2%)	0.005
Adolescents (11–17 y)	108 (13%)	122 (12%)	94 (9%)		138 (12%)	186 (11%)	
Adults (≥18 y)	696 (84%)	847 (86%)	951 (90%)		938 (85%)	1,556 (88%)	
Females	425 (51%)	493 (50%)	524 (49%)	0.739	578 (52%)	864 (49%)	0.09
Caucasians	792 (95%)	923 (94%)	999 (94%)	0.344	1,053 (95%)	1,661 (94%)	0.258
Ischemic time ± SD (h)	5.3 ± 2.1	5.7 ± 1.7	5.6 ± 1.6	<0.001	5.4 ± 2.0	5.7 ± 1.6	<0.001
Pre-transplant ventilator use	37 (5%)	59 (6%)	121 (11%)	<0.001	47 (4%)	170 (10%)	<0.001
Pre-transplant steroid use	227 (27%)	317 (32%)	297 (28%)	0.038 <sup>a</sup>	315 (28%)	526 (30%)	0.439
Pre-transplant FEV <sub>1</sub>	28 ± 13	27 ± 15	25 ± 14	<0.001	28 ± 13	26 ± 14	<0.001
Pan-resistant bacterial infection	82 (10%)	195 (20%)	231 (22%)	<0.001	128 (11%)	380 (21%)	<0.001
ECMO at listing	0 (0%)	1 (0.4%)	19 (1.8%)	<0.001	0 (0%)	20 (1.1%)	<0.001
ECMO at transplant	4 (0.5%)	4 (0.4%)	44 (4.1%)	<0.001	4 (0.4%)	48 (2.7%)	<0.001
Mean LAS		42.9 ± 12.5	49.0 ± 18.1	<0.001			

CF, cystic fibrosis; ECMO, extracorporeal membrane oxygenation; FEV<sub>1</sub>, forced expiratory volume in 1 second; LAS, lung allocation score; LTx, lung transplantation.  
 Values are presented as mean ± SD or number (%).

<sup>a</sup>The differences between early era and mid era (*p* = 0.023) and mid era and current era (*p* = 0.036) are significant, but the differences between not early era and current era (*p* = 0.75) are not significant.



**Table 2** Pre-LTx Characteristics of Pediatric CF Patients With CF in Different Eras

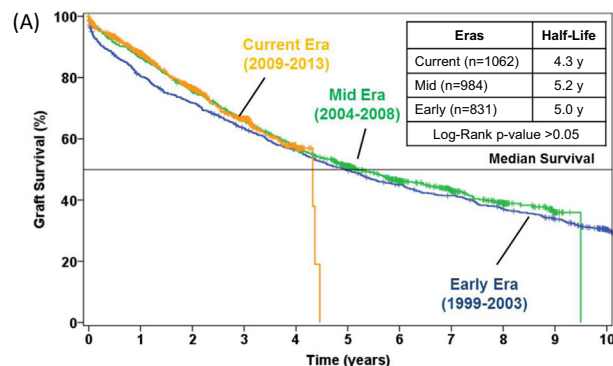
Variables	Early era (1999–2003), n = 135	Mid era (2004–2008), n = 137	Current era (2009–2013), n = 111	Pre-LAS (Jan 1999–May 2005), n = 171	Post-LAS (Jun 2005–Sep 2013), n = 212	p-value
Age (y)	14 ± 3	14 ± 3	14 ± 3	14 ± 3	14 ± 3	0.154
Height (cm)	146 ± 16	150 ± 15	148 ± 16	146 ± 16	149 ± 15	0.067
Age group						
Children (1–10 y)	27 (20%)	15 (11%)	17 (15%)	33 (19%)	26 (12%)	0.065
Adolescents (11–17 y)	108 (80%)	122 (89%)	94 (85%)	138 (81%)	186 (88%)	
Females	81 (60%)	88 (64%)	65 (59%)	105 (61%)	129 (61%)	0.917
Caucasians	125 (93%)	110 (80%)	88 (79%)	155 (91%)	168 (79%)	0.003
Mean ischemic time (h)	4.2 ± 1.9	5.4 ± 1.6	5.6 ± 1.5	4.4 ± 1.9	5.5 ± 1.6	0.001
Pre-transplant ventilator use	4 (3%)	5 (4%)	9 (8%)	4 (2%)	14 (7%)	0.055
Pre-transplant steroid use	32 (25%)	49 (36%)	23 (22%)	43 (27%)	203 (30%)	0.487
Pre-transplant FEV <sub>1</sub>	29 ± 13	32 ± 18	31 ± 14	29 ± 13	32 ± 17	0.037
Pan-resistant bacterial infection	14 (11%)	34 (26%)	28 (27%)	24 (14%)	52 (26%)	0.026
Mean LAS		38.6 ± 12.3	43.1 ± 18.9			

CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in 1 second; LAS, lung allocation score; LTx, lung transplantation.

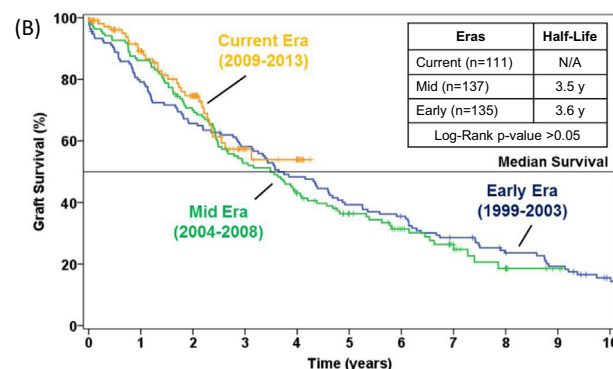
Values are presented as mean ± SD or number (%).

<sup>a</sup>The differences between early era and mid era ( $p = 0.03$ ) and mid era and current era ( $p = 0.009$ ) were significant, but the differences between not early era and current era ( $p = 0.58$ ) were not significant.

## Survival by Eras in CF Patients

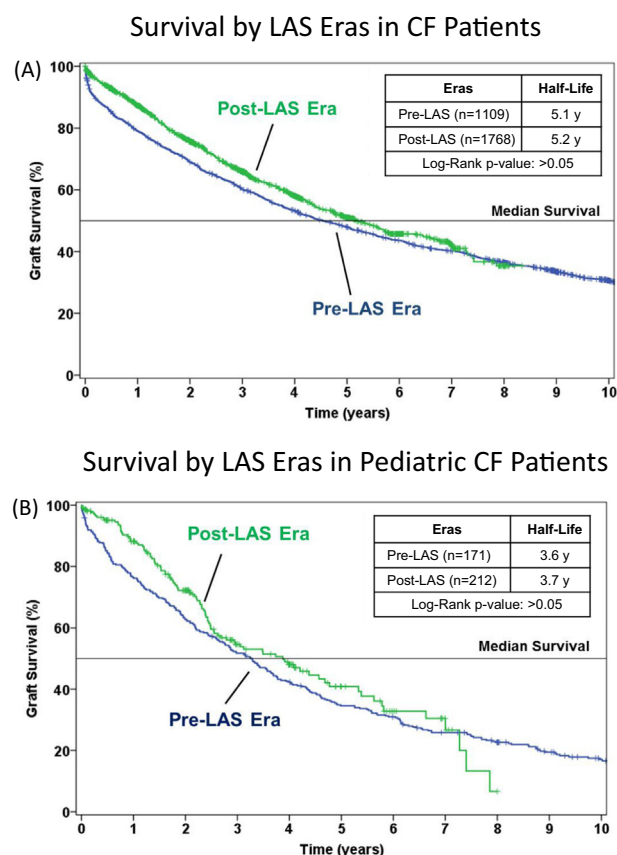


## Survival by Eras in Pediatric CF Patients

**Figure 3** (A) Graft survival by eras in patients with CF. (B) Graft survival by eras in pediatric patients with CF.

infrequent treatment choice, if not delayed the need for LTx. This explains why patients are older and why more adults and less children with CF proportionally are undergoing LTx. The absolute number of pediatric transplants (approximately 50 per year) is very small compared with the number performed in adults and has remained relatively consistent.

The proportion of pediatric LTx for CF showed a similar decreasing trend from early to current era to that seen in adults (60% vs 47%,  $p = 0.009$ ). Early reports supported a surgical benefit from LTx for pediatric patients with CF<sup>12,13</sup>; however, Liou et al<sup>14</sup> reported that only 5 of 514 pediatric patients with CF on the waitlist for LTx had improved survival after LTx, and they questioned the validity of LTx for this patient cohort. These findings remain controversial, and several authors have challenged the results.<sup>15,16</sup> The results of the present study for pediatric patients with CF may reflect these circumstances; surgeons appear to be conservative about LTx in this population. This is also likely related to better management of pediatric patients with CF, leading to fewer of them needing immediate LTx. This may reflect the reduced number of Caucasian patients in the pediatric population and that Caucasian children with CF may undergo LTx less often at a young age. Another possible reason is that non-Caucasian children may be more likely to get listed and receive LTx in the current era probably because Caucasian children could get better care than non-Caucasians that allowed them to delay LTx.



**Figure 4** (A) Graft survival by LAS eras in patients with CF. (B) Graft survival by LAS eras in pediatric patients with CF.

The study results indicated that the average age of patients with CF undergoing LTx has been increasing in adult and pediatric groups. A similar trend was reported previously,<sup>17</sup> and we have confirmed that it has continued after 2008. Pre-LTx characteristics showed decreased FEV<sub>1</sub>, increased pre-transplant ventilator use, and increased incidence of pan-resistant bacterial infection, suggesting that more clinically ill patients have been undergoing LTx in the current era. Nevertheless, graft survival has remained consistent across the eras. Improved medical treatment and management, better patient care, improved patient selection, refinement of surgical procedures including donor organ treatment, decreased numbers of deaths among patients on waitlists, and shorter waiting time after LAS implementation all are factors associated with the results of the current era. Given that the increased incidence of pre-transplant pan-resistant bacterial infection was the most visible change across eras, management of infectious disease in patients with CF has significantly improved across eras. In addition, the increased age of patients with CF undergoing LTx in the post-LAS era may have a protective effect against post-operative infection, rejection, and bronchiolitis obliterans syndrome during follow-up.<sup>17</sup> Adolescence as a risk factor for poor graft survival is well documented for heart and lung transplantation. Because more patients with CF undergoing LTx are out of their teenage years, better patient compliance to treatment secondary to behavioral independence and emotional maturation may help explain the improved survival in the post-LAS era.<sup>7</sup>

The LAS has dramatically affected LTx strategies. The interaction between the LAS and LTx outcomes is significant; higher LAS is typically associated with increased survival benefit of LTx.<sup>9</sup> However, some authors have warned that very high LAS (approximately  $\geq 50$ ) was associated with worse survival in LTx recipients with CF<sup>7,8</sup> and that the LAS should be considered an important tool for judging the appropriateness of patient candidacy.<sup>7</sup> Pre-transplant ventilator use is strongly associated with high LAS; our results showed higher mean LAS (42.9 vs 49.0) and higher pre-transplant ventilator use (5% vs 11%) in the current era, although graft survival was similar in the post-LAS era. This observation may support the current timing of placing patients with CF on waitlists even though they are more ill than in the earlier eras; we must consider that perhaps patients with CF were placed on the list too early in the past. However, this trend should be followed carefully to avoid patients being too sick (i.e., some have proposed a LAS  $>50$  to be too late) and negatively affecting LTx outcomes; all agree that the timing of transplant listing with adequate LAS is very important for obtaining good surgical benefits from LTx. In children, the rate of pan-resistant bacterial infection has increased by 2.5-fold, but the FEV<sub>1</sub> also has increased. This may demonstrate that in the current era many children are undergoing LTx for unremitting infections that require continuous intravenous antibiotic therapy and that significantly decrease quality of life rather than for the classic indication of a decreasing FEV<sub>1</sub>.

This study has several limitations. First, this was a retrospective review of a national database. Second, limited clinical data, especially post-LTx data, were collected. Third, the absolute differences in the demographics of patients with CF were relatively small even though there were statistically significant differences between them. For example, although the change in FEV<sub>1</sub> was statistically significant, we are unsure how clinically significant this difference is. Finally, we could not identify the exact reasons for the changing trends, which were beyond the scope of the database; thus, the results might have been confounded by unmeasured factors.

In conclusion, the proportion of patients with CF undergoing LTx has decreased in the past 15 years in adult and pediatric patient populations. Patients with CF undergoing LTx are increasingly older, more ill, and more likely to have resistant bacterial infections than before, although graft survival is unaffected. The implementation of the LAS has decreased waitlist times in adult and pediatric CF cohorts. Most importantly, despite the current more ill state of patients with CF undergoing LTx, outcomes remain unchanged.

## Disclosure statement

The authors have no conflicts of interest to disclose.

This study used data provided by UNOS as a contractor for the OPTN. All data were analyzed and interpreted by the authors, who have all responsibility for this study, and not by the OPTN or the US government.

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