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Lung transplantation for cystic fibrosis

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KEYWORDS:
cystic fibrosis;
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bridging

BACKGROUND: The contribution of lung transplantation to the treatment of patients with end-stage cystic fibrosis (CF) has been debated. We aimed to describe achievable outcomes from high-volume CF and lung transplant programs. This study reports on the largest single-center experience of lung transplantation for adult and pediatric patients with CF. It also highlights the evolution of practice and outcomes over time.

METHODS: A retrospective analysis of the prospectively collected Toronto Lung Transplant database was carried out. Post-transplant survival in CF was calculated using the Kaplan−Meier method and analyzed with log-rank tests.

RESULTS: From 1983 to 2016, a total of 1,885 transplants were performed at our institution, where 364 (19.3%) were CF recipients and another 39 (2.1%) were CF retransplants. The mean age at first transplant was 29.5 ± 9.7 years where 56.6% were males and 91.5% were adults. Pre-transplantation, 88 patients (24.2%) were *Burkholderia cepacia* complex (BCC)-positive, 143 (39.3%) had diabetes mellitus, and the mean forced expiratory volume in one second was 26.0 ± 7.2%, as predicted at listing. The 1-, 5-, and 10-year probabilities of survival in adults who were BCC-negative were 94%, 70%, and 53%, respectively. Pediatric, BCC-positive, and retransplant recipients had worse survival than adult patients who were BCC-negative. Strategies to improve the donor pool did not affect survival but possibly reduced waitlist mortality. For the entire cohort, the most common causes of death after lung transplant were infection and chronic lung allograft dysfunction.

CONCLUSIONS: Lung transplantation for CF provides excellent short- and long-term outcomes. These results strongly support lung transplantation as the standard of care for patients with CF having advanced lung disease.

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Cystic fibrosis (CF) is the most common lethal genetic disease among Caucasians.[1] The pulmonary component of the disease is characterized by progressive airway inflammation and recurrent respiratory infections, leading to

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bronchiectasis and chronic respiratory failure.[2] Indeed, pulmonary disease is the leading cause of morbidity and mortality in this population.

In 1988, the Toronto Lung Transplant Program performed the first double lung transplant (LTx) for a patient with CF, and this success subsequently revolutionized the care of patients with CF. End-stage patients who previously had no therapeutic option and were managed solely with palliation now had reason for aggressive medical therapy. Similarly, patients with early stage CF now had additional hope and incentive to adhere to treatment regimes.

Lung transplantation, however, is not a panacea. The shortage of donor organs limits access to lung transplantation, and chronic lung allograft dysfunction (CLAD) historically limits the overall median survival of lung transplant recipients to only 5 to 6 years.[3] Moreover, patients with CF who are underweight, infected with Burkholderia cepacia complex (BCC), young (aged <18 years), have Medicaid insurance, and are sicker at the time of transplant have been shown to have additional risk for poor survival.[4–7] Hence, survival depends upon the competing risks of CF end-stage lung disease mortality, transplant waitlist mortality, and post-transplant mortality.

The Toronto Program is the largest and oldest CF lung transplant program and is intimately associated with the Toronto Adult CF program, which treats majority of patients with CF in the area. Decision for referral to lung transplantation is guided by the CF program. Listing is a shared decision between the CF and the transplant programs. Therefore, we can achieve a better determination of the appropriate time for transplant and better support for sick patients with CF, leading to transplant. When patients with CF do ultimately deteriorate, our program is aggressive in bridging patients with ventilation and extracorporeal life support (ECLS), if needed, to lung transplantation.[8] Canada does not have a national priority allocation score for listed patients and center-specific medical priority drives transplant allocation, where the sickest bridged patients are the highest priority. Opportunity for transplant is further expanded by using donation after cardiac death (DCD) lungs and the Toronto ex vivo lung perfusion (EVLP) program, which can recover injured donor lungs previously not considered for clinical use.[9] Finally, when post-transplant patients with CF develop CLAD, we would consider retransplantation to further extend survival and quality of life for appropriate candidates.

In this study, we reported the Toronto experience with patients with CF, looking at both the pediatric and adult population with a focus on post-transplant survival. Programmatic changes that occurred over time and aimed at improving outcomes were examined. To the best of our knowledge, this is the largest single-center CF LTx experience to be reported to date.

Methods

All patients with CF who received LTx in our program from 1983 to December 31, 2016 were included. The pediatric (aged <18 years) lung transplant activity in our program started at Toronto General Hospital in 1988 and moved to the Hospital for Sick Children in 1996. Adult lung transplant activity remained at Toronto General Hospital. Patients were cared for by 1 team as a combined adult and pediatric program.

Data were retrospectively extracted from the prospectively collected database of the Toronto Lung Transplant Program. The study was approved by the University Health Network Research Ethics Board. A waiver for informed consent was provided because of the nature of the study.

Our study population was divided into 3 eras: 1984 to 1995, 1996 to 2005, and 2006 to 2016. This division was intended to separate out the early experience from the more modern experience and to examine the effect of recent innovations in practice, such as bridging to lung transplantation with ECLS and expansion of the donor pool with EVLP and DCD donors. For waitlist mortality analysis purposes, the study population was divided into 2 eras—1998 to 2005 and 2006 to 2016—as data were unavailable from 1984 to 1998.

All patients received triple-drug immunosuppression as previously published.[10] Patients who were crossmatch-positive[10] and BCC-positive (BCC+)[11] were treated with modified immunosuppressive regimens detailed elsewhere. A multiantibiotic regimen was given based on recent sensitivity testing.[11]

Post-transplant survival was calculated using the Kaplan–Meier method, and comparisons between groups were performed using log-rank test. Continuous variables in groups of 2 were compared using Student's unpaired *t*-test, whereas those in groups of 3 or more were compared using analysis of variance. Statistical analysis was conducted using R 3.3.2.

Results

From the initiation of our lung transplant program to December 31, 2016, CF accounted for 364 cases of 1,885 procedures performed (19.3%). There were 31 pediatric transplants (8.5%). Among the 333 adults receiving primary transplantation, 245 (74%) were BCC-negative (BCC−) and 87 (26%) were BCC+. There was 1 pediatric patient who was BCC+ in our cohort. Thirty-nine patients, all adults, underwent retransplantation (Figure 1). The demographics of the adult and pediatric patients are displayed in Table 1.

Adult population

The 1-, 5-, and 10-year post-transplant survival probabilities for the adult patients who were BCC− were 94%, 70%, and 53%, respectively. This favorably compares with unadjusted survival for other indications (53%, 58%, and 56% for 5-year survival for pulmonary hypertension, interstitial lung disease, and emphysema, respectively). The BCC+ patients experienced significantly worse survival with 1-, 5-, and 10-year survival of 59%, 33%, and 16%, respectively ($p < 0.001$) (Figure 2). Among the 88 patients who were BCC+, genotyping data were available for 73 (83%), with 66 (90% of genotyped cases) representing B *cenocepacia* (Genomovar III), 3 representing B *multivorans* (Genomovar II), 2 representing B *vietnamiensis* (Genomovar V), and 2 representing B *gladioli.* The main cause of death in this population was BCC infection (44% of deaths), followed by CLAD (34%), as opposed to the patients who were BCC− and had CLAD as the most frequent

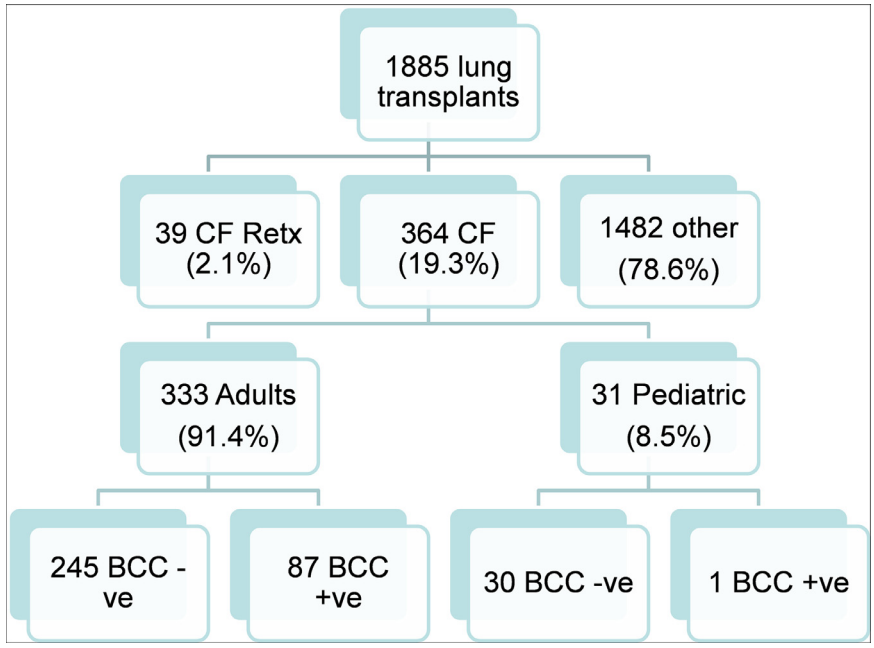

Figure 1 Overview of study population. BCC, *Burkholderia cepacia* complex; BCC +ve, BCC-positive; BCC −ve, BCC-negative; CF, cystic fibrosis.

cause of death (41%), followed by bacterial infection (27%). Overall, septic causes of death were higher than other indications (22%, 24%, and 21% for pulmonary hypertension, interstitial lung disease, and emphysema, respectively). Over the years, there has been a significant decrease from 46% (1984–95) to 32% (1996–2005) and 15% (2006–2016) in the percentage of patients in our transplant program who are BCC+ ($p < 0.001$).

Pediatric population

In the study period, 30 pediatric patients who were BCC− underwent LTx for CF, with a mean age at transplant of 13.7 ± 2.6 years and no gender predominance (17 males and 14 females). Survival of pediatric patients was lower than that of adults, with 1-, 5-, and 10-year survival probabilities of 90%, 62%, and 33%, respectively ($p = 0.01$) (Figure 3). Majority of our pediatric population consisted of adolescents (77% for age 12–17 years; 23% for age <12 years), and adolescent survival was similar to that of the adult BCC− population, with 1-, 5-, and 10-year survival probabilities of 91%, 73%, and 45%, respectively ($p = 0.22$). When adolescence was defined according to Paraskeva et al[12] (10−24 years), adolescent transplant demonstrated a survival detriment (adolescent: $n = 101$; 94%, 61%, and 43% for 1-, 5-, and 10- year survival vs adult: $n = 170$; 93%, 75%, and 57% for 1-, 5-, and 10-year survival; $p = 0.03$). However, further analysis by looking at survival of patients from 18 to 24 years did not show a difference compared with adults ($p = 0.1$); thus, this survival detriment is likely driven by the age group of 10 to 12 years.

As CF care improves and patients live longer, the age at which transplant is required should go up. Our data supported this trend. For the 2 eras where pediatric transplant was offered, the mean age increased from 27.6 years (1996–2005) to 30.4 years (2006–2016) ($p = 0.02$).[13]

Retransplantation

A total of 39 patients developed CLAD and underwent retransplantation after a mean age of 5.1 years (range: 0.7–

Table 1 Demographics of Study Population

Clinical values	First-time Tx($n = 364$)	Adults($n = 333$)	Children($n = 31$)	p-Value (adults vs children)
Age, years (SD)	29.5 (9.7)	31 (8.7)	13.7 (2.6)	<0.001
Gender male (%)	206 (56.6)	189 (56.8)	17 (54.8)	0.99
Pneumothorax (%)	76 (20.9)	73 (21.9)	3 (9.7)	0.17
Hemoptysis (%)	85 (23.4)	83 (24.9)	2 (6.5)	0.04
FEV1 % (SD)	26 (7.2)	25 (7.2)	31 (5.9)	<0.001
CFRDM (%)	143 (39.3)	133 (39.9)	10 (32.3)	0.52
Pancreatic insufficiency (%)	241 (66.3)	227 (68.2)	14 (45.2)	0.02
BCC (%)	88 (24.2)	87 (26.1)	1 (3.2)	<0.001

Abbreviations: BCC, *Burkholderia cepacia* complex; CFRDM, cystic fibrosis−related diabetes mellitus; FEV1, forced expiratory volume in one second; Tx, transplant

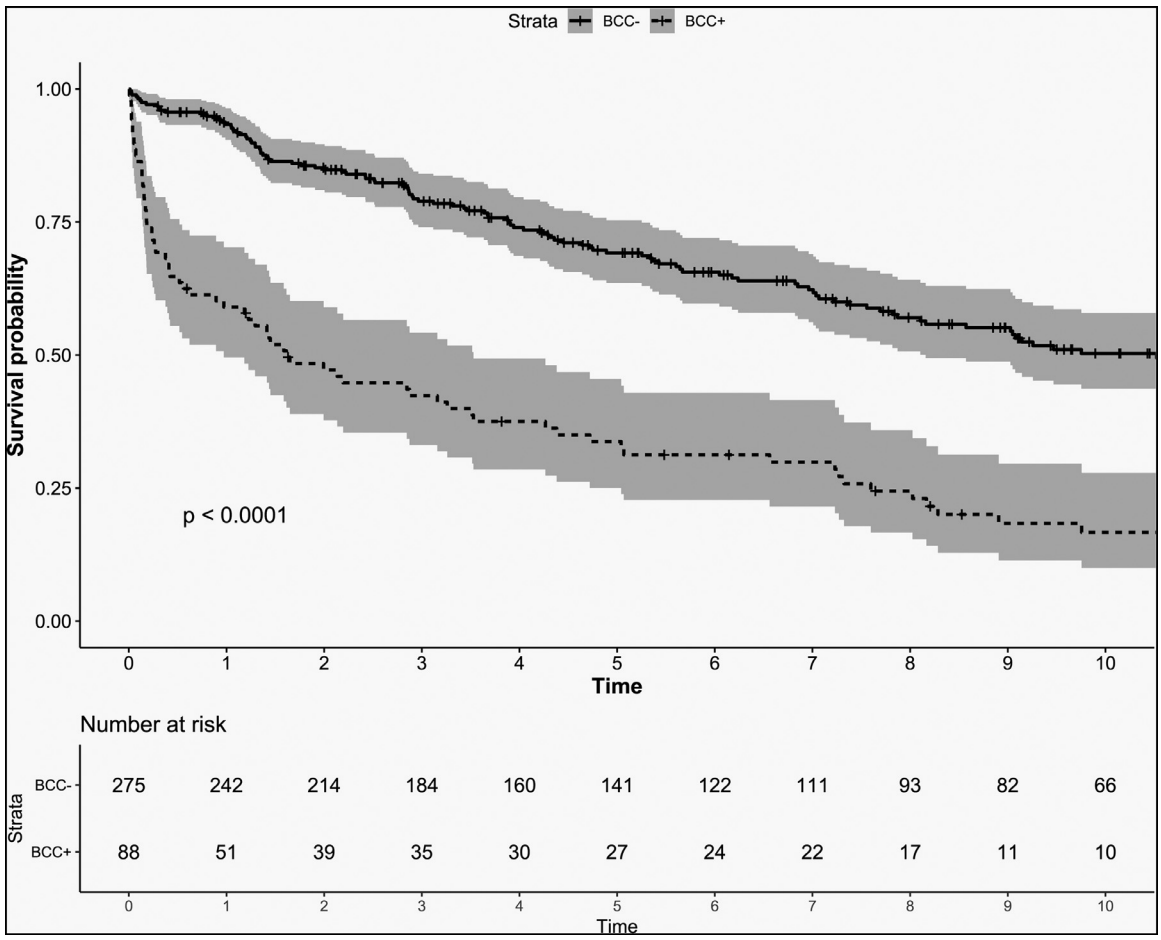

Figure 2 Survival curve of adult patients with cystic fibrosis following lung transplant stratified by BCC status. BCC, *Burkholderia cepacia* complex; BCC+, BCC-positive; BCC−, BCC-negative.

16.5 years). Retransplant patients were similar in age compared with first-time transplant patients (30.8 years and 28.9 years for retransplant and first-time transplant patients, respectively; $p = 0.20$). Short-term end-points such as intensive care unit and hospital stays were longer in retransplant patients than in first-time transplant patients (median intensive care unit stay: 10 days vs 3 days; median hospital stay: 36 days vs 23 days, respectively; $p < 0.0001$). Survival at 1, 5, and 10 years for retransplant patients was 73%, 47%, and 30%, respectively and was lower than survival in patients of first-time BCC− transplant ($p = 0.0008$) (Figure 4).

Bridging to transplant

Our program began bridging patients to lung transplantation in 2003, initially with non-invasive techniques and subsequently with mechanical ventilation. Starting in 2007, we added ECLS to the bridging armamentarium whenever listed patients presented with severe hypercapnic and/or hypoxemic respiratory failure. The modes of ECLS were (1) femoral artery to femoral vein pumpless Novalung in 5 patients, 2 of which required hemodynamic support and were switched to veno-arterial ECLS and ventilated; and (2) veno-venous ECLS with a dual-lumen or bicaval cannulas in 8 patients, 4 of which were ventilated. The mean period of ECLS was 12.8 days, ranging from 2 days to 31 days. A total of 4 of 16 patients (25%) were bridged to transplant with ECLS without being intubated. Some patients (5 of 20; 25%) were placed on ECLS support but did not survive the lung transplantation. The overall 30-day post-transplant mortality in this very sick pre-transplant group needing bridging was 10.5%, and the 1- and 5-year survival probabilities were 81% and 49%, respectively, with no statistically significant difference to non-bridged patients ($p = 0.24$).

Expansion of the donor pool was achieved using EVLP ($n = 28$), DCD ($n = 19$), and lobar transplantation ($n = 12$), with a total of 45 cases (12 cases of both DCD and EVLP, 1 case of lobar transplant and EVLP, and 1 case of lobar transplant and DCD). Outcomes were not compromised by these strategies because the patients who received grafts from this expanded donor pool presented similar 1- and 5-year survivals as patients who were BCC− (91% and 62%; $p = 0.86$).

In the adult population, a significant drop in waitlist mortality from 13.0% (12 of 92) to 5.9% (14 of 237) was observed ($p = 0.03$) between the 2 eras. In the pediatric cohort, the waitlist mortality decreased from 18% (4 of 22) to 4.8% (1 of 21) from the first to the second era ($p = 0.36$). Era did not have a significant effect on the survival of BCC +, BCC−, or pediatric patients. For adult patients who were

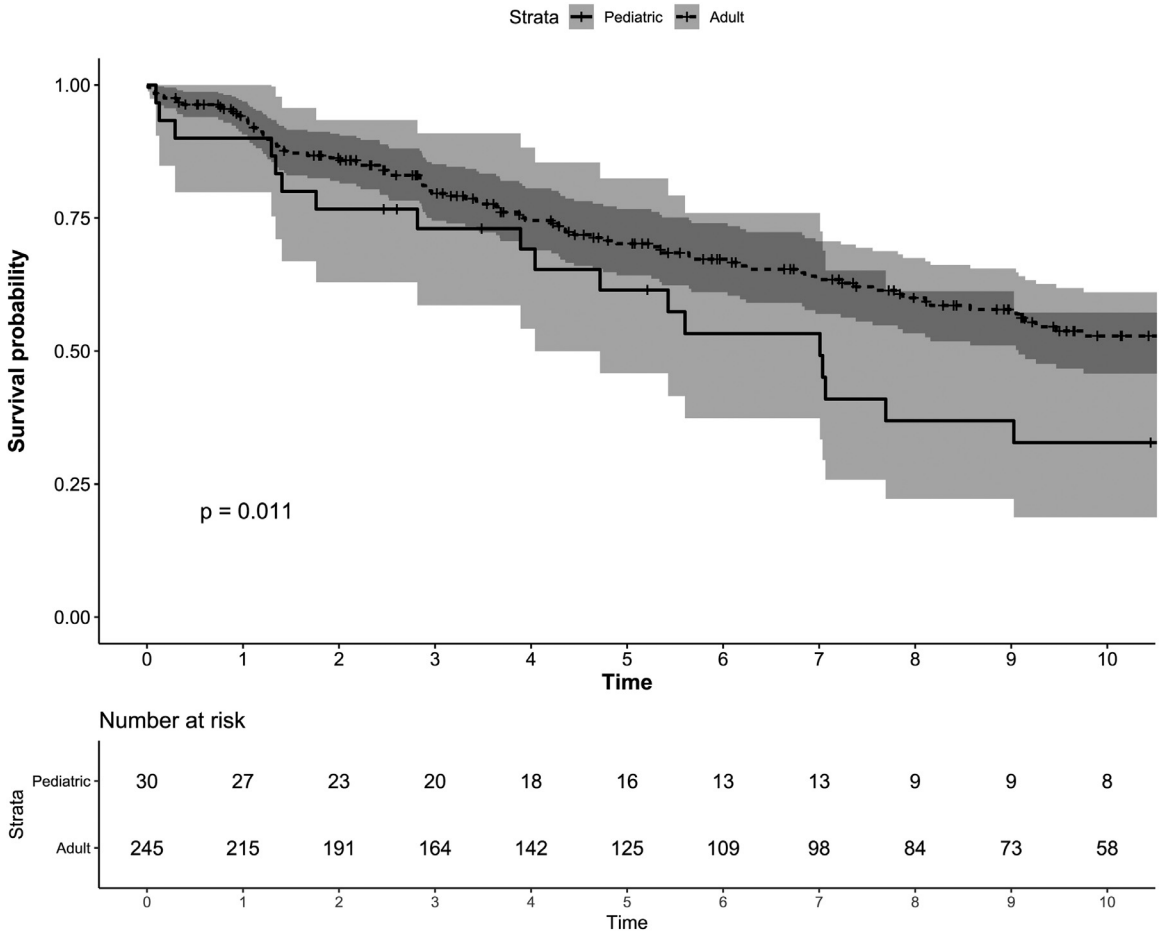

Figure 3 Survival curve of adult vs pediatric patients with cystic fibrosis following lung transplant.

BCC−, 1-, 5-, and 10-year survivals were 89%, 78%, and 44%, respectively, for the era 1984 to 1995 ($n = 27$); 95%, 67%, and 54%, respectively, for the era 1996 to 2005 ($n = 61$); and 94%, 70%, and 56%, respectively, for the era 2006 to 2016 ($n = 157$; $p = 0.89$). For adult patients who were BCC+, 1-, 5-, and 10-year survivals were 61%, 30%, and 13%, respectively, for the era 1984 to 1995 ($n = 14$); 56%, 33%, and 17%, respectively, for the era 1996 to 2005 ($n = 20$); and 62%, 36%, and 25%, respectively, for the era 2006 to 2016 ($n = 17$) ($p = 0.6$). For pediatric patients, 1-, 5-, and 10-year survivals were not available for the era 1984 to 1995 ($n = 0$); 88%, 65%, and 41%, respectively, for the era 1996 to 2005 ($n = 17$); and 93%, 61%, and 25%, respectively, for the era 2006 to 2016 ($n = 14$; $p = 0.4$).

Discussion

Survival of patients with CF in Canada is reportedly one of the highest worldwide. As the sole intervention that can immediately influence survival, lung transplantation likely plays a central role in this outcome.[14] This report presents a single-center experience of patients with CF who have undergone lung transplantation from 1988 to 2016 in this context and demonstrates excellent overall survival and a significant fall in waitlist mortality.

Combined expertise in the pre-transplant management of CF disease at our adult and pediatric CF centers maximizes pre-transplant outcomes and minimizes pre-mature listing of patients with CF. Indeed, in this 28-year experience, only 8% were pediatric; the remainder survived to adulthood before requiring lung transplantation.

Once listed, patients have a high probability of receiving an LTx at our center. We have seen a steady reduction in waitlist mortality of patients with CF over time. This is in part related to the close communication between the referring CF team and the transplant program regarding patient status and also relates to our program's initiatives in the advanced bridging of patients and in expanding the donor pool.

Bridging to LTx with ECLS has been associated with an increasing trend toward reduced waitlist mortality. Because of relatively younger age and increased risk for acute decompensation of the chronic respiratory failure, patients with CF represent an ideal population to consider bridging with ECLS. In the ECLS bridge-to-transplant series of Toyoda et al[15] and Hoopes et al,[16] CF was the indication for 21% and 22.5% of successfully bridged patients and represented a significant percentage of bridged patients,[17,18] if not the absolute majority, in other studies.[19,20] In addition, patients with CF are well-suited for support with dual-lumen veno-venous ECLS. This mode keeps the groin free so the patient can be actively mobilized or ambulated while addressing the hypoxemic component of the respiratory failure. This strategy has been shown to improve survival

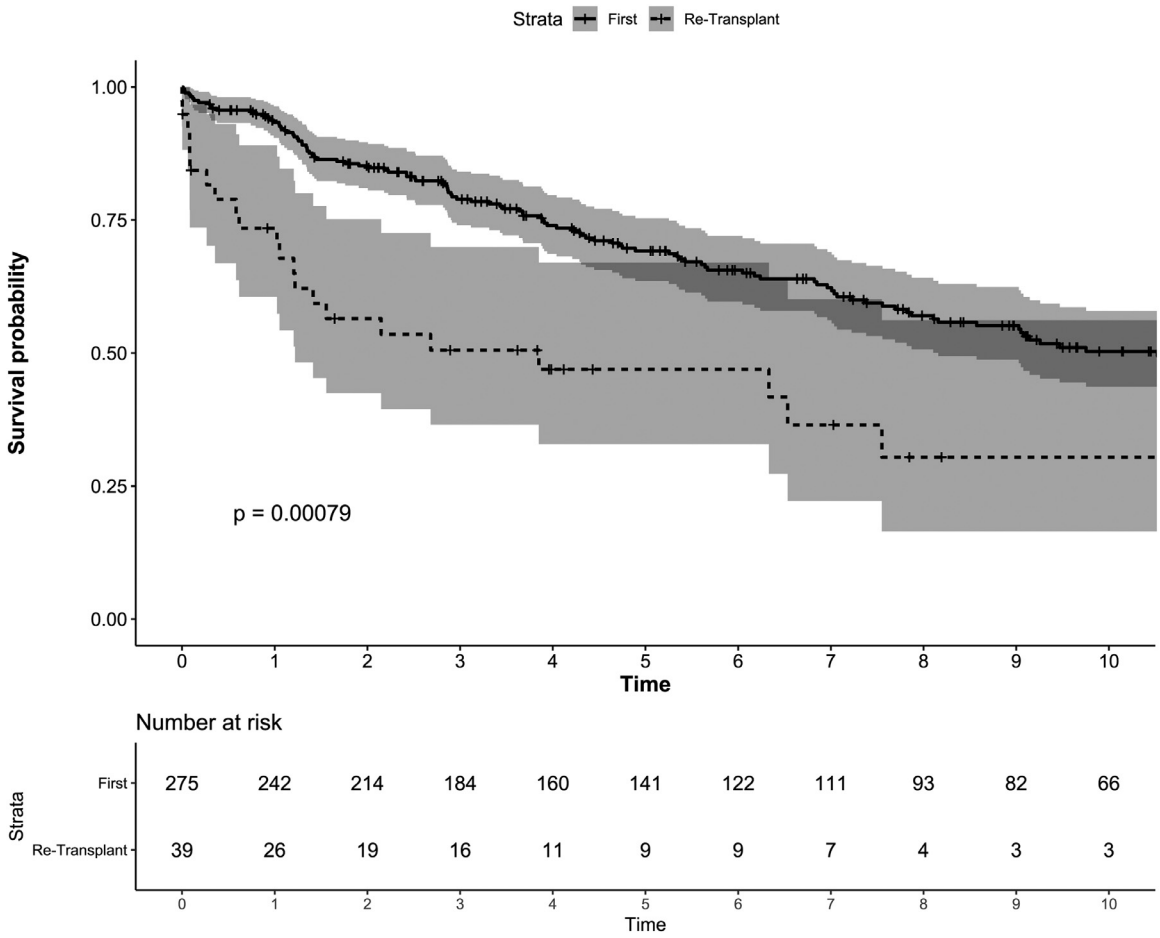

Figure 4 Survival curve of patients with cystic fibrosis following first lung transplant vs lung retransplant.

and potentially shorten the early post-transplant recovery when compared with patients bridged with mechanical ventilation.[17,21] The current report reinforces this observation, with a clear shift from mechanical ventilation to ECLS, and shows that there is no significant difference in survival compared with non-bridged patients.

The terminal event in bridged patients with CF is usually multisystem organ failure related to pulmonary sepsis. In order to prevent this, we have resorted to aggressive physical therapy and ambulation where possible while on ECLS or performance of early tracheostomy for aggressive bronchial toilet with bronchoscopy and suctioning. We recently performed a bilateral pneumonectomy for source sepsis control in a patient with CF with unrelenting Pseudomonas septicemia and bridged the patient without lungs for 6 days on ECLS to a successful bilateral lung transplant.[22]

It is noteworthy that the ECLS bridging algorithm was temporarily linked to aggressive expansion of the donor lung pool by means of lobar transplantation, DCD,[23] and EVLP.[9] Even though improving technology has certainly made long-term support feasible, better outcomes after ECLS bridge-to -LTx have been linked to shorter waiting times.[24] High resource utilization should also be expected with long ECLS runs, including a repeated need for blood product transfusion and circuit exchanges.[25] However, in the current report, the use of ECLS bridging strategies coupled with expansion of the donor pool coincided with a significant overall decrease in our waitlist mortality for patients with CF after 2005. This observation is similar to that which we previously reported with the application of ECLS pulmonary artery−left atrium Novalung bridging in lung transplant for pulmonary arterial hypertension, demonstrating a waitlist mortality going from 22% to virtually zero.[26]

BCC continues to be a significant barrier to LTx success in patients with CF. Single-center data clearly showed that worse outcomes are associated with the *B. cenocepacia* species.[6,27,28] B. *cenocepacia* corresponded to 90% of our cases that were genotyped. Contrary to BCC−, in our experience, most of the patients who were BCC+ died from infection and not CLAD. Fortunately, there has been a decrease in the prevalence of BCC among patients with CF in Canada, with the number of patients who were BCC+ in our program dropping from 47% to 12% after 2007.[14] In our experience, patients who were BCC+ had a 33% 5-year survival. Critical interpretation of these results should take into account the negative impact that BCC also has on the survival probability of non-transplanted patients as it represents the single strongest factor associated with mortality. While recognizing the increased risk presented by this population of patients, we continued to believe that LTx consideration should not be denied to this population. We

have continued to focus our efforts on measures to avoid post-operative infectious complications and on expansion of the donor pool.[9,23,29]

Adolescent patients with CF have been reported to have worse post-transplant outcomes than younger children and adults.[12,30,31] However, this was not supported by our data. Even though we have not specifically evaluated the reasons leading to this finding, one can speculate that the close collaboration of the CF and LTx programs, the establishment of a pediatric–adult transplant transition process, and the overlap of physicians working as one team all play an important role in patient selection and maintenance of adherence. Despite historical ambivalence of the LTx benefit for the pediatric population, our report, along with others,[32] illustrated that excellent outcomes can be obtained in highly specialized centers. A recent study has also shown that the worse outcomes observed with pediatric patients in the U.S. can be partially explained by children and adolescents being transplanted at adult programs.[33]

Because patients with CF generally undergo lung transplantation at a relatively young age, they may be suitable candidates for a retransplant procedure if their graft starts to fail with CLAD. Despite modern reports still showing worse outcomes for retransplantation than first-time LTx, judicious patient selection plays a crucial role in allocation of such a scarce resource.[34,35] Our program will consider retransplantation on a case-by-case basis with complete evaluation and risk assessment as done for first-time transplantation. Considerations include fitness, renal function, and social support. Type of CLAD (bronchiolitis obliterans syndrome vs restrictive allograft syndrome) is not a major consideration. However, we recognize that patients with restrictive allograft syndrome bridged to retransplant are high risk candidates. In our study, 39 patients underwent lung retransplantation for CLAD at a mean age of 30.8 years with increased risk but acceptable survival when compared with first-time LTx. The small cohort relative to the total number of patients that developed CLAD, as well as the young age, suggests that this population was highly selected. Moreover, the mean interval from first transplant to retransplantation was 5.1 years (range: 0.7–16.5 years). This is concordant with previous reports, suggesting that improved outcomes are obtained when retransplantation is performed more than 1 year from the primary operation.[34]

The current study reinforces the role of LTx in the treatment of end-stage lung disease secondary to CF. Clearly, outcomes have continued to improve, and the 50% 5-year survival rule no longer applies to this population. CF-specific outcome data should be used whenever informing patients or referring physicians that are considering this therapy. More importantly, the survival benefit conferred by LTx comes with significantly increased quality of life.[36]

The limitations of this study are its retrospective nature, the long study period, and the evolution in medical protocols. Nevertheless, our large sample size, comprehensive database, and minimal loss to follow-up allow us to demonstrate how our program and the field have evolved and how current medical and technological advances have allowed us to transplant sicker patients while maintaining good outcomes and a significant reduction in waitlist mortality.

In conclusion, lung transplantation for patients with CF provides excellent long-term survival in the range of a 10-year median survival. Specific populations such as children, adolescents, retransplant, and bridge-to-transplant candidates can also enjoy this benefit when carefully selected and managed in experienced centers. A significant reduction in waitlist mortality can be expected with improving bridging and donor lung preservation strategies. This experience supports lung transplantation as the standard of care for patients with CF having an advanced lung disease.

In this retrospective analysis of patients with CF receiving lung transplantation, excellent short- and long-term outcomes were achieved. This supports lung transplantation as the standard of care for patients with CF having end-stage lung disease.

Disclosure statement

S.K., T.K.W., and M.C. are founders of Perfusix Canada (PXCA). This company provides ex vivo lung perfusion (EVLP) services and training to University Health Network. Owing to conflict of interest relative to EVLP activities as lung transplant surgeons in the institution, S.K., T.K.W., and M.C. do not receive any payments from PXCA. Furthermore, with respect to the provision of EVLP services, PXCA is a non-profit company that does not generate profit from EVLP activities provided for patients of University Health Network.

S.K., T.K.W., and M.C. are founders of XOR Labs Toronto, a company dedicated to development of EVLP machines. The XOR Labs Toronto EVLP machine is in development phase and was not used on any patients reported in this study.Lung Bioengineering (LBI), a subsidiary of United Therapeutics: LBI acquired Perfusix USA in 2015, a company that was co-founded by S.K., T.K.W., and M.C. Currently S.K., T.K.W., and M.C. are paid consultants for LBI. They give strategic advice to LBI lung perfusion center as members of its Scientific Advisory Board. The remaining authors have no conflicts of interest to declare. None of the authors have a financial relationship with any commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

References

1. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet 2009;373:1891-904.
2. Grasemann H, Ratjen F. Early lung disease in cystic fibrosis. Lancet Respir Med 2013;1:148-57.
3. Chambers DC, Yusen RD, Cherikh WS, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant 2017;36:1047-59.
4. Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. Am J Respir Crit Care Med 2001;163:1331-7.

5. Snell GI, Bennetts K, Bartolo J, et al. Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. J Heart Lung Transplant 1998;17:1097-103.
6. De Soyza A, Meachery G, Hester KL, et al. Lung transplantation for patients with cystic fibrosis and Burkholderia cepacia complex infection: a single-center experience. J Heart Lung Transplant 2010;29: 1395-404.
7. Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. Am J Respir Crit Care Med 2005;171:1053-9.
8. Granton JT, Shapiro C, Kesten S. Noninvasive nocturnal ventilatory support in advanced lung disease from cystic fibrosis. Respir Care 2002;47:675-81.
9. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011;364:1431-40.
10. Tinckam KJ, Keshavjee S, Chaparro C, et al. Survival in sensitized lung transplant recipients with perioperative desensitization. Am J Transplant 2015;15:417-26.
11. Chaparro C, Keshavjee S. Lung transplantation for cystic fibrosis: an update. Expert Rev Respir Med 2016;10:1269-80.
12. Paraskeva MA, Edwards LB, Levvey B, et al. Outcomes of adolescent recipients after lung transplantation: an analysis of the International Society for Heart and Lung Transplantation Registry. J Heart Lung Transplant 2018;37:323-31.
13. Benden C, Goldfarb SB, Stehlik J. An aging population of patients with cystic fibrosis undergoes lung transplantation: an analysis of the ISHLT Thoracic Transplant Registry. J Heart Lung Transplant 2019;38:1162-9.
14. Stephenson AL, Tom M, Berthiaume Y, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. Eur Respir J 2015;45:670-9.
15. Toyoda Y, Bhama JK, Shigemura N, et al. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg 2013;145:1065-71.
16. Hoopes CW, Kukreja J, Golden J, Davenport DL, Diaz-Guzman E, Zwischenberger JB. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg 2013; 145:862-8.
17. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763-8.
18. Hayanga AJ, Aboagye J, Esper S, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation in the United States: an evolving strategy in the management of rapidly advancing pulmonary disease. J Thorac Cardiovasc Surg 2015;149:291-6.
19. Lafarge M, Mordant P, Thabut G, et al. Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. J Heart Lung Transplant 2013;32:905-13.
20. Lang G, Taghavi S, Aigner C, et al. Primary lung transplantation after bridge with extracorporeal membrane oxygenation: a plea for a shift in our paradigms for indications. Transplantation 2012;93:729-36.
21. Hoetzenecker K, Donahoe L, Yeung JC, et al. Extracorporeal life support as a bridge to lung transplantation—experience of a high-volume transplant center. J Thorac Cardiovasc Surg 2018;155:1316-28. e1.
22. Cypel M, Waddell T, Singer LG, et al. Bilateral pneumonectomy to treat uncontrolled sepsis in a patient awaiting lung transplantation. J Thorac Cardiovasc Surg 2017;153:e67-9.
23. Machuca TN, Mercier O, Collaud S, et al. Lung transplantation with donation after circulatory determination of death donors and the impact of ex vivo lung perfusion. Am J Transplant 2015;15:993-1002.
24. Crotti S, Iotti GA, Lissoni A, et al. Organ allocation waiting time during extracorporeal bridge to lung transplant affects outcomes. Chest 2013;144:1018-25.
25. Kon ZN, Wehman PB, Gibber M, et al. Venovenous extracorporeal membrane oxygenation as a bridge to lung transplantation: successful transplantation after 155 days of support. Ann Thorac Surg 2015;99:704-7.
26. de Perrot M, Granton JT, McRae K, et al. Impact of extracorporeal life support on outcome in patients with idiopathic pulmonary arterial hypertension awaiting lung transplantation. J Heart Lung Transplant 2011;30: 997-1002.
27. Alexander BD, Petzold EW, Reller LB, et al. Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. Am J Transplant 2008;8:1025-30.
28. Aris RM, Routh JC, LiPuma JJ, Heath DG, Gilligan PH. Lung transplantation for cystic fibrosis patients with Burkholderia cepacia complex. Survival linked to genomovar type. Am J Respir Crit Care Med 2001;164: 2102-6.
29. Chaparro C, Maurer J, Gutierrez C, et al. Infection with Burkholderia cepacia in cystic fibrosis: outcome following lung transplantation. Am J Respir Crit Care Med 2001;163:43-8.
30. Hayes D Jr, McCoy KS, Whitson BA, Mansour HM, Tobias JD. High-risk age window for mortality in children with cystic fibrosis after lung transplantation. Pediatr Transplant 2015;19:206-10.
31. Oshrine K, McGrath D, Goldfarb S. Transplanting the adolescent cystic fibrosis patient: can we do it? Ther Adv Respir Dis 2013;7:101-9.
32. Schmid FA, Inci I, Bürgi U, et al. Favorable outcome of children and adolescents undergoing lung transplantation at a European adult center in the new era. Pediatr Pulmonol 2016;51:1222-8.
33. Hayes D Jr, Glanville AR, McGiffin D, Tobias JD, Tumin D. Age-related survival disparity associated with lung transplantation in cystic fibrosis: an analysis of the registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2016;35:1108-15.
34. Thomas M, Belli EV, Rawal B, Agnew RC, Landolfo KP. Survival After lung retransplantation in the United States in the current era (2004 to 2013): better or worse? Ann Thorac Surg 2015;100:452-7.
35. Verleden SE, Todd JL, Sato M, et al. Impact of CLAD phenotype on survival after lung retransplantation: a multicenter study. Am J Transplant 2015;15:2223-30.
36. Singer LG, Chowdhury NA, Faughnan ME, et al. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. Am J Respir Crit Care Med 2015;192:965-73.