EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

The impact of the high emergency lung transplantation program in cystic fibrosis in France: insight from a comparison with Canada

Adèle Coriati, Jenna Sykes, Lydie Lemonnier, Xiayi Ma, Sanja Stanojevic, Clémence Dehillotte, Nicolas Carlier, Anne L. Stephenson

Please cite this article as: Coriati Aèle, Sykes J, Lemonnier L, *et al*. The impact of the high emergency lung transplantation program in cystic fibrosis in France: insight from a comparison with Canada. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00014-2021).

The Impact of the High Emergency Lung Transplantation program in Cystic Fibrosis in France: insight from a comparison with Canada

Adèle Coriati[1], Jenna Sykes[1], Lydie Lemonnier[2], Xiayi Ma[1], Sanja Stanojevic[3], Clémence Dehillotte[2], Nicolas Carlier[4,5], Anne L. Stephenson*[1,6,7], Pierre-Régis Burgel*[4,5, 8] and *co-senior authors

[1]Department of Respirology, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada, M5B 1W8
[2] Association Vaincre la Mucoviscidose, Paris, France
[3] Department of Community Health and Epidemiology; Dalhousie University; Halifax, NS, Canada B3H 1V7
[4] Hôpital Cochin, Assistance Publique Hopitaux de Paris, Paris, France
[5] ERN-Lung Cystic Fibrosis network
[6] Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, Toronto, Ontario, Canada M5T 3M6
[7] Keenan Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, 209 Victoria Street, Toronto, Ontario, Canada M5B 1T8
[8] Université de Paris and Institut Cochin, Inserm U1016, Paris, France

Corresponding Author

Prof Pierre-Régis Burgel, Hôpital Cochin, Assistance Publique Hopitaux de Paris, 27 rue du Faubourg Saint Jacques, Paris, France, Email: pierre-regis.burgel@aphp.fr Tel: +33 1 5841 2367 Fax: +33 1 46338253

Abstract

Introduction: France implemented a high emergency lung transplantation (HELT) program nationally in 2007. A similar program does not exist in Canada. The objectives of our study were to compare health outcomes within France as well as between Canada and France before and after the HELT program in a population with Cystic Fibrosis (CF).

Methods: This population-based cohort study utilized data from the French and Canadian CF registries. A cumulative incidence curve assessed time to transplant with death without transplant as competing risks. The Kaplan-Meier method was used to estimate post-transplant survival.

Results: Between 2002 and 2016, there were 1075 (13.0%) people with CF in France and 555 (10.2%) people with CF in Canada who underwent lung transplantation. The proportion of lung transplant increased in France after the HELT program was initiated (4.5% vs. 10.1%) whereas deaths pre-transplant decreased from 85.3% in the pre-HELT to 57.1% in the post-HELT period. Between 2008-2016, people in France were significantly more likely to receive a transplant (Hazard Ratio (HR) 1.56, 95% CI 1.37-1.77, $p<0.001$) than die (HR 0.55, 95% CI 0.46-0.66, $p<0.001$) compared to Canada. Post-transplant survival was similar between the countries and there was no difference in survival when comparing pre- and post-HELT period in France.

Conclusion: Following the implementation of the HELT program, people living with CF in France were more likely to receive a transplant than die. Post-transplant survival in the post-HELT period in France did not change compared to the pre-HELT period, despite potentially sicker patients being transplanted, and is comparable to Canada.

Introduction

The probability of receiving a transplant, and how long someone will live following lung transplantation varies between countries, in part because each country has its own system for transplant referral and donor lung allocation[1, 2]. Furthermore, differences in transplant recipient characteristics, waitlist mortality and post-transplant survival have been reported between countries[3, 4]. In France, prioritization of donor lung allocation has historically relied on transplant physician assessment of patient severity without specific criteria. In an effort to increase access to lung transplantation and reduce deaths on the waiting list, France formally implemented a high emergency lung transplantation (HELT) program at a national level in July 2007, which prioritized critically ill patients on the transplant waiting list based on specific criteria [5, 6]. The HELT program is a dedicated national emergency program with specific criteria laid out for enrolment in order to select those at highest risk for death unless they have rapid access to lung transplantation. These criteria are focused on hypercarbic and hypoxic respiratory failure and are limited to specific diseases, including cystic fibrosis (CF) and bronchiectasis, idiopathic pulmonary fibrosis and pulmonary hypertension. This program prioritizes patients with the highest need and this results in a transplant ultimately for the vast majority of people soon after being enrolled in the program. The overall purpose of the HELT program is to avoid mortality in those at highest risk of death within two weeks. Once the person is enrolled in the program, the application is systematically reviewed and approved by 2 experts and the patient is listed in the program for 8 days which can be renewed once. For people with CF, those requiring invasive ventilation, and/or extracorporeal membrane oxygenation, or patients at high risk for intubation (e.g. on non-invasive ventilation >18h per day for at least 3 days with arterial $PaCO_2$ >80 mmHg) are potential candidates for the HELT program.

Initial studies suggested the HELT program resulted in fewer deaths on the waiting list; however, these reports included people with various underlying diseases [5, 7]. Therefore, the impact of HELT on the CF population has yet to be established. Furthermore, outcomes in the CF population continue to improve, regardless of transplant, therefore analysis of temporal trends within a country may not measure the true impact of a given program. France and Canada have well-established CF registries, they both provide universal government-funded health care, they also contain data post-transplantation. In addition, the demographics of the two CF populations have been shown to be comparable [8]. Although Canada does prioritize the sickest patients, there is no universal and systematic program and regional variation exists [2]. Therefore, comparing transplant rates and outcomes between two distinct CF populations may provide insight into the impact of these different approaches.

The objectives of our study were to compare the proportion of deaths without lung transplant as well as post-transplant survival in France before and after implementation of the HELT program in the CF population. To account for medical advancement in CF care that occurred during this period, we compared similar metrics between France and Canada over the same timeframe. We hypothesized that the HELT program will result in (1) proportionally more lung transplants in France with fewer deaths without transplant compared to Canada, and (2) lower post-transplant survival in France after implementation of the HELT program since patients in this program are sicker at the time of lung transplantation.

Materials and Methods

Design

This population-based cohort study utilized data from two longitudinal national CF registries: the French CF registry (FCFR) and the Canadian CF registry (CCFR).

Study period

National CF registry data from Jan 1, 2002 – December 31, 2016 were used in this study. Two study periods were established based on the year the HELT program began: pre-HELT (2002-2006) and post-HELT (2008-2016). The year 2007 was not included in the study as the HELT program started in the middle of that year.

Data resources

The FCFR, managed by Vaincre la Mucoviscidose, was established in 1992 and follows patients with CF from 47 CF centers. It is estimated that over 95% of the French CF population is captured within the CF registry with a low rate of lost-to-follow-up (less than 3%)[9]. The CCFR, established in the early 1970s, is managed by CF Canada, and records data on individuals with CF who are followed in one of 42 Canadian CF clinics. It is estimated that 95% of the Canadian CF population is represented within the registry with a low rate of lost-to-follow-up (~5%)[10, 11]. Both clinical and demographic data are recorded annually on all included patients. Registry data undergo routine validation checks to ensure that they are free of duplicates and errors. All individuals within both registries provided informed consent to have their data collected and be used for research purposes. The research ethics board approval for this study has been obtained from Unity Health Toronto (UHT) (REB #17-312) and approval for use of the proposed registry data has been granted by CF Canada and Vaincre la Mucoviscidose. This study was in compliance with the International Society for Heart and Lung Transplantation ethic statement.

Variable definitions

The most recent clinical measurements up to 3 years before lung transplant were summarized to compare the lung transplant recipients in both countries. Body mass index (BMI) was calculated using the WHO guidelines for adults [12] and the Centre for Disease Control growth charts were used to calculate BMI centiles for children[13]. Patients were categorized as underweight (BMI <19 kg⁄m^2 or BMI%≤12%), overweight (BMI >24.9 kg⁄m^2 or BMI%≥85%), or normal (BMI between ≥19 kg⁄m^2 and ≤24.9 kg⁄m^2 or BMI% between >12% and <85%). The presence of *Burkholderia cepacia (B. cepacia)* complex or *Pseudomonas aeruginosa* (*P. aeruginosa*) were assessed in sputum samples and considered positive if the bacteria were identified at least once within the time period. CF genotype was classified as: Phe508del homozygous, Phe508del heterozygous, other or missing. CF-related diabetes (CFRD) was based on the CF guidelines[14]. Therapies such as feeding tube, bi-level positive airway pressure (BiPAP) and supplemental oxygen were recorded if administered during the reported year. A pulmonary exacerbation was defined as the administration of intravenous antibiotic (IV Ab) in the hospital and⁄or at home. Forced expiratory volume in 1 sec (FEV_1) percent predicted FEV_1 ($ppFEV_1$) was calculated using Global Lung Function Initiative (GLI) reference equations[15]. FEV_1 values from patients < 6 years of age were not used, as this age group does not reliably perform this manoeuvre.

Statistical analysis

Median and interquartile ranges were used to summarize continuous variables whereas frequency and proportion were used to summarize categorical variables. The standardized mean difference was calculated to assess the difference between the two countries, and a standardized mean difference (SMD) greater than 10 was interpreted as a relevant difference[16, 17]. Patient characteristics between countries

were compared using the Mann-Whitney test for continuous variables and the Chi-squared test for categorical variables. We calculated the number of transplants to deaths as a ratio over time using a five-year rolling window. A difference-in-difference analysis was used to compare the change in ratio of lung transplants to pre-transplant deaths after the HELT program between France and Canada.

Time to lung transplant with death without transplant as a competing risk was modeled using the Fine and Gray cumulative incidence curves in the pre-HELT era (2002-2006) and the post-HELT era (2008-2016) and compared using Gray's test. Data were left truncated at January 1st in the first year of each study window unless born or diagnosed with CF within the window. Competing risk regression models were used to estimate the sub-distribution hazard of receiving a transplant or dying after adjusting for gender, age at diagnosis, pancreatic status, genotype, in addition to the following variables measured at the time of entry into the cohort: patient age, BMI, infection with *B. cepacia*, CFRD, the number of pulmonary exacerbations in a year and ppFEV$_1$.

Time to death was calculated from the date of lung transplant until death or last known follow-up and represented using Kaplan-Meier survival curves and compared using a log-rank test. A sensitivity analysis excluding patients with *B. cepacia* complex was done given these patients have a worse prognosis and *B. cepacia* is more common in Canada. All statistical analysis were done using the R software (version 3.4.3)[18]. All p-values were two-sided and assessed for significance at $p<0.05$ unless otherwise stated.

Results

Overall Study Population

Between 2002 and 2016, 8266 French and 5451 Canadian individuals with CF were included in the study (Table 1). A total of 826 (10.0%) deaths and 1075 (13.0%) lung transplants were recorded in the FCFR compared to 692 (12.7%) deaths and 555 (10.2%) lung transplants in the CCFR (Table 1S).

Although the populations were largely comparable, France had a higher percentage of patients with "other" mutations and fewer homozygous Phe508del patients. The proportion of *B. cepacia* patients and the proportion of patients categorized as normal or overweight were higher in Canada compared to France (Table 1).

Pre- and Post-HELT lung transplants and deaths

Characteristics of all patients (with and without a lung transplant) pre- and post-HELT period are summarized in Table 2S. Table 2 summarizes the lung transplants and deaths (classified as pre- and post-transplant) between the two time periods by country. The proportion of lung transplants doubled in France after the HELT program was initiated (4.5% pre-HELT compared to 10.1% post-HELT). A higher proportion of lung transplants were done in pediatric patients in France compared to Canada in both time periods (Table 2). The proportion of deaths without transplant decreased in France between the two time periods (85.3% vs. 57.1%). Comparing France and Canada, a similar proportion of deaths without transplant was seen in the pre-HELT period (85.3% vs. 86.9%; $p = 0.25$); however, in the post-HELT period the proportion of deaths without transplant for France decreased to 57.1% while the Canadian proportion was 77.7% ($p < 0.001$ between countries in the post-HELT period). In France, the proportion of deaths that occurred after lung transplant increased 2.9 times between the pre-HELT and post-HELT time periods (14.7% to 42.9%) suggesting more patients were receiving lung transplantation. Although the proportion of post-transplant deaths in Canada also increased, the magnitude was less compared to France (13.1% to 22.3% which represented a 1.7 increase).

The ratio of lung transplants to pre-transplant deaths increased at a higher rate in France compared to Canada (0.24 vs. 0.06 per year respectively, $p<0.001$; Figure 1). The ratio of lung transplants to pre-transplant deaths prior to 2007 was, on average, similar between the two countries (0.645 for Canada vs

0.643 for France, p=0.99, Figure 1). Using a difference-in-difference analysis, this ratio significantly increased for France compared to Canada after 2007 (difference in ratio between France and Canada in post-HELT relative to the difference in ratio in pre-HELT: 1.27, 95% CI 0.49-2.05, p=0.0026). We observed that, prior to 2007 (pre-HELT), the proportion of deaths without transplant between the countries was comparable. However, in the post-HELT era, a decrease in the proportion of deaths without transplant in those with advanced lung disease (FEV_1<40%) was observed in France, whereas the proportions of deaths in Canada remained stable (Figure 1S).

The subset of people included in the competing risk analysis is described in Figure 2S. Patients were more likely to die without a transplant in both Canada and France in the pre-HELT period (Figure 2A & Table 3S) with no significant differences found between the countries. However, in the post-HELT period, receiving a lung transplant was significantly more likely to occur than death without a lung transplant in both countries (Figure 2B). When comparing the countries, patients were more likely to receive a transplant in France compared to Canada (Gray's test for lung transplant between Canada and France p<0.001, Gray's test for death before transplant between Canada and France p<0.001). Also, multivariable competing risk regression models identified a decreased risk of death (Hazard ratio (HR) 0.55, 95% CI 0.46-0.66; p<0.001) and increased probability of receiving a lung transplant (HR 1.56, 95% CI 1.37-1.77; p<0.001) in France compared to Canada (Table 3S). The increased probability of receiving a transplant compared to death in France in the post-HELT period was seen early as the two curves in Figure 2B separate soon after time zero.

Post-transplant survival

Characteristics of transplant recipients pre- and post-HELT period in France and Canada are summarized in Table 4S. The 1-, 3- and 5-year probability of survival post-transplant in France were 86.7%, 76.9% and 69.6% in the pre-HELT period compared to 85.2%, 76.7%, and 73% in the post-HELT period (Figure 3) with no significant difference in post-transplant survival between the time periods. Comparing post-transplant survival between Canada and France, no statistically significant difference was found in either the pre-HELT (P=0.64) or the post-HELT (P=0.76) period (Figure 4). These results were unchanged after excluding patients infected with *B. cepacia* complex (Figure 3S).

Discussion

In the present study, we examined the impact of the HELT program on transplantation and death in France in CF. To account for the temporal effects of medical progress, including increased access to lung transplantation, we compared outcomes between France and Canada. Our study showed that after implementation of the HELT program in France, proportionally more patients received lung transplants and the risk of death without a transplant was lower for French patients. Such improvement was not observed to the same magnitude in Canada. Further, post-transplant survival in France was similar in the pre- and post-HELT period despite including potentially sicker CF patients enrolled in the HELT program. Comparison with Canadian transplant rates demonstrate that the magnitude of the improvements in France was greater than what would be expected due to temporal effects of increased access to transplant. Lastly, post-transplant survival between the countries was similar despite French patients being potentially sicker.

One purpose of the French HELT program was to reduce deaths on the lung transplant waitlist and there is limited literature on the impact of the HELT program on the CF population specifically. We observed a significant decrease in the rate of deaths without transplant in CF patients following the implementation of the HELT program. A previous study showed, regardless of underlying disease, a decrease in waitlist death rate from 19% to 2% since the HELT program began [7] with CF accounting for 81.1% of cases. A study published in 2012 by Boussaud et al. examined outcomes pre- and post-HELT era of various diseases. They reported a decrease in survival rate post-transplant in the entire cohort in the post-HELT period (55% survival rate at one year) compared to the pre-HELT period (76.6% survival rate at one year) but did not present data by disease [6]. One study by Savale et al. reported the impact of the HELT program in patients with pulmonary hypertension specifically and found a decrease in death rate on the waiting list in the post-HELT era, and no significant difference in overall survival between the pre- and post-HELT period [19]. Saueressig *et al.* published a retrospective single-center study assessing the impact of the HELT program in a small CF population of 15 HELT patients and reported a significant decrease in death rate on the lung transplant waiting list from 29.4% to 9.6% following the implementation of the HELT program[20]. Roussel *et al.* studied 503 HELT patients (47% had CF) compared to 1041 non-HELT transplant recipients, and also found a significant increase in the rate of transplant following the implementation of the HELT program [21]. Our study revealed a unique comparison by quantifying the rate of transplants and deaths pre- and post-HELT in France compared to Canada, a country that does not apply the HELT program. We reported that the change in the ratio of transplants to deaths was not as large in Canada and the risk of death was higher in Canada compared to France in the post-HELT period demonstrating the positive impact of the French HELT program. As there was also a slight increase in the rate of lung transplants in Canada post-HELT, we suggest that factors other than the improvement in

transplant access via the HELT program also contribute to the increasing rate of lung transplant in France during this study period. Strategies to increase organ availability may contribute to an increasing rate of transplant in France. Ex-vivo lung perfusion for lung transplants was implemented in 2011 in France [22]. However, given that it was performed in only one of the ten transplant centers in France, it is unlikely to explain the results. Finally, in the post-HELT era, the age at transplant increased and the proportion of children who received a transplant decreased compared to the pre-HELT era, regardless of the country, which could be explained by increased overall CF prognosis.

For people with end-stage CF lung disease, lung transplant remains a key treatment option to prolong survival. Previous studies have shown a decrease in post-transplant survival for those on the HELT program [6, 21] while others have shown no change [7] in post-transplant survival. Because patients eligible for transplant within the HELT program are potentially more unstable (e.g. intubated, on ECMO etc.), it is important to assess the impact of this program on post-transplant survival both within France and compared to Canada. We did not see lower survival in France in the post-HELT period and furthermore, the survival between Canada and France was similar. This is similar to one study that focused on CF patients specifically which showed no difference in post-transplant survival (1 and 2.5 years follow-up) between the HELT-CF group and the group of patients with CF who were selected for the regular lung transplantation program[20]. Moreover, despite differences in the prevalence of BCC between the countries, our results showed no difference in post-transplant survival overall or after excluding individuals infected with BCC in both countries. This may be due to the fact that the proportion of BCC who received a lung transplant is low in both countries [2, 23]. Unfortunately, we were not able to identify French patients transplanted in the HELT program vs. those transplanted without the HELT program specifically because this data is not being captured in the FCFR registry. However, it should be noted that the proportion of patients being referred to the HELT program in France is approximately 20% of the total lung transplants, including CF and non-CF

patients [21, 24]. Therefore, analyzing post-transplant survival of CF patients in the HELT program and comparing to those in the regular lung transplant program will be important to assess in the future.

There is no universal consensus on the criteria for prioritization of people awaiting lung transplantation. Italy took a similar approach to France and implemented the Italian Urgent lung transplant program (IULTp) in 2010, where patients could be transferred from the regular lung transplant program to the IULTp if they were < 50 years of age and required mechanical ventilation and/or extracorporeal lung support [25]. In 2018, the Italian CF lung transplantation group reported no difference in mortality while on the waitlist regardless of whether or not they were listed in the IULTp or not [26]. However, they observed a higher percentage of deaths at 1-year post-transplant for patients who were in the IULTp [26]. Moreover, studies showed that in the US, after the lung allocation score (LAS) was implemented, there was a 30% decrease in waitlist mortality in all comers with no change in 1-year post-transplant survival [27]. Interestingly, the variables included in the LAS score are not CF specific, in other words, the characteristics that predict death in CF are not necessarily incorporated in the LAS score [28]. Consequently, some argue that the LAS disproportionally limits lung transplant in CF patients [10]. Our data showed a 33% decrease in the rate of death pre-transplant and no change in post-transplant survival in the post-HELT period compared to the pre-HELT period suggesting the effectiveness of the HELT program in the context of the French healthcare system. In contrast to the HELT program, the LAS compares the statistical probability of a patient's survival in the next year without a transplant, and the projected length of survival post-transplant in order to prioritize patients for organs.

This study has several strengths. We utilized two well-characterized longitudinal national CF registries for this population-based cohort study. Both registries contain data on all CF patients, including those who have received lung transplants. In addition, both registries report a very low rate of lost-to-follow-up and missing data for clinical characteristics. To ensure the accuracy and completeness of the

information in the registries, quality checks are performed regularly. Finally, both countries have well-established universal CF healthcare systems and there are many similarities between these systems in France and Canada.

However, there are several limitations that need to be mentioned. First, prior literature has shown that approximately 30% of patients with CF in France who died without lung transplantation were never referred for lung transplantation even though most of them were eligible [29]. It will be important in a future study to determine the proportion of patients who died and were not referred or felt to not be an eligible candidate as these pre-transplant deaths could have possibly been prevented. Also, we acknowledge that we report the death rate pre-transplant, not necessarily the death rate on the waitlist, as the date of listing was not available for the French cohort. Determining how many of these pre-transplant deaths occurred while on the waitlist is important to further assess the effectiveness of the HELT program. Since the French CF registry does not capture referral data for lung transplants, we could not determine the number of patients with severe CF who were not referred for consideration of transplant in France. However, the decrease in the proportion of deaths observed in those with advanced lung disease in the post-HELT era supports the assumption that the HELT program has contributed to reducing the proportion of deaths in severe CF patients. Future studies are necessary to evaluate changes to lung transplant referral practices that are a result of HELT. Finally, our study does not allow us to determine if lung transplant prolongs life for patients (regardless of the HELT program) compared to not receiving a transplant. While this is a very important question, it is a very challenging one to answer because we do not know exactly how long a person would have lived had they not received a transplant. Comparing survival of transplanted patients to those who do not receive a transplant is challenging because of differences in disease severity and confounding by indication.

In conclusion, an increase in the rate of transplants as well as a decrease in the deaths without transplant were found in the CF population following the implementation of the HELT program in France. Furthermore, the HELT program did not appear to have a negative impact on overall post-transplant survival and was similar to the Canadian CF population. Further studies are needed to better understand the differences between the countries and whether or not a similar prioritization strategy such as the HELT program would be advantageous in countries that have different geographical distribution and healthcare systems.

Acknowledgments

We would like to acknowledge and thank all of the CF patients and families in France and Canada who consent to be part of their respective national CF patient registries as well as the CF clinic staff who spend many hours inputting the data.

Financial support

We would like to acknowledge the support of the Cystic Fibrosis Canada research grant held by A.L.S. and the Vaincre la Mucoviscidose research grant held by P.R.B. which made this study possible. A.C. was supported by a Post-Doctoral Fellowship from the Canadian Lung Association.

Financial Disclosure Statement

The authors declare that there are no financial conflicts of interest.

References

1. Merlo CA, Weiss ES, Orens JB, Borja MC, Diener-West M, Conte JV, Shah AS. Impact of U.S. Lung Allocation Score on survival after lung transplantation. J Heart Lung Transplant. 2009;28(8):769-75.
2. Yeung JC, Machuca TN, Chaparro C, Cypel M, Stephenson AL, Solomon M, Saito T, Binnie M, Chow CW, Grasemann H, Pierre AF, Yasufuku K, de Perrot M, Donahoe LL, Tikkanen J, Martinu T, Waddell TK, Tullis E, Singer LG, Keshavjee S. Lung transplantation for cystic fibrosis. J Heart Lung Transplant. 2020;39(6):553-60.
3. Quon BS, Sykes J, Stanojevic S, Marshall BC, Petren K, Ostrenga J, Fink A, Elbert A, Faro A, Goss CH, Stephenson AL. Clinical characteristics of cystic fibrosis patients prior to lung transplantation: An international comparison between Canada and the United States. Clinical transplantation. 2018;32(3):e13188.
4. Stephenson AR, K.J; Sykes, J.; Stanojevic, S.; Ostrenga, J.; Fink, A.; Quon, B.; Marshall, B.; Faro, A.; Petren, K.M.; Elbert, A.; Goss, C.H. Bridging the survival gap in Cystic Fibrosis between Canada and the United States: an in-depth look at lung transplant. (Abstract). Pediatric pulmonology. 2019;54(S2):S470.
5. Orsini B, Sage E, Olland A, Cochet E, Tabutin M, Thumerel M, Charot F, Chapelier A, Massard G, Brichon PY, Tronc F, Jougon J, Dahan M, D'Journo XB, Reynaud-Gaubert M, Trousse D, Doddoli C, Thomas PA. High-emergency waiting list for lung transplantation: early results of a nation-based study. Eur J Cardiothorac Surg. 2014;46(3):e41-7; discussion e7.
6. Boussaud V, Mal H, Trinquart L, Thabut G, Danner-Boucher I, Dromer C, Raymond CS, Reynaud-Gaubert M, Kessler R, Philit F, Dorent R, Stern M. One-year experience with high-emergency lung transplantation in France. Transplantation. 2012;93(10):1058-63.
7. Roux A, Beaumont-Azuar L, Hamid AM, De Miranda S, Grenet D, Briend G, Bonnette P, Puyo P, Parquin F, Devaquet J, Trebbia G, Cuquemelle E, Douvry B, Picard C, Le Guen M, Chapelier A, Stern M, Sage E, Group FLT. High Emergency Lung Transplantation: dramatic decrease of waiting list death rate without relevant higher post-transplant mortality. Transpl Int. 2015;28(9):1092-101.
8. Reynaud Q, Boudreau V, Touzet S, Desjardins K, Bourdy SP, Blond E, Berthiaume Y, Rabasa-Lhoret R, Durieu I. Glucose tolerance in Canadian and French cystic fibrosis adult patients. Sci Rep. 2019;9(1):4763.
9. Burgel PR, Bellis G, Olesen HV, Viviani L, Zolin A, Blasi F, Elborn JS, Europe. EETFoTPoCfAwCFi. Future trends in cystic fibrosis demography in 34 European countries. The European respiratory journal. 2015;46(1):133-41.
10. Stephenson AL, Sykes J, Stanojevic S, Quon BS, Marshall BC, Petren K, Ostrenga J, Fink AK, Elbert A, Goss CH. Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study. Annals of internal medicine. 2017;166(8):537-46.
11. Corey M, Farewell V. Determinants of mortality from cystic fibrosis in Canada, 1970-1989. American journal of epidemiology. 1996;143(10):1007-17.
12. BMI classification. Geneva: World Health Organization. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.
13. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. Adv Data. 2000(314):1-27.
14. Riggs AC, Seaquist ER, Moran A. Guidelines for the diagnosis and therapy of diabetes mellitus in cystic fibrosis. Current opinion in pulmonary medicine. 1999;5(6):378-82.

15. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, Initiative ERSGLF. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. The European respiratory journal. 2012;40(6):1324-43.
16. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. Communications in Statistics - Simulation and Computation. 2009;38(6):1228-34.
17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107.
18. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing Vienna, Austria2012. Available from: http://www.R-project.org/.
19. Savale L, Le Pavec J, Mercier O, Mussot S, Jais X, Fabre D, O'Connell C, Montani D, Stephan F, Sitbon O, Simonneau G, Dartevelle P, Humbert M, Fadel E. Impact of High-Priority Allocation on Lung and Heart-Lung Transplantation for Pulmonary Hypertension. Ann Thorac Surg. 2017;104(2):404-11.
20. Saueressig MG, Pelluau S, Sermet I, Souilamas R. Urgent lung transplantation in cystic fibrosis patients: experience of a French center. Eur J Cardiothorac Surg. 2011;40(3):e101-6.
21. Roussel A, Sage E, Massard G, Thomas PA, Castier Y, Fadel E, Le Pimpec-Barthes F, Maury JM, Jougon J, Lacoste P, Claustre J, Dahan M, Pirvu A, Tissot A, Thumerel M, Drevet G, Pricopi C, Le Pavec J, Mal H, D'Journo XB, Kessler R, Roux A, Dorent R, Thabut G, Mordant P, French Groups of Lung T. Impact of donor, recipient and matching on survival after high emergency lung transplantation in France. The European respiratory journal. 2019;54(5).
22. Sage E, Mussot S, Trebbia G, Puyo P, Stern M, Dartevelle P, Chapelier A, Fischler M, Foch Lung Transplant G. Lung transplantation from initially rejected donors after ex vivo lung reconditioning: the French experience. Eur J Cardiothorac Surg. 2014;46(5):794-9.
23. Burgel PR, Lemonnier L, Dehillotte C, Sykes J, Stanojevic S, Stephenson AL, Paillasseur JL. Cluster and CART analyses identify large subgroups of adults with cystic fibrosis at low risk of 10-year death. The European respiratory journal. 2019;53(3).
24. Biomédecine. RaAdl. 2017. Available from: http://www.agence-biomedecine.fr/annexes/bilan2013/donnees/organes/04-coeur-poumon/pdf/pcp.pdf. .
25. Boffini M, Venuta F, Rea F, Colledan M, Santambrogio L, D'Armini AM, Bertani A, Voltolini L, Parisi F, Marinelli G, Nanni Costa A, Rinaldi M. Urgent lung transplant programme in Italy: analysis of the first 14 months. Interact Cardiovasc Thorac Surg. 2014;19(5):795-800; discussion
26. Borchi B, Barao Ocampo M, Cimino G, Pizzamiglio G, Bresci S, Braggion C, Italian Cystic Fibrosis Lung Transplantation G. Mortality rate of patients with cystic fibrosis on the waiting list and within one year after lung transplantation: a survey of Italian CF centers. Ital J Pediatr. 2018;44(1):72.
27. Kozower BD, Meyers BF, Smith MA, De Oliveira NC, Cassivi SD, Guthrie TJ, Wang H, Ryan BJ, Shen KR, Daniel TM, Jones DR. The impact of the lung allocation score on short-term transplantation outcomes: a multicenter study. J Thorac Cardiovasc Surg. 2008;135(1):166-71.

28. Lehr CJ, Skeans M, Dasenbrook E, Fink A, Fernandez G, Faro A, Valapour M. Effect of Including Important Clinical Variables on Accuracy of the Lung Allocation Score for Cystic Fibrosis and Chronic Obstructive Pulmonary Disease. American journal of respiratory and critical care medicine. 2019;200(8):1013-21.
29. Martin C, Hamard C, Kanaan R, Boussaud V, Grenet D, Abely M, Hubert D, Munck A, Lemonnier L, Burgel PR.

Causes of death in French cystic fibrosis patients: The need for improvement in transplantation referral strategies!

Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2016;15(2):204-12.

Table 1: Characteristics of patients in France and Canada at the most recent measurement within the study window (2002-2016)*.

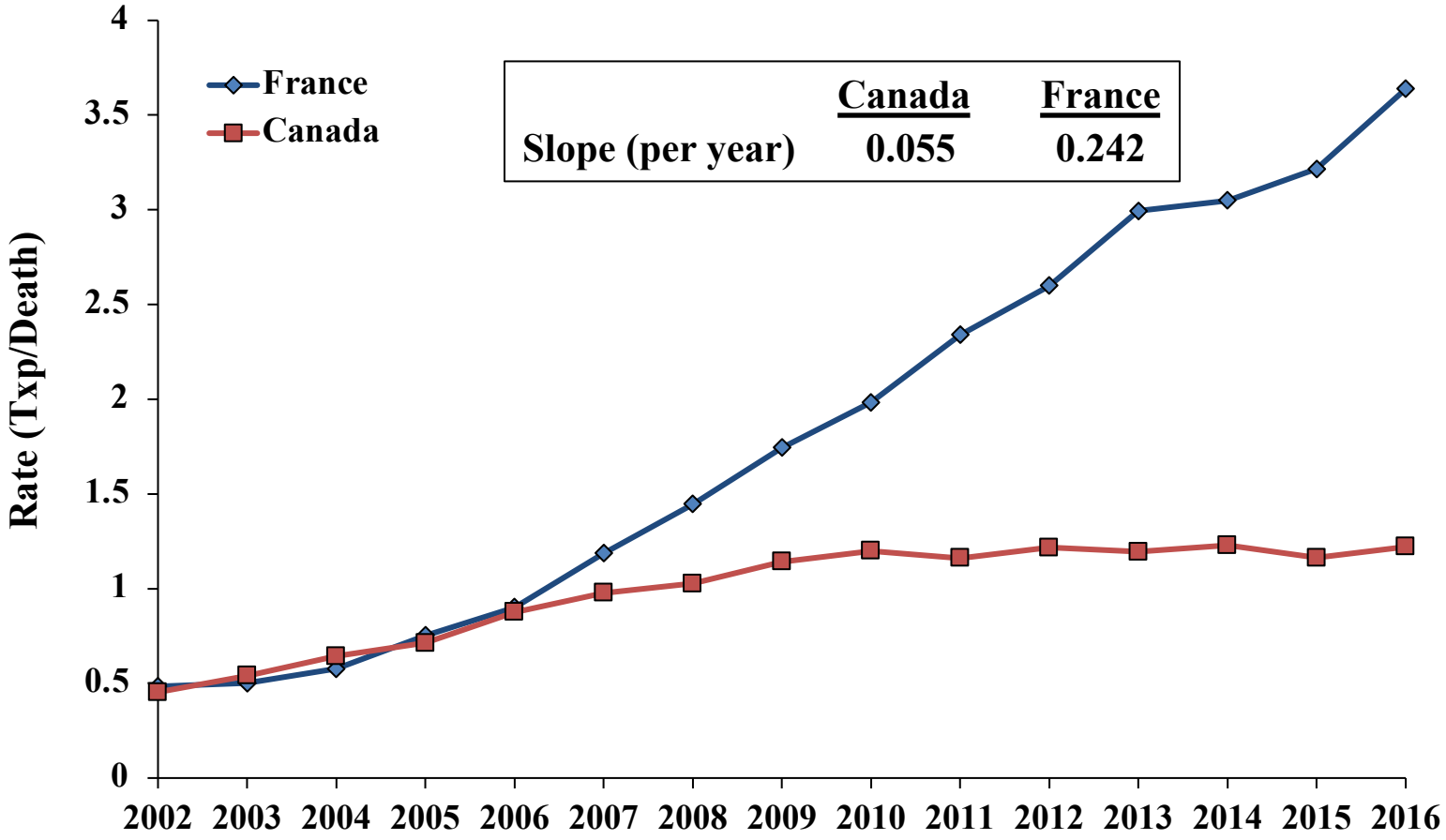
	France	Canada	P value	SMD
Total number of patients, n	8266	5451		
Sex				
Women, n (%)	3938 (47.6)	2544 (46.7)	0.273	1.9
Men, n (%)	4328 (52.4)	2907 (53.3)		
Genotype				
Phe508del homozygote, n (%)	3274 (39.6)	2557 (46.9)	< 0.001	14.8
Phe508del heterozygote, n (%)	3469 (42.0)	2140 (39.3)		5.5
Other, n (%)	1295 (15.7)	619 (11.4)		12.6
Missing, n (%)	228 (2.7)	135 (2.5)		1.8
Pancreatic status, ever/never				
Insufficient, n (%)	7048 (85.3)	4531 (83.1)	< 0.001	6.0
Sufficient, n (%)	1214 (14.7)	920 (16.9)		
Missing, n(%)	4 (0)	0 (0)		
CFRD, ever/never				
Yes, n (%)	2124 (25.7)	1393 (25.6)	0.262	0.4
No, n (%)	6138 (74.3)	4058 (74.4)		
Missing, n (%)	4 (0)	0 (0)		
Microbiology, ever/never				
P. aeruginosa, n (%)	5976 (72.5)	4076 (74.9)	0.002	5.5
B. cepacia complex, n (%)	430 (5.2)	564 (10.4)	< 0.001	19.3
Nbr Pulmonary Exacerbations/year				
0, n (%)	5369 (65.1)	3494 (64.2)	< 0.001	1.9
1-2, n (%)	1769 (21.5)	1436 (26.4)		11.6
≥ 3, n (%)	1107 (13.4)	512 (9.4)		12.7
Medication				
Feeding tube, n (%)	776 (9.4)	347 (6.4)	< 0.001	11.3
BiPAP, n (%) * as of 2011	534 (6.5)	69 (1.3)	< 0.001	27.2
Oxygen, n (%)	1415 (17.2)	607 (11.2)	< 0.001	17.3
ppFEV1	72.0 (40.5-94.6)	68.7 (40.3-92.7)	< 0.001	4.8
<40, n (%)	1604 (19.5)	1017 (18.7)	< 0.001	0.5
40-69, n (%)	1546 (18.8)	1104 (20.3)		7.4
≥70, n (%)	3405 (41.3)	1998 (36.7)		6.9
NA, n (%)	1690 (20.5)	1323 (24.3)		
BMI categories (adult and children)				
Underweight, n (%)	1919 (23.3)	733 (13.5)	< 0.001	26.3
Normal, n (%)	4869 (59.1)	3284 (60.3)		5.7
Overweight, n (%)	702 (8.5)	835 (15.3)		23.2
NA, n (%)	755 (9.2)	590 (10.8)		

Data are presented as Median (Interquartile range). ppFEV1 values were calculated using the GLI equations. * The last recorded clinical measurement (or most recent) within the study window was recorded for subjects who did not receive a transplant in order to reflect the current situation in case they have developed complications or have deteriorated overtime. For subject who received a transplant, we used the last recorded clinical data prior to transplant, BMI: body mass index, ppFEV1: percent predicted forced expiratory volume in 1 second, SMD: standard mean difference. P. aeruginosa: pseudomonas aeruginosa, B. cepacia complex: *Burkholderia cepacia* complex, BiPAP: bilevel positive airway pressure. P value was assessed using the Mann-Whitney test for continuous variables and the Chi-squared test for categorical variables.

Table 2: Deaths and transplants pre-high emergency lung transplantation (HELT) (2002-2006) and post-HELT (2008-2016) in Canada and France.

	Pre-HELT				Post-HELT			
	France	**Canada**	**SMD**	**P Value**	**France**	**Canada**	**SMD**	**P Value**
Total number of patients, n	5505	3908			7442	4929		
Number of transplants, n (%)	248 (4.5)	173 (4.4)	0.4	0.896	755 (10.1)	340 (6.9)	11.6	< 0.001
Pediatric, n(% of total transplants)	51 (20.6)	16 (9.2)	32.2	0.003	105 (13.9)	22 (6.5)	24.8	< 0.001
Adult, n(% of total transplants)	197 (79.4)	157 (90.8)			650 (86.1)	318 (93.5)		
Age at transplant (yrs)	24.9 (19.8-30.6)	27.5 (23.0-35.0)	41.6	< 0.001	26.7 (21.7-33.5)	29.6 (24.0-37.0)	29.2	< 0.001
Pediatric (yrs)	16.2 (13.1-18.1)	15.6 (13.7-17.9)	5.2	0.8	16.7 (14.7-17.9)	16.4 (13.1-17.8)	21.6	0.54
Adult (yrs)	26.5 (22.6-33.2)	28.5 (24.2-36.1)	30.7	0.011	28.4 (23.8-34.4)	30.2 (24.9-37.7)	21.6	0.002
Age at death (yrs)	21.8 (16.4-28.7)	26.1 (20.1-34.0)	40.2	< 0.001	25.9 (20.9-34.1)	30.5 (23.5-43.2)	30.8	< 0.001
Age at death after transplant (yrs)	23.6 (19.4-27.5)	27.3 (23.3-33.7)	56.8	0.022	25.4 (21.4-32.1)	30.5 (24.2-39.2)	57.5	< 0.001
Age at death without transplant (yrs)	21.6 (15.7-28.7)	25.6 (20.0-34.0)	38.2	< 0.001	27.3 (20.0-37.9)	30.6 (23.4-43.6)	18.7	0.0018
Number of deaths, n(%)	285 (5.2)	222 (5.7)	2.2	0.308	415 (5.6)	363 (7.4)	7.3	< 0.001
Death after transplant, n(% of total deaths)	42 (14.7)	29 (13.1)	0.2	1.000	178 (42.9)	81 (22.3)	5.3	0.005
Death without transplant, n(% of total deaths)	243 (85.3)	193 (86.9)	2.5	0.253	237 (57.1)	282 (77.7)	12.3	< 0.001

Data are presented as Median (Interquartile range). SMD: standard mean difference. P value was assessed using the Mann-Whitney test for continuous variables and the Chi-squared test for categorical variables.



France	Transplant (n)	118	130	153	200	227	268	298	326	341	379	408	440	439	434	422
	Death (n)	244	260	265	266	252	226	206	187	172	162	157	147	144	135	116
Canada	Transplant (n)	117	127	144	152	169	177	189	200	205	202	197	184	188	178	177
	Death (n)	258	235	224	213	193	181	184	175	171	174	162	154	153	153	145

Figure 1. Rate of transplant over death in Canada and France over the entire time period (2002-2016). The number of transplants to deaths as a ratio over time was calculated using a five-year rolling window. Death refers to deaths without a lung transplant. Txp: lung transplant.

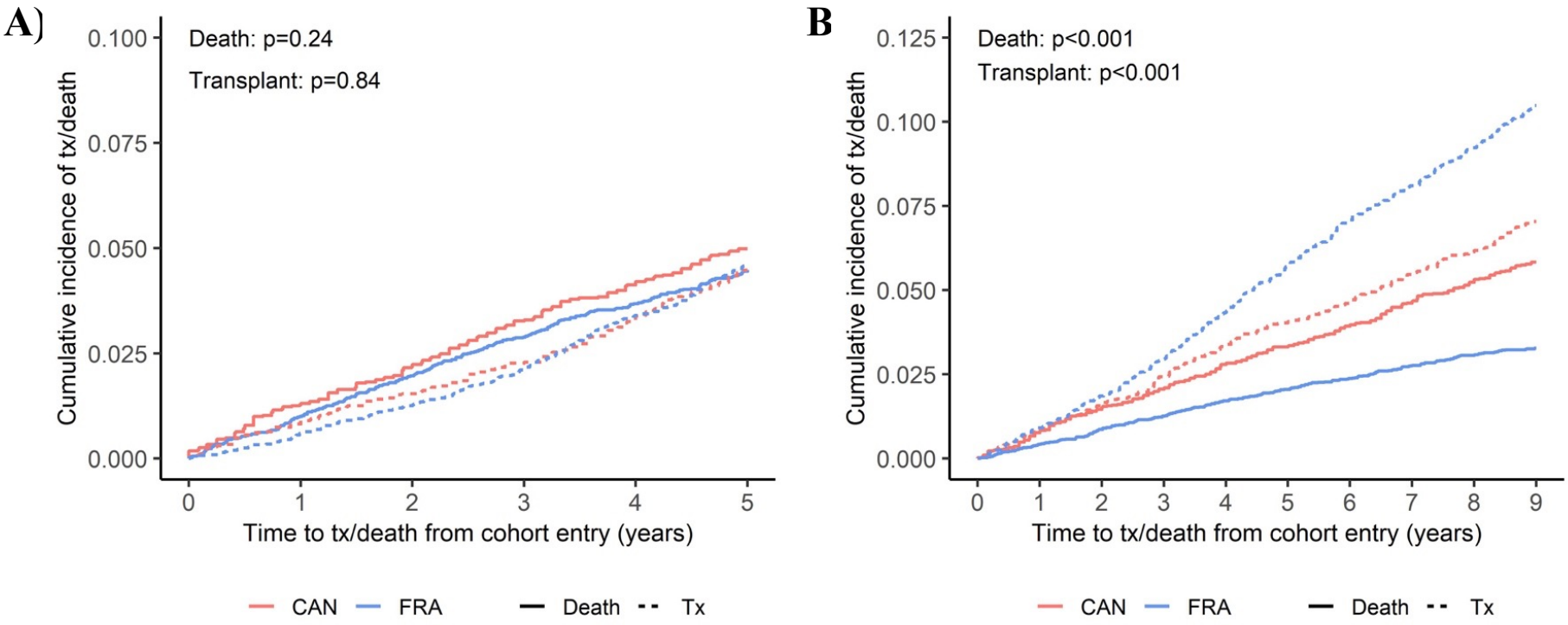


Figure 2. Competing risk analysis of receiving lung transplant or death without lung transplant a) pre-high emergency lung transplantation (HELT, 2002-2006) and b) post-HELT (2008-2016) program in France and Canada. Tx: transplant, CAN: Canada, FRA: France. Death refers to deaths without a lung transplant.

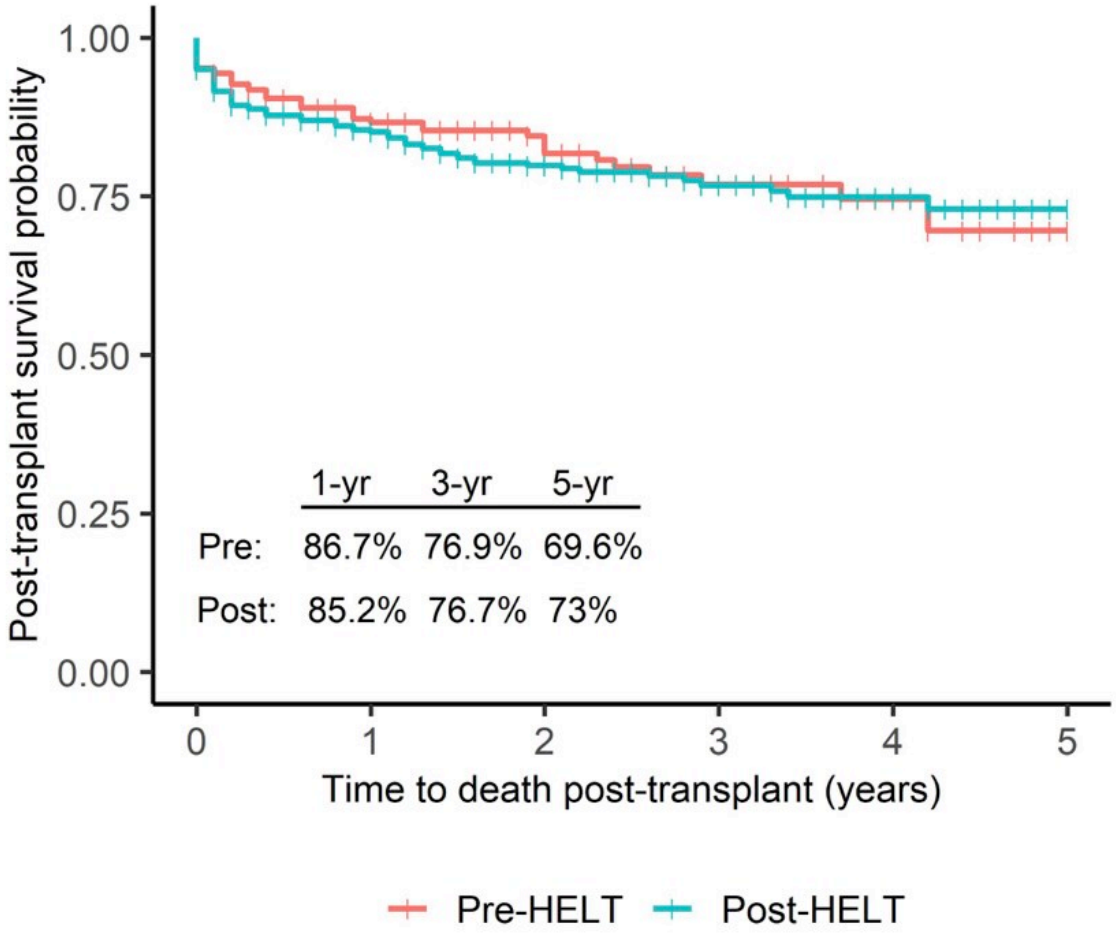


Figure 3. Post-transplant survival pre-high emergency lung transplantation (HELT) (2002-2006) and post-HELT (2008-2012) program in France using 5 years of follow-up.

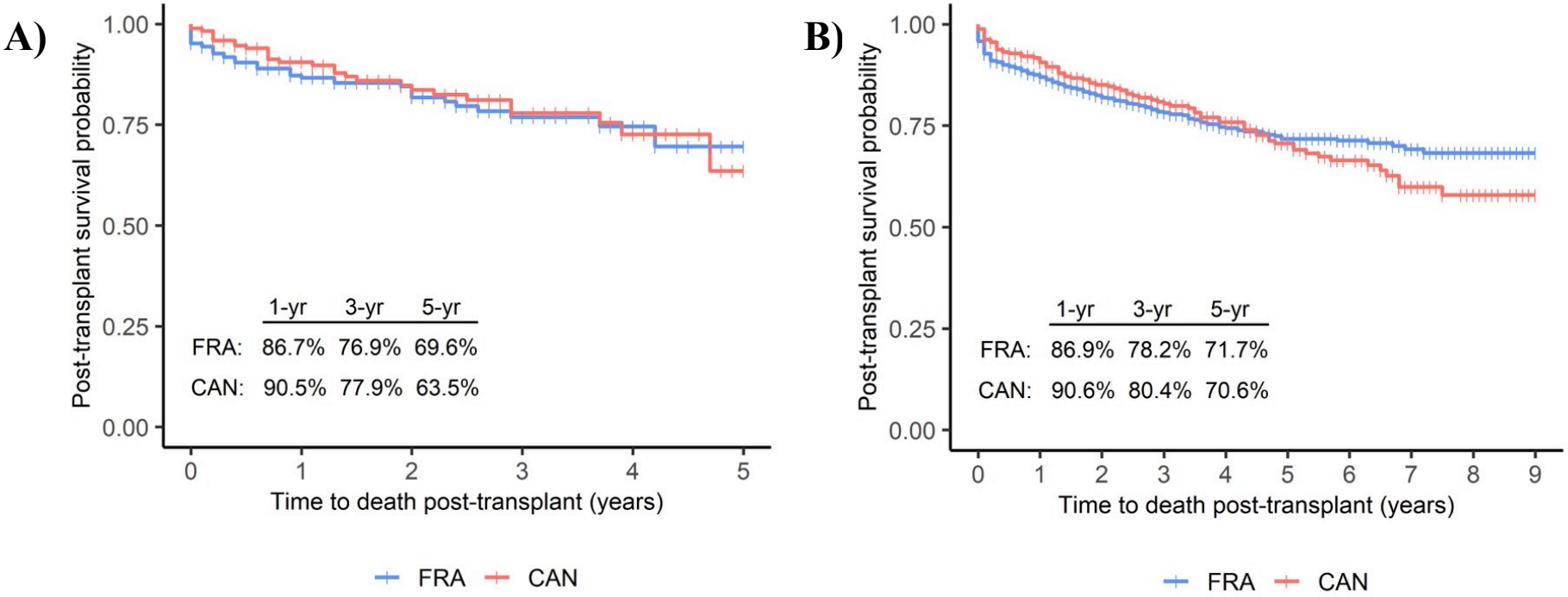


Figure 4. Post-transplant survival of CF patients in Canada and France A) pre-high emergency lung transplantation (HELT) (2002-2006) and B) post-HELT (2008-2016).

Data Supplement

The Impact of the High Emergency Lung Transplantation program in Cystic Fibrosis in France: insight from a comparison with Canada

Adèle Coriati, Jenna Sykes, Lydie Lemonnier, Xiayi Ma, Sanja Stanojevic, Clémence Dehillotte, Nicolas Carlier, Anne L. Stephenson, Pierre-Régis Burgel

Registry Variables

Variables in the FCFR and CCFR were harmonized. The most recent measurements within the study window, including both the transplanted and non-transplanted patients, were summarized in both countries. The CCFR started recording BiPAP since 2011; therefore proportions are calculated as of 2011 for both France and Canada for this variable.

Transplant programs

There are a total of 4 transplant programs in Canada, 2 of which also do pediatric transplants. It is estimated that between 50-60% of Canadian transplants are done at the Toronto transplant center. In France, there are 10 lung transplant programs. Contrary to France, Canada does not have a national, standardized priority allocation system for listed patients. However, center-specific medical priority drives transplant allocation where the sickest patients are the highest priority [1]. In Canada, patients with CF < 18 years of age are prioritized for lung allocation in the same way as adults. However in France, children with CF < 18 years of age have national priority over adults with CF.

Additional Tables Referenced in the Text

Table 1S. Deaths and transplants in Canada and France (2002-2016).

	France	Canada	P value	SMD
Total number of patients, n	8266	5451		
Number of deaths, n(%)	826 (10.0)	692 (12.7)	< 0.001	8.5
Death after transplant				
Yes, n (% of total deaths)	314 (38.0)	180 (26.0)	0.139	2.7
No, n (% of total deaths)	512 (62.0)	512 (74.0)	< 0.001	12.0
Age at death (yrs)	24.7 (19.4-32.2)	28.9 (22.3-39.2)	< 0.001	32.7
Age at death with transplant (yrs)	25.9 (21.2-32.3)	30.5 (24.4-39.3)	< 0.001	50.0
Age at death without transplant (yrs)	23.5 (18.0-32.1)	28.2 (21.3-39.0)	< 0.001	28.6
Number of transplants, n (%)	1075 (13.0)	555 (10.2)		8.8
Pediatric, n (% of total transplants)	174 (16.2)	43 (7.7)	< 0.001	26.2
Adult, n (% of total transplants)	901 (83.8)	512 (93.3)		26.2
Age at transplant (yrs)	26.1 (20.9-32.9)	28.6 (23.7-36.2)	< 0.001	31.0
Pediatric (years)	16.5 (14.1-18.0)	15.9 (13.2-17.9)	0.619	8.4
Adult (years)	28.1 (23.6-34.0)	29.8 (24.8-36.2)	< 0.001	22.1

Data are presented as Median (Interquartile range). SMD: standard mean difference. P value was assessed using the Mann-Whitney test for continuous variables and the Chi-squared test for categorical variables.

Table 2S. Characteristics of all patients (with and without a lung transplant) pre-high emergency lung transplantation (HELT) (2002-2006) and post-HELT (2008-2016) at the most recent measurement of study window and are censored at date of transplant in Canada and France.

	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
	France	**Canada**	**SMD**	**P Value**	**France**	**Canada**	**SMD**	**P Value**
Total number of patients, n	5505	3908			7442	4929		
Sex								
Women, n(%)	2633 (47.8)	1818 (46.5)	2.6	0.218	3525 (47.4)	2288 (46.4)	1.9	0.310
Men, n(%)	2872 (52.2)	2090 (53.5)			3917 (52.6)	2641 (53.6)		
Genotype								
Phe508del homozygote, n(%)	2409 (43.8)	1981 (50.7)	13.9	< 0.001	2959 (39.8)	2305 (46.8)	14.2	< 0.001
Phe508del heterozygote, n(%)	2213 (40.2)	1466 (37.5)	5.5		3147 (42.3)	1966 (39.9)	4.9	
Other, n(%)	750 (13.6)	392 (10.0)	11.1		1181 (15.9)	565 (11.5)	12.9	
Missing, n(%)	133 (2.4)	69 (1.8)	4.5		155 (2.1)	93 (1.9)	1.4	
Pancreatic status, ever/never								
Insufficient, n(%)	5077 (92.2)	3460 (88.5)	12.6	< 0.001	6373 (85.6)	4073 (82.6)	8.3	< 0.001
Sufficient, n(%)	427 (7.8)	448 (11.5)			1066 (14.3)	856 (17.4)		
NA, n(%)	1 (0)	0 (0)			3 (0)	0 (0)		
CFRD, ever/never								
Yes, n(%)	844 (15.3)	602 (15.4)	0.2	0.698	1760 (23.7)	1150 (23.3)	0.8	0.339
No, n(%)	4660 (84.7)	3306 (84.6)			5679 (76.3)	3779 (76.7)		
NA, n(%)	1 (0.0)	0 (0)			3 (0.0)	0 (0)		
Microbiology, ever/never								
P. aeruginosa, n(%)	3435 (62.4)	2702 (69.2)	14.3	< 0.001	5174 (69.6)	3531 (71.6)	4.6	0.014
B. *cepacia* complex, n(%)	196 (3.6)	300 (7.7)	18.0	< 0.001	332 (4.5)	450 (9.1)	18.6	< 0.001
Nbr Pulmonary Exacerbations/year								
0, n(%)	3939 (71.6)	2813 (72.1)	1.1	< 0.001	5049 (68.0)	3305 (67.2)	1.8	< 0.001
1-2, n(%)	1072 (19.5)	862 (22.1)	6.4		1542 (20.7)	1232 (25.0)	10.2	
≥ 3, n(%)	488 (8.9)	226 (5.8)	11.8		837 (11.3)	385 (7.8)	11.7	
Medication								
Feeding tube, n(%)	408 (7.4)	172 (4.4)	12.8	< 0.001	569 (7.7)	265 (5.4)	9.2	< 0.001
BiPAP, n(%)* as of 2011	-	-	-	-	535 (7.2)	69 (1.4)	28.9	< 0.001
Oxygen, n(%)	615 (11.2)	219 (5.6)	20.2	< 0.001	943 (12.7)	419 (8.5)	13.6	< 0.001
ppFEV1	67.7 (42.0-89.6)	71.2 (48.2-89.9)	10.5	< 0.001	75.3 (46.6-95.8)	72.1 (45.9-94.0)	4.7	< 0.001
<40, n(%)	872 (15.9)	520 (13.3)	13.5	< 0.001	1193 (16.1)	760 (15.4)	0.1	0.002
40-69, n(%)	1132 (20.6)	928 (23.8)	3.3		1487 (20.0)	1060 (21.5)	6.9	
≥70, n(%)	1789 (32.5)	1510 (38.7)	7.8		3300 (44.4)	1979 (40.2)	6.2	
NA, n(%)	1706 (31.0)	943 (24.2)			1448 (19.5)	1123 (22.8)		

	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
BMI categories (adult and children)								
Underweight, n(%)	1443 (26.2)	542 (13.9)	37.2	< 0.001	1562 (21.0)	614 (12.4)	24.3	< 0.001
Normal, n(%)	3003 (54.6)	2524 (64.7)	15.6		4567 (61.5)	3075 (62.5)	2.4	
Overweight, n(%)	274 (5.0)	494 (12.7)	27.3		665 (9.0)	811 (16.5)	24.0	
NA, n(%)	779 (14.2)	341 (8.7)			634 (8.5)	422 (8.6)		

Data are presented as Median (Interquartile range). FEV1 percent predicted values were calculated using the GLI equations HELT: high emergency lung transplantation, CFRD: cystic fibrosis-related diabetes, BMI: body mass index, ppFEV1: percent predicted forced expiratory volume in 1 second, SMD: standard mean difference. P. aeruginosa: pseudomonas aeruginosa, B. cepacia complex: burkholderia *cepacia complex*, BiPAP: bilevel positive airway pressure. P value was assessed using the Mann-Whitney test for continuous variables and the Chi-squared test for categorical variables.

Table 3S. Competing risk regression model, analysis for receiving a lung transplant or death (without a lung transplant), for pre-HELT (2002-2006) and post-HELT (2008-2016) program.

The competing risk regression models were used to estimate the subdistribution hazard of receiving a transplant or dying by country after adjusting for gender, age at diagnosis, pancreatic status, genotype, and the following information at the time of entry into the cohort: patient age, BMI, infection with B. *cepacia*, CFRD, the number of pulmonary exacerbations in a year and ppFEV$_1$.

	Transplant				**Death**			
	Pre-HELT		**Post-HELT**		**Pre-HELT**		**Post-HELT**	
Variables	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**
Country (France vs Canada)	1.08 (0.89-1.32)	0.44	1.56 (1.37-1.77)	<0.001	0.99 (0.81-1.21)	0.91	0.55 (0.46-0.66)	<0.001
Gender (men vs women)	1.19 (0.98-1.45)	0.08	1.15 (1.02-1.29)	0.03	1.29 (1.05-1.57)	0.01	1.28 (1.07-1.53)	0.01
Age at diagnosis (≥2 yrs)	0.88 (0.71-1.09)	0.23	0.82 (0.72-0.94)	0.004	0.72 (0.58-0.9)	0.004	1.07 (0.89-1.3)	0.45
Pancreatic Status (PI vs PS)	3.68 (1.96-6.89)	<0.001	7.11 (4.75-10.66)	<0.001	1.51 (0.99-2.31)	0.05	1.76 (1.27-2.44)	<0.001
B *cepacia* complex	1.97 (1.45-2.69)	<0.001	1.21 (0.98-1.51)	0.08	3.41 (2.63-4.43)	<0.001	2.91 (2.29-3.68)	<0.001
CFRD	9.13 (7.42-11.23)	<0.001	10.4 (9.01-12.01)	<0.001	2.73 (2.23-3.36)	<0.001	2.31 (1.93-2.77)	<0.001
Heterozygote vs Homozygote	0.63 (0.5-0.78)	<0.001	0.62 (0.55-0.71)	<0.001	0.93 (0.75-0.1.16)	0.54	0.85 (0.7-1.04)	0.11
Other vs Homozygote	0.46 (0.31-0.69)	<0.001	0.57 (0.47-0.7)	<0.001	0.95 (0.68-1.33)	0.76	0.77 (0.57-1.03)	0.08
Age	1.04 (1.04-1.05)	<0.001	1.03 (1.03-1.03)	<0.001	1.03 (1.03-1.04)	<0.001	1.05 (1.04-1.05)	<0.001
Overweight vs Normal	0.5 (0.29-0.88)	0.02	0.42 (0.3-0.58)	<0.001	0.72 (0.44-1.16)	0.18	0.89 (0.64-1.25)	0.51
Underweight vs Normal	2.81 (2.3-3.44)	<0.001	2.91 (2.57-3.3)	<0.001	2.85 (2.32-3.49)	<0.001	2.18 (1.8-2.65)	<0.001
percent predicted FEV$_1$	0.92 (0.92-0.93)	<0.001	0.93 (0.93-0.94)	<0.001	0.95 (0.94-0.95)	<0.001	0.96 (0.95-0.96)	<0.001
PEx/year	1.37 (1.31-1.44)	<0.001	1.29 (1.2-1.39)	<0.001	1.38 (1.32-1.45)	<0.001	1.26 (1.18-1.35)	<0.001

HELT: high emergency lung transplantation, CFRD: Cystic fibrosis related diabetes, FEV_1: forced expiratory volume in 1 second, PI: pancreatic insufficient, PS: pancreatic sufficient, PEx: pulmonary exacerbation.

Table 4S. Characteristics of patients who received a lung transplant pre-high emergency lung transplantation (HELT) (2002-2006) and post-HELT (2008-2016) as most recent value 3 years prior to transplant in Canada and France.

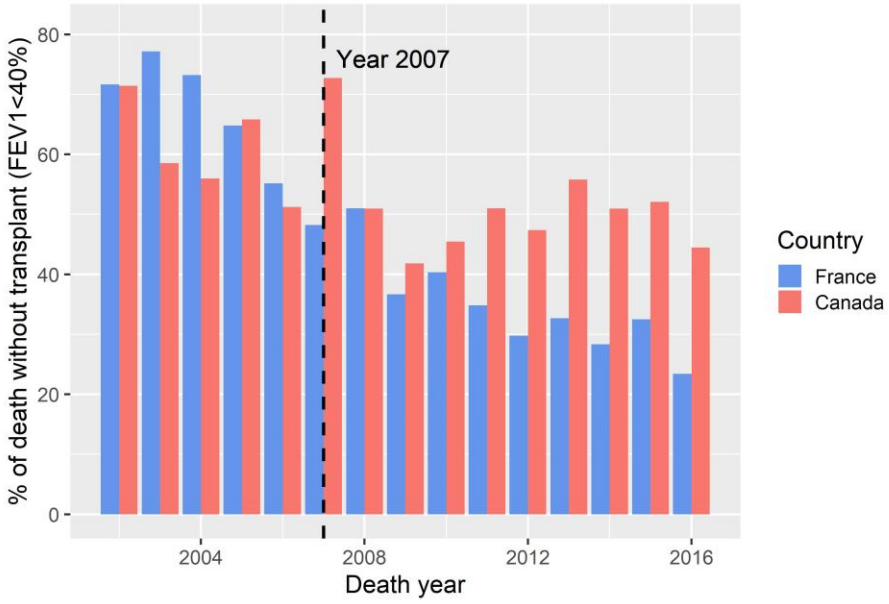
	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
	France	**Canada**	**SMD**	**P Value**	**France**	**Canada**	**SMD**	**P Value**
Total number of patients, n	248	173			755	340		
Pediatric, n(%)	51 (20.6)	16 (9.2)	32.2	0.003	105 (13.9)	22 (6.5)	24.8	< 0.001
Adult, n(%)	197 (79.4)	157 (90.8)			650 (86.1)	318 (93.5)		
Sex								
Women, n(%)	133 (53.6)	83 (48.0)	11.3	0.297	387 (51.3)	165 (48.5)	5.5	0.441
Men, n(%)	115 (46.4)	90 (52.0)			368 (48.7)	175 (51.5)		
Genotype								
Phe508del homozygote, n(%)	140 (56.5)	108 (62.4)	12.2	0.181	404 (53.5)	204 (60.0)	13.1	0.188
Phe508del heterozygote, n(%)	78 (31.4)	52 (30.0)	3.0		266 (35.2)	100 (29.4)	12.5	
Other, n(%)	25 (10.1)	8 (4.6)	21.0		79 (10.5)	32 (9.4)	3.5	
Missing, n(%)	5 (2.0)	5 (2.9)	5.7		6 (0.8)	4 (1.2)	3.9	
Pancreatic status, ever/never								
Insufficient, n(%)	244 (98.4)	165 (95.4)	17.4	0.126	746 (98.8)	324 (95.3)	20.9	< 0.001
Sufficient, n(%)	4 (1.6)	8 (4.6)			9 (1.2)	16 (4.7)		
CFRD, ever/never								
Yes, n(%)	133 (53.6)	76 (43.9)	19.5	0.063	454 (60.1)	169 (49.7)	21.1	0.002
No, n(%)	115 (46.4)	97 (56.1)			301 (39.9)	1711 (50.3)		
Microbiology, ever/never								
P. aeruginosa, n(%)	236 (95.2)	160 (92.5)	11.1	0.351	737 (97.6)	330 (97.1)	3.5	0.739
B. *cepacia* complex, n(%)	28 (11.3)	29 (16.8)	15.8	0.142	61 (8.1)	57 (16.8)	26.6	< 0.001
Nbr Pulmonary Exacerbations/year								
0, n(%)	36 (15.3)	30 (18.0)	7.3	< 0.001	95 (12.8)	73 (21.7)	23.6	< 0.001
1-2, n(%)	79 (33.5)	85 (50.9)	35.8		236 (31.8)	147 (43.6)	24.5	
≥ 3, n(%)	121 (51.3)	52 (31.1)	41.8		410 (55.3)	117 (34.7)	42.3	
Medication								
Feeding tube, n(%)	83 (35.2)	39 (23.4)	26.2	0.015	234 (31.6)	67 (19.9)	27.0	< 0.001
BiPAP, n(%)* as of 2011	-	-	-	-	263 (35.5)	38 (11.3)	59.7	< 0.001
Oxygen, n(%)	201 (85.2)	103 (61.7)	55.2	< 0.001	571 (77.1)	222 (65.9)	25.0	< 0.001

	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
	France	**Canada**	**SMD**	**P Value**	**France**	**Canada**	**SMD**	**P Value**
ppFEV1	21.7 (17.6-27.9)	23.3 (19.6-29.7)	6.5	0.131	26.0 (20.9-33.2)	25.1 (20.4-30.5)	23.3	0.039
<40, n(%)	186 (78.8)	138 (82.6)	32.6	0.019	610 (82.3)	273 (81.0)	22.3	0.009
40-69, n(%)	12 (5.1)	2 (1.2)	24.0		74 (10.0)	16 (4.7)	18.9	
≥70, n(%)	5 (2.1)	0 (0)	22.5		11 (1.5)	1 (0.3)	12.7	
NA, n(%)	33 (14.0)	27 (16.2)			46 (6.2)	47 (14.0)		
BMI categories, (adult and children)								
Underweight, n(%)	141 (59.7)	41 (24.6)	62.4	< 0.001	396 (53.4)	96 (28.5)	47.3	< 0.001
Normal, n(%)	84 (35.6)	97 (58.1)	20.1		319 (43.0)	184 (54.6)	34.7	
Overweight, n(%)	4 (1.7)	8 (4.8)	71.5		9 (1.2)	21 (6.2)	29.2	
NA, n(%)	7 (3.0)	21 (12.6)			17 (2.43)	36 (10.7)		

Data are presented as Median (Interquartile range. FEV1 predicted values were calculated using the GLI equations. HELT: high emergency lung transplantation, CFRD: cystic fibrosis-related diabetes, BMI: body mass index, ppFEV1: percent predicted forced expiratory volume in 1 second, SMD: standard mean difference, P. aeruginosa: pseudomonas aeruginosa, B. cepacia complex: burkholderia *cepacia complex*, BiPAP: bilevel positive airway pressure. P value was assessed using the Mann-Whitney test for continuous variables and the Chi-squared test for categorical variables.

Additional Figure Referenced in the text

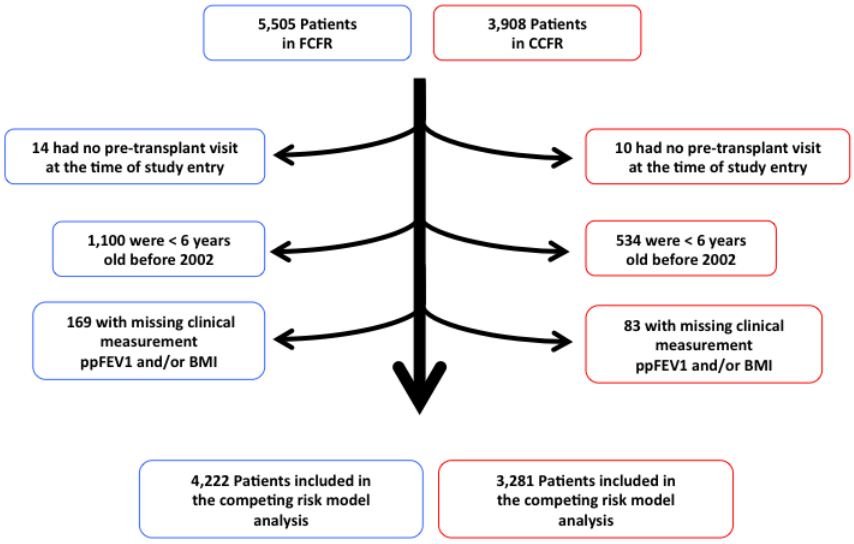
Figure 1S. Proportion of deaths in French and Canadian CF patients with low lung function (FEV_1<40%) who did not received a lung transplant throughout the study period (2002-2016).



Footnote: Year 2007 is the year that the high emergency lung transplant program was implemented in France. FEV_1: forced expiratory volume in 1 second.

Figure 2S. Patient selection from the French (FCFR) and Canadian (CCFR) CF registries for the competing risk analysis in the A) pre-HELT (2002-2006) and the B) post-HELT (2008-2016) periods. HELT: high emergency transplantation, BMI: body mass index, ppFEV1: percent predicted forced expiratory volume in 1 sec.

A)



B)

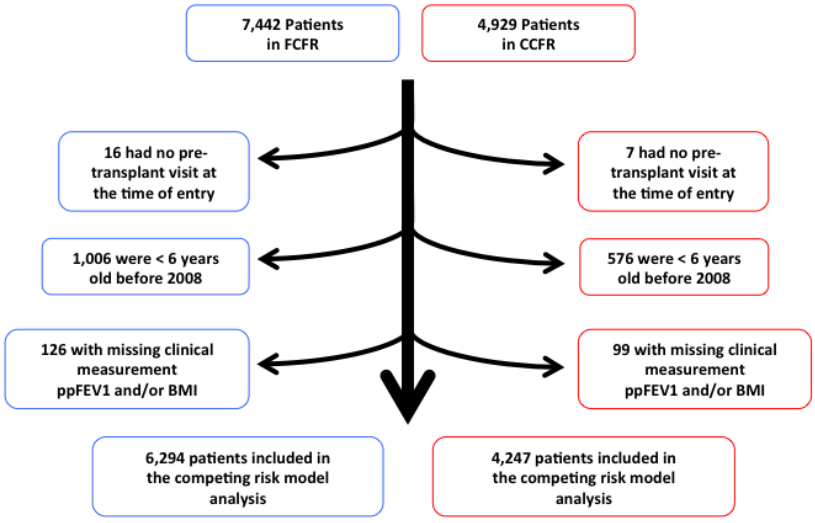
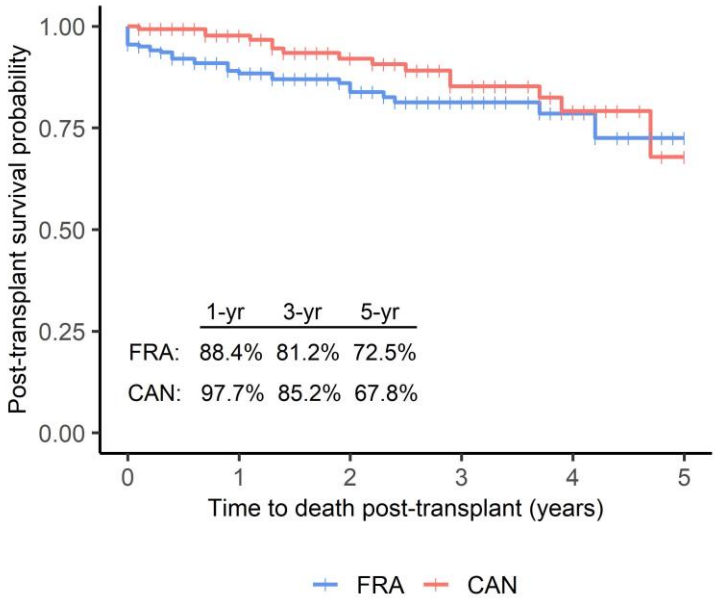
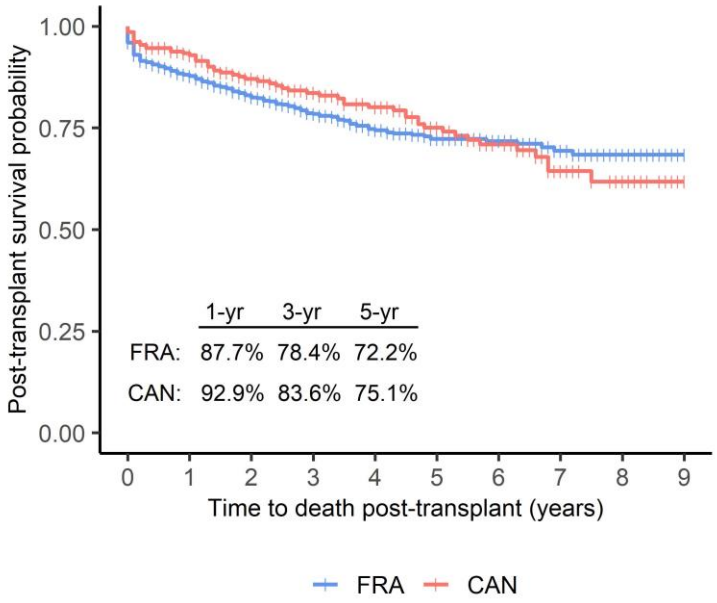


Figure 3S. Post-transplant survival of CF patients without B. *cepacia* complex in Canada and France A) pre-HELT (2002-2006) and B) post-HELT (2008-2016) program. HELT: high emergency lung transplantation.

A)



B)



References

1. Yeung JC, Machuca TN, Chaparro C, Cypel M, Stephenson AL, Solomon M, Saito T, Binnie M, Chow CW, Grasemann H, Pierre AF, Yasufuku K, de Perrot M, Donahoe LL, Tikkanen J, Martinu T, Waddell TK, Tullis E, Singer LG, Keshavjee S. Lung transplantation for cystic fibrosis. J Heart Lung Transplant. 2020;39(6):553-60.