Impact of a high emergency lung transplantation programme for cystic fibrosis in France: insight from a comparison with Canada

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A high emergency lung transplantation programme in the French cystic fibrosis population led to an increased number of lung transplants. Post-transplant survival was not changed despite sicker patients being transplanted and was comparable to Canada. https://bit.ly/2ScK7vv

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Abstract

Background France implemented a high emergency lung transplantation (HELT) programme nationally in 2007. A similar programme 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 programme in a population with cystic fibrosis (CF).

Methods This population-based cohort study utilised 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 transplants increased in France after the HELT programme was initiated (4.5% *versus* 10.1%), whereas deaths pre-transplant decreased from 85.3% in the pre-HELT period to 57.1% in the post-HELT period. Between 2008 and 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 with Canada. Post-transplant survival was similar between the countries, and there was no difference in survival when comparing pre- and post-HELT periods in France.

Conclusions Following the implementation of the HELT programme, 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 with the pre-HELT period, despite potentially sicker patients being transplanted, and was 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, prioritisation 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) programme at a national level in July

2007, which prioritised critically ill patients on the transplant waiting list based on specific criteria [5, 6]. The HELT programme is a dedicated national emergency programme 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. The programme prioritises patients with the highest need and this ultimately results in a transplant for the vast majority of people soon after being enrolled in the programme. The overall purpose of the HELT programme is to avoid mortality in those at highest risk of death within 2 weeks. Once the person is enrolled in the programme, the application is systematically reviewed and approved by two experts, and the patient is listed in the programme for 8 days, which can be renewed once. For people with CF, those requiring invasive ventilation and/or extracorporeal membrane oxygenation (ECMO) or patients at high risk for intubation (*e.g.* on noninvasive ventilation >18 h per day for at least 3 days with arterial carbon dioxide tension >80 mmHg) are potential candidates for the HELT programme.

Initial studies suggested the HELT programme resulted in fewer deaths on the waiting list; however, these reports included people with various underlying diseases [5, 7]. Therefore, the impact of the HELT programme on the CF population has yet to be established. Furthermore, outcomes in the CF population continue to improve, regardless of transplant, and therefore analysis of temporal trends within a country may not measure the true impact of a given programme. France and Canada have well-established CF registries, they both provide universal government-funded healthcare, and the registries also contain data post-transplantation. In addition, the demographics of the two CF populations have been shown to be comparable [8]. Although Canada does prioritise the sickest patients, there is no universal and systematic programme, 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 programme in the CF population. To account for medical advances in CF care that occurred during this period, we compared similar metrics between France and Canada over the same timeframe. We hypothesised that the HELT programme would result in 1) proportionally more lung transplants in France with fewer deaths without transplant compared with Canada, and 2) lower post-transplant survival in France after implementation of the HELT programme since patients in this programme are sicker at the time of lung transplantation.

Materials and methods

Design

This population-based cohort study utilised data from two longitudinal national CF registries: the French CF Registry and the Canadian CF Registry.

Study period

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

Data resources

The French CF Registry, managed by Vaincre la Mucoviscidose (Paris, France), was established in 1992 and follows patients with CF from 47 CF centres. It is estimated that >95% of the French CF population is captured within the registry, with a low rate of loss to follow-up (<3%) [9]. The Canadian CF Registry, established in the early 1970s, is managed by CF Canada (Toronto, ON, 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 loss 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. Research ethics board approval for this study has been obtained from Unity Health Toronto (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 ethics statement [12].

Variable definitions

The most recent clinical measurements up to 3 years before lung transplant were summarised to compare lung transplant recipients in both countries. Body mass index (BMI) was calculated using the World Health Organization guidelines for adults [13]; US Centers for Disease Control and Prevention growth charts were used to calculate BMI centiles for children [14]. Patients were categorised as underweight (BMI <19 $kg \cdot m^{-2}$ or BMI% ⩽12%), overweight (BMI >24.9 $kg \cdot m^{-2}$ or BMI% ⩾85%) or normal (BMI between ⩾19 and ⩽24.9 $kg \cdot m^{-2}$ or BMI% between >12% and <85%). The presence of *Burkholderia cepacia* complex or *Pseudomonas aeruginosa* was 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 was based on CF guidelines [15]. Therapies such as feeding tube, bilevel positive airway pressure and supplemental oxygen were recorded if administered during the reported year. A pulmonary exacerbation was defined as the administration of intravenous antibiotic in the hospital and/or at home. Forced expiratory volume in 1 s (FEV_1) % predicted was calculated using Global Lung Function Initiative reference equations [16]. 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 (interquartile range) was used to summarise continuous variables and frequency (proportion) was used to summarise categorical variables. The standardised mean difference (SMD) was calculated to assess the difference between the two countries and SMD >10 was interpreted as a relevant difference [17, 18]. 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 5-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 programme between France and Canada.

Time to lung transplant with death without transplant as a competing risk was modelled using Fine–Gray cumulative incidence curves in the pre-HELT (2002–2006) and post-HELT (2008–2016) periods and compared using Gray's test. Data were left truncated at 1 January in the first year of each study window unless born or diagnosed with CF within the window. Competing risks regression models were used to estimate the subdistribution hazard of receiving a transplant or dying after adjusting for sex, age at diagnosis, pancreatic status and genotype, in addition to the following variables measured at the time of entry into the cohort: patient age, BMI, infection with *B. cepacia*, CF-related diabetes, number of pulmonary exacerbations in a year and FEV_1 % pred.

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 the 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 analyses were performed using R version 3.4.3 [19]. 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 French CF Registry compared with 692 (12.7%) deaths and 555 (10.2%) lung transplants in the Canadian CF Registry (supplementary table S1). 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 categorised as normal or overweight were higher in Canada compared with France (table 1).

Pre- and post-HELT lung transplants and deaths

Characteristics of all patients (with and without a lung transplant) for the pre- and post-HELT periods are summarised in supplementary table S2. Table 2 summarises 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 programme was initiated (4.5% pre-HELT compared with 10.1% post-HELT). A higher proportion of lung transplants was done in paediatric patients in France compared with Canada in both time periods (table 2). The proportion of deaths without transplant decreased in France between the two time periods (85.3% *versus* 57.1%). Comparing France and Canada, a similar proportion of deaths without transplant was seen in the pre-HELT period (85.3% *versus* 86.9%; p=0.25); however, in the post-HELT period the proportion of deaths without transplant for France decreased to

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
Patients	8266	5451		
Sex				
Women	3938 (47.6)	2544 (46.7)	0.273	1.9
Men	4328 (52.4)	2907 (53.3)		
Genotype				
Phe508del homozygous	3274 (39.6)	2557 (46.9)	<0.001	14.8
Phe508del heterozygous	3469 (42.0)	2140 (39.3)		5.5
Other	1295 (15.7)	619 (11.4)		12.6
Missing	228 (2.7)	135 (2.5)		1.8
Pancreatic status (ever/never)				
Insufficient	7048 (85.3)	4531 (83.1)	<0.001	6.0
Sufficient	1214 (14.7)	920 (16.9)		
Missing	4 (0)	0 (0)		
CFRD (ever/never)				
Yes	2124 (25.7)	1393 (25.6)	0.262	0.4
No	6138 (74.3)	4058 (74.4)		
Missing	4 (0)	0 (0)		
Microbiology (ever/never)				
Pseudomonas aeruginosa	5976 (72.5)	4076 (74.9)	0.002	5.5
Burkholderia cepacia complex	430 (5.2)	564 (10.4)	<0.001	19.3
Pulmonary exacerbations per year				
0	5369 (65.1)	3494 (64.2)	<0.001	1.9
1–2	1769 (21.5)	1436 (26.4)		11.6
⩾3	1107 (13.4)	512 (9.4)		12.7
Medication				
Feeding tube	776 (9.4)	347 (6.4)	<0.001	11.3
BiPAP (as of 2011)	534 (6.5)	69 (1.3)	<0.001	27.2
Oxygen	1415 (17.2)	607 (11.2)	<0.001	17.3
FEV_1 (% pred)[¶]	72.0 (40.5–94.6)	68.7 (40.3–92.7)	<0.001	
<40	1604 (19.5)	1017 (18.7)	<0.001	4.8
40–69	1546 (18.8)	1104 (20.3)		0.5
⩾70	3405 (41.3)	1998 (36.7)		7.4
Not available	1690 (20.5)	1323 (24.3)		6.9
BMI categories (adult and children)				
Underweight	1919 (23.3)	733 (13.5)	<0.001	26.3
Normal	4869 (59.1)	3284 (60.3)		5.7
Overweight	702 (8.5)	835 (15.3)		23.2
Not available	755 (9.2)	590 (10.8)		

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. CFRD: cystic fibrosis-related diabetes; BiPAP: bilevel positive airway pressure; FEV_1: forced expiratory volume in 1 s; BMI: body mass index; SMD: standardised mean difference. [#]: 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 had developed complications or deteriorated overtime. For subject who received a transplant, we used the last recorded clinical data prior to transplant. [¶]: FEV_1 % pred values were calculated using the Global Lung Function Initiative reference equations [16]. p-value assessed using the Mann–Whitney test for continuous variables and the Chi-squared test for categorical variables.

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 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 with France (13.1% to 22.3%, which represented a 1.7 times increase).

The ratio of lung transplants to pre-transplant deaths increased at a higher rate in France compared with Canada (0.24 *versus* 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 *versus* 0.643 for France; p=0.99) (figure 1). Using a difference-in-difference analysis, this ratio significantly increased for France compared with Canada after 2007 (difference in ratio between France

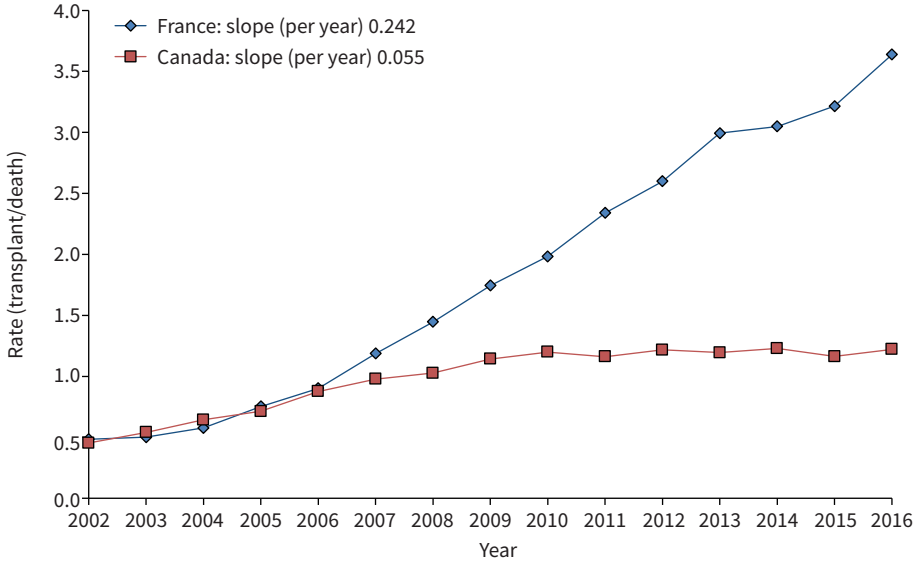
TABLE 2 Deaths and transplants pre-high emergency lung transplantation (HELT) (2002–2006) and post-HELT (2008–2016) in Canada and France

	Pre-HELT				Post-HELT			
	France	Canada	SMD	p-value	France	Canada	SMD	p-value
Patients	5505	3908			7442	4929		
Transplants	248 (4.5)	173 (4.4)	0.4	0.896	755 (10.1)	340 (6.9)	11.6	<0.001
Paediatric	51 (20.6)	16 (9.2)	32.2	0.003	105 (13.9)	22 (6.5)	24.8	<0.001
Adult	197 (79.4)	157 (90.8)			650 (86.1)	318 (93.5)		
Age at transplant (years)	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
Paediatric	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	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 (years)	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
After transplant	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
Without transplant	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
Deaths	285 (5.2)	222 (5.7)	2.2	0.308	415 (5.6)	363 (7.4)	7.3	<0.001
After transplant	42 (14.7)	29 (13.1)	0.2	1.000	178 (42.9)	81 (22.3)	5.3	0.005
Without transplant	243 (85.3)	193 (86.9)	2.5	0.253	237 (57.1)	282 (77.7)	12.3	<0.001

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. SMD: standardised mean difference. p-value assessed using the Mann–Whitney test for continuous variables and the Chi-squared test for categorical variables.

and Canada post-HELT relative to the difference in ratio 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 period, a decrease in the proportion of deaths without transplant in those with advanced lung disease (FEV_1 <40% predicted) was observed in France, whereas the proportions of deaths in Canada remained stable (supplementary figure S1).

The subset of patients included in the competing risk analysis is described in supplementary figure S2. Patients were more likely to die without a transplant in both Canada and France in the pre-HELT period



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
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 lung 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 5-year rolling window. Death refers to deaths without a lung transplant.

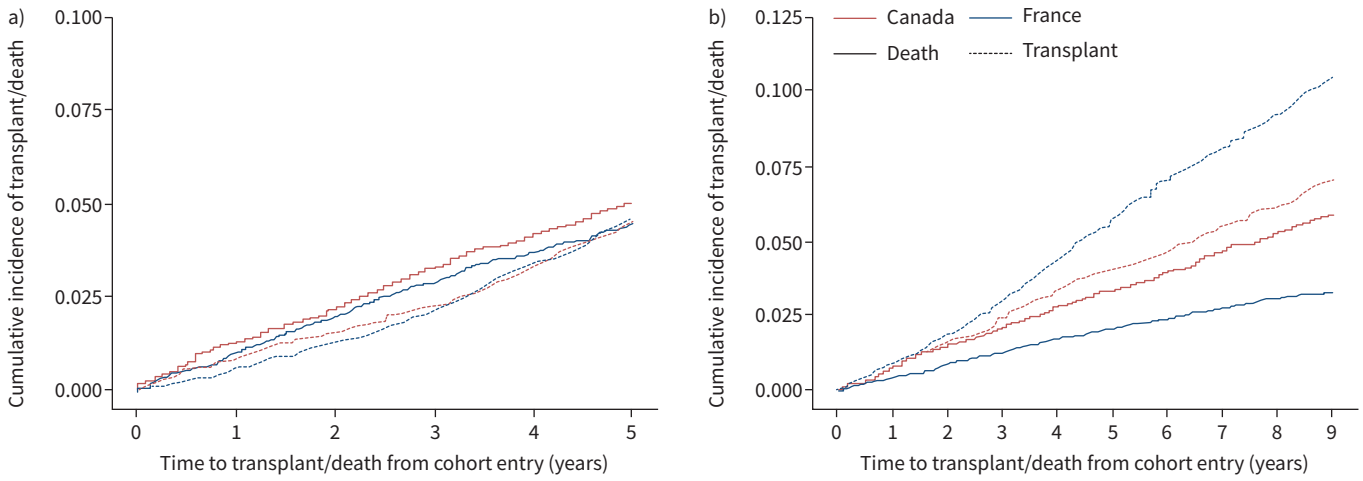


FIGURE 2 Competing risks analysis of receiving lung transplant or death without lung transplant: a) pre-high emergency lung transplantation (HELT) (2002–2006) (death p=0.24; transplant p=0.84) and b) post-HELT (2008–2016) (death p<0.001; transplant p<0.001) in France and Canada. Death refers to deaths without a lung transplant.

(figure 2a and supplementary table S3), 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 with 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 risks 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 with Canada (supplementary table S3). The increased probability of receiving a transplant compared with death in France in the post-HELT period was seen early as the two curves in figure 2b separate soon after time 0.

Post-transplant survival

The characteristics of transplant recipients pre- and post-HELT in France and Canada are summarised in supplementary table S4. The 1-, 3- and 5-year probability of survival post-transplant in France was 86.7%, 76.9% and 69.6%, respectively, in the pre-HELT period compared with 85.2%, 76.7% and 73.0%, respectively, in the post-HELT period (figure 3), with no significant difference in post-transplant survival

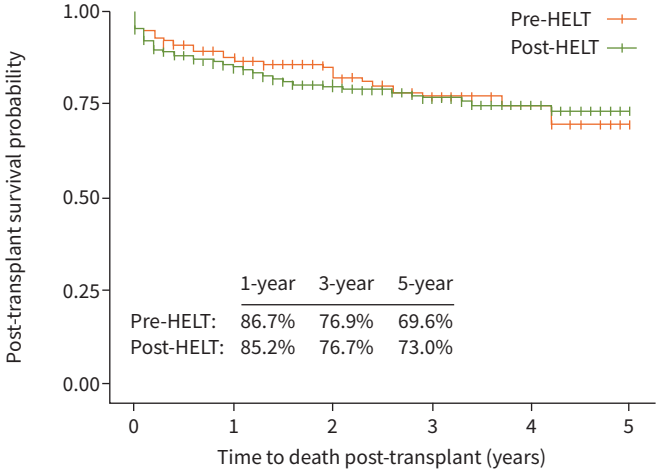


FIGURE 3 Post-transplant survival pre-high emergency lung transplantation (HELT) (2002–2006) and post-HELT (2008–2012) in France using 5 years of follow-up. The 1-, 3- and 5-year survival probabilities (%) are indicated.

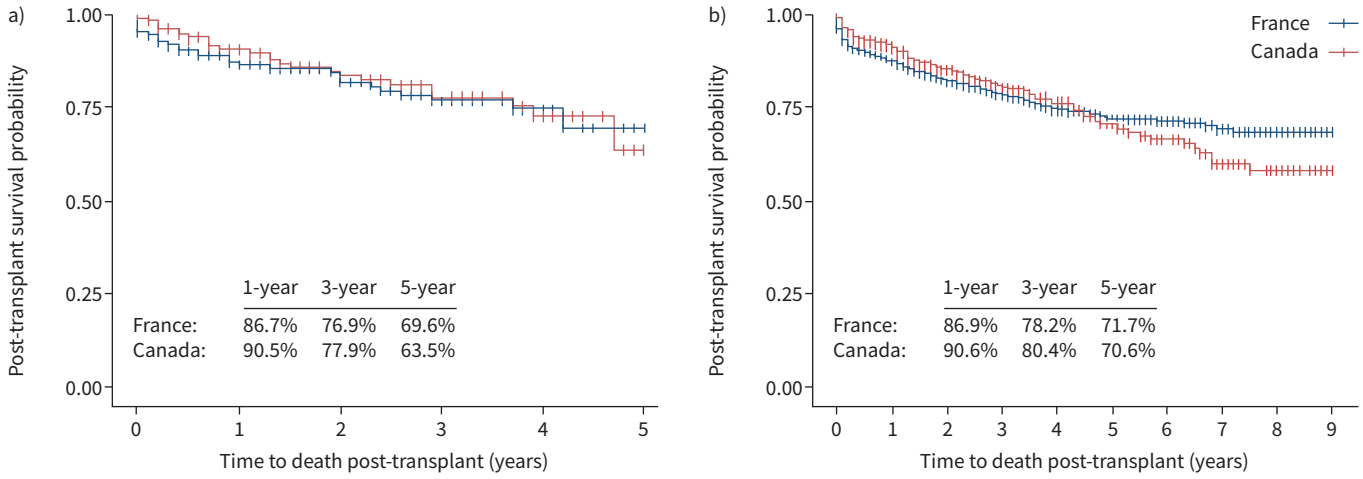


FIGURE 4 Post-transplant survival of cystic fibrosis patients in Canada and France a) pre-high emergency lung transplantation (HELT) (2002–2006) and b) post-HELT (2008–2016). The 1-, 3- and 5-year survival probabilities (%) are indicated.

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 post-HELT (p=0.76) period (figure 4). These results were unchanged after excluding patients infected with *B. cepacia* complex (supplementary figure S3).

Discussion

In the present study, we examined the impact of the HELT programme 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 programme in France, proportionally more patients received lung transplants and the risk of death without a transplant was lower for French patients. Such an improvement was not observed to the same magnitude in Canada. Furthermore, post-transplant survival in France was similar in the pre- and post-HELT periods despite including potentially sicker CF patients enrolled in the HELT programme. Comparison with Canadian transplant rates demonstrates 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 programme was to reduce deaths on the lung transplant waiting list and there is limited literature on the impact of the HELT programme 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 programme. A previous study showed, regardless of underlying disease, a decrease in the waitlist death rate from 19% to 2% since the HELT programme began [7], with CF accounting for 81.1% of cases. A study published in 2012 by Boussaud *et al.* [6] examined outcomes pre- and post-HELT for various diseases. They reported a decrease in survival rate post-transplant in the entire cohort in the post-HELT period (55% survival rate at 1 year) compared with the pre-HELT period (76.6% survival rate at 1 year) but did not present data by disease. One study by Savale *et al.* [20] reported the impact of the HELT programme 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 periods. Saueressig *et al.* [21] published a retrospective single-centre study assessing the impact of the HELT programme 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 programme. Roussel *et al.* [22] studied 503 HELT patients (47% had CF) compared with 1041 non-HELT transplant recipients and also found a significant increase in the rate of transplant following the implementation of the HELT programme. Our study revealed a unique comparison by quantifying the rate of transplants and deaths pre- and post-HELT in France compared with Canada, a country that does not apply the HELT programme. 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 with France in the post-HELT period, demonstrating the positive impact of the French HELT

programme. As there was also a slight increase in the rate of lung transplant in Canada post-HELT, we suggest that factors other than the improvement in transplant access *via* the HELT programme also contributed 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 [23]. However, given that it was performed in only one of the 10 transplant centres in France, it is unlikely to explain the results. Finally, in the post-HELT period, the age at transplant increased and the proportion of children who received a transplant decreased compared with the pre-HELT period, 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 programme [6, 22], while others have shown no change in post-transplant survival [7]. Because patients eligible for transplant within the HELT programme are potentially more unstable (*e.g.* intubated, on ECMO, *etc.*), it is important to assess the impact of this programme on post-transplant survival both within France and compared with Canada. We did not see lower survival in France in the post-HELT period, and 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-year follow-up) between the HELT-CF group and the group of patients with CF who were selected for the regular lung transplantation programme [21]. Moreover, despite differences in the prevalence of *B. cepacia* complex between the countries, our results showed no difference in post-transplant survival overall or after excluding individuals infected with *B. cepacia* complex in both countries. This may be due to the fact that the proportion of *B. cepacia* complex-infected individuals who received a lung transplant is low in both countries [2, 24]. Unfortunately, we were not able to identify French patients transplanted in the HELT programme *versus* those transplanted without the HELT programme specifically because this data is not captured in the French CF Registry. However, it should be noted that the proportion of patients being referred to the HELT programme in France is ∼20% of the total lung transplants, including CF and non-CF patients [22, 25]. Therefore, analysing post-transplant survival of CF patients in the HELT programme and comparing survival with those in the regular lung transplant programme will be important to assess in the future.

There is no universal consensus on the criteria for prioritisation of people awaiting lung transplantation. Italy took a similar approach to France and implemented the Italian Urgent Lung Transplant Programme (IULTp) in 2010, where patients could be transferred from the regular lung transplant programme to the IULTp if they were <50 years of age and required mechanical ventilation and/or extracorporeal lung support [26]. In 2018, the Italian CF Lung Transplantation Group reported no difference in mortality while on the waiting list regardless of whether patients were listed in the IULTp or not [27]. However, they observed a higher percentage of deaths at 1-year post-transplant for patients who were in the IULTp [27]. Moreover, studies showed that in the USA, 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 [28]. 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 [29]. 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 with the pre-HELT period, suggesting the effectiveness of the HELT programme in the context of the French healthcare system. In contrast to the HELT programme, 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 prioritise patients for organs.

This study has several strengths. We utilised two well-characterised 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 loss 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 ∼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 [30]. 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 waiting list, as the date of listing was not available for the French cohort. Determining how many of these pre-transplant deaths occurred while on the waiting list is important to further assess the effectiveness of the HELT programme. 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 period supports the assumption that the HELT programme 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 the HELT programme. Finally, our study does not allow us to determine if lung transplant prolongs life for patients (regardless of the HELT programme) compared with 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 programme in France. Furthermore, the HELT programme did not appear to have a negative impact on overall post-transplant survival, which 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 prioritisation strategy such as the HELT programme would be advantageous in other countries that have different healthcare systems.

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