

## **Data Supplement**

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

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## **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).**

	<b>France</b>	<b>Canada</b>	<b>P value</b>	<b>SMD</b>
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								
<i>P. aeruginosa</i> , n(%)	3435 (62.4)	2702 (69.2)	14.3	< 0.001	5174 (69.6)	3531 (71.6)	4.6	0.014
<i>B. cepacia</i> 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	

	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
NA, n(%)	1706 (31.0)	943 (24.2)			1448 (19.5)	1123 (22.8)		
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-HELТ (2002-2006) and post-HELТ (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<sub>1</sub>.

Variables	Transplant				Death			
	Pre-HELТ		Post-HELТ		Pre-HELТ		Post-HELТ	
	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 ( $\geq 2$ 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
<i>B cepacia</i> 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 <sub>1</sub>	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

HELТ: high emergency lung transplantation, CFRD: Cystic fibrosis related diabetes, FEV<sub>1</sub>: 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.**

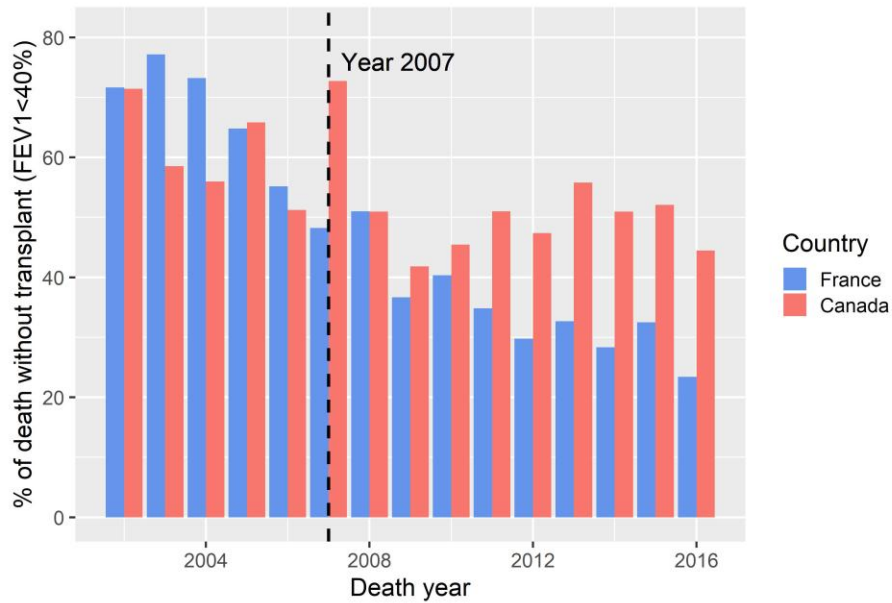
	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
	France	Canada	SMD	P Value	France	Canada	SMD	P Value
Total number of patients, n	248	173			755	340		
Pediatric, n(%)	51 (20.6)	16 (9.2)	32.2	0.003	105 (13.9)	22 (6.5)	24.8	< 0.001
Adult, n(%)	197 (79.4)	157 (90.8)			650 (86.1)	318 (93.5)		
Sex								
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								
<i>P. aeruginosa</i> , n(%)	236 (95.2)	160 (92.5)	11.1	0.351	737 (97.6)	330 (97.1)	3.5	0.739
<i>B. cepacia</i> 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
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	

	Pre-HELT (2002-2006)				Post-HELT (2008-2016)			
	France	Canada	SMD	P Value	France	Canada	SMD	P Value
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).**

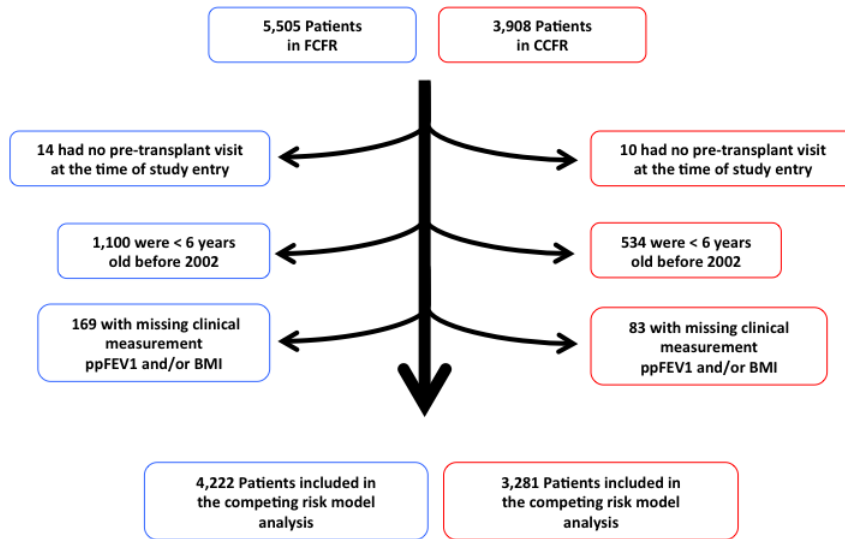


Footnote: Year 2007 is the year that the high emergency lung transplant program was implemented in France.  $FEV_1$ : forced expiratory volume in 1 second.

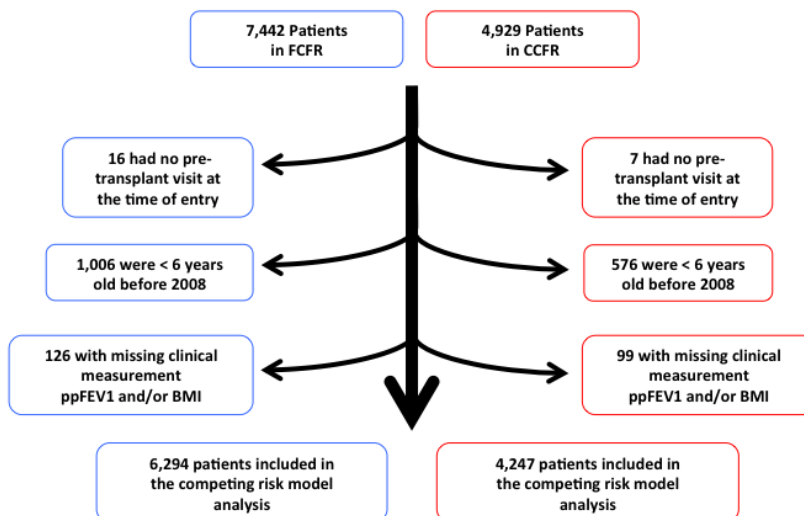


**Figure 2S. Patient selection from the French (FCFR) and Canadian (CCFR) CF registries for the competing risk analysis in the A) pre-HELT (2002-2006) and the B) post-HELT (2008-2016) periods.** HELT: high emergency transplantation, BMI: body mass index, ppFEV1: percent predicted forced expiratory volume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

A)

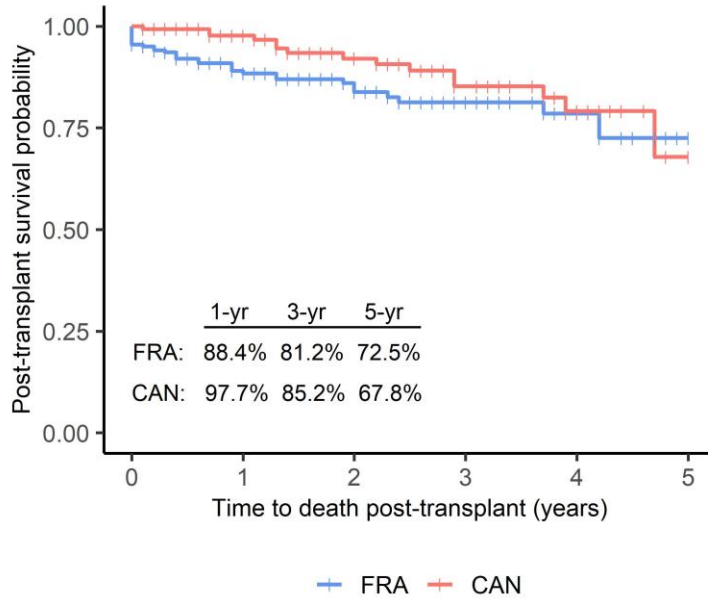


B)

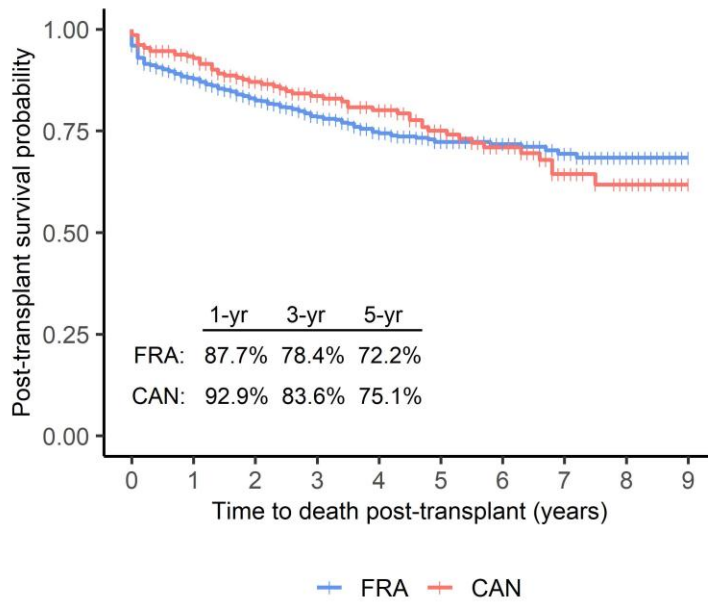


**Figure 3S. Post-transplant survival of CF patients without *B. cepacia* complex in Canada and France A) pre-HELT (2002-2006) and B) post-HELT (2008-2016) program. HELT: high emergency lung transplantation.**

A)



B)



## References

1. Yeung JC, Machuca TN, Chaparro C, Cypel M, Stephenson AL, Solomon M, Saito T, Binnie M, Chow CW, Grasmann 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.