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Clinical Characteristics of Cystic Fibrosis Patients Prior to Lung Transplantation: An International Comparison between Canada and the United States

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Abstract

Background—Cystic fibrosis (CF) patients from Canada have better reported post lung transplant survival compared to patients from the U.S. We hypothesized the clinical characteristics of CF patients prior to lung transplant differ between the two countries.

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Methods—Population-based cohort study utilizing combined Canadian CF Registry and U.S. CF Foundation Patient Registry data from 1986 to 2013. Demographic and clinical variables were analyzed prior to lung transplant.

Results—Between 1986 and 2013, 607 (10.2%) CF patients underwent lung transplantation in Canada and 3,428 (7.5%) in the U.S. A lower proportion of recipients had growth of *B. cepacia* complex prior to transplant in the U.S. compared to Canada (0.8% vs. 4.3%). Lung function was similar between recipients from the two countries. The proportion of patients classified as underweight was significantly higher in the U.S. compared to Canada (39.8% vs. 28.0%; SD 26.1) despite higher rates of feeding tube use (42.5% vs. 28.6%; SD 29.0).

Conclusions—CF lung transplant recipients from the U.S. have similar lung function, lower rates of *B. cepacia* complex, and worse nutritional parameters prior to transplant compared to counterparts in Canada. Future studies are necessary to evaluate the impact of these differences on post-transplant survival.

Introduction

Cystic fibrosis (CF) is the third most common indication for lung transplantation in adults and the most common indication in children.[1,2] Among the disease indications, adult CF lung transplant recipients have the longest post-transplant survival based on International Society for Heart and Lung Transplantation (ISHLT) statistics.[2] However, CF survival post-lung transplant has been reported to vary by country of residence.[3,4] Based on Canadian CF Registry data from 1988 to 2012, median post-transplant survival was estimated at 10 years.[3] Comparatively, based on United States UNOS/OPTN data from 2000 to 2011, the median survival for privately insured CF recipients was 7.9 years and 4.7 years for the publicly insured.[4] Median survival estimates from the U.K. are similar to the privately insured in the U.S. at 8.1 years.[4]

The reasons for national disparities in CF lung transplant outcomes are complex and likely involve differences in both pre- and post-transplant clinical factors. Pre-transplant factors include the process of selecting candidates (including timing of referral) and severity of illness at the time of transplant. For instance, selecting higher-risk candidates and/or prioritizing sicker patients at the time of transplant could result in worse post-transplant survival. The objective of this study was to use population-based national CF registry data to compare the pre-transplant clinical characteristics of lung transplant recipients in Canada and the U.S. We hypothesized CF lung transplant recipients in the U.S. would have more advanced lung disease and worse nutritional status prior to transplant potentially contributing to some of the differences in post-transplant survival reported in prior studies.

Methods

This population-based cohort study utilized a combined Canada-U.S. registry data set derived from the Canadian CF Registry (CCFR) and U.S. CF Foundation Patient Registry (CFFPR). The process of harmonizing and combining the national data sets has been described in detail in a recent publication.[5] The combined data set encompasses 42 Canadian and over 110 U.S. CF care centers from 1986 to 2013. The CCFR captures virtually all CF

patients in Canada[6] and the CFFPR captures approximately 94% of patients from accredited CF care centers in the U.S.[7] For this study, patients who underwent their first lung transplant in each country from 1986 to 2013 were selected for analysis. Subjects with prior non-lung transplants (e.g. liver, kidney, other) were excluded. The study was approved by the Ethics Review Boards of St. Michael's Hospital (Toronto, Ontario) and Seattle Children's Hospital (Seattle, WA).

Demographic, clinical, and treatment variables collected in the year prior to lung transplant were analyzed as the exact date of transplant was missing for 52% of CFFPR cases. In the combined data set, these variables corresponded to the first visit of the year in both countries as the CCFR only reported first annual visit clinical measurements prior to 2012. There were 110 patients (2.7%) whose FEV_1 was above 53% predicted, the highest pre-transplant FEV_1 documented in a prior analysis using the CCFR.[3] For these patients, the FEV_1 % predicted was set to missing as they represented potential errors.

The GLI reference equations were used to calculate FEV_1 % predicted. CDC growth charts were used to calculate BMI percentile for children aged 2–19, and for adults BMI was calculated using weight in kg/height in m^2. Patients were classified as underweight if their BMI percentile was less than 12% (for children aged ≤19 years) or if their BMI was less than 18.5 kg/m^2 for adults (>19 years) according to the WHO classification. Adult patients were classified as severely underweight if their BMI was less than 17 kg/m^2. Overweight was classified as a BMI over 25 kg/m^2 or a BMI percentile over 84%.

Patients were classified as receiving non-invasive bi-level positive airway pressure (BiPAP) ventilation support, home oxygen, and feeding tubes if they had any history of use in the three years prior to transplant. Treatment variables were collected for different periods in the two registries. BiPAP was first recorded in 2006 in the U.S. and 2011 in Canada. Feeding tubes and home oxygen were both recorded beginning in 2001 for the Canadian registry and 1989 in the U.S. registry. To ensure comparability of these variables, we have restricted the data to the latest year of availability in both countries. Given that the lung allocation score (LAS) was introduced in 2005 in the U.S. but not in Canada, a sub-group analysis was performed comparing clinical characteristics prior to lung transplantation in the five years pre- and post-2005.

Continuous variables were summarized using median and range. Categorical variables were summarized as frequency and proportions. Differences between the two countries were assessed using the Mann-Whitney-Wilcoxon test for continuous variables and the chi-square test for categorical variables. P-values are two-sided and due to the large sample size, a standardized difference (SD) was also calculated. Tests were deemed statistically significant if the p-value was less than 0.001 and SD>10.[8] All analyses were performed in R version 3.3.0.

Results

Between 1986 and 2013, 630 CF patients underwent lung transplantation in Canada and 3,428 in the U.S. The median time between clinical measurements and known date of

transplant was 347 (IQR: 318–362) days in Canada and 342 (IQR: 303–363) days in the U.S. As a proportion of patients followed during the corresponding time period in each registry, 10.2% underwent lung transplant in Canada compared to 7.5% in the U.S. A higher proportion of U.S. CF lung transplant recipients had a combined lung and other organ transplant (mostly heart-lung or liver-lung) compared to Canada (3.2% vs. 0.7%, SD 18.6). The sex and ethnic breakdown of CF lung transplant recipients in Canada and the U.S. was similar (Table 1). However the median age of transplant was lower in the U.S. compared to Canada, with a higher proportion undergoing transplant at <18 years of age (13.8% vs. 6.4%; SD 24.7) although the difference has decreased since 2010 (8.8% vs. 4.5%; SD 17.5).

There were higher rates of missing CF genotype information in the U.S. compared to Canada (24.3% vs. 7.1%), particularly prior to 1990, but of those patients with documented genotype, a similar proportion of recipients were homo- or heterozygous for the F508del mutation from each country. Rates of diabetes were slightly higher in the U.S. compared to Canada but the proportion of pancreatic insufficient patients was similar. While the prevalence of *P. aeruginosa* from sputum cultures over a lifetime was similar for transplant recipients from the two countries, there were much higher prevalence rates of MRSA in the U.S. and higher rates of *Burkholderia cepacia* complex in Canada.

For parameters reflecting lung disease severity prior to lung transplant, lung function based on FEV_1 and forced vital capacity (FVC) % predicted was similar between recipients from Canada and the U.S. including the proportion of patients with a FEV_1 % predicted of <20% (13.7% vs. 16.4%; SD 7.8). Furthermore, there were similar rates of home oxygen (73.6% vs. 69.5%; SD 10.2) and BiPAP (25.0% vs. 26.7%; SD 3.8) use for transplant recipients from Canada and the U.S., respectively.

CF patients from the U.S. had worse nutritional parameters prior to lung transplant compared to recipients from Canada. The proportion of patients classified as underweight (BMI percentile <12% for ≤19 years or BMI<18.5 kg/m^2 for >19 years) was significantly higher in the U.S. compared to Canada (39.8% vs. 28.0%; SD 26.1). Furthermore the proportion of adult patients classified as severely underweight (BMI<17.0 kg/m^2) was significantly higher in the U.S. compared to Canada (16.7% vs. 12.1%; SD 13.0), despite higher rates of feeding tube use in the U.S. compared to Canada (42.5% vs. 28.6%; SD 29.0).

A sensitivity analysis was performed comparing FEV_1 % predicted and BMI for patients with known exact date of transplant from each country (52% of cases from the CFFPR and 100% of cases from the CCFR). Values for FEV_1 % predicted and BMI were similar to the main analysis (data not reported). An additional analysis restricted to five years pre- and post-2005 to evaluate the impact of the lung allocation score on pre-transplant clinical characteristics revealed no significant differences between countries with the exception of higher rates of CF-related diabetes reporting in the post-LAS period in the U.S. relative to Canada (Supplementary Table 1).

Discussion

This combined CF registry study is the first to compare the clinical characteristics of lung transplant recipients from Canada and the U.S. Lower BMI and higher rates of feeding tube use indicate worse nutritional parameters for U.S. recipients relative to Canada. However, there has been a steady decrease in the proportion of patients classified as underweight over time in the U.S., such that the proportion of patients being classified as underweight before lung transplant are now similar between the two countries. The data from this study suggest that improvements can be made in optimizing nutritional parameters for CF patients prior to lung transplant in both countries since about 1 in 3 patients are classified as underweight.

Marked differences were observed in the rates of lifetime sputum culture positivity for *B. cepacia* complex between CF transplant recipients from the two countries. Patients with *B. cepacia* complex were underrepresented among transplant recipients from the U.S. compared to Canada (0.8% vs. 4.3%), relative to the rates of *B. cepacia* complex observed in the overall CF population in the U.S vs. Canada (4.5% vs. 7.2%).[9] While some *Burkholderia spp.* (specifically *B. cenocepacia* and *B. gladioli*) are considered relative contraindications to lung transplant[10] due to worse post-transplant outcomes,[3,10–15] these only represent a minority of *Burkholderia spp.* isolates (< 1/3) in the U.S.[16] As this study was not specifically designed to compare access to lung transplant between the two countries, future studies are warranted to understand why recipients with *B. cepacia* complex are underrepresented among transplant recipients from the U.S. compared to Canada.

A higher proportion of CF patients underwent lung transplantation prior to the age of 18 years in the U.S. compared to Canada. The number of pediatric lung transplants performed in Canada was small which limits statistical comparisons of clinical characteristics between the two countries for this age group but there were no obvious differences in this subgroup relative to the overall group comparison (Supplementary Table 2). As a result, the higher rates of pediatric CF transplants in the U.S. presumably reflect national differences in lung disease severity (and greater need for transplant) during the pediatric years as opposed to being reflective of differences in transplant referral practices. The proportion of pediatric patients transplanted out of all patients transplanted in the U.S. has decreased steadily over time potentially reflecting improvements in clinical outcomes and reduced need for transplant for pediatric CF patients in the U.S.

While lung function and the rates of end-stage lung disease treatments (home oxygen and BiPAP use) appeared similar prior to transplant for recipients from both countries, physiologic parameters (e.g. hypoxemia, hypercapnia) and need for mechanical ventilation were not available in the registries to fully assess severity of illness of CF recipients at the time of transplant. Furthermore, we could not perform a reliable comparison of post-transplant survival in Canada and the U.S. using CF registry data as loss to follow-up post-transplant was much higher in the U.S. compared to Canada (20% vs. 2%). Using simulation experiments, we have previously reported that survival analysis tends to underestimate actual survival as the loss to follow-up rate increases.[17] As a result, future studies directly comparing post-transplant survival will need to incorporate linkage between the U.S. CFFPR and UNOS/OPTN databases.

The year of transplant was known for all recipients but the exact date was missing for 54% of recipients from the CFFPR which is a study limitation. Therefore, to exclude the possibility of including post-transplant clinical measurements in the U.S., we analyzed clinical measurements from the first annual visit in the year prior to the transplant year in a sensitivity analysis. This resulted in a longer than desired time interval between clinical measurement and transplant. However, we do not believe this altered the results of our study as the clinical measurements ($FEV_{1\ \%}$ predicted, BMI) from patients with known exact date of transplant was similar to our primary analysis. Lastly, the rates of CFRD increased to a larger extent in the 5 years post-LAS (vs. pre-LAS) in the U.S. compared to Canada. This increase mirrors the increased reporting of CFRD in the non-transplanted adult CF population in the U.S. during the same time period (data not presented) and, therefore, does not appear to be the result of CF and/or transplant clinics trying to 'game' the LAS system by re-classifying patients with impaired glucose tolerance as having CFRD to inflate their LAS priority score.

In summary, this is the first study to compare pre-transplant clinical characteristics for CF lung transplant recipients in the U.S. and Canada. CF patients from the U.S. have similar lung function but are younger, have lower rates of B. cepacia, and have worse nutritional parameters prior to lung transplant compared to counterparts in Canada. Future studies are planned to directly examine the potential impact of these differences on post-transplant survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

B. cenocepacia	*Burkholderia cenocepacia*
BCC	*Burkholderia cepacia* complex
BiPAP	bi-level positive airway pressure
BMI	body mass index
CCFR	Canadian Cystic Fibrosis Registry
CF	cystic fibrosis
CFFPR	U.S. Cystic Fibrosis Foundation Patient Registry
FEV_1	forced expiratory volume in 1 second

GLI	Global Lung Initiative
IQR	interquartile range
ISHLT	International Society for Heart and Lung Transplantation
MRSA	methicillin-resistant *Staphylococcus aureus*
OPTN	Organ Procurement and Transplantation Network
P. aeruginosa	*Pseudomonas aeruginosa*
SD	standardized difference
U.K	United Kingdom
UNOS	United Network for Organ Sharing
U.S	United States
WHO	World Health Organization

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Table 1

Comparison of pre-transplant factors in Canada and the U.S.

Variable	Categories	Canada	%	U.S.	%	p-value	SD
Overall	N	607	100.0	3,428	100.0		
Type of Transplant	Lung	603	99.3	3,318	96.8	**<0.0001**	**18.6**
	Lung-Other	4	0.7	110	3.2		
Gender	F	276	45.5	1679	49.0	0.11	7.0
	M	331	54.5	1749	51.0		
Race	Non-Caucasian	13	2.1	75	2.2	>0.99	0.2
	Caucasian	588	96.9	3353	97.8		
	Unknown	6	1.0	0	0		
Age at transplant	Median (range)	28.9	(8.3–61.7)	27.7	(0.7–66.9)	**<0.0001**	**16.7**
	<18 years	39	6.4	474	13.8	**<0.0001**	**24.7**
	Pediatrics[1], <2000	10	7.8	193	19.2	**0.0009**	**33.8**
	Pediatrics, 2000–2010	23	6.7	208	13.0	**0.0007**	**21.5**
	Pediatrics 2010+	6	4.5	73	8.8	0.12	**17.5**
	≥18 years	568	93.6	2954	86.2		
Age at diagnosis	Median (range)	0.76	(0–57.9)	0.7	(0–60.9)	0.13	4.3
	<2 yrs	392	64.6	2227	65.0	0.85	0.8
	≥2 yrs	215	35.4	1201	35.0		
Genotype[2]	Homozygous dF508	328	58.2	1384	53.3	0.11	9.7
	Heterozygous dF508	189	33.5	985	38.0		9.3
	Other	47	8.3	226	8.7		1.3
Pancreatic Status	Sufficient	48	7.9	165	4.8	0.003	**12.7**
	Insufficient	559	92.1	3261	95.1		
	Unknown	0	0	2	0.1		
CF-Related Diabetes	No	323	53.2	1521	44.4	**<0.0001**	**17.8**

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Variable	Categories	Canada	%	U.S.	%	p-value	SD
	Yes	284	46.8	1907	55.6		
FEV_1 % Predicted	Median (range)	26.1	(9.8–51.8)	26.1	(9.1–52.9)	0.61	0
	<20%	83	13.7	563	16.4	0.22	7.8
	20–30%	276	45.5	1481	43.2		6.6
	≥30%	158	26.0	914	26.7		0.7
	Missing	90	14.8	470	13.7		
FVC % Predicted	Median (range)	46.0	(19.5–137.4)	44.5	(13.3–108.4)	0.033	8.3
	<20%	1	0.2	30	0.9	0.098	10.4
	20–30%	42	6.9	292	8.5		5.4
	≥30%	481	79.2	2737	79.8		8.0
	Missing	83	13.7	369	10.8		
BMI[3]	Normal weight	328	54.0	1589	46.4	**<0.0001**	**20.1**
	Overweight	32	5.3	103	3.0		**12.6**
	Underweight	170	28.0	1365	39.8		**26.1**
	<2000	38	29.7	494	49.2	**0.0001**	**39.9**
	2000–2010	94	27.2	609	38.2	**0.0007**	**22.1**
	2010+	38	28.4	262	31.6	0.21	**13.4**
	Missing	77	12.7	371	10.8		
	Median (range)	19.6	(13.3–30.1)	18.89	(12.8–46.2)	**<0.0001**	**20.0**
	BMI <17 kg/m^2 (adults)	69	12.1	493	16.7	0.011	**13.0**
Microbiology (ever/never)	MRSA	37	6.1	968	28.2	**<0.0001**	**62.3**
	B. cepacia complex	26	4.3	28	0.8	**<0.0001**	**51.9**
	P. aeruginosa	580	95.6	3310	96.6	0.0046	**11.7**
	Not cultured	3	0.5	51	1.5		
Treatment[4]	Feeding Tubes	130	28.6	966	42.5	**<0.0001**	29.0
	Total Eligible	455		2273			
	Home O_2	335	73.6	1580	69.5	0.055	10.2
	Total Eligible	455		2273			
	BiPAP	25	25.0	171	26.7	0.81	3.8

Variable	Categories	Canada	%	U.S.	%	p-value	SD
	Total Eligible	100		641			

[1]Pediatrics defined as <18 years of age. Time period divided into the following categories: year <2000, 2000–2010, 2010+.

[2]The proportion of patients missing genotypes was 7.1% in Canada (n=43) and 24.3% in the U.S. (n=833).

[3]BMI: underweight defined as BMI percentile <12% for ≤19 years or BMI<18.5 kg/m^2 for >19 years; overweight defined as BMI percentile over 84% for ≤19 years or BMI over 25 kg/m^2 for >19 years; and normal weight is measurements between underweight and overweight. Time period divided into the following categories: year <2000, 2000–2010, 2010+.

[4]Use of home oxygen and feeding tubes were calculated from 2001 onwards. Use of BiPAP was calculated from 2011 onwards.

Abbreviations: B. cepacia complex, *Burkholderia cepacia* complex; BiPAP, bilevel positive airway pressure; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MRSA, methiciliin-resistant *Staphylococcus aureus; P. aeruginosa*, *Pseudomonas aeruginosa*; SD, standardized difference.