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Clinical and demographic factors associated with post–lung transplantation survival in individuals with cystic fibrosis

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cystic fibrosis;
survival;
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B. cepacia complex

BACKGROUND: Contemporary studies evaluating post-transplant survival are limited and often include data from single centers or selected sub-groups. The purpose of this study was to evaluate overall transplant survival and to identify risk factors associated with death after transplant.

METHODS: The Canadian Cystic Fibrosis Registry, a population-based cohort, was used to describe survival after lung transplant. Pre-transplant factors associated with post-transplant survival were estimated using Cox proportional hazards models.

RESULTS: Between 1988 and 2012, 580 patients received a lung transplant. In the entire cohort, post–lung transplant 1-year survival was 87.8%, 5-year survival was 66.7%, and 10-year survival was 50.2%. Median post-transplant survival was 3.3 years (95% confidence interval [CI] = 2.13–6.56) in patients infected with *Burkholderia cepacia* complex compared with 12.36 years (95% CI = 10.34–17.96) in patients without *B cepacia* infection (hazard ratio [HR] = 2.63, 95% CI = 2.0–3.44). After adjustment, there was a non-significant trend toward better post-transplant survival with increasing year of transplant (HR = 0.98, 95% CI = 0.96–1.00). Pancreatic sufficiency (HR = 2.13, 95% CI = 1.41–3.20) and age at transplant such that youngest and oldest had the poorest survival ($p < 0.001$) were significant negative predictors of survival. The risk of death after transplant for patients infected with *B cepacia* was highest within the first year (HR = 6.29, 95% CI = 3.87–10.21) but remained elevated >1 year after transplant (HR = 1.92, 95% CI = 1.33–2.77) compared with patients without *B cepacia* infection.

CONCLUSIONS: After lung transplantation, 5-year survival in Canadians with CF is 67%, and 50% of patients live >10 years. Despite these impressive probabilities, age at transplant, pancreatic sufficiency and *B cepacia* infection remain important determinants of survival after lung transplantation.

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The median age of survival in cystic fibrosis (CF) has steadily increased over the last 2 decades.[1,2] This increase is likely due to several factors, including optimization of nutrition, aggressive antibiotic therapy for pulmonary

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exacerbations, and the availability of lung transplantation for progressive respiratory failure. Since the first heart-lung transplant for CF performed in 1984, there have been significant advances in the surgical technique (i.e., en bloc double-lung transplants, bilateral sequential lung transplants) and the post-transplantation medical management, and overall post-transplant survival has improved.[3]

Several published reports described single-center experiences[4–6]; however, population-based studies characterizing health outcomes after lung transplant in CF are scarce. Thabut et al[7] used United Network for Organ Sharing data (2005–2009) and reported the 1-year and 3-year post-transplant survival for 454 patients with CF in the United States was 88.4% and 67.8%, respectively. An earlier study published in 2009 used United Network for Organ Sharing data from 1987 to 2007 and demonstrated that patients who underwent transplant at older ages (28–34 years and $\geq$35 years of age) had a statistically significant reduction in risk of death compared with patients who underwent transplant between the ages of 7 and 20 years.[8]

Several factors, such as sex, malnutrition, and CF-related diabetes (CFRD), have been shown to have a negative impact on health outcomes in the general CF population[9–15]; however, their effects on the post-transplant population are unclear. For example, depending on the study, investigators found that individuals with CFRD have better survival post-transplant,[16,17] found that individuals with CFRD have an increased risk of death after lung transplant,[8] or found no association with post-transplant survival.[7] Furthermore, female sex and the presence of malnutrition have been shown to have a negative impact on overall CF survival, but it is uncertain if these are important predictors in the post-transplant patient population.[1,18]

Accurately predicting life expectancy post-transplant in patients with CF is important to allow caregivers to intervene to change modifiable risk factors and to outline accurately the risks and benefits of transplantation, which can guide decision making. The objectives of this study were to describe the Canadian transplant experience over the past 2 decades, to identify risk factors associated with post-transplant survival, and to identify sub-groups of CF patients at highest risk for death after transplant.

Methods

Data sources

This population-based cohort study used Canadian Cystic Fibrosis Registry data between 1988 and 2012. Individuals with CF are followed closely by 43 CF accredited clinics across Canada. There are 5 lung transplant centers in Canada (Vancouver, Edmonton, Winnipeg, Toronto, and Montreal). The Canadian Cystic Fibrosis Registry contains detailed demographic and annual clinical information on all patients with CF across Canada. Nutritional markers and lung function are recorded from the first stable clinic visit of the year, whereas other variables, such as sputum bacteriology and CF-related complications, reflect events that occurred within a calendar year. Date of transplant, transplanted organ, date of death, and cause of death are recorded in the registry. Registry data undergo routine validation checks to ensure that they are free of errors, and discrepancies are resolved by cross-referencing with original sources at the reporting CF center. In 2013, all CF clinics were provided with a list of transplanted individuals from their center to confirm their vital statistics as of December 31, 2012. If an individual underwent more than 1 lung transplant, the first transplant date was used with the first recorded lung transplant starting in 1988. The type of transplant was categorized as "lung" or "other," with "lung" referring to bilateral lung, heart-lung, and liver-lung transplants.

All individuals within the registry provided informed consent to have their data collected and used for research purposes. The study was approved by the Research Ethics Board at St. Michael's Hospital, Toronto, Ontario (REB No. 12-158C).

Risk factors

Genotype was classified as homozygous for delta F508, heterozygous for delta F508, other, or missing. Age at diagnosis was categorized into <2 years and ≥ 2 years groups. Pancreatic insufficient or pancreatic sufficient classification was based on enzyme usage.

Clinical measurements of forced expiratory volume in 1 second (FEV_1) and body mass index (BMI) were obtained from either the year of transplant or the year just before transplant. The date of the clinical measurements was used to ensure the testing was done before the transplant. FEV_1 was expressed as a percentage of the normal predicted values for height, age, and sex.[19,20] BMI was calculated using weight (kg)/height $(m)^2$. BMI percentiles were calculated for children between the ages of 2 and 17 years using U.S. Centers for Disease Control growth charts.[21] BMI was categorized into underweight and adequate weight; children were then classified based on the BMI percentile as underweight (BMI percentile $\leq$12%) or adequate weight (BMI percentile $>$12%), whereas adults $\geq$18 years old were classified into underweight (BMI <18.5 kg/m^2) and adequate weight (BMI ≥ 18.5 kg/m^2) based on BMI values. CFRD was defined as hyperglycemia based on oral glucose tolerance testing results or random blood sugar measurements requiring insulin therapy.[22] For sputum bacteriology, clinics report any positive culture in the year for the following bacteria: *Burkholderia cepacia* complex (BCC), *Pseudomonas aeruginosa, Staphylococcus aureus, Stenotrophomonas maltophilia,* and methicillin-resistant *S aureus*. Any history of previous infection before transplant for each of the bacteria was summarized as ever/never for each patient.

Statistical analysis

Characteristics of the CF transplant population were summarized using simple descriptive statistics (mean, median, proportions). Post-transplant survival was measured from the date of first lung transplant to date of death or December 31 of the year of the last recorded visit. The probability of surviving 1, 5, or 10 years post-transplant was calculated using the Kaplan-Meier method. Univariate predictors of survival were calculated using the Cox proportional hazards model. The most appropriate functional form of continuous predictors was chosen by examining Martingale residuals. Schoenfeld residuals were investigated to determine if the proportional hazards assumption was satisfied for all variables. When the proportional hazards assumption failed, a time-varying coefficient was used to explain the relationship of the hazard over time. For BCC status, the change in hazard 1 year post-transplant was modeled because immunosuppression is highest and infection risk is greatest in the first year after transplant. The multiple